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ABSTRACT BOOK

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0001

PREDICTING THE EMERGENCE OF PIPERAQUINE-RESISTANT *PLASMODIUM FALCIPARUM* MALARIA IN AFRICA

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Global efforts to control and eliminate *Plasmodium falciparum* (Pf) malaria have been thwarted by the emergence of resistance to first-line antimalarials. Resistance to piperaquine (PPQ) in Southeast Asia is primarily mediated by mutations in the drug efflux transporter PfCRT. In Africa, PPQ has been identified as a promising partner drug for chemoprevention with artemisinin-based combination therapies, based on its potency against asexual blood stage parasites, extended plasma half-life (2-3 weeks), and good safety profile. However, the emergence of artemisinin-resistant parasites in areas in Africa increases selective pressure for PPQ resistance, so it will be important to predict whether resistance can arise in this region. Here we have used gene editing to introduce the most common chloroquine-resistant *pfcrt* alleles in Africa into Dd2 (Asian) parasites: GB4 (Dd2 without N326S/I356T), Cam783 (Dd2 without N326S), and FCB (Dd2 without I356T). We then edited the most prevalent PPQ-resistant PfCRT mutations from Southeast Asia (T93S and I218F) into Dd2$^{GB4,\ Cam783,\ or\ FCB\ crt}$ parasites. In PPQ survival assays, these mutations only confer high-grade PPQ resistance (~10% survival at 200 nM) on the FCB PfCRT background. Parasites expressing GB4+T93S or Cam783+T93S exhibited increased survival only at lower PPQ concentrations (~25 nM). This suggests that N326S, absent in both GB4 and Cam783 but present in Dd2 and FCB, is necessary for these mutations to confer PPQ resistance. All T93S and I218F mutant parasites showed increased susceptibility to chloroquine and monodesethyl-chloroquine, relative to parental Dd2. Ongoing fitness assays will reveal the impact of our set of mutant *pfcrt* alleles on parasite growth rates *in vitro*. The interplay between the degree of drug resistance and parasite fitness is an important determinant of which strains can dominate regionally. Our findings help proactively predict the emergence of PPQ resistance in Africa, which is especially relevant to global health efforts to identify region-specific antimalarial treatments and to combat the spread of multidrug-resistant Pf parasites.

0002

CLASSICAL GENETICS IDENTIFIES MULTIPLE GENETIC LOCI INFLUENCING RESPONSE TO ANTIMALARIAL DRUG COMBINATIONS

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Triple artemisinin combination therapies (TACT) are currently being evaluated to replace artemisinin combination therapies (ACT) due to the burgeoning spread of antimalarial drug resistance. Since artemisinin derivatives have short serum half-lives, there is a greater demand on partner drugs to clear residual infections. Partner drugs, and antimalarials in general, often act on heme detoxification pathways leading to potential cross resistance and failure of clinically relevant drugs. To ensure the long-term success of TACTs, ideal partner drugs will have high synergy or produce collateral sensitivity, such that resistance to one drug results in greater sensitivity to the other. Identification of ideal drug combinations would rely on knowledge of the genetic determinants affecting susceptibility to each drug individually and in combination. To achieve this, we tested 102 unique recombinant progeny from a *Plasmodium falciparum* genetic cross in a high throughput screen against 14 drug combinations and used the result to carry out quantitative trait loci (QTL) mapping. The cross utilized a multidrug resistant, KEL1/PLA1 parasite isolated from western Cambodia in 2016, representing a contemporary Southeast Asian genetic background. The second parent is a drug sensitive, African parasite isolated from Malawi in 2016. With the recent emergence of Kelch13 mutations in east Africa, this cross will be valuable to assess the function and interactions of mutations associated with drug resistance in an African genetic background. Results for the piperaquine/amodiaquine drug combination identified a highly significant locus on chromosome 7 centered on *pfcrt*, as well as two significant loci on chromosome 10, a suggestive locus on chromosome 2 and a minimal signal on chromosome 14. Results for piperaquine/pyronaridine in combination also produced a very similar linkage scan to piperaquine/amodiaquine. Further investigation into these loci using unique progeny with varying Plasmepsin copy numbers and *pfcrt* alleles will elucidate their potential interactions that result in differential drug response.

0003

DECREASED EX VIVO SUSCEPTIBILITY OF *PLASMODIUM FALCIPARUM* TO BOTH DIHYDROARTEMISININ AND LUMEFANTRINE IN NORTHERN UGANDA

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The emergence of artemisinin (ART) resistance (delayed clearance after therapy) in northern (N) Uganda may facilitate selection of *Plamodium falciparum* resistant to ART-based combination therapy (ACT) partner drugs, as seen in southeast Asia. We compared genotypes and drug susceptibility phenotypes of *P. falciparum* isolates collected in June-July, 2021 from Tororo and Mbale, Districts in eastern (E) Uganda, where markers of ART resistance have been uncommon, and Agago District in N Uganda, where the resistance-associated PfK13 469Y and 675V mutations have emerged. Genotypes were determined using molecular inversion probe techniques. Drug susceptibilities were measured with IC_{50} (SYBR green) and ring survival assay (RSA) methods. We successfully assayed ring survival, IC_{50}s, and K13 genotypes in 75, 74, and 84 samples, respectively. As seen previously, the prevalences of PfK13 mutations associated with ART resistance were higher in N than E Uganda (469Y 33% vs. 7%, p = 0.01; 675V 16% vs. 4%, p = 0.16). Increased copy number of the *pfmdr1* and *pmp-2/3* genes was very uncommon. Susceptibilities to dihydroartemisinin (DHA) by RSA and to chloroquine, monodesethyl amodiaquine, piperaquine, mefloquine, DHA, quinine, and pyronaridine by IC_{50} were similar in the two regions. However, susceptibility to lumefantrine (LM) was decreased in N (IC_{50} 14.6 nM for 49 samples) compared to E (7.0 nM for 25 samples) Uganda (p <0.0001). 14 of 49 isolates from N, but none of 25 from E Uganda had LM IC_{50} >20 nM (p=0.002). The 469Y mutation was associated with abnormal DHA RSA (median survival 1.7% for WT, 2.5% for mixed, and 7.3% for pure mutant isolates; p = 0.01 for WT vs pure mutant) and trended toward elevated LM IC_{50} (11.4 nM for WT, 11.8 nM for mixed, and 14.8 nM for pure mutant isolates; p = 0.09). Significant associations were not seen for the 675V mutation, but sample size was limited (only two pure mutant 675V parasites were studied). Our results indicate loss of activity of both DHA and LM in N Uganda and suggest concern regarding the activity of artemether-LM, the first-line antimalarial in Uganda. Studies to assess the antimalarial efficacy of ACTs in N Uganda are urgently needed.

0004

IDENTIFICATION OF PIPERAQUINE RESISTANCE IN SOUTH AMERICA HIGHLIGHTING AN EVOLUTION OF MOLECULAR MARKERS CONTRASTING WITH THE SOUTHEAST ASIAN SITUATION

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Plasmodium falciparum malaria (*Pf*) is nowadays treated using six artemisinin-based combination therapies (ACTs) recommended by the WHO. Their efficiency is threatened by the emergence of parasite resistance. Recently, the combination dihydroartemisinin - piperaquine (DHA-PPQ) has been discontinued in Southeast Asia following the emergence of parasites resistant to both DHA and PPQ. In French Guiana, South America, we identified piperaquine resistance at a prevalence of 45.3% based on *in vitro* survival assays (n=86). This resistance was significantly associated with the mutation PfCRT^{C350R} and *Pfpm2/3* gene amplifications (p<0.001). It was also responsible for therapeutic failures in patients. However, no signs of artemisinin partial resistance (phenotype or genotype) were detected. Genomic data identified recurrent *de novo* emergence of this mutation. It has already spread at the sub-regional level in the Guiana Shield and requires improved guidelines for treatment recommendations. A temporal analysis was also performed to understand PPQ resistance evolution over a 20-year period. It revealed the emergence of PfCRT^{C350R} mutation, first, followed, years later, by the amplification of *Pfpm2/3*. *In vitro* assay results suggested that PfCRT^{C350R} mutation is required for PPQ resistance in this region. This situation will be compared to the evolution of resistant markers described in Southeast Asia to emphasize the different mutational pathways and genetic architectures of drug resistance in different parasite genetic backgrounds.

0005

EVALUATION OF THE IMPLEMENTATION AND EFFECTIVENESS OF INTERMITTENT PREVENTIVE TREATMENT FOR MALARIA USING DIHYDROARTEMISININ-PIPERAQUINE ON REDUCING MALARIA BURDEN IN SCHOOL-AGED CHILDREN IN TANZANIA: AN IMPLEMENTATION RESEARCH CLUSTER RANDOMIZED TRIAL

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In high malaria endemic areas of sub-Saharan Africa, school-age children (5-15 years) have become increasingly more vulnerable and contribute significantly as reservoirs to onward malaria transmission in the population. An effectiveness-implementation hybrid trial was conducted to evaluate the implementation of the intermittent preventive treatment of malaria in schoolchildren (IPTsc) using Dihydroartemisinin-Piperaquine(DP), for evidence of the operational feasibility and effectiveness of IPTsc on clinical malaria incidence at a high endemic area in Handeni District Council (DC), Handeni Town Council (TC), and Kilindi DC of Tanga region, Tanzania. Wards in the three study districts were the randomisation unit (clusters). Each ward was randomised to implement IPTsc or not (control). All schoolchildren in primary schools located in the IPTsc arm were given DP three times a year in liaising with transmission seasonality. For the impact of the intervention, in each district, 24 randomly selected wards (12 per study arm, one school per ward) were chosen as representatives. Three rounds of drug dispensing (in Aug 2020, Nov 2020, and Mar 2021), covered 127 primary schools with around 80,000 schoolchildren involved. The average respective coverage of completed dose per round was; 77% (range 68%-83%), 76% (range 69%-82%), and 79%(range 77%-83%). The drugs were well tolerated by the schoolchildren. For impact evaluation, 3752 schoolchildren (1971 DP arm and 1781 control arm) were enrolled. Baseline asymptomatic malaria parasitaemia was 58% for Handeni DC, 20% for Kilindi DC, and 18% for Handeni TC. The average attributable reduction of malaria parasitaemia across all districts was 62% and the effectiveness of IPTsc in preventing clinical malaria over the course of a year was 41% (95%CI 31%-49% *p<0.001*). Implementation of IPTsc was feasible and well accepted by the communities and teachers. IPTsc reduces malaria parasitemia, prevents clinical malaria, and is feasibly implementable through schoolteachers. The addition of IPTsc to school health policy is desirable in improving the health and academic achievement of schoolchildren.

0006

THE POTENTIAL IMPACT OF POINT-OF-CARE RESISTANCE DIAGNOSTICS ON SPREAD OF ANTIMALARIAL RESISTANCE WITHIN A MULTI-DRUG POPULATION TREATMENT STRATEGY

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Rapid 'resistance diagnostic' tests are an emerging technology consisting of user-friendly sample-to-result DNA tests, which detect not only malaria infection, but also drug resistance-associated mutations in the parasite. These point-of-care tests could allow clinicians to choose an antimalarial according to the resistance profile of a patient's infection. This technology has direct benefits for the patient, but also has potential to alter spread of resistance if the diagnostics become widely used. Here, we use multi-strain malaria transmission models tracking sensitive and resistant parasites over time to test the potential for resistance management by diagnostics. First, we explore proof-of-principle within an ODE deterministic model framework. If two drugs, A and B, are used in a standard multiple first-line therapy population treatment strategy, and allocated to patients at random, resistance to each drug will eventually spread to 100% frequency. By contrast, in an idealised scenario where resistance diagnostics are used to guide all treatment decisions and operate perfectly (i.e. patients with the strain resistant to drug A are always given drug B instead, and vice versa), the advantage of single-drug resistance is negated and resistant strains cannot spread. We are currently developing an individual-based model to include real-life factors such as imperfect sensitivity of the diagnostic, lower coverage of diagnostic use (currently ~40% for standard RDTs in many areas), lower test sensitivity for minor clones within multi-clonal infections, varied and off-policy informal antimalarial use, residual drug levels, partial resistance and multi-drug resistance among others. Nonetheless in initial results we so far find that resistance diagnostics could substantially increase the useful lifespan of an antimalarial drug compared to a standard multiple first line therapy policy. Furthermore, they may allow continued use of drugs to which there is moderate resistance already present, conserving efficacy of newer antimalarials.

0007

CONTRASTING DRUG POLICY INTERVENTIONS TO DELAY THE FIXATION OF 561H ARTEMISININ RESISTANT *PLASMODIUM FALCIPARUM* IN RWANDA

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While artemisinin combination therapies (ACTs) have been instrumental in reducing the global public health burden due to malaria, the identification of 561H artemisinin-resistant *Plasmodium falciparum* in Rwanda is the latest signal that the parasite is rapidly evolving resistance. The lack of a WHO approved replacement for ACTs necessitates the need for a drug policy intervention to delay the spread and fixation of 561H while simultaneously meeting the public health goal of effective treatment of uncomplicated malaria. In this study, we employed a national-scale, individually-based stochastic model of malaria, calibrated for the ground conditions in Rwanda to evaluate various drug policy interventions. Following model validation, we developed a menu of interventions based upon four broad policy interventions: artemether-lumefantrine (AL) extension, AL replacement, multiple first-line therapies (MFT), and drug rotation. We found that over short time horizons (i.e., three to five years) options incorporating dihydroartemisinin-piperaquine (DHA-PPQ) minimizes treatment failures, although the evolution of partner drug resistance to piperaquine results higher treatment failures over a ten-year time horizon. In contrast, policy options incorporating artesunate-amodiaquine (ASAQ) or AL had higher treatment failure rates in the short term, while having a two-fold or better difference in treatment failures over the long-term, compared to full DHA-PPQ deployment. These findings highlight the need for awareness both the time horizons involved, and partner drug resistance when developing drug policy responses to the of artemisinin resistance while awaiting the deployment of next generation therapies for uncomplicated malaria.

0008

MATERNAL CHILD HEALTH VULNERABILITY DURING THE COVID-19 PANDEMIC IN LUSAKA, ZAMBIA

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Infectious disease outbreaks and natural disasters often have indirect impacts on essential health services, which can lead to significant excess morbidity and mortality. Anecdotal experience, qualitative studies, and mathematical modeling studies have raised serious concerns about the potential impact of the COVID-19 pandemic on essential health services in sub-Saharan Africa, but quantitative estimates of service disruption remain limited. We quantified the change in health service utilization for a variety of health services at a referral hospital in Lusaka, Zambia. We compared the monthly number of patients receiving various services before and after the start of the COVID-19 pandemic by student's t-test. The most dramatic decreases in utilization were found to be in child weight checks (-56.6% [95% CI: -37.5%, -75.7%]) and the number of cervical cancer screenings performed (-43.3% [95% CI: -21.9%, -64.7%]). Obstetric services and childhood vaccinations demonstrated more modest declines. Our study provides quantitative measures for the decline in several health service which can be used for modeling the long-term impacts of the pandemic. Our findings also highlight the particular vulnerability of preventative health services during disaster scenarios.

0009

IMPACT OF COMMON GENETIC VARIANTS ON CYTOKINE RESPONSE HETEROGENEITY UPON BCG VACCINATION IN INFANTS FROM GUINEA-BISSAU

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Mycobacterium tuberculosis (TB) continues to be one of the leading causes of mortality worldwide. Over 25% of TB deaths occur in the African Continent. Bacillus Calmette-Guerín (BCG) being TB vaccine also provides non-specific protective effects against other infections through "trained innate immunity". Several studies have demonstrated that the host genetic variation has a strong influence on the immune response, e.g to influenza, Hepatitis B or measles vaccination. However, which genetic variants affect cytokine responses to secondary infections upon BCG vaccination is unknown. Moreover, while studies in European populations have demonstrated the role of genetic polymorphisms in the inter-individual variability in cytokine responses upon stimulation, it is not clear whether these findings are transferable to non-Europeans. We utilized an African trial cohort (Guinea-Bissau) of low-birth-weight (<2.5 kg) infants (~400

samples) randomized to BCG vaccination or no BCG-vaccination. In vitro stimulation of whole blood was done using five different stimuli followed by seven different cytokine measurements. We performed genome-wide SNP cytokine QTL (cQTL) mapping followed by pathway enrichment and functional annotation. The results were compared using a European BCG-vaccinated adult cohort (n=300).In the African samples, we identified 9 independent cQTLs ($P < 5 \times 10^{-8}$) affecting cytokine responses specifically in the BCG group but not in the control group. Interestingly, these cQTLs show pleiotropic effects. Also, nominal cQTLs ($p < 0.05$) between European and African samples showed very limited overlap (1.4% to 1.5%), indicating either age or ethnicity-associated genetic effects. We identified several causal genes at these loci and implicated complement pathway in regulating cytokine response after BCG vaccination, which was confirmed through functional validation. Our study shows that distinct genetic loci affect cytokine response in BCG-vaccinated African infants; the same associations were not seen in otherwise similar BCG-unvacciantedinfants or in European BCG-vaccinated adults.

0010

TRADITIONAL UVULECTOMY: PREVALENCE AND ASSOCIATED FACTORS IN A PREGNANCY BIRTH COHORT IN NORTH SHEWA ZONE, ETHIOPIA

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Traditional uvulectomy is a procedure which consists of cutting part or all of the uvula. It takes place in informal settings in the community without any clinical assessment or indication, usually for fear of obstructed breathing in infants leading to death. The procedure is performed by local traditional healers using unsterilized sharp equipment and is known to expose individuals to complications such as excessive bleeding, sepsis, tetanus and infectious diseases like Hepatitis and HIV. Despite efforts to counsel and educate the community on the dangers of this practice, it still persists in some developing countries. In Ethiopia, this practice is commonly observed in the Amhara region where the community attributes nearly all infant and neonatal illnesses to uvular swelling or elongation. This region also bears one of the highest infant and neonatal morbidity and mortality rates in the country. Few hospital-based studies have been conducted to describe prevalence and complications of this practice but there is dearth of information on the magnitude of this problem in the community. The BIRHAN pregnancy and birth cohort study is based in the Amhara region and follows a cohort of children from birth up to two years of age through scheduled visits on days 6, 28 and 42 after birth as well as months 6, 12 and 24. This study aims to assess the prevalence and timing of traditional uvulectomy among a largely rural community and describe social, obstetric and neonatal factors associated with the observation of this practice. A total of 2,290 live births were enrolled and followed during the period of December 2018 to December 2021. The prevalence of traditional uvulectomy in the study population was high at 14.1%; n=322. Of those who were subject to the procedure, 8.7%; n= 28 were performed by day 6 of birth and 74.2%; n=239 were done by the age of 12 months. Further analysis will describe factors associated with this harmful practice. The results of this study will help to describe the current burden of this problem as well as identify risk populations and areas for targeted interventions that will help to reduce neonatal and early childhood morbidity and mortality.

0011

ASSOCIATIONS BETWEEN BRAIN VOLUMETRY IN CHILDHOOD AND EARLY CHILDHOOD STUNTING

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Early childhood stunting affects over 200 million young children worldwide and is associated with suboptimal childhood development and cognition. There are limited data on the effects of early childhood stunting on human brain volumetry. We evaluated childhood brain volumes at 9 years of age and its association with stunting at 2 years, in a community-based birth cohort in Vellore, south India. Volumetric T1 weighted magnetic resonance imaging (MRI) images were acquired using Siemens Skyra 3T MRI scanners without sedation, and automated segmentation performed using FreeSurfer version 6. For analysis, volumes of total brain, cerebellum, regional cerebral cortices, subcortical brain structures and corpus callosum at 9 years were compared between those stunted and not stunted at 2 years of age using univariate analysis with further adjustments for age, sex, and total brain volume. Of 251 new-borns recruited into the MAL-ED birth cohort, 205 (81.7%) children were available for the 9-year follow-up. Of 178 children included in this analysis, 83 (46.6%) children were stunted at 2 years. Children stunted at 2 years of age had smaller left and right cerebellar cortices when compared to those not stunted (left - 52,032 mm^3 Vs 53,348 mm^3; p = .03 and right - 52,369 mm^3 Vs 53,688 mm^3; p = .04 respectively), when adjusted for age, sex, and total brain volume. Stunted children also had significantly smaller posterior corpus callosum when compared to those not stunted (744 mm^3 Vs 783 mm^3 respectively; p = .04). Follow up of an Indian birth cohort showed that early childhood stunting was associated with lower childhood cerebellar cortical brain volumes which may influence information integration and motor co-ordination, as well as smaller posterior corpus callosum which could affect higher order association brain regions. Future research should explore concurrent and predictive nutrition-brain associations in children.

0012

CHARACTERIZING THE BURDEN OF HYALINE MEMBRANE DISEASE AMONG DECEASED INFANTS ENROLLED IN THE KENYA CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE NETWORK (CHAMPS) PROGRAM

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Hyaline membrane disease (HMD) is a life-threatening clinical syndrome whose true prevalence is still unknown in many African countries. Furthermore, diagnosis and therapy remain a challenge in developing countries. Child Health and Mortality Prevention Surveillance (CHAMPS) is a multi-country surveillance program that systematically identifies causes of under-five mortality from defined catchment areas in seven countries. Here, we described prevalence, diagnosis, management, and maternal risk factors for hyaline membrane disease among neonates enrolled in the CHAMPS Kenyan site. Causes of death (COD) were determined by a panel of experts using data from post-mortem conducted through minimally invasive tissue specimen testing, clinical records, and verbal autopsy. Between May 2017 and April 2021, 124 deceased neonates had their COD determined. Thirty (24.2%) had HMD as immediate COD or other significant condition causing death. Slightly more than half (17 [56.6%]) had a clinical diagnosis of HMD antemortem—none of the cases had the often routinely required investigations such as chest X-ray, electrocardiogram, blood culture or blood gases analyses done prior to

death. Supplemental oxygen was given in all cases, with the amount of oxygen administered being sup-optimal (0.5L/min). No case received surfactant replacement therapy, continuous positive airway pressure, mechanical breathing machine, and endotracheal tube placement. HMD was commonest in neonates with low birth weight (26 [86.6%]) and preterm births (25 [83.3%]). The prevalence of HMD is high among Kenya CHAMPS cases, with significant antemortem gaps in diagnosis and clinical management of cases identified. Given medical complexity of diagnosing and managing children with HMD, a high index of clinical suspicion coupled with training on optimal management can be considered to reduce HMD associated neonatal deaths.

0013

FACTORS ASSOCIATED WITH DISCHARGE AGAINST MEDICAL ADVICE AMONG CHILDREN TREATED FOR SUSPECTED OR PROVEN INFECTIONS AT UGANDAN HOSPITALS

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Discharge against medical advice (DAMA) is a known risk factor for adverse outcomes in children. An improved understanding of its impact on outcomes and its risk factors is essential to the development of programs to address DAMA. The aim of this study was to (1) assess the impact of DAMA on post-discharge outcomes and (2) to identify key socioeconomic and clinical risk factors for DAMA. This secondary analysis of a multisite observational study included children 6-60 months of age hospitalized with suspected or proven infections enrolled from July 2017 to July 2019. Children received follow-up for 6 months after discharge to determine outcome. Seventy-seven clinical and socio-demographic variables, collected at admission, were assessed as potential risk factors. Univariate logistic regression was performed to identify significant risk factors for DAMA, as well as its impact on post-discharge readmission and mortality. Of the 3,673 children who survived to hospital discharge, 483 (13%) were discharged against medical device, and 53 (11%) of them died within 6 months. DAMA was highly associated with post-discharge mortality (HR: 3.62, 95% CI: 2.60-5.05). Malnutrition, HIV and anemia were key clinical risk factors of DAMA, while lower maternal education, higher distance from hospital, and the children being brought to the hospital by their father (compared to their mother) were key social risk factors. DAMA is common and is a key risk factor for poor post-discharge outcomes. Programs to address DAMA, especially for socially vulnerable children, are urgently required.

0014

CLINICAL DECISION SUPPORT ALGORITHM ADHERENCE AT A PEDIATRIC TELEMEDICINE AND MEDICATION DELIVERY SERVICE IN A LOW-RESOURCE SETTING

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In low-resource settings the application of telemedicine coupled with medication delivery has considerable potential to overcome healthcare access barriers. We piloted a telemedicine and medication delivery service (TMDS) called 'MotoMeds' for pediatric patients with acute illness at night in Haiti. In this study, a paper-based clinical decision-support algorithm was developed for call center case management. We assessed the algorithm's performance by comparing call center exams with paired in-person exams (reference standard). In this sub-analysis, algorithm adherence was the primary outcome measure. Inclusion criteria were age 10 years or less and parental contact with a TMDS provider. Workflow: A parent of an ill child contacted the call center. A TMDS provider used the algorithm to gather information to triage the child for danger signs and generate an assessment and plan. Cases included a severity (mild, moderate, severe) and disposition assessment; plans included oral or topical medications and/or oral fluids. For households within the delivery zone, a provider and driver transported medications/fluids to the child's home where the paired exam was performed. Two independent physicians reviewed the charts for algorithm non-adherence: severity mis-categorizations, failure to identify danger signs, prescription of a non-indicated antibiotic and/or failure to prescribe an indicated antibiotic. A total of 382 cases were enrolled; 86% (327) of cases at the call center and 88% of cases (296) at the household exhibited full adherence. Among cases with deviations, mis-categorization between mild and moderate severity was the most common type at both the call center (13%, 48) and household (10%, 35). A missed danger sign occurred in <1% (1) of cases at the call center and 3% (10) of cases at the household. Prescription of non-indicated antibiotics occurred in 1% (5) and 5% (16) of cases and failure to prescribe an antibiotic occurred in 1% (2) and <1% (1) of cases at the call center and household, respectively. The data reveal areas for improvement and suggest adherence can be optimized with digitization, a critical step towards scalability.

0015

WHOLE PROTEOME DIFFERENTIAL SCREENING IDENTIFIES HELMINTH DEFENSE MOLECULE AS NOVEL SCHISTOSOMIASIS JAPONICA VACCINE CANDIDATE

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To identify vaccine candidates for Schistosomiasis japonica, differential screening of an adult worm cDNA library was employed using sera and epidemiologic data from a praziquantel treatment reinfection cohort (N = 300) in a holoendemic region of the Philippines. This approach enables the identification of schistosome antigens recognized by antibodies expressed by resistant, but not susceptible, individuals. 1 x 106 clones were differentially screened of which 32 were recognized by antibodies in both resistant sera (RS) and susceptible sera (SS), 38 were recognized by antibodies in SS, and five were uniquely recognized by RS. Of the five uniquely recognized clones, four were identified as SjHDM-1, a helminth innate immune cell modulator. The population profile of rSjHDM-1-specific antibodies in the praziquantel treatment reinfection cohort was assessed using a bead-based assay. Cohort participants demonstrated a 2.7-fold increase in rSjHDM-1-specific IgG antibody responses compared to SWAP-

specific IgG responses (p<0.0001) and a 3.7-fold increase compared to SEA-specific IgG responses (p<0.0001). Compared to North American controls, study participants displayed a significant increase of rSjHDM-1-specific IgG antibody responses (p=0.007). Immunofluorescence staining of SjHDM-1 in adult *Schistosoma japonicum* worms exhibited localization to the tegument in female and male worms. Mouse protection studies will be conducted to characterize SjHDM-1 as a vaccine candidate, with efficacy assessed in a buffalo challenge study. SjHDM-1 yields promise as a novel schistosome vaccine antigen given its host immune accessibility and its antigen-specific IgG profile in holoendemic populations.

0016

MATERNAL SCHISTOSOMIASIS AND ALTERATIONS IN BREAST MILK COMPOSITION

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Human breast milk is the preferred nutritional source for babies and is recommended for at minimum 6 months and, ideally, up to 24 months. Breastfeeding is associated with reduced risks of infant acute otitis media, gastroenteritis, and lower respiratory tract infections. Human milk is composed of macronutrients including carbohydrates such as lactose, micronutrients, and components conferring immune protection including immunoglobulins, predominantly secretory IgA. IgA-secreting plasma cells of the breast are thought to originate in the intestine. In a mouse model of schistosomiasis, egress of eggs through the gut lymphoid tissue led to vascular remodeling and a reduction in secretory IgA producing lymphocytes. The effect of maternal schistosomiasis on human breast milk composition has yet to be investigated. To elucidate this question, a cohort of 240 pregnant women in Leyte, Philippines were enrolled and followed until their infants were 2 years of age. Helminth infection was evaluated by Kato-Katz method at enrollment (less than 20 weeks gestation) and at 32 weeks gestation. Women were offered anthelmintic treatment, but all declined. Breast milk samples were evaluated at periodic time points throughout the study. At six months postpartum, exclusively breastfeeding women who were infected with *Schistosoma japonicum* were found to have a 29% decrease in IgA in their breastmilk (p<0.05). We postulate that this is the result of damage to the gut lymphoid tissue during schistosome egg migration. Additionally, in mothers with evidence of gut integrity disruption and bacterial translocation, as measured by endotoxin in blood collected at 32 weeks gestation, there was an association with both decreased IgA (p<0.01, R^2=0.024) as well as decreased lactose content (p<0.01, R^2=0.023) in the breastmilk at 6 months postpartum. This is the first study to investigate alterations in human breast milk, in particular demonstrating impairment in the immune properties of breast milk, in maternal schistosomiasis. Future work will investigate associations between altered milk components and infant growth in the context of maternal schistosomiasis.

0017

COMPARATIVE GENOMICS AND GENETIC MAPPING BUILT ON A NEW SNAIL MODEL PROVIDE INSIGHTS INTO SCHISTOSOME-RESISTANCE IN THE SNAIL *BIOMPHALARIA GLABRATA*

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Schistosomiasis, caused by Schistosoma parasites transmitted by freshwater snails, still plagues 237 million people in the world. *Biomphalaria glabrata* has served as the only model snail for studies of schistosomes in snails. To better understand schistosome vector snail biology and help develop innovative snail control strategies, we have developed a new snail model consisting of two homozygous *B. glabrata* lines (iM line and iBS90) with sharply contrasting schistosome-resistance phenotypes. We produced and compared high-quality genome sequences for iM line and iBS90 which were assembled from 255 (N50 = 22.7 Mb) and 346 (N50 = 19.4 Mb) scaffolds, respectively. Using F2 offspring bred from the two lines and the newly generated genome sequences, we constructed 18 linkage groups covering 96% of the genome and identified three new QTLs (quantitative trait loci), two involved in snail resistance and one relating to body pigmentation. This study provides excellent genomic resources for understanding complex vector snail biology, reveals genomic difference between resistant and susceptible lines, and offers novel insights into genetic mechanism of snail resistance to schistosomiasis.

0018

INTERLEUKIN-4-INDUCING PRINCIPLE FROM *SCHISTOSOMA MANSONI* EGGS IS IMPORTANT IN BLADDER CANCER: DNA RECOGNITION AND BINDING SPECIFICITY OF THE *S. HAEMATOBIUM* HOMOLOGUE

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Urogenital schistosomiasis, caused by *Schistosoma haematobium* is the most common form of schistosomiasis worldwide and is well-known for its association with bladder cancer; incidence rates estimated at about 3-4 cases per 100,000. However, the underlying mechanisms for the causal link between *S. haematobium* and bladder cancer, are poorly understood. Interleukin-4-inducing principle from *Schistosoma mansoni* eggs (IPSE) is the most abundant secreted protein from eggs of all schistosome species and plays a major role in modulating host pathology. We have previously demonstrated that H-IPSE, the *S. haematobium* homolog of IPSE, is internalized by both endothelial and urothelial cells, drives endothelial and urothelial proliferation, and is thus involved in *S. haematobium*-related carcinogenesis. Here, we used Protein binding microarray (PBM) technology and bioinformatics approaches to determine the specific DNA binding motifs of H-IPSE, and the downstream transcriptional events that result. Our results showed that DNA binding of H-IPSE is highly specific, and a DNA-binding motif of GGGTGGG was determined. The GGGTGGG sequence is recognized by the transcription factors PuF and Sall2, which are involved in tumor suppression. Concurrent experiments with M-IPSE (the *S. mansoni* homolog) showed that M-IPSE has the DNA binding motif resembling GGGGGAAAA and is different from H-IPSE, although similar in their affinity for G-rich sequences. Together, our results enabled us to identify novel targets of H-IPSE and its role in carcinogenesis and tumor progression through DNA recognition and binding of transcription factor sequence motifs involved in tumor suppression, and thus expand the understanding of the *S. haematobium*-associated pathology. The differences in DNA binding motifs for H-IPSE and M-IPSE may likely explain the unique carcinogenic properties of S. *haematobium* but not *S. mansoni*.

0019

HARNESSING THE POTENTIAL OF ANTI-GLYCAN ANTIBODIES INDUCED IN SCHISTOSOMIASIS FOR DEVELOPMENT OF HIGHLY SENSITIVE AND SPECIFIC SEROLOGICAL TOOLS

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The WHO 2030 roadmap for schistosomiasis clearly identifies an expanded portfolio of highly sensitive and specific diagnostic tools as essential

for continued and sustained progress towards elimination. Serological assays are excellent for sensitive detection of primary infections with schistosomes and for schistosomiasis surveillance in very low endemic, near- and post-elimination settings. However, many existing assays are based on crude soluble egg, cercarial or worm antigen preparations, which suffer from batch-to-batch variation and contain cross-reactive epitopes. Many glycan elements present in the schistosome glycoprotein and glycolipid repertoire elicit high antibody titres upon infection. Here we aim to exploit the antigenicity of glycan motifs for development of highly sensitive and specific schistosomiasis serology, while also benefitting from the added advantage of glycans being highly stable compared to protein antigens. Tailor-made glycan microarrays combined with well-characterised sample sets (n>500 individuals) were used to evaluate target performance. Sensitivity was determined using two controlled human schistosome infection (CSI) studies, primary infection samples from travellers, and samples from schistosomiasis endemic areas. Specificity was confirmed using helminth naïve and soil-transmitted helminth positive samples. From >80 targets, a single native schistosome glycan performed with high sensitivity and specificity for both IgG and IgM (≥95%). Observations from natural primary (traveller) and low dose CSI (10-30 cercariae) single exposure infections show dose dependent timing of IgG response initiation. Current preliminary data indicates that synthetic glycans can mimic the native material. In conclusions, a glycan target candidate for development of highly sensitive and specific schistosomiasis diagnostic tool(s) with use cases for travellers and in low endemic, near and post-elimination settings has been identified. Importantly, the glycan antigen shows promise for scalable production and hence future standardised test development.

0020

SOIL-TRANSMITTED HELMINTHIASIS IS NO LONGER A PUBLIC HEALTH PROBLEM IN BURKINA FASO

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Baseline mapping conducted between 2004 and 2005 showed Burkina Faso was endemic for soil-transmitted helminths (STH) and co-endemic with schistosomiasis (SCH) and lymphatic filariasis (LF) in a number of health districts. Overall, 48 out of 70 health districts (HDs) had STH prevalence among school age children (SAC) ranging 1.8-48.7%. Mass drug administration (MDA) for STH started in 2001 in the Sud-Ouest region and reached all endemic HDs by 2005, integrated with LF and/or SCH MDA. Population 5 years and older were targeted with albendazole during LF/MDA and SAC were targeted with albendazole during SCH/MDA and since 1999, deworming of children under five years has been conducted biannually with vitamin A supplementation (VAS) campaigns. To assess multiple years of treatment on STH endemicity, impact assessments were conducted in 2016-2019 during both SCH sentinel site surveys and LF transmission assessment surveys (TAS) with support from USAID's END in Africa and Act | West programs. SCH-STH surveys were carried out in 77 sentinel and spot check sites, with a total of 11,065 children aged 5 to 15 years evaluated. TAS-STH integrated surveys were conducted in 20 LF evaluation units (EUs), with a total of 6,927 children aged 6 to 7 evaluated in 650 sites. Kato-Katz was used to diagnose STH infections in stool. In total, 727 sites across 66 HDs were assessed by either SCH-STH or TAS-STH surveys, although only 48 of these were endemic for STH at baseline. The STH prevalence findings ranged from 0.00 to 4.49% (median prevalence 0.00%). Among them, 12 HDs evaluated through TAS-STH surveys were classified as having a prevalence of <2%, and 30 HDs were classified as having a prevalence between 2% and 10%. No moderate or heavy intensity infection was found in any HD. The results showed that multiple years of deworming may have successfully eliminated STH as a public health problem in Burkina Faso. STH MDA is no longer needed, but to maintain the progress made in controlling STH, targeted deworming will be implemented in collaboration with the Nutrition Directorate and the Family Health Directorate for pregnant women and women of childbearing age at health facilities.

0021

CIRCULATING ANODIC ANTIGEN (CAA) AS A DIAGNOSTIC MARKER FOR MEASURING TREATMENT SUCCESS IN UROGENITAL SCHISTOSOMIASIS

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Monitoring of anthelmintic efficacy constitutes a challenge, as diagnostics are mainly based onmeasuring the excretion of eggs. Therefore, sensitive and accurate tools are needed to improve theassessment of the efficacy of anthelmintic interventions. Diagnosis of schistosomiasis is alsocomplemented by the detection of *circulating anodic antigen* (CAA), an antigen that is released by*Schistosoma* worms into the bloodstream of the host and excreted via urine. As part of the freeBILy-GAB study, we compared CAA detection in urine vs. urine filtration method to assess the efficacy ofpraziquantel treatment for urogenital schistosomiasis during pregnancy. We evaluated the efficacy ofpraziquantel (40mg/kg single dose) within 82 infected pregnant women. Schistosomiasis wasdiagnosed and monitored through urine filtration and CAA detection multiple days post-treatment. Detection of CAA was based on an up-converting reporter particle-based lateral flow test. Wecalculated cure rates (CR), geometric mean (GM), and intensity reduction rate (IRR) for bothprocedures. CRs by microscopy were higher compared to that of CAA detection at days 21 (96.8% vs.81.1%) and 41 (96.8% vs. 80.3%) following treatment. Decrease of urine CAA levels appeared to befaster than urine egg counts, as CAA GM dropped below the positivity threshold 4-6 days aftertreatment, while the GM of egg counts only reached negativity after 14-21 days. Egg count IRRcontinued to increase after treatment for many days and reached the WHO threshold of 90% fortreatment success on day 14. Meanwhile, CAA IRR remained lower, showed greater dispersal and thesteady decline reversed on day 28. The CAA is a prospective tool for monitoring praziquantel-basedtreatment. The CAA detects the effect of treatment at an earlier time point as compared tomicroscopy. However, we recorded higher variability of CAA levels during follow up where wesuspected that antigen levels would remain at a low level. The CAA detection might be more sensitiveto immature worms than egg-based microscopy, therefore detecting treatment failure or reinfection more accurately.

0022

COMMUNITY-WIDE DEWORMING LEADS TO A LOWER BURDEN OF STH INFECTION IN SCHOOL-AGED CHILDREN COMPARED WITH SCHOOL-BASED DEWORMING ALONE: RESULTS ROM THE COMMUNITY-DEWORMING AGAINST SOIL-TRANSMITTED HELMINTHS (CODE-STH) TRIAL

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STH infections cause significant morbidity worldwide. The main control strategy is deworming of school-aged children (SAC). Community-wide deworming may reduce reinfection in SAC further as reducing the STH reservoir in adults may also reduce transmission. CoDe-STH is the first trial in the world comparing school-based versus community-wide deworming on STH infections in SAC. It is the largest ever trial using qPCR for STH diagnostics. Conducted in 64 primary schools in Dak Lak province, Vietnam, over 21,000 albendazole doses were given to SAC in both trial arms, and over 70,000 doses given to community members in the intervention arm at baseline. Stool samples were collected from SAC in both arms at baseline and at 1 year. More than 15,000 samples were analysed by qPCR. The primary outcome was prevalence of *Necator americanus*, the dominant STH species in the region; the main secondary outcome was infection intensity of *N. americanus*. Generalised linear mixed models with an interaction term of arm/timepoint were used to compare study outcomes. Unadjusted and adjusted odds ratios (OR) of *N. americanus* infection in SAC did not differ between trial arms at follow-up indicating that community-wide deworming had no impact on reducing reinfection of SAC one year after deworming. However, the odds of high/moderate intensity *N. americanus* infection was significantly lower in the community arm (uOR 0.29, p=0.001; aOR 0.30, p=0.001), demonstrating that community-wide deworming meant reinfections in SAC one year after deworming were of a lower intensity. In a sensitivity analysis, whereby schools with baseline *N. americanus* prevalence of <5% were excluded, the incident rate ratio (IRR) of infection intensity was also significantly lower in the community group (uIRR 0.42, p=0.008; aIRR 0.48, p=0.009). CoDe-STH is the first demonstration that community-wide deworming lowers burden of STH infection in SAC more than school-based deworming alone. This trial demonstrates the health benefit of expanding deworming programs to include the wider community after 12 months and only one round of treatment.

0023

GENETIC DIFFERENCES AMONG HUMAN TRICHURIS POPULATIONS WITH DIFFERING RESPONSES TO ALBENDAZOLE-IVERMECTIN COMBINATION TREATMENT

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Trichuris trichiura, one of the most important Soil Transmitted Helminth (STH) species, infects over 500 million people globally. Mass drug administration treatment programs use either albendazole or mebendazole but these benzimidazole drugs have very low efficacy against *T. trichiura,* with egg reduction rates (ERR) typically below 50%. Combination albendazole-ivermectin treatment has shown considerable improvement in efficacy. An albendazole-ivermectin combination treatment trial was performed in three regions - Laos, Tanzania, and Cote d'Ivoire, revealing high efficacy with ERR above 98% in Tanzania and Laos but much lower efficacy in Cote d'Ivoire with ERR below 70%. To explore whether this difference in efficacy could be due to genetic differences in the parasite populations, we performed Illumina short-read deep amplicon sequencing of multiple mitochondrial and ribosomal DNA loci on *T. trichiura* PCR positive fecal samples from the three regions. Primers targeting the mitochondrial *nad1*, *nad4, cox-1,* and the major β-tubulin gene generated haplotypes mapping to the appropriate reference sequences from all the samples from Tanzania and Laos, but not from Cote d'Ivoire. Phylogenetic analysis of the ribosomal ITS-1 and ITS-2 loci revealed that haplotypes from the samples in Cote d›Ivoire clustered separately from those found in Tanzania and Laos populations in a clade containing *Trichuris* sequences from non-human primates and *Trichuris suis*. This study demonstrates that the *Trichuris* population in Cote d›Ivoire is genetically divergent to those from Tanzania and Laos, likely a cryptic species, and has a lower sensitivity to albendazole-ivermectin combination treatment.

0024

HUMAN GUT MICROBIOME CHANGES ARE ASSOCIATED WITH SINGLE DOSE ALBENDAZOLE TREATMENT OUTCOMES OF HOOKWORM INFECTIONS

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Microbes play an important role in human gut homeostasis, metabolic, immunologic and physiopathology of the body. Active helminth infections cause host gut dysbiosis, which should restore after successful treatment. Our longitudinal study conducted during 2018-2021 in the Kintampo North Municipality in Ghana recorded low cure rates with treatment with a single dose of 400 mg albendazole in some communities. To investigate the involvement of the gut microbiome we obtained fecal samples from consented hookworm positive participants who were either successfully treated or failed. At each sampling event, the samples were collected prior to and 10-14 days post albendazole treatment. We used 16S rRNA amplicon sequencing of DNA extracted from stool to investigate the composition and biodiversity of the gut microbiota and to identify potential microbial biomarkers associated with treatment outcomes. The results showed significant variation in microbiota diversity between individuals successful and unsuccessful after albendazole treatment (ADONIS; R^2= 0.10 p= 0.001). A significant compositional increase in Firmicutes (Metastats; p= 0.005) was observed among individuals who failed treatment and a corresponding increase in Proteobacteria (Metastats; p= 0.04) within cured individuals. The diversity analysis also revealed a significant increase in microbial diversity (ANOSIM; R= 0.21, p= 0.001) among successfully treated individuals. This study suggests a relationship between human gut microbiota and albendazole therapy outcomes of hookworm infection. Moving forward, we will conduct further studies to hone in on specific biomarkers identified within this study to establish their potential for assessment of pharmacological responses to anthelminthic therapies.

0025

THE BENZIMIDAZOLES OXFENDAZOLE AND FLUBENDAZOLE ELIMINATE ADULT FILARIAE OF *LITOMOSOIDES SIGMODONTIS* IN AN IMMUNE SYSTEM-DEPENDENT MANNER

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Preclinical research is hampered by the fact that drugs with known efficacy in human filarial patients as well as filarial rodent models are less active *in vitro* and require increased concentrations for efficacy. In the present study, we investigated to what extent the efficacy of the benzimidazoles flubendazole and oxfendazole in the *Litomosoides sigmodontis* mouse model depends on the immune system. Both flubendazole and oxfendazole are direct acting drugs and treatment with either compound can lead to complete elimination of adult worms in the *L. sigmodontis* mouse model after subcutaneous (flubendazole) or oral (oxfendazole) application. Wild-type BALB/c, eosinophil-deficient dblGATA, IL-4R/IL-5-deficient, antibody-deficient μMT, and B-, T-, and NK-cell-deficient RAG2/IL-2Rγ mice were infected with *L. sigmodontis*. Following adult worm development (35 dpi), mice were treated with optimal and suboptimal doses of flubendazole subcutaneously and oxfendazole orally, respectively, and worm burdens were determined 70 days post infection and compared to vehicle controls. In a separate experiment, animals were treated with a combination of oxfendazole and IL-4, IL-5, or IL-33 for 3 days. Wild-type animals showed a reduction in adult worm burden of >98% compared with vehicle controls after 5-day treatment with flubendazole and oxfendazole. In contrast, treatment with either benzimidazole in knockout mice resulted in no reduction (RAG2/IL-2Rγ) or significantly impaired reduction in worm burden (dblGATA, IL-4R/IL-5$^{-/-}$, μMT). In addition, the efficacy of a suboptimal 3-day treatment with oxfendazole (17% reduction in adult worms) was increased to 70% reduction in adult worms when combined with IL-5, but not IL-4 (37%) and IL-33 (39%). Our results suggest that various components of the immune system support the filaricidal effect of benzimidazoles *in vivo* and represent a way to increase treatment efficacy *in vivo* and may allow the development of *in vitro* assays with a better prediction of drug efficacy.

0026

PROCESS DEVELOPMENT OF SJ-P80: A LOW-COST TRANSMISSION-BLOCKING VETERINARY VACCINE FOR ASIATIC SCHISTOSOMIASIS

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Asiatic schistosomiasis caused by *Schistosoma japonicum* is a neglected tropical disease resulting in significant morbidity to both humans and animals - particularly bovines - in endemic areas. Infection with this parasite leads to less healthy herds, causing problems in communities which rely on bovines for farming, milk and meat production. Additionally, excretion of parasite eggs in feces perpetuates the life cycle and can lead to human infection. We endeavored to develop a minimally purified, inexpensive, and effective vaccine based on the 80 kDa large subunit of the calcium activated neutral protease (calpain) from *S. japonicum* (Sj-p80). Here we describe the production of veterinary vaccine-grade Sj-p80 at four levels of purity and demonstrate in a pilot study that minimally purified antigen provides protection against infection in mice when paired with a low-cost veterinary adjuvant, Montanide™ ISA61 VG. Preliminary data demonstrate that the vaccine is immunogenic with robust antibody titers following immunization, and vaccination resulted in a reduction of parasite eggs being deposited in the liver (23.4-51.4%) and intestines (1.9-55.1%) depending on antigen purity as well as reducing the ability of these eggs to hatch into miracidia by up to 31.6%. We therefore present Sj-p80 as a candidate vaccine antigen for Asiatic schistosomiasis which is now primed for continued development and testing in bovines in endemic areas. A successful bovine vaccine could play a major role in reducing pathogen transmission to humans by interrupting the parasitic life cycle and improving quality of life for people living in endemic countries.

0027

INTERLEUKIN-4-INDUCING PRINCIPLE OF *SCHISTOSOMA MANSONI* EGGS (IPSE), A SCHISTOSOME IMMUNOREGULATORY PROTEIN, PREVENTS SEPSIS

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Urogenital and hepatoenteric schistosomiasis transmission depend upon the successful transit of eggs across the bladder and intestinal walls, respectively. However, egg passage disrupts local tissues and can lead to bacterial translocation, sepsis, and host death, an undesirable outcome for schistosomes that rely on continuous oviposition to maximize reproductive success. There is evidence that schistosomes may immunoregulate their hosts to prevent sepsis. *Schistosoma mansoni*-infected mice develop endotoxemic sepsis and die if their myeloid cells lack the IL-4 receptor. Mice whose bladders are injected with *Schistosoma haematobium* eggs also develop endotoxemia and die if phagocytic cells are depleted. *Schistosoma* eggs secrete large amount of the interleukin-4-inducing principle of *S. mansoni* eggs (IPSE). These findings led us to hypothesize that IPSE may be a schistosome molecule that prevents host sepsis. To test this hypothesis, mice underwent intravenous IPSE or vehicle injection followed by intraperitoneal injection with cecal slurry a day later to induce sepsis. Mice were then assigned clinical sepsis scores every 2 hours for 18 hours in a blinded fashion (maximum score of 28). Both groups of mice had similar baseline scores. Whereas mice given vehicle injections developed progressively severe sepsis with an average score of 16 at 18 hours, IPSE-treated mice did not exceed a score of 14 at any time point. Additionally, at time of euthanasia (18 hours post-sepsis induction), there was a decrease in average sepsis scores in the IPSE-treated group compared to vehicle-treated mice, that continued to have a worsening clinical course. A 48-plex cytokine analysis of mouse plasma collected at time of euthanasia was performed using the Luminex platform. This revealed significant changes in multiple cytokines, consistent with IPSE's known immunoregulatory mechanisms. These findings support the hypothesis that IPSE may contribute to prevention of schistosomiasis-associated sepsis likely via preconditioning, and suggest that IPSE could be developed as a therapeutic agent for other forms of sepsis.

0028

ECO-CLIMATIC FACTORS SHAPING THE DISTRIBUTION OF *ANOPHELES COLUZZII* AND *AN. GAMBIAE* MALARIA VECTORS AND OF THEIR PUTATIVE HYBRIDS ACROSS THEIR SYMPATRIC RANGE

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Anopheles coluzzii (CO) and *An. gambiae* (GA), the main Afrotropical malaria vectors, have recently diverged and believed to be isolated due to imperfect pre-mating isolation mechanisms, as shown by records of putative hybrids (H) characterized by heterozygous CO/GA genotypes of diagnostic markers in chromosome-X centromeric region. We here report the results of the systematic review of the existing (2001-2021) literature on field samples of CO, GA and H distribution across their sympatric range in west and central Africa. This allowed to create a database with >170k individuals from >1,900 sampling sites; of these individuals approximately 119k were collected and identified as adults, 5k as larvae and 47k were collected as larvae, but genotyped after emergence in the laboratory.

Overall, H-frequency was highest in the far-west region (up to 25%), 10-fold lower (up to 1.9%) in western countries and again 10-fold lower (<0.2%) in central Africa. Unexpectedly, H-frequency was overall lower in samples collected as larvae but emerged in the lab and genotyped as adults (which we expected to have escaped selective mechanism against H-larvae in the field), than in samples collected as adults. Preliminary results of Generalized Additive Model carried out on the latter sample highlight temperature and rainfall (and not land cover) as major climatic determinants of H-frequencies. In addition, it is predicted that H-frequency is higher where CO and GA frequencies are balanced and in proximity to the coast, confirming at continental level previous results from Burkina Faso and far-west region, respectively.

0029

LOCAL THERMAL ADAPTATION IN MOSQUITO POPULATIONS AND THE POTENTIAL IMPLICATIONS FOR IMPACTS OF CLIMATE CHANGE

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Local thermal adaptation in mosquito populations and the potential implications for impacts of climate change Environmental temperature impacts many aspects of mosquito life history. Consequently, there is considerable concern that increases in temperature due to climate change could lead to shifts in the dynamics and distribution of *Aedes aegypti*, the primary vector of arbovirus diseases like dengue, Zika, and yellow fever. Many current mechanistic models that examine the effects of temperature on transmission tend to assume there are 'average' thermal performance curves that are representative for a given vector species. However, this 'one size fits all' assumption ignores the potential for local thermal adaptation to create population-level differences in thermal performance. In this study, we explored thermal performance of five field populations of *Ae. aegypti* from Mexico, together with a standard laboratory strain. We reared these six populations at a range of temperatures between 13°C and 37°C to generate thermal performance curves for a suite of life-history traits including development rate, fecundity, and survival. We then integrated these traits into a composite fitness measure to characterize the effects of temperature on overall population growth rates. The results provide strong evidence for the potential for local thermal adaptation in *Ae. aegypti* populations and challenge the prevailing of application of 'one size fits all' thermal performance models to explore the current and future impact of climate on mosquito borne diseases.

0030

WHY DO HUMANS DIFFER IN ATTRACTIVENESS TO MALARIA MOSQUITOES?

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Malaria morbidity and mortality have increased in the past years, underlining the need for fundamental knowledge to develop new or improved vector surveillance and control tools, such as odour-baited traps. Malaria mosquitoes are attracted to humans using cues such as volatiles emanating from the human body. Earlier research has shown that human individuals differ in their attractiveness to the malaria mosquito *Anopheles coluzzii*, which correlates with human skin microbial composition. The human skin interacts in a complex manner with the immune system that on one hand defends the skin against pathogens and on the other hand facilitates the balance of commensal bacteria. However, it is unknown which selection pressure drives this preference from mosquitoes for specific humans. We hypothesize that mosquitoes prefer those humans whose blood is most beneficial for their reproduction and/or survival. To test this hypothesis, an observational study with 49 human subjects was conducted. During four visits, *An. coluzzii* mosquitoes were allowed to take blood meals from subjects *in vivo* and *in vitro*. Odour samples and skin swabs for analysis of microbial composition were collected from each subject during each visit. After feeding, mosquito oviposition and survival were monitored up to 14 days after feeding. Furthermore, from whole blood of the subjects, peripheral blood mononuclear cells were isolated and then stimulated *in vitro* with three selected species of commensal bacteria to study individual variation in cytokine production as immunological parameters. Individual attractiveness of the human odour samples to *An. coluzzii* mosquitoes was studied in a dual-choice olfactometer. Preliminary results show substantial variation across participants in the parameters measured. Statistical modelling is ongoing to investigate effects of subject traits on mosquito attraction and reproduction.

0031

GENOTYPING OF *ANOPHELES* MOSQUITO BLOOD MEALS REVEALS NONRANDOM HUMAN HOST SELECTION: IMPLICATIONS FOR *PLASMODIUM FALCIPARUM* TRANSMISSION, MALAWI

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Genotyping of human blood in arthropod vector blood meals allows identification of individual humans who were fed upon. This approach has improved understanding of parasite transmission in several vector-borne disease systems, including malaria. We used microsatellite-based genotyping to identify which humans were naturally transmitting *Plasmodium falciparum* to *Anopheles* vector mosquitoes. Household surveys (n=46) were conducted in two districts of moderate-to-high malaria transmission in southeastern Malawi. Demographic information and blood spots on filter paper were collected from consented participants. Indoor resting, blood-fed, female *Anopheles* mosquitoes were repeatedly sampled from inside participants' houses every two weeks during peak transmission (Jan-Apr 2020) by pyrethroid spray catches and CDC light traps. Genomic DNA from human blood spots and mosquito blood meals was genotyped and unique profiles identified and matched using a program in RStudio. *P. falciparum* DNA was detected in human and mosquito samples by PCR. Human blood was detected in 370 mosquito samples, of which 12% (n=44) contained more than one human genotype. Few individuals contributed most of the blood meals to the *Anopheles* vector population. 46 unique human genotypes from the at-risk human participants (n=250) were found among the 370 mosquito blood meals. The number of blood meals taken from individual people ranged from 1 to 49. More blood meals (60%) came from males than females even though males were a smaller fraction of the population. Among blood meals that matched genotyped participants, vectors fed more frequently on school-age children (SAC) (6-15 years old) than younger children and adults. Mosquitoes that had fed upon male SAC had the highest *P. falciparum* infection prevalence in their abdomens. Results support the hypothesis that SAC, particularly males, are important reservoirs of *P. falciparum* transmission from humans to mosquitoes. Thus, interventions aimed at reducing *P. falciparum* transmission should preferentially target this population.

0032

DOES HOST PREFERENCE DRIVE OBSERVED FEEDING PATTERNS OF *AEDES ALBOPICTUS* ACROSS GEOGRAPHIC POPULATIONS?

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Aedes albopictus is an invasive mosquito species capable of transmitting over 20 different pathogens with a variety of reservoir hosts. Its capacity to transmit these pathogens in nature is unclear, in part due to uncertainty surrounding its feeding behavior. Blood meal analyses from field-captured mosquitoes have shown vastly different feeding patterns, with a range of anthropophagy and host diversity levels. We sought to investigate whether innate host preference influences observed feeding patterns in nature. Low generation *Aedes albopictus* colonies were established with field-collected mosquitoes from 3 locations with high reported anthropophagy (Thailand, Cameroon, and Florida) and 3 locations with low reported anthropophagy (New York, Maryland, and Virginia). These mosquitoes were compared against anthropophilic (Thai *Ae. aegypti*) and zoophilic (Ugandan *Ae. aegypti*) control colonies. Host preference was assessed via dual-port olfactometer, which allows simultaneous presentation of two hosts (human arm and guinea pig). After 10 minutes of odor exposure, the number of mosquitoes that chose each host were recorded. All 6 *Ae. albopictus* colonies were significantly less likely ($P < 0.05$) to choose human than Thai *Ae. aegypti* (anthropophilic control) and did not exhibit significantly different host choice from the Ugandan *Ae. aegypti* (zoophilic control). There were no significant differences in host choice between low anthropophagy and high anthropophagy *Ae. albopictus* colonies. Our results suggest that differences in natural feeding patterns were not driven by differences in innate host preference for this species. Variation in feeding patterns are more likely the result of differences in host availability in each location. Our work is the first to compare *Ae. albopictus* and *Ae. aegypti* host preference directly and provides insight into differential vectorial capacity and human feeding risk.

0033

EXPANDED GEOGRAPHIC DISTRIBUTION AND HOST PREFERENCE OF *ANOPHELES GIBBINSI* (*AN. SPECIES 6*) IN NCHELENGE DISTRICT, ZAMBIA

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Nchelenge District in northern Zambia suffers from holoendemic malaria transmission despite a decade of yearly IRS and ITN distributions. One hypothesis for this lack of impact is that some vectors may forage in the early evening or outdoors. *Anopheles gibbinsi* was identified in early evening mosquito collections and we gleaned further insight into this taxon, including characterizing its genetic identity, feeding preferences and potential role as a malaria vector. Mosquitoes were collected with CDC light traps in indoor sitting rooms, outdoor gathering spaces and animal pens from 16:00-22:00. Host detection by PCR, COI and ITS2 PCR, and CSP ELISA were performed on all samples morphologically identified as *An. gibbinsi* (n = 453), and a subset of specimens (n = 24) were selected for COI and ITS2 sequencing. Comparison of COI and ITS2 *An. gibbinsi* reference sequences to the NCBI database revealed >99% identity to "*An. sp. 6*" from Kenya. More than 97% of specimens were morphologically and molecularly consistent with *An. gibbinsi*. Specimens were primarily collected in animal pen traps (59.2%), followed by traps outdoors near where humans gather (24.3%), and traps set indoors (16.5%). Host DNA detection revealed a high propensity for feeding on goats, but 5% of specimens with detected host DNA (n = 4) had fed on humans. None of the specimens were positive for *Plasmodium falciparum* sporozoites. In order to determine risk factors for increased abundance of *An. gibbinsi,* a negative binomial generalized linear mixed-effects model was performed. Animal pens and inland households >3 km from Lake Mweru were both associated with increased *An. gibbinsi* abundance. This is the first report of *An. gibbinsi* in Nchelenge District, Zambia. This study provided a species identity for "*An. sp. 6*" from sequences deposited in the NCBI database - a species implicated in malaria transmission in Kenya. Composite data suggest that this species is largely zoophilic and exophilic, but opportunistically feeds on humans and ingests the malaria parasites they carry. This species should continue to be monitored in Zambia and neighboring countries as a potential malaria vector.

0034

ANOPHELES LEUCOSPHYRUS GROUP PHYLOGENY REVEALS ORIGINS OF THE MAJOR FOREST MALARIA VECTORS IN SOUTHEAST ASIA

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The *Anopheles leucosphyrus* group of mosquitoes belonging to the *Neomyzomia* series has a wide range spanning from southwestern India to mainland and insular Southeast Asia (SEA). The group comprises 20 known species to date, all of which are highly forest dependent typically breeding in forest ground pools. Many species within the group including *An. baimaii*, *An. dirus*, *An. scanloni*, *An. cracens* and *An. balabacensis* are highly competent vectors of human malaria in India and SEA. Other members of the group such as *An. macarthuri*, *An. pujutensis*, and *An. nemophilous* spread primarily simian malaria and feed preferentially on monkeys. Using a phylogenomics approach involving the whole genome sequencing of 10 species of both human and simian/ape feeding species we studied the evolution of host feeding in the group. The phylogeny revealed a single origin of a human blood feeding clade that contains most species of the *Anopheles dirus* complex, major vectors of human forest malaria in Southeast Asia. The estimated timing of this switch indicates this occurred in response to early hominin dispersals to SEA rather than to the more recent arrival of anatomically modern humans. This phylogeny coupled with an understanding of host switching therefore serves as an archaeological tool that can date and place the arrival of early hominins. Host switching from primates to hominins most likely occurred in insular Southeast Asia where the majority of ancestral monkey and ape feeding species are found. Following the host switching event, human-feeding mosquitoes spread from insular to mainland SEA during the Pleistocene when there were multiple phases when the Sunda Shelf was exposed joining the islands of Borneo, Sumatra and Java to the mainland. Dispersal across the mainland was associated with multiple speciation events likely involving adaptation to different habitats. These recently derived species continue to have a strong preference for human blood making them extremely effective malaria vectors in the forested regions of SEA.

0035

MOXIDECTIN COMBINATION THERAPY FOR LYMPHATIC FILARIASIS IS SUPERIOR TO IVERMECTIN PLUS ALBENDAZOLE FOR CLEARANCE OF MICROFILAREMIA AT 12 MONTHS POST-TREATMENT

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An improved treatment regimen for lymphatic filariasis (LF) that provides prolonged microfilaria (Mf) clearance could accelerate LF elimination by reducing the number of rounds of mass drug administration required to interrupt transmission. We now report preliminary efficacy data from the first randomized clinical trial of moxidectin combination therapy for LF. We enrolled 121 patients with *W. bancrofti* night blood counts of >40 Mf/mL into four treatment arms: (i) ivermectin + albendazole (IA, current standard of therapy), (ii) ivermectin + diethylcarbamazine (DEC) + albendazole (IDA), (iii) moxidectin + albendazole (MoxA), and (iv) moxidectin + DEC + albendazole (MoxDA). To date, 105 participants (87%) have been reevaluated 12 months post-treatment. Complete Mf clearance was achieved and sustained through 12 months in 100% of MoxA (15/15) and MoxDA (20/20) participants, compared with 19/22 (86%) IDA and 6/21 (29%) IA (control) participants ($p<0.001$). Semiquantitative filariasis test strip (FTS) scores, (related to adult worm burdens) decreased in 8 (36%) IDA and 9 (45%) MoxDA participants, compared to 2 (13%) MoxA and 1 (5%) IA participants ($p=0.008$). Among those with scrotal worm nests detectable by ultrasound at baseline, 11/12 (92%) IA participants had detectable worm nests at 12 months vs 3/10 (30%) after IDA, 3/8 (38%) after MoxA, and 4/10 (40%) after MoxDA ($p = 0.01$). These data show that MoxA is superior to IA and comparable to IDA and MoxDA for sustained clearance of Mf through 12 months post-treatment. Greater reduction in FTS scores after treatments that included DEC is consistent with that drug's known macrofilaricidal effect. IDA, MoxDA, and MoxA all appear superior to IA for inactivating adult worm nests. The primary endpoint for the study (24 months) has not yet been reached. However, these preliminary data suggest that a single dose of MoxA may lead to prolonged Mf clearance without DEC. That would be a game-changer for LF elimination programs in onchocerciasis-endemic countries where IDA cannot be used because of safety concerns.

0036

PARTIAL MACROFILARICIDAL ACTIVITY OF IVERMECTIN, DIETHYLCARBAMAZINE AND ALBENDAZOLE COMBINATION TREATMENT FOR HUMAN ONCHOCERCIASIS

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Onchocerciasis ("river blindness") has been targeted for elimination. New treatments that kill or sterilize female worms could accelerate this process. Prior studies have shown that a triple drug treatment comprised of ivermectin plus diethylcarbamazine and albendazole (IDA) leads to prolonged clearance of microfilaremia in persons with lymphatic filariasis. We now report results from a randomized clinical trial that compared the macrofilaricidal effects of IDA vs. a comparator treatment (ivermectin plus albendazole, IA) in persons with onchocerciasis. The study was performed in the Volta region of Ghana. Persons with microfiladermia and palpable subcutaneous nodules were pre-treated with two doses of ivermectin (150 ug/kg) that were separated by 6 months prior to treatment with either a single dose of IA (150 ug/kg, 400 mg), a single dose of IDA (IDA1, 150 ug/kg, 6mg/kg, 400 mg) or 3 daily doses of IDA (IDA3). These treatments were tolerated equally well, and there were no severe or serious adverse events. Skin microfilariae were cleared or greatly reduced by all three treatments for 18 months, at which time nodules were excised for histological assessment. Nodules were barcoded, embedded in paraffin, and at least two sections per nodule were stained, scanned and analyzed by two independent assessors. 64% (127 of 198) adult female worms were alive in 116 nodules recovered from 41 IA recipients. 52% (142 of 274) of female worms in 149 nodules from 47 IDA1 recipients and 53% (159/300) worms in 167 nodules from 47 IDA3 recipients were alive. This reduction in female worm viability after IDA (IDA1 and IDA3) vs IA was statistically significant. 28% of female worms in nodules from IA recipients were alive and fertile at 18 months compared to only 15% after IDA1 and 12% after IDA3. Results from this pilot study suggest that IDA was superior to IA for killing or sterilizing female *O. volvulus* worms. These results are superior to those reported to date with other short term oral treatments. However, additional studies will be needed to confirm these promising findings.

0037

SAFETY AND PHARMACOKINETICS OF A SINGLE ORAL DOSE OF MOXIDECTIN IN SUBJECTS AGED 4 TO 17 YEARS WITH (OR AT RISK OF) ONCHOCERCIASIS, TO IDENTIFY AN OPTIMAL DOSE FOR TREATMENT OF CHILDREN 4 TO 11 YEARS: RESULTS OF AN OPEN LABEL STUDY

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Community-directed treatment with ivermectin over decades has controlled and eliminated onchocerciasis in some foci, but alternative strategies are required to achieve elimination across Africa. Moxidectin (MOX), a milbemycin-class macrocyclic lactone with broad activity against filarial and ecto-parasites, has demonstrated superior skin microfilariae suppression compared to ivermectin. MOX 8 mg is approved by the United States Food and Drug Administration for the treatment of onchocerciasis in patients 12 years and older. However, to achieve onchocerciasis elimination, all age groups that serve as a reservoir for infection should be included in treatment programs. We are conducting a prospective, age-stratified, adaptive, open-label, single-dose, pharmacokinetic (PK) and safety study at the University of Health and Allied Sciences Research Centre, Hohoe, Ghana. The study aims to determine the PK of MOX in children and adolescents aged 4 to 17 years and select a suitable dose to treat children younger than 12 years. Participants from villages in the Kpassa sub-district in Nkwanta North, an area endemic for onchocerciasis, were recruited into three age-based cohorts: 12 to 17 years (Cohort I, n=9), 8 to 11 years (Cohort II, n=18) and 4 to 7 years (Cohort III, n=9). Cohort I and the first 9 participants in Cohort II were enrolled concurrently and received 8 mg MOX, based on simulations in a population PK (popPK) model. PK sampling and safety follow-up was completed to Week 24. Following Day 28 PK sample analysis, a Safety Monitoring Board review of safety, non-compartmental PK and updated popPK modelling incorporating body weight effects on clearance recommended evaluating a 6 mg dose in children 8 to 11 years (Cohort II, n=9) and initiating evaluation of a 4 mg dose in children 4 to 7 years (Cohort III). As of 31 Mar 2022, all subjects have been dosed and PK sampling and safety monitoring is continuing. MOX was well-tolerated with only mild or moderate adverse events, all assessed as unrelated to treatment, reported to date. The results of Week 24 follow-up and PK sample analysis for all participants, to be completed in August 2022, will be presented.

0038

AUTOMATED ANALYSIS OF HISTOLOGICAL SLIDES FROM ONCHOCERCA NODULES USING ARTIFICIAL INTELLIGENCE (AI)

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Onchocerciasis is a neglected tropical disease caused by the filarial worm *Onchocerca volvulus*. The adult worms reside in nodules under the human host's skin, where they can reproduce for 15 years. Macrofilaricidal drugs that kill or sterilize adult worms are urgently needed to eliminate onchocerciasis by 2030. One hurdle to rapid drug development is the histological evaluation of the nodules, which can only be done by a few experts worldwide. We aim to automate this time-consuming task by developing an AI tool that is faster and less dependent on human assessors. Over 1,000 digitalized nodule slides were used to train separate AI models to detect worm sections (Faster R-CNN) and subsequently classify the detected sections (EfficientNet). First, binary classification models (e.g., alive vs. dead and unclear) were trained on the following attributes: vitality, sex, presence of *Wolbachia* (endosymbiotic bacteria) and fertility of female worms. Then, these models were refined with more classes per attribute (e.g., alive vs. dead vs. unclear). In addition, a classification model was trained to detect microfilariae (Mf) in the nodule tissue. Most models reached accuracies of over 90%: detection of worm sections 92% mAP; classification on single sections for vitality: 96.9%, sex: 98.1%, *Wolbachia*: 90.0% and fertility: 95.1%. The recently started training to detect Mf in the nodule tissue showed an accuracy of around 80%. Preliminary data on the refined models indicate a similar performance to the binary models. Finally, all models were combined in a single tool that provides a complete nodule analysis. The first test with binary classification on 15 images, which were not included in the training, showed 81.4-98.6% agreement between a human expert and the AI, depending on the attribute. The first validation of the combined tool shows similar results as the individual models. Based on these results, the focus is now on the tool's robustness to ensure similar outcomes on new data from different sources. After validation and approval of the tool for clinical trials, the human experts will focus on the quality checks of the AI and the assessment of complex cases.

0039

NINETEEN ONCHOCERCIASIS BIOMARKER CANDIDATES IDENTIFIED DIRECTLY IN HUMAN SERUM AND URINE

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Onchocerca volvulus, the causative agent of onchocerciasis, infects over 20 million people and can cause severe dermatitis and ocular conditions including blindness. Current mass drug administration treatments do not kill female *O. volvulus* worms, and common diagnostic tests cannot reliably assess the viability of adult worms. This lack of sensitivity for active infections presents an urgent need for better diagnostic tests to monitor the efficacy of new treatments and ongoing mass drug administration. Serum samples from individuals infected with *O. volvulus* (n = 8), and from uninfected individuals (n = 7) were examined by deep scale proteomics, including the use of a timsTOF Pro mass spectrometer. Data were interrogated for *O. volvulus* proteins present in infected but not uninfected samples. Among all detected proteins, 19 high-priority candidate biomarkers were identified in the serum of 3 or more *O. volvulus*-infected samples (not present in uninfected) that were supported by two or more unique peptides. Comprehensive functional annotation, RNA-seq based transcriptional profiling and taxonomic conservation/diversification characterized the detected proteins in more detail. 15 peptides from 11 of the top 19 proteins were validated by parallel MS/MS (Orbitrap) with isotope-labeled synthetic peptides. One candidate was detected with eight unique peptides in five different serum samples. Additional MS/MS samples have shown that peptides from 4 of the top 6 candidate biomarkers were also detected in urine samples from onchocerciasis patients. We are now working to develop practical assays for the most promising candidates that may be useful for diagnosis of active infections and for monitoring efficacy of new treatments in clinical trials.

0040

CHARACTERIZING VIRAL-SPECIFIC B CELL RESPONSES IN HUMAN FILARIAL INFECTION USING VIRSCAN, A NOVEL SEROSURVEY TOOL

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Filarial infections have been shown to alter bystander CD4+ and CD8+ T cell memory responses to a variety of non-filarial antigens including virally-encoded proteins. We have previously found that in filarial-cytomegalovirus (CMV) coinfections, filarial infections may limit the ability of T-effector cell to transition to long lived memory cells; moreover, these infections appear to induce T cell exhaustion that may insufficient control of persistent antigens. To understand whether these T cell-associated outcomes of filarial infections extend to the B cell compartment, serum from 20 healthy and 186 *Loa loa*-infected individuals were assessed using VirScan, a viral peptide phage display library, that allows for the simultaneous assessment of human immunoglobulin G (IgG) response to all major viruses of humans (n=206) through sequencing of the immunoprecipitated phage. By comparing total IgG raw read counts among all samples tested, it could be seen that there was significant virus-specific seroreactivity to 135 distinct viral species. Among the 20 most prevalent viruses recognized by human IgG in all subjects, the filarial-infected individuals demonstrated markedly lower viral-specific IgG responses for Human herpesvirus 6A (p=.022), Enterovirus B (p=0.004), Rhinovirus A (p=.007), and Rhinovirus B (p=.004)) when compared to the healthy individuals. When testing for differences among microfilariae positive (Mf+) and microfilariae negative (Mf-) Loa loa- infected individuals, viral-specific IgG raw read counts were significantly lower among Mf+ patients for Rhinovirus A (p=0.005). We are further analyzing the diversity of viral epitopes among filarial-infected individuals to determine how broadly epitope restriction occurs at the B cell level. Our data suggest filarial infections may modify not only T cell-based viral bystander responses, but also those driven by B cells.

0041

TOWARDS TELOMERE TO TELOMERE FILARIAL GENOMES

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Filarial genomics have largely accelerated over the last decade with the rapid advances in sequencing technologies and genome assembly pipelines. Among the filarial worms, *Brugia malayi* and *Onchocerca volvulus* genomes are at near chromosomal level. Because repetitive elements are part of the filarial genomes that we frequently exploit for molecular diagnostics we sought to better characterize the organization of these and other non-coding DNAs. Over the last decade, the *L. loa* genome improved from 5443 contigs (SOLID 454) to 2250 contigs

(Illumina and PacBio) with scaffold N50 values ~175-180 Kb. Using ultra-high molecular weight (UHMW) DNA extracted from microfilaria of *L. loa* obtained during apheresis of a single patient, we performed long-read sequencing using Oxford nanopore technology (ONT). The ONT reads (~130 x coverage) with average read N50 values ~40-60 Kb were assembled with multiple long-read assemblers (e.g. FLYE, CANU, WENGAN, SHASTA, WTDBG2, NECAT, NEXTDENOVO, RAVEN). After merging the best assemblies and removal of haplotigs, we condensed the genome to 12 contigs with scaffold N50 ~16 Mb. 6 of the 12 contigs were smaller repeat elements that comprised ~0.6% of the 91.8 Mb assembled genome, while the 6 larger contigs and the mitochondrial genome made up 99.3% of the genome. Synteny with other filarial genomes and Nigon element mapping resulted in the identification of 5 autosomes and an X-chromosome, with BUSCO scores of ~99%. Moreover, all the 6 chromosomes had the canonical telomeric repeats "TTAGGC" at both ends. Long-read sequencing and assembly of the Brugia malayi and Wuchereria bancrofti is in progress and will be compared to the Loa loa chromosome level assembly.

0042

WHAT PREDICTS PEOPLE'S ADHERENCE TO COVID-19 MISINFORMATION? A RETROSPECTIVE STUDY USING A NATIONWIDE ONLINE SURVEY AMONG ADULTS RESIDING IN THE UNITED STATES

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Tackling infodemics with flooding misinformation is key to managing the COVID-19 pandemic. Yet only a few studies have attempted to understand the characteristics of the people who believe in and adhere to misinformation. Our study objective was to identify the factors associated with adherence to certain types of COVID-19 misinformation among US adults during the early phase of the pandemic. We used the data from an online survey that was administered in April 2020 to 6,518 English-speaking adult participants in the United States. We created binary variables to represent four misinformation categories related to COVID-19: general COVID-19-related, vaccine/anti-vaccine, COVID-19 as an act of bioterrorism, and mode of transmission. Using binary logistic regression and the LASSO regularization, we then identified the important predictors of adherence to each type of misinformation. Nested vector bootstrapping approach was used to estimate the standard error of the LASSO coefficients. About 30% of our sample reported adhering to at least one type of COVID-19-related misinformation. Adherence to one type of misinformation was not strongly associated with adherence to other types. We also identified 58 demographic and socioeconomic factors that predicted people's susceptibility to at least one type of COVID-19 misinformation. Different groups, characterized by distinct sets of predictors, were susceptible to different types of misinformation. There were 14 predictors for general COVID-19 misinformation, 23 for COVID-19 vaccine, 37 for COVID-19 as an act of bioterrorism, and 14 for mode of COVID-transmission. Our findings confirm the existence of groups with unique characteristics that adheres to different types of COVID-19 misinformation. Findings are readily applicable by policymakers to inform careful targeting of misinformation mitigation strategies.

0043

SUPPLY OR SERVICE? FACTORS AFFECTING DELIVERY OF INTERMITTENT PREVENTIVE TREATMENT FOR MALARIA IN PREGNANCY IN DRC

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National data suggested many missed opportunities for delivery of intermittent preventive treatment for malaria in pregnancy (IPTp) during ANC visits in DRC. This study, conducted in March 2021 in the Lualaba and Tanganyika provinces, examined ANC registry records, conducted facility assessments, and used qualitative methods to triangulate on data quality and reasons for missed IPTp delivery. While ANC registry findings revealed missed IPTp provision at 44% of all ANC visits, data quality sub-analyses suggest frequent under recording of IPTp provision along with ample missing data. Specifically, data quality verifications revealed 41% variation between clients recorded receiving SP compared to observed, and 19% variation between those recorded vs. recalling receipt of SP during their ANC visit. In both cases, registries under-recorded SP provision compared to the data verification approach. Two strong predictors of SP provision at every ANC visit were stock in a pharmacy/storeroom (OR 6.99, SE 1.00) and having 1+ supervisory visits in the past year (OR 2.35, SE 0.30), while not receiving SP stock in the past month or longer significantly reduced odds of SP provision at every ANC visit (OR 0.60, SE 0.06). Qualitative data reiterated challenges with record keeping as providers noted they have many forms to complete and an inadequate number of staff to do the work correctly. Providers also described challenges in counseling clients on how to manage common side-effects of SP. From facility inventories, the study found major SP supply disruptions between September 2020 and January 2021, coinciding with the emergence of COVID-19 in DRC. The study findings underscore problems with data recording, counseling efficacy, and SP stock management that overemphasize the scope of missed opportunities for IPTp delivery while suggesting the necessity of interventions to improve IPTp provision. Provincial malaria control staff reviewed the data and offered potential recommendations, including increased supervision of ANC providers, job aids to support counseling about management of side-effects, and improved IPTp stock alert and restocking systems.

0044

IS IT POSSIBLE TO ACCURATELY PREDICT RISK OF PRETERM DELIVERY IN A RURAL SETTING IN ETHIOPIA?

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Prematurity is the principal cause of death among children under five years, globally leading to over 900,000 deaths per year. To effectively reduce the prevalence of preterm deliveries, interventions should be targeted at high-risk pregnancies. However, most proposed predictive models for preterm birth require information collected with tools that are not available in low-resource areas. We evaluated whether risk of preterm delivery can be predicted using readily available data. This study uses data from a maternal and child health cohort in North Shewa, Ethiopia. All women were enrolled in the cohort between December 2018 and March 2020. The study outcome was preterm delivery, defined as any delivery occurring before week 37 of gestation regardless of vital status of the fetus or neonate. Sociodemographic, clinical, environmental, and pregnancy-related factors were included in the models. Predictors that were not available but important for risk prediction — mainly ultrasound measurements and biomarkers — were not considered. Both standard

time-to-event analysis methods (Cox and accelerated failure time models) and machine learning models (decision tree ensembles) were used to predict the risk of preterm delivery. Model discrimination was estimated using the area-under-the-curve (AUC). A total of 2493 pregnancies were included in the analysis. Of those, 138 women were censored for being lost to follow-up before delivery. The predictive performance of all models was poor. The AUC was highest for the tree ensemble classifier (0.59, 95%CI [0.56, 0.63]). When models were calibrated so that 90% of women who experienced a preterm delivery were classified as high risk, at least 80% of those classified as high risk did not experience preterm delivery. Neonatal sex, multiple gestation and education were among the factors which contributed most strongly to the models. It may not be possible to accurately predict risk of preterm delivery without collecting key predictors such as cervical length or fetal fibronectin during pregnancy, and the feasibility and cost-effectiveness of collecting such data in low-resource areas should be explored.

0045

COST EFFECTIVENESS ANALYSIS OF EXPANDING TUBERCULOSIS PREVENTIVE THERAPY TO HOUSEHOLD CONTACTS AGED 5-14 YEARS IN THE PHILIPPINES

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There has been limited uptake of the newest national guidelines encouraging the expansion of tuberculosis preventive therapy (TPT) to children aged 5-14 years who are household contacts (HHCs) of index pulmonary tuberculosis (TB) cases. In this analysis we provide input on the most cost-effective strategy to expand latent TB testing and treatment among HHCs aged 5-14 years of index TB patients in the Philippines. In the model, eligible HHCs are screened for latent TB infection (LTBI) with either tuberculin skin test (TST) or interferon gamma release assay (IGRA) and those who test positive will then be simulated to receive one of the following strategies: 6 months of daily isoniazid (6H), 3 months of daily isoniazid plus rifampicin (3HR), 3 months of weekly isoniazid and rifapentine (3HP) or the current practice of no testing or treatment for LTBI (NTT). The analysis adds up the projected costs of the program to the Philippines public healthcare system and compares them to the quality-adjusted life years (QALY) gained over a time horizon of 20 years. An intervention will be considered cost-effective if its incremental cost-effectiveness ratio (ICER) falls below the Philippines gross domestic product per capita of $3,298.33. Our model estimates that expanding TPT coverage to HHCs aged 5-14 years would be cost effective when using TST. The most cost-effective strategy combines TST with 6H with an ICER of 2,296 $/QALY gained (Uncertainty range: 1,274 - 4,875), closely followed by combining TST with 3HP which had an ICER of 2,374 $/QALY gained (Uncertainty range: 1,343-4,923). In a high prevalence scenario with LTBI prevalence exceeding 50% among HHCs, all testing and regimen combinations became cost-effective with TST and 6H again achieving the lowest ICER. These findings were robust to sensitivity analyses over a wide range of parameter values. In conclusion, expanding TPT coverage to HHCs aged 5-14 years is cost effective when using TST and 6H closely followed by a strategy combining TST and 3HP especially in a high prevalence scenario. IGRA cost will require significant reduction to achieve results similar to TST.

0046

ELUCIDATING PNEUMOCOCCAL MIGRATION IN SOUTH AFRICA USING GENETIC AND HUMAN MOBILITY DATA

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Streptococcus pneumoniae is a globally endemic, human obligate bacteria, and a leading cause of pneumonia and meningitis worldwide. The pneumococcal conjugate vaccine targets a subset of the 100 pneumococcal serotypes. Despite the enormous public health burden, the extent and mechanisms of pneumococcal spread across spatial scales remains largely unknown, as does the variability of spread driven by the vaccine. We analyzed 6910 geolocated whole genome pneumococcal genome sequences from patients, collected from 2000-2014 from throughout South Africa. We developed mechanistic phylogeographic models to reconstruct pathogen spread, incorporating the generation time distribution, human mobility data provided by Facebook, population size, and underlying heterogeneities in sampling. We found that pairs of sequences that had a most recent comment ancestor (MRCA) within one year were separated by an average of 186km, rising to 287km for pairs separated by 10 years. We were able to accurately recover this pattern of spatial spread using our mechanistic model. We estimated that most transmission events were local (85% within municipality), with occasional long-distance transmissions, mainly between population hubs. Overall, the pneumococcus was 20 times more likely to have travelled to a major population hub (population >3-million) than elsewhere after one year of sequential person-to-person transmission. We found that the introduction of the vaccine in 2009 had a marked impact on serotype distribution. Serotypes not included in the vaccine were subsequently more mobile, with individuals infected by non-vaccine types being located in significantly more municipalities after just 2 years of transmission than individuals infected by the serotypes in the vaccine. Although most transmission events remain local in South Africa there is variability in its rate of spread determined by serotype fitness. Our framework provides an opportunity to explore whether similar patterns of spread are observed elsewhere with differing mobility patterns as well as the impact of vaccine introductions on patterns of spread across pneumococcal serotypes.

0047

SAVING YOUNG LIVES: TRIAGE AND MANAGEMENT OF SEPSIS IN CHILDREN USING SMART TRIAGE

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Sepsis is the leading cause of child death and disability. Triage can improve outcomes by detecting those most at-risk, but is not the norm in many low- and middle- income countries. We evaluated whether Smart Triage, a digital triage platform, improves time to treatment for children with sepsis at a regional referral facility in Eastern Uganda. Smart Triage includes a mobile triage application integrating pulse oximetry and a clinical risk prediction model, a Bluetooth patient and treatment tracking system, and a clinical dashboard. Model development was completed using a baseline cohort enrolled from March 2020 to March 2021 and usability testing was done with healthcare workers prior to implementing the platform. From April 2021 to December 2021 all children presenting to the outpatient department (OPD) with an acute illness were triaged and stratified as emergency, priority, or non-urgent based on anthropometric data, vital signs and pulse oximetry, using the model integrated into the mobile application. Our primary outcome was time to first treatment. In the baseline cohort, 1,612 children were triaged, with a 22.4% (95% CI 20.4 to 24.3) admission rate. After implementation, 1,948 children were triaged, with a 15.0% (95% CI 13.4 to 16.6) admission rate. The mean time to treatment decreased by 20%, from 5.1 hours (95% CI 4.7

to 5.5) to 4.1 hours (95% CI 3.9 to 4.4).e improvement was greater for emergency cases. These results indicate that risk stratification at triage using a simple digital triage tool can reduce the time to treatment and improve the quality of care for children with sepsis.

0048

DEVELOPMENT OF A NON-CONTACT HANDWASHING DEVICE TO PREVENT THE SPREAD OF COMMUNICABLE DISEASES IN NIGERIA

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According to a report issued by UNICEF on World Water Day 2022, Nigeria has the world's highest number of deaths from waterborne disease among children under five years old. The factors contributing to this problem are numerous, but among the reasons is a lack of adequate handwashing infrastructure. To address this deficiency, public and private institutions have deployed their own makeshift solutions. The most common solution consists of a bucket of water, mounted at hand height, with a tap fixed at the bottom of the bucket. When the tap is opened by hand, water flows out of the bucket and on to the user's hands which are placed beneath the tap. The user can then wash his/her hands. This solution, called a Veronica Bucket, grew immensely in popularity following the outbreak of the Covid-19 pandemic as proper hand-hygiene was identified as an important strategy in stemming the spread of the coronavirus. However, this solution, while simple and effective, does have several drawbacks. Firstly, users must physically manipulate the tap on the Veronica bucket to access flowing water. This task serves as a small, yet real, hurdle in using the handwashing solution. The tap can also serve as a point of transmission for communicable diseases. Another deficiency with the Veronica Bucket is that the dispensation of soap is not inherently built into the design. A drop of soap diluted in water is sufficient to rupture and kill many types of viruses and bacteria, but the Veronica Bucket does not dispense soap. And users of the Veronica Bucket can choose to wash their hands for only several seconds rather than the 40 seconds advised by the WHO. To address these problems, a team of engineering faculty, students, and staff at the University of Ibadan in Ibadan, Nigeria, developed a device which replaces the manually operated tap on a Veronica Bucket. This battery-powered and rechargeable device automatically detects when a user places his/her hands underneath the bucket and then dispenses water and liquid soap on to the user's hands. The device then pauses, allows the user to lather with soap, and then distributes water from the bucket for rinsing. The entire operation takes 40 seconds.

0049

PARTICIPATORY APPROACH IN MODELLING OF THE POTENTIAL IMPACT OF INTERVENTIONS ON THE COVID19 EPIDEMIC IN THE KYRGYZ REPUBLIC

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Modelling of potential effects of non-pharmaceutical interventions and vaccination on the course of COVID-19 pandemic was widely applied in informing the global health strategies in light of the novelty of the disease and related uncertainties and unknowns. Along with many other countries, Kyrgyzstan constantly needed prompt evidence, prognosis and projections of the disease spread and mortality. Vaccination was expected to dramatically change the epidemic, however, the initial demand in the world exceeded manufacturing capacities, and thus, it caused new challenges in the country in planning the vaccination with limited delivery. The Kyrgyz modelling group in cooperation with International COVID-19 Modelling (CoMo) Consortium and the Kyrgyz Ministry of Health (MoH) conducted two modelling rounds. Such participatory approach allowed us to promptly share our projections with key decision-makers, including MoH and the Cabinet of Vice-Prime Minister. Eventually, we proposed several scenarios of lockdown release interventions and vaccination strategies. Each scenario projected the potential impact of interventions on the course of the epidemic, mortality and health system. However, the policy decisions were driven not only by existing evidence and research tools but also by social pressure. Thus, our proposed "managed lockdown release" scenario was acknowledged as an optimal approach to balance between health and economic/social destruction. However, the decision was to fully release the lockdown due to the above pressures, which was followed by a significant wave of morbidity and mortality as projected in our baseline scenario "full release". Considering the above, our group decided to share the information on the importance of social distancing, mask-wearing, vaccination and other interventions with a broader audience via participating in public discussions, press conferences and other mass media channels. I believe, through such a participatory approach we managed to significantly contribute to informing the national policy decisions and improving the public acceptance of related public health interventions.

0050

THE DEVELOPMENT OF A MACHINE LEARNING-DRIVEN CLINICAL DECISION SUPPORT TOOL FOR THE MANAGEMENT OF DENGUE IN VIETNAM

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Seasonal dengue epidemics exert significant pressure on healthcare settings worldwide. Clinical decision-making is a dynamic process and central to patient outcomes. However existing tools and guidelines tend to be static, and focus mainly on early management. The adoption of appropriate clinical decision-support systems (CDSS) at patient point-of-care could improve the quality and consistency of care delivery. We present work in the development of a CDSS intended for use by clinicians managing dengue in Vietnam. This work is done in the context of a multi-disciplinary collaboration in the application of technological innovations in low- and middle-income country settings. We performed process mapping, task analysis and semi-structured interviews at the Hospital for Tropical Diseases (HTD), Ho Chi Minh City, Vietnam in order to understand and characterise clinician needs for the management of acute febrile illnesses. In parallel, clinical data from 4,131 patients admitted with dengue were used to train a set of machine learning models to predict clinical outcomes. Workshops and focus groups adopting human-centred design principles informed the development of CDSS prototypes. We identified potential areas in the patient pathway at the HTD where CDSS introduction could be impactful. Clinical decision-making for acute infection is complex and variation in approaches to patient management and risk assessment are described. The optimal functions for the CDSS were identified and prioritised in small group sessions - a system emphasising usability, ease of access to guidelines, dashboard summary functions and risk prediction for shock have been chosen for incorporated into a web-based CDSS, accessible through desktop and mobile devices. Translation of these findings into a CDSS is currently underway and usability testing in end-users in Vietnam planned for Q3 2022.

0051

CHALLENGES FOR PRECISE ESTIMATION OF CHILD IMMUNIZATION COVERAGE AND DROP-OUT RATE IN MANDERA COUNTY IN KENYA

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Precision in estimating child immunization coverage and drop-out rates is dependent on census data, specifically on estimating population in an area which leads to set the target for immunizing children in that particular area. Achieving the precision in child immunization report becomes challenging more specifically in the area where in- and out-migration rate is higher, for example in areas with abundant nomadic population or in the informal settlement or slum areas. Child immunization coverage in such areas often suffers low precision which may include coverage estimates far beyond or below 100%. Similarly, inaccuracy in drop-out reporting is also noticed in reported immunization data from those areas. We conducted a community population based survey in 2020 in three sub-counties (Mandera North, Mandera South and Mandera West) in Kenya and compared the survey results with reported data through District Health Information System (DHIS) for same period. Our survey results revealed fully immunization coverage among children below 1 year as 61% which was reported through DHIS data as 97.6%; a similar difference was shown for DPT-Hepatitis-Hib drop-out rate, while survey result (17.6%) and DHIS data (4.3%) were compared. The DHIS sets immunization targets using census data which are obtained usually every 10 years. Census data are then used to project population data in a specific area for later years until another round of census is conducted. Such projections often misestimate real population data which leads to under- or over-estimated coverage and drop-out rate in a specific area. The significant differences we found between survey results and DHIS reported data between child immunization coverage and drop-out rates are greatly misleading the project managers and implementers in those sub-counties to plan the implementation focus, especially for prioritizing needs to address the real inadequacy of immunization services in the area.

0052

MULTIAGENT SIMULATION MODEL OF THE COVID-19 EPIDEMIC PROCESS WITH SOCIAL FACTORS

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Agent-based approach to simulation is an effective tool for studying the spread of COVID-19. Modeling makes it possible to identify the parameters that affect the development of the epidemic process and to understand social aspects influencing COVID-19 propagation. To build a multi-agent model of the epidemic process, we used data provided by the Public Health Center under the Ministry of Health of Ukraine on the incidence of COVID-19 distributed by age and incorporated the results of a sociological study on adherence to vaccination against COVID-19 and other control measures (437 blood plasma donors, 797 healthcare workers, 150 students). The agent-based model was realized using C# language. The objects of the model were age, gender, and knowledge base, including adherence to vaccination and readiness to comply with control measures. We simulated the spread of COVID-19 through an artificial population with the same characteristics of our study population. Transmission occurred probabilistically based on traits of the individual agents (e.g., vaccination status and adherence, control measure acceptance, age, etc.). The model was verified by comparing the retrospective forecast with registered cases of COVID-19. The simulation results showed that the population can be divided into three groups concerning vaccination: skeptics (43%), conformists (32%), and loyalists (25%). This division is observed in all three groups of respondents (plasma donors, healthcare workers, and students). But within each social group, the ratio of these subgroups varied. Using sociological data and methods of intelligent decision-making in conditions of uncertainty, we found that attitude to vaccination correlates with the attitude to compliance with control measures. Our model allows us to study the effectiveness of control measures, accounting for important individual traits such as attitudes toward vaccination, which is an important advantage over other models. The model can also be useful in the development of educational programs aimed at certain social groups.

0053

SYSTEMATIC REVIEW OF MATHEMATICAL MODELING OF INFECTIOUS DISEASE WITH HUMAN MOVEMENT DATA

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Human movement plays a key role in determining the dynamics of infectious disease epidemiology. Population mixing rates and travel affect the rate of epidemic growth, distribution of infections, and total population size. Therefore, we conducted a systematic review of studies using human movement data in mathematical mechanistic models of infectious disease. We searched PubMed until July 11th, 2021, and retrieved over 1,700 articles. After review, we identified 107 articles that met inclusion criteria. We extracted metadata for each included article including modeling approach, type of mobility data used, location of study, and disease system of interest. Airborne transmission was the most studied transmission route with COVID19 with 62% of studies and influenza being the most frequently studied diseases with 23% of the articles[NK1] . Historically, census data or population counts were the most utilized data types to parameterize movement models, but location-based services - software monitoring location date -- are increasingly common[NK2] . Considering this, most studies were set in the US, Europe, and China. While mobility is fundamental to all infectious disease, the literature has been skewed to disease systems and locations where such studies are the most easily implemented - airborne transmission in high-income settings. [NK3] This highlights the need to increase the study of the role of human movement in infectious disease dynamics in Africa, Asia, and Latin America as they bear disproportionate burden. Furthermore, research needs to expand beyond airborne transmission as enteric and vector-borne diseases comprise a large proportion of the burden of infectious diseases and human movement has implications on population dynamics for these diseases. Our review provides an atlas of current literature as a reference to enable future studies by showcasing implementation of in areas of greatest burden.

0054

COMPARATIVE REPRESENTATIVENESS OF A MOBILE PHONE-BASED VS. IN PERSON SURVEY-BASED COVERAGE EVALUATION SURVEYS FOLLOWING MASS DRUG ADMINISTRATION FOR SOIL-TRANSMITTED HELMINTHS: INDIA

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With increasing mobile phone subscriptions in low- and middle-income countries, telephone-based surveys are becoming increasingly popular for public health programs and research. Despite advantages, such as cost-effectiveness, time efficiency, reach, sharing of information, and comparable quality to in-person data collection, systematic exclusion of participants without access to mobile phones, or for other reasons, may limit representativeness. For DeWorm3, a large, ongoing randomized,

controlled multi-country trial including India, we regularly conducted coverage evaluation surveys to measure coverage of mass drug administration in two sub-sites, Timiri (rural area), and Jawadhu hills (tribal area), located in south India. The COVID-19 pandemic led to a nationwide lockdown in 2020, which necessitated a change in protocol to use a mobile phone-based survey instead of in-person coverage surveys. Here we examine the representativeness of the mobile phone-based survey to the previous in-person survey conducted in 2019. During the in-person survey, 88% of sampled households participated, while only 57% of sampled households participated in the phone-based survey. Notably, 17% of households in 2020 were not able to be contacted at all, as they did not provide a telephone number during the census. Larger households, households with higher socioeconomic status, and those with younger, more educated household heads were over-represented in the phone-based survey. Non-response in the phone-based survey, defined as households that refused to participate or were unable to consent or could not be contacted, was lower in Jawadhu hills, higher in households from the poorest SES quintile, and lower in households with heads who completed secondary school or higher education. Phone-based interviews took a shorter time, but more attempts were required to complete surveying all household members. The in-person coverage evaluation survey better represented the population than the phone-based survey, though the latter permitted an assessment of treatment coverage when circumstances during the pandemic precluded household visits.

0055

WORLD HEALTH ORGANIZATION COORDINATED SCIENTIFIC ADVICE FOR HEALTH PRODUCT RESEARCH AND DEVELOPMENT

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The current global disease landscape is an ever-evolving challenge to health product developers focusing their efforts on tackling the prevention, treatment and control of tropical infectious diseases. Vaccines, diagnostics, medicines and vector control products adapted to the specific context in which they are intended to be used are key to reducing the overall burden of infectious diseases and incorporating specifications to meet these requirements needs to happen at the research & development (R&D) stage. The World Health Organization (WHO) Science Division has a mandate to optimize R&D processes, including the provision of scientific advice to external parties to support the development of appropriate health products in areas of unmet public health needs. Product developers may contact WHO to obtain Coordinated Scientific Advice (CSA), a new standardized service for joint advice delivered by WHO Prequalification and the WHO disease-focused technical department(s). CSA is open to innovative products and existing products when new data are generated for a new indication, for example. The entire process is expected to take approximately ten weeks and the outcome is a consolidated WHO advice report. CSA is confidential and prospective in nature. The optimal time for a CSA is before the start of pivotal phase III trials but will ultimately depend on the needs of the product developer. WHO is conducting a time-limited pilot and inviting product developers to apply. The overall impact will be evaluated through user feedback, follow-up of the product development, future relevant guidelines and prequalification outcomes. Initial observations show particular interest from developers across different disease areas and different health product categories. CSA provides comprehensive advice to developers to best anticipate applications for WHO prequalification and policy recommendations, aiming to improve quality of submissions through adequate study design and accelerate timely access to quality priority health products.

0056

DEVELOPING A COMMUNITY OF PRACTICE FOR NEGLECTED TROPICAL DISEASE (NTD) PROGRAM MANAGERS IN AFRICA

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Neglected tropical disease (NTD) Program Managers have numerous responsibilities including coordination and partnerships, resource mobilization, intervention and service delivery, and data management, surveillance, monitoring, evaluation and research. In 2019, a group of Program Managers in Africa advocated for opportunities to collaborate and learn from one another in deriving best practices to overcome shared professional challenges. In 2020, the African NTD Community of Practice (CoP) for Program Managers in Africa was launched to support the pursuit of this goal. The purpose of this abstract is to describe the process of co-designing the CoP in partnership with Program Managers. In 2020, a CoP Development Team based at the University of Washington (USA) and University of Global Health Equity (Rwanda) met with a group of nine Program Managers to begin learning about Program Manager priorities for an African Program Managers CoP. Over a series of three meetings, Program Managers were presented with key decisions to make for the CoP, including voting on features to include in an online CoP and other design components. After the co-design meetings were concluded, a Beta version of an online CoP was developed that included features that Program Managers met consensus on. In February 2021, the Program Managers participated in one-to-one usability testing exercises with CoP facilitators. During these meetings, Program Managers navigated the Beta CoP using a "talk aloud" method. Experiences and feedback from the usability testing were pooled and used to refine the platform, particularly to improve the translation features that allow Program Managers to communicate with one another in their own language without any need for manual translation. The final CoP, named Kikundi, includes key features such as direct messaging, group messaging, discussion forums, curated resources, a Program Manager directory, program updates, an NTD events calendar, and professional development trainings. By engaging in a rigorous co-design process, the CoP is well matched to meet Program Manager needs moving forward.

0057

COMMUNITY READINESS ASSESSMENT OF MALNUTRITION AND DIETARY INCLUSION OF RICE BRAN IN RURAL SOUTHWEST GUATEMALA

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Rice bran is a globally accessible, nutrient-rich agricultural co-product of rice processing that can support nutrient absorption and reduce frequency of, and recovery time from, diarrhea episodes. Rice bran is underutilized in regions where the vicious cycle of malnutrition and diarrheal disease

contribute to increased childhood morbidity and mortality. This study assessed baseline community readiness to address malnutrition in rural Guatemalan households, in a region where 40% of children suffer from chronic malnutrition. In September 2021, thirteen key respondents of varied social roles and demographics residing in the Trifinio region of southwest Guatemala were selected. In-person semi-structured interviews were conducted in Spanish using the Community Readiness Model with 6 domains: (A) Community efforts, (B) Community knowledge of efforts, (C) Leadership, (D) Community climate, (E) Knowledge about the issue, and (F) Resources for efforts. Interviews were recorded and observational field notes were taken by a second Spanish speaking team member. Interview responses were scored by a native Guatemalan Spanish speaker who did not conduct the interviews. The overall readiness score was 4.26 (SD 1.52). This score indicates the community is in the pre-planning stage for addressing malnutrition, in which there is clear recognition that something must be done about the issue of childhood malnutrition, and there is awareness of groups addressing diarrhea and child growth faltering, but efforts to address malnutrition are not yet focused or detailed. Rice Bran was not consumed as part of the diet in this community. To address malnutrition beyond the "pre-planning stage" in this community, we need to reduce stigma and raise general awareness of rice bran and malnutrition among local leaders. Local focus groups on dietary habits across the lifespan may also inform household-level interventions. In an effort to develop a sustainable malnutrition prevention intervention, we have initiated a 3-month feasibility trial of household-level dietary rice bran supplementation.

0058

HEALTH CARE SEEKING BEHAVIOR FOR ILLNESSES IN CHILDREN AGED UNDER FIVE YEARS IN WESTERN KENYA: A QUALITATIVE STUDY

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Health care seeking behavior by caregivers for childhood illnesses is an important determinant of child survival, and delayed healthcare is associated with high child mortality. Acquiring health information and making use of the information can moderate inaccurate assessment and response to childhood diseases. The Child Health and Mortality Prevention Surveillance (CHAMPS) Kenya team assessed factors affecting caregivers' Health care seeking behavior for childhood illness in western Kenya by conducting a qualitative study of 88 community members between April 2017 and February 2018 using purposive sampling in an informal urban settlement in Kisumu County, and in rural Siaya County. Key informant interviews, semi-structured interviews and focus group discussions were audio-recorded and transcribed. All participants provided verbal consent. Data management was completed on *Nvivo 11*. Iterative analysis process was utilized and themes were identified and collated. Our findings reveal three broad thematic areas: cultural beliefs, religious beliefs and economic factors. Often, caregivers prefer not to take children with measles symptoms to the hospital because of a belief that the child will die upon medical intervention. In other instances, caregivers would take their children to traditional healers for illness believed to be caused by witchcraft. Caregivers would seek prayers for their children illness and wellbeing because of the belief in the healing power of prayers. Caregivers low income and perception of prohibitive cost of clinical care attributes to seeking over the counter medication first, which further delays care. Pain relievers were the most commonly reported medication purchased by caregivers to relieve symptoms of illness in children. To improve timely health care seeking behavior, it is important to increase health literacy in caregivers and improve their ability to accurately assess the timing and importance of clinical health care. Education should include a focus on danger signals in childhood illness which should prompt immediate clinical healthcare-seeking.

0059

ATTITUDES AND EXPERIENCES REGARDING MENSTRUAL HYGIENE MANAGEMENT AMONG MOZAMBICAN OF SCHOOL-AGE GIRLS

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Some scientific evidence suggests that poor Menstrual Hygiene Management (GHM) is a factor that influences absenteeism and poor school performance among girls. There is little research related to GHM in Mozambique. This study aimed to understand the challenges faced by school-age girls in the practice of GHM in Mozambique. A mixed study was conducted in the provinces of Inhambane, Tete and Nampula in 2018/19. Were conducted 12 observations in schools, 24 interviews with teachers and 60 focus group discussions with different community members. Interviews were recorded and transcribed before the thematic analysis using Nvivo 12. Data from observations was entered in Ms Excel and frequencies of each indicator was generated. Menstruation is perceived as a sign of growth, a passage into adulthood. Menstruation information is obtained from teachers, mothers and other actors who are not necessarily prepared to respond to girls' needs. Menstruating girl does not necessarily miss classes, but may be temporarily absent from the classroom or school. Norms and practices associated with menstruation guide behaviour during this period which include negative perceptions about menstruation and the culture of silence around the subject. The schools have robust structures, but the bathrooms were not aligned with the type of construction of the other school structures. Schools lack basic hygiene conditions, with a lack of water and soap. The lack of privacy in the bathrooms, the discomfort of colic, the fear of being discovered are some of the challenges faced by girls during menstruation. Posing risks for girls to miss school. The main source of information about menstruation is the school. Cultural norms and practices associated with menstruation guide secret behaviour resulting in limited exchange of information about menstruation and menstrual hygiene. The lack of hygiene and sanitation conditions is one of the challenges faced by girls in school during menstruation. Teachers do not have accurate information on menstruation and menstrual hygiene and training is needed in this area.

0060

IS 'SPEEDING UP' A FEASIBLE AND BENEFICIAL LONG-TERM STRATEGY IN DRUG AND VACCINE DEVELOPMENT? OPPORTUNITIES, RISKS, BENEFITS AND DRAWBACKS OF SYSTEMATIC ACCELERATION

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The covid-19 pandemic has shown that the acceleration of clinical trials of both vaccines and pharmacotherapeutics is feasible and may not lead to unfavorable registration process outcomes. Clinical trial and registration trajectory, from beginning to end, would have normally taken at least a decennium, while the first covid-19 vaccines were developed in less than two years. Similar accelerations of clinical trials have been preceded a few times, mainly in situations of global health emergencies: the Ebola vaccine clinical trialing during the West African Ebola virus disease outbreak in 2013-2016; and fast-tracking of multidrug-resistant tuberculosis (MDR-TB) clinical drug development (bedaquiline, delamanid) when the MDR-TB epidemic became a global emergency. These successful examples of clinical trial accelerations could be used to identify the components which are beneficial and essential in enabling acceleration of clinical trials,

such as resources, priority (i.e., covid-19 is a public health risk for high income countries) and risk assessment (i.e., introducing mRNA vaccines posed a potentially higher safety risk due to more 'unknowns' than introducing an existing vaccine platform with more safety experience). Once these components are determined, a new clinical trial trajectory could be developed in which time and eventually costs might be reduced in comparison to the current clinical trial trajectories. We hypothesize that it should be possible to re-model the clinical trial trajectory in a - flexible - scheme also for diseases and settings beyond emergency responses, thereby benefiting global health by making pharmaceutical development more accessible. We are currently testing this hypothesis by means of a literature search in which we will examine examples of acceleration of drug and vaccine development for global health programs such as are mentioned earlier, and use the gained knowledge to re-model the current clinical trial trajectory. Results of the work currently underway will be presented during the meeting.

0061

ASSESSING THE ECONOMIC IMPACT OF COVID-19 IN THE LARGEST TOWNSHIP IN SOUTH AFRICA: SOWETO

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The implementation of lockdown measures posed a huge threat to economies globally, more so in resource limited settings such as South Africa. In March 2020, following the initial Covid-19 cases in South Africa, a hard lockdown was implemented with only essential services and workers allowed to operate. In the third quarter of 2021, the unemployment rate was reported at 34.9%, the highest official unemployment rate recorded since 2008. Furthermore, South Africa is experiencing food insecurity due to COVID-19 and high inflation rates, with about 16% of the population reported to have experienced food insecurity. This study aims to examine the economic impact of COVID-19, using data from CHAMPS Soweto/Thembelihle Health Demographic Surveillance Site collected during the level three and four lockdown period February 2021 - June 2021. The outcome variable economic impact is defined as any individual reporting loss of income or who perceived basic needs (i.e. medicine, food) as expensive. Analysis included descriptive and adjusted logistic regression to identify factors associated with economic impact of COVID-19. Among adults aged 18-59 years (55 542), 29% reported having experienced economic impact of COVID-19. About 18% (10 041) experienced loss of income and 15 932 (29%) reported that basic needs were expensive during the COVID-19 period. Those permanently employed (OR 3.74, CI 3.56-4.92) and those temporarily employed (OR 4.04 CI 3.79-4.31) were at a higher risk of experiencing the economic impact of COVID-19 compared to those who were students. By age group, those who were between 51-55 years (OR 1.93, CI 1.76-2.11) and 56-59 years old (OR 2.03; CI 1.84-2.25) were more likely to experience the economic impact of COVID-19 compared to those 19-24 years. We show that COVID-19 has severe economic impact on the Soweto population; a community already struggling socio-economically. These findings show the need to balance outbreak response with economic productivity. There is now an urgent need to create employment and business opportunities as well as to subsidize the food basket.

0062

COMPARISON OF PREGNANCY AND BIRTH OUTCOMES USING ARCHIVAL MEDICAL RECORDS BEFORE AND DURING THE FIRST WAVE OF THE COVID-19 PANDEMIC IN KINSHASA, DEMOCRATIC REPUBLIC OF CONGO: A DESCRIPTIVE, LONGITUDINAL ANALYSIS

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Little research has been conducted on the impact of the coronavirus disease 2019 (COVID-19) pandemic on either pregnancy/birth outcomes or the ability of archival medical records to capture such outcomes. Our study objective is to compare the frequency of preterm birth (PTB), stillbirth, low birth weight (LBW), small for gestational age (SGA), microcephaly, and neonatal bloodstream infection (NBSI) before and during the COVID-19 pandemic in Kinshasa, Democratic Republic of Congo. We conducted a facility-based retrospective cohort study in which identified cases of pregnancy/birth outcomes were tabulated at initial screening and subcategorized according to level of diagnostic certainty using Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) definitions. Documentation of birth complications, delivery type, and maternal vaccination history were also evaluated. The frequency of each pregnancy/birth outcome was compared in the pre- (i.e., July 2019-February 2020) and intra-COVID-19 (i.e., March-August 2020) periods via two-sample *z*-test for equality of proportions. In total, 14,300 birth records were abstracted. Pregnancy/birth outcomes were identified among 22.0% and 14.3% of pregnancies in the pre- and intra-COVID-19 periods, respectively. For stillbirth, LBW, SGA, microcephaly, and NBSI, estimates were similar across study periods. However, the frequency of PTB in the intra-COVID-19 period was significantly lower than that reported in the pre-COVID-19 period (8.6% vs. 11.5%, $p < 0.0001$). Furthermore, the level of diagnostic certainty declined slightly across all outcomes from the pre- to the intra-COVID-19 period. Nonetheless, diagnostic certainty was especially low for certain outcomes (i.e., stillbirth and NBSI) regardless of period; other outcomes (i.e., PTB and LBW) had moderate to high levels of diagnostic certainty. Results were mostly consistent when the analysis was focused on the facilities designated for COVID-19 care. Overall, our study adds crucial real-world data to the literature regarding the impact of the COVID-19 pandemic on maternal/neonatal services and outcomes in Africa.

0063

CONGENITAL BIRTH DEFECTS AMONG PERINATAL DEATHS: FINDINGS FROM CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) BANGLADESH

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Nearly 240,000 newborns die globally per year within the first 28 days of life from congenital birth defects (CBD). About 90% of children born with CBDs come from low- and middle-income countries. Worldwide CBDs contribute to over 20% of stillbirth and neonatal deaths. CHAMPS is a multi-country program aiming to recognize and track the causes of stillbirths and childhood deaths in seven countries, through postmortem minimally invasive tissue sampling (MITS) and other information. We aimed to estimate the prevalence and explore the common presentations of CBDs using MITS in Bangladesh. From March 2018 to February 2022, an expert

panel determined the causes for 298 perinatal deaths based on data from MITS, histopathology, molecular and microbiological diagnostics, clinical data abstraction, photographs and verbal autopsies. We found 21 (7%) cases with CBDs in the causal chain and, of these, 10 (48%) were stillbirths and 11 (52%) were early neonatal deaths. A CBD was considered the underlying cause in 10 deaths and antecedent or morbid cause in 11 others. Congenital malformation syndrome affecting multiple systems (7/21), neural tube defect (NTD) (3/21) and malformation of the musculoskeletal system (4/21) were the most common. Anencephaly and gastroschisis were the main NTD and musculoskeletal system abnormality, respectively. Shared maternal characteristics include maternal age <30y (91%), hypertension (19%), previous delivery of a baby with congenital abnormality (9%), and gestational diabetes (5%). Twelve mothers had a history of ultrasound investigation during pregnancy; and the CBD was detected in ultrasound reports of six cases. Seventeen mothers (68%) received at least one ANC visit. The panel opined 60% of cases were preventable (6 out of 10 where congenital malformation was the underlying condition) through preconception counselling, folic acid supplementation, or ultrasound for pregnancy profile for early detection. Our findings highlight the need for appropriate folic acid supplementation, quality antenatal care during pregnancy and strengthening research on major CBDs to understand the risk factors for prevention.

0064

CHARACTERISTICS OF CALLERS WHO SOUGHT FREE HEALTH SERVICES FROM CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) CALL CENTRE IN BALIAKANDI, A RURAL SUB-DISTRICT OF BANGLADESH

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In September 2017, Child Health and Mortality Prevention Surveillance (CHAMPS) Bangladesh established a 24/7 physician's operated call-in centre to address illness-related inquiries for Baliakandi population, which is a rural subdistrict in Bangladesh. It is specially designed to assess illness of under-5 children and maternal complication. Physicians provide advice to the family for management of illness and refer to appropriate health facility. All calls are recorded, and referrals are followed up using an android application. Caller information was later linked with ongoing Demographic Surveillance System (DSS) covering 56005 ever-married women of reproductive age and 22395 under-5 children. This study assessed the characteristics of callers taking recent data between January to December 2021. Call centre received total 3160 calls from Baliakandi residents on selected period where 2256 (71%) were health-related calls of any nature. Among 2256 calls, 1802 (80%) calls were for illness; 813 (45%) calls were for under-5 children and 449 (25%) were for maternal complications. 791 (63%) illness-related calls from total 1262 for under-5 children and pregnant/postpartum women could be linked to DSS; of them 477 (60%) calls were from households (HH) of fourth and highest wealth quintile; 456 (58%) were from HHs where mothers had education for more than 10 years; and majority of calls (73%) from HHs with younger mothers (15-29 years). Out of 791, 30 maternal and under-5 children complications were urgently referred to health facility for immediate management. 14 (47%) of them visited recommended hospital. Among non-compliance of referral (16), 14 (88%) women had secondary or higher level of education and 8 (50%) HHs were from fourth quintile group. They preferred to have treatments at home or in private hospital. 465 (58%) mothers who used the call centre services had higher education and 585 (74%) HHs using call centre were from middle to higher quintile groups. Considering the high non-usage of the call centres, we recommend further studies to identify the barriers for using call-in centre services and recommended referral facilities.

0065

ACCELERATING UNIVERSAL HEALTH COVERAGE THROUGH CONTINUOUS PERFORMANCE IMPROVEMENT OF PRIVATE HEALTH FACILITIES IN BENIN

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In Benin, 65% of people seek care in private health facilities (PHFs) and 14% of women give birth in PHFs. However, all Ministry of Health (MOH) capacity building interventions are aimed at public health facilities. The unfavorable regulatory environment, coupled with a low demand for, and awareness of, quality services, contribute to an inefficient and uneven quality of services in the private sector. To improve the quality of reproductive, maternal, newborn and child health care (RMNCH) in the PHFs, USAID's Benin Private Sector Health Partnership Activity project worked with the MOH to conduct a capacity building intervention composed of (i) training nurses, midwives and clinicians using a High Impact Intervention Package (PIHI in French) on key RMNCH topics, followed by (ii) evaluation visits to assess their performance using a dedicated clinical checklist and provide tailored recommendations. The PIHI training was provided to 157 staff from 120 PHFs in 9 districts, and a pool of 45 evaluators were trained on the evaluation process to conduct the intervention from August 2020 to September 2021. The PHFs received a baseline visit and up to 3 evaluation visits during the intervention period. Scores for PHFs receiving at least 2 visits (N=118) increased by 15.94% (95% CI 13.75-18.11, p<0.0001) from 41.25% at baseline to 57.19% during the follow-up visit. Scores for PHFs receiving 4 visits (N= 36) increased (p<0.0001) from 40.70%, at baseline to 54.55%, 66.99%, and 68.81% during the 3 follow-up visits, respectively. The difference in scores between the 3rd and 4th visit was not statistically significant (p=0.39). Of the 118 PHFs receiving at least one follow-up visit, only 3 PHFs (0.03%) scored at least 80% at baseline for satisfactory quality services compared to 27 PHFs (22.81%) at the final visit. These results suggest that this approach can effectively improve the quality of services provided in a sector that has long been neglected and needs stronger support to help achieve universal health coverage in Benin. The many lessons learned in this project could be useful for other countries where PHFs play a similarly important role in service coverage.

0066

EXTREMOPHILES AND THE SEARCH FOR EXTRA-TERRESTRIAL LIFE.

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Extremophiles - are species of microorganisms that have adapted themselves to live in extremes of cold or hot temperatures like hot springs and glacial environments. How they uniquely survive the harshness of those environments - in niches, on fossil remains, rocks and now in outer space, have been the subject of much research for Microbiologists, environmentalists, archeologists, modern astronauts and scientists searching for life outside of our planet - Earth. Several spore-forming *Bacillus* species (*B. stearothermophilus, B. subtilis, B. coagulans, B. cereus, B. anthracis*, etc.) have long been isolated from the soil and identified as contaminants of food and water reservoirs. Majority of industrially useful microorganisms have been isolated from the soil where they uniquely contribute to enriching the soil - trapping and transforming the energy of the sun into useful nutrients. Their survival has been attributed to their unique ability to produce dipicolinic acid, a calcium ion chelator found only in spores. Recently, some novel microbial species have been isolated from the International Space Station (ISS) and belong to the - Methylobacteriaceae family. Of these, *Methylorubrum rhodesianum* was the first to be named and a close specie with *Methylobacterium indicum*.

"The new strains may be "bio-technologically useful genetic determinant" to assist with the growth of plants in space. Another extremophile named - *Deinococcus radiodurans* which was exceptionally resistant to high levels of radiation and pressures simulated to International Space Station conditions has also been isolated. These and a few other such endeavors stand out to usher a new era of research that help scientists to try to understand extra-terrestrial life and the peculiar traits needed to enable humans learn to adapt to life outside of our planet - Earth.

0067

SARS-COV-2 SEROPREVALENCE, COVID-19 VACCINATION, AND HESITANCY IN AGRICULTURAL WORKERS IN RURAL GUATEMALA

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During the COVID-19 pandemic, serological tests to screen populations have provided better estimates of the cumulative incidence of infection. In addition, little is known about the confidence, acceptability, and uptake of COVID-19 vaccines in rural areas of low and middle-income countries. This study evaluated the seroprevalence of SARS-CoV-2 in agricultural workers in rural Guatemala, their COVID-19 vaccine uptake and vaccination attitudes. A cross-sectional study was undertaken from August to November of 2021 in agricultural workers at a sugar plantation in rural Guatemala. A questionnaire was used to collect demographic, previous COVID-19 infection, attitudes towards and receipt of COVID-19 vaccines. Serological testing was performed to detect SARS-CoV-2 IgM and IgG using STANDARD™ Q COVID-19 IgM/IgG Plus assay. Of 4,343 workers, 1,279 (29.4%) were seropositive for SARS-CoV-2 IgG and/or IgM compared to 2.3% reporting having COVID-19 infection in the past; 85% had received the first dose of the COVID-19 vaccine and 21.9% the second dose at the time. The majority were men (99.5%), who worked in the sugar cane fields (99.9%), with an average age of 34 years. Vaccine refusal was 0.6%, and 13.9% expressed some degree of vaccine hesitancy. Vaccine hesitancy and refusal was inversely associated with uptake of any dose of COVID-19 vaccine and their interest in protecting the family, coworkers, and their community. Most non-hesitant workers (57.3%) reported receiving enough information about COVID-19 vaccines, compared to 39.1% of those with some hesitancy and 15.4% of those refusing ($p<0.001$). Most workers trusted health care providers and the Ministry of Health on COVID-19 vaccine information, followed by their employer; vaccine refusers were significantly likely to trust on their family, friends, or religious leaders. Agricultural workers in countries like Guatemala, have suffered high incidence of asymptomatic and undetected SARS-CoV-2 infection. Most have received the COVID-19 vaccine, but there are moderate degrees of vaccine hesitancy that require better public health information to overcome it.

0068

SOCIOECONOMIC DISRUPTIONS CREATED BY THE COVID-19 PANDEMIC IN AN URBAN SLUM COMMUNITY

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Urban slum communities are particularly vulnerable to the socioeconomic disruptions created by the COVID-19 pandemic. We sought to evaluate the impact of the pandemic and emergency social protection interventions on employment and food security among inhabitants of an urban slum community in Salvador, Brazil. Additionally, we assessed the impact of "Auxilio Emergencial", a financial assistance program created to alleviate the economic impact of COVID-19 emergency among informal workers. We conducted household-based surveys before (September to November 2019) the emergence of COVID-19, and after the first (November 2020 to February 2021) and second (July to October 2021) COVID-19 epidemic waves in Brazil. Of the 2988 individuals who participated in at least one of the surveys, 1,726 (57.8%) were female, and most self-identified as Black (48.3%) or Brown (44.9%). The prevalence of unemployment among women increased from 52.0% in the first pre-pandemic survey to 61.7% and 68.1% in the second and third surveys. Among men, unemployment increased from 30.9% in the first survey to 35.4% and 45.9% in the second and third surveys. Based on a standardized 2-item screening tool, 50.7% of households reported food insecurity in the pre-pandemic survey. Overall, 632/943 (67.0%) households reported receiving support through Auxilio Emergencial during the second survey. Between the first and second surveys, the prevalence of food insecurity decreased by 5.1% (95% CI -13.2 – 2.9%) among households receiving Auxilio Emergencial, whereas it increased by 6.0% (95% CI -5.1 – 17.1%) among non-recipient households. These findings indicate that, within this setting of informal settlements and high socioeconomic deprivation, women were particularly vulnerable to economic instability during the COVID-19 pandemic. Although social support programs partially alleviated food insecurity among recipients, the overall prevalence of food insecurity remained high in this population. This highlights the need for additional social protection interventions to mitigate economic and food insecurity in urban slum communities.

0069

GENOMIC CHARACTERIZATION OF *KLEBSIELLA PNEUMONIAE* ISOLATES FROM DEATHS IN CHILDREN UNDER 5 YEARS OF AGE IDENTIFIED THROUGH THE CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) NETWORK

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Klebsiella pneumoniae (KP) was identified as the predominant organism attributed to deaths at Child Health and Mortality Prevention Surveillance (CHAMPS) sites in sub-Saharan Africa and South Asia. Recent data indicate a rise in multidrug resistant and hypervirulent KP. We performed genomic characterization of KP isolates from CHAMPS cases to investigate diversity, virulence, and antimicrobial resistance (AMR) with the goal of informing development of vaccines and other therapeutics. KP isolates cultured from post-mortem blood and/or cerebrospinal fluid (CSF) specimens from Bangladesh (n=19), Mali (n=13), Kenya (n=32) and Sierra Leone (n=13) underwent whole genome sequencing (WGS) at icddr,b and CDC, Atlanta. Sequence types (STs) were determined using Institute Pasteur multi-locus sequence type database. Clinically relevant information, including K (capsular polysaccharide) and O (lipopolysaccharide) antigen loci, AMR elements, and virulence factors, was extracted using KP specific genomic tools Kleborate and Pathogen watch. Among 77 isolates identified as KP by various microbiological methods at CHAMPS site laboratories, 61 (79%) were identified as KP by WGS. Among these, 35 STs were identified, including novel types in Sierra Leone (n = 1) and Mali (n = 5). In total, 34 K-loci and 6 O-loci types were detected. Diverse K-loci (5-13 unique types) were observed within each country. O1/O2v1 comprised the majority of isolates in Bangladesh (57%), Kenya (48%), and Sierra Leone (50%) while O1/O2v2 was dominant in Mali (66%). Over 60% of strains from Bangladesh and Sierra Leone possessed yersiniabactin siderophores, a virulence factor common among hospital-associated KP strains. Extended-spectrum beta-lactamase genes were detected in 40-100% of KP isolates from each country; a carbapenem resistance gene was identified in 57% of Bangladeshi isolates. Virulence factors and AMR are common among KP isolates associated with child deaths in low-and-middle-income countries. Ongoing surveillance utilizing genomics tools is crucial for the development of vaccine candidates and antimicrobial treatments for this important pathogen.

0070

INTEGRATED DELIVERY OF HOUSEHOLD MALARIA INTERVENTIONS DURING THE COVID PANDEMIC IN ZAMFARA STATE, NIGERIA

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Globally, 2/3 of the additional malaria deaths recorded in 2020 were attributed to service disruptions from COVID-19. To prevent further delays in the implementation of planned campaigns for life-saving interventions such as insecticide treated nets (ITN) and seasonal malaria chemoprevention (SMC), the Government of Zamfara State, Nigeria and its partners creatively reorganized ITN & SMC delivery as an integrated campaign, despite the involvement of different target groups and commodities. However, implementing a mass campaign had the potential to increase the number of COVID-19 cases. We deployed a combined ITN-SMC campaign involving modified community and house-to-house commodity distribution strategies, and integrated COVID-19, SMC, and ITN-related messaging. The strategy included fixed distribution posts in selected areas (80% of nets) and door to door distribution in others (20% of nets) tailored to local logistical challenges and the capacity of authorities to manage gatherings. To reduce crowding, the number of days for net distribution was extended from five to ten. A multi-channel demand creation strategy as well as advocacy was used to ensure political, community and media support for the campaign. Messages focused on the importance of malaria prevention; correction of myths and misconceptions for ITNs, SMC, and COVID-19; and prompt care-seeking in the COVID-19 context. Bottom-up mechanisms were put in place to minimize the spread of rumors. These efforts yielded impressive results; 2.9 million ITNs reached beneficiaries, and 1,030,000 SMC doses were administered to eligible children (91% coverage). There was an unprecedented level of government buy-in at all levels (at least $353,925). The net card redemption rate was 96%, and net use rates among children under five, pregnant women and the general population was 90%, 92% and 74% respectively. The COVID-19 infection live count in Zamfara State did not spike during the campaign period. This experience shows that with some modifications, mass distribution campaigns and the promotion of healthy malaria behaviors can successfully continue despite the COVID-19 pandemic.

0071

EFFECTS OF CLIMATIC FACTORS ON COVID19 TRANSMISSION IN ETHIOPIA

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Climate conditions may affect the transmission and pathophysiology of respiratory tract infections in many ways. However, its impact on the COVID-19 pandemic's propagation is not well studied. This study aimed to evaluate the effects of environmental parameters such as temperature, rainfall, relative humidity, sunshine length, and wind speed on COVID-19 daily cases in Addis Ababa, Ethiopia. Data for confirmed COVID-19 cases between 10th March 2020 and 31st October 2021 were obtained from the National Data Management Center at the Ethiopian Public Health Institute. Data for climatic factors were obtained from the Ethiopia National Meteorology Agency. The Spearman rank correlation test was used to estimate the correlation between daily confirmed COVID-19 cases and climatic factors, and the log-link negative binomial regression model was used to fit the effect of climatic factors on COVID-19 transmission, from lag0 to lag14 days. A total of 245,101 COVID-19 cases were reported in Addis Ababa during the study period, with a median of 337 and a maximum of 1903 new cases per day. A significant association between COVID-19 cases and humidity was observed with a 1% increase in relative humidity was associated with a 1.1% [IRRs (95%CI): 0.98, (0.97-0.99)] and 1.2% [IRRs (95% CI): 0.98, (0.97-0.99)] decrease in COVID-19 cases for 4 and 5 lag days prior to detection, respectively. The highest increase in the effect of wind speed and rainfall on COVID-19 was observed at 14 lag days prior to detection with IRRs of 1.854 (95%CI: 1.26 - 2.74) and 1.078 (95%CI: 1.04 - 1.12), respectively. The lowest IRR was 1.109 (95%CI: 0.93-1.31) and 1.007 (95%CI: 0.99-1.02) both in lag 0, respectively. The transmission of COVID-19 was substantially associated with climate factors in Addis Ababa, Ethiopia. The number of reported cases has shown seasonal variations, the highest in rainy and the lowest in dry seasons. This highlights COVID-19 prevention and control strategies should consider seasons. Further study might be required to understand the virological and pathophysiologic impact of climatic factors in Ethiopia.

0072

HISTORICAL GOLD MINING INFECTIOUS DISEASE EPIDEMICS IN AUSTRALASIA

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Lethal infectious disease epidemics have historically occurred in military, refugee and mining camps where crowded conditions promote the spread of enteric, respiratory and insect-borne infections. The early history of gold mines around Palmer River, Queensland in the 1870s, Kalgoorlie, Western Australia in the 1890s and Papua on the island of New Guinea in the 1910s are recounted specifically as it relates to infectious disease deaths.

Despite large diagnostic gaps, it is likely that malaria was the predominate problem in Palmer River, typhoid in Kalgoorlie and bacillary dysentery in Papua. Nearly two-thirds of all recorded deaths in the Palmer River district from 1873-1883 were due to infections predominately "fevers". Typhoid fever likely killed >2000 Australians in the early phases of the Western Australian goldfields in the 1890s. Severe dysentery outbreaks killed up to a majority of the local workforce in the Lakekema goldfields of Papua resulting in the colonial authorities stopping mining activity in the second decade of the twentieth century. In the absence of public health measures and specific chemotherapy, large mortality rates in miners reflected the over-riding economic drivers of gold miners and their lack of any understanding of microbial disease and its interruption by public health measures. Similar infectious disease epidemics are likely to reoccur when large numbers of impoverished miners use low-technology methods to work alluvial gold deposits in conflict areas as has been seen in modern Africa and Latin America.

0073

EXEMPLARS IN DIAGNOSTICS: LESSONS FROM PROGRAMS OR INNOVATIONS THAT HAVE CLOSED THE GAP IN DIAGNOSTICS SERVICE DELIVERY

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Forty seven percent of the global population have little or no access to appropriate diagnostic services. Access to appropriate diagnostics for 6 conditions (HIV, TB, Malaria, HBV, hypertension, and diabetes) could prevent 1.1 million premature deaths in low- and middle-income countries (LMICs) every year, while inappropriate diagnosis results in poor health outcomes, increases the cost of care, and contributes to the development of antimicrobial resistance. Moreover, many countries have yet to develop country-specific diagnostic strategic plans and national essential diagnostics lists (EDLs). The Exemplars in Global Health (EGH) program seeks to address this challenge by studying country or global-programs and innovations that contributed to closing the gap in diagnostics. Diagnostics alone cannot help strengthen any disease program and the outcome measures are interlinked to the downstream processes in the cascade of care, such as linkage to treatment, follow up etc. Therefore, we used empirical analysis, structured interviews with experts, policy analysis to assess the success of diagnostics. Early findings highlight the importance of point-of-care and self-testing, use of digital solutions to retain people in the care cascade, multi-disease testing platforms and integrated testing strategies. In partnership with downstream audiences, including country decision-makers, norm-setting bodies, and funders, findings from this project will be disseminated and learnings from success stories will be leveraged where appropriate, to support the successful implementation of diagnostic programs in comparable settings.

0074

COVID-19 LOCKDOWNS AND FOOD INSECURITY: ASSESSING HOUSEHOLD INDICATORS OF VULNERABILITY IN HARAR AND KERSA, ETHIOPIA

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COVID-19 is associated with one of the largest disruptions to life in the 21st century. To quell disease spread, national governments implemented lockdowns that likely created hardships for households around the world. To improve knowledge of the consequences of these lockdowns, we examined food insecurity and economic hardships such as job loss or business closure during the pandemic in a remote region of Ethiopia. Data were collected from Health and Demographic Surveillance Systems in Harar and Kersa, Ethiopia, using a cross-sectional survey that was implemented between August and September 2021. The questionnaire was administered to a simple random sample of 880 households (5 households were excluded as respondents were less than 18 years old). Of 875 households, 139 (15.9 %) reported not having enough food to eat since March 2020, an increase of 5.8 % from households that reported not having enough food to eat prior to the pandemic. In bivariate logistic regression analyses, households were less likely to have reported food insecurity if they lived in urban compared to rural areas (OR = 0.54, p-value = 0.001) and more likely to have reported food insecurity if they had more than 8 household members (OR = 3.27, p-value = 0.021). After adjusting for additional covariates, households were less likely to have reported food insecurity if they had a household member with secondary level education or greater compared to no education (AOR = 0.28, p-value = 0.003) or reported a monthly household income greater than 4,000 Birr (highest quartile) compared to households with a monthly income less than 1,350 Birr (lowest quartile) (AOR = 0.29, p-value = 0.005). Households were more likely to have reported food insecurity if they had a family member lose employment (AOR= 2.33, p-value <0.001) or reported an increase in local food prices (AOR= 4.00, p-value <0.001). These results are consistent with the premise that the pandemic exacerbated socioeconomic inequalities to increase disparities in food security. This knowledge will help inform future policies seeking to mitigate disease outbreaks without fomenting other unintended hardships or health problems.

0075

MOLECULAR EPIDEMIOLOGY OF *UREAPLASMA* SPECIES ISOLATED FROM NEONATES IN THE GLOBAL MULTI-CENTER CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE NETWORK (CHAMPS)

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Ureaplasma species, including *U. urealyticum* and *U. parvum,* are infectious causes of stillbirth, neonatal sepsis, and preterm labor. Recent studies in South Asia and South Africa suggest *Ureaplasma* species are an underrecognized cause of neonatal infections in low- and middle-income countries. Diagnostic testing of neonatal clinical specimens for *Ureaplasma* is rarely done, and bacterial factors associated with birth complication and infection remain unclear. We performed additional testing on post-mortem blood, cerebrospinal fluid (CSF), and tissue specimens from Child Health and Mortality Prevention Surveillance (CHAMPS) cases in South Africa from May 2017 to January 2018. *Ureaplasma* species were initially detected by real-time reverse transcription polymerase chain reaction (RT-PCR) using custom TaqMan Array Cards. Specimens from CHAMPS cases in which *Ureaplasma* was detected in one or more specimen types were transferred to the Centers for Disease Control and Prevention (CDC) for culture, real-time PCR, and whole genome sequencing (WGS). Ten isolates (5 *U. urealyticum*, 5 *U. parvum*) were recovered from 22 primary specimens, including lung tissue (n=5), blood (n=2), and CSF (n=3), from 6 cases where *Ureaplasma* was detected but not attributed to the cause of death. Genome assemblies were generated for 8 isolates and species identified by WGS matched real-time PCR species identification for all isolates. Expanded multi-locus sequence typing revealed diversity of isolates. Four (50%) isolates matched known sequence types (STs) (STs 38, 95, 48) which clustered in clonal complexes corresponding to species. Of these, 2 isolates from 2 different cases matched the same ST (ST 38). Novel allelic profiles were identified in the remaining 4 (50%) isolates. Sequence

evaluation for antimicrobial resistance revealed 1 isolate as tetracycline resistant through *tet (M)* gene acquisition. Analysis of additional specimens from cases enrolled at all CHAMPS sites is ongoing to further investigate the molecular epidemiology of *Ureaplasma* spp. and to identify relevant features that may contribute to poor clinical outcomes.

0076

SEROPREVALENCE BASED MAP OF VULNERABILITY TO ZIKA VIRUS BASED ON ENVIRONMENTAL SUITABILITY

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The 2015-17 Zika virus (ZIKV) epidemic in the Americas subsided faster than expected and evolving population immunity was postulated to be the main reason. Herd immunization is suggested to occur around 60-70% seroprevalence, depending on demographic density and climate suitability. However, this was only documented for a few cities in South America, meaning a substantial portion of the population might still be vulnerable to a future Zika virus outbreak. The aim of our study was to determine the vulnerability of populations in South America and Africa by comparing the environmental suitability of ZIKV transmission to the observed seroprevalence, based on published and unpublished studies. We collected seroprevalence and geospatial data of 89 unique locations from 34 studies. Extracting the environmental suitability at each location and converting to a hypothetical expected seroprevalence, we were able to determine the discrepancy between observed and expected. This discrepancy was used to evaluate the level of risk that each location still has for an outbreak to occur. Of the 89 unique locations, 58 (65%) exhibited an expected seroprevalence higher than what was observed. 19 locations (21%) even showed a discrepancy of -0.5 or less as an indicator of high risk. The considerable heterogeneity between environmental suitability and seroprevalence potentially leaves a large population vulnerable to future infection. Vulnerability seems to be especially pronounced at the fringes of the environmental suitability for ZIKV (e.g., Sao Paulo, Brazil). The discrepancies between observed and expected seroprevalence raise the question why the ZIKV epidemic stopped with large populations unaffected. This lack of understanding also highlights that future ZIKV outbreaks currently cannot be predicted with confidence.

0077

A SUSPECTED CASE OF EBOLA IN BURKINA FASO: WHAT IF IT HAD BEEN TRUE?

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On August 22 2021, in a sub-regional context marked by a recent outbreak of Ebola Virus Disease (EVD) in the Republic of Guinea and a suspected imported case in the Republic of Côte d'Ivoire, a 22-year-old male patient who returned from Côte d'Ivoire was received at the Bogodogo University Hospital (CHU B) and was suspected to be a case of Ebola. An after action review (AAR) that focused on seven (07) thematic areas (coordination and finance; surveillance; risk communication and community engagement; laboratory system; infection prevention and control; case management and continuity of services; logistics and procurement) was conducted. The methods consisted of a workshop with the direct stakeholders of emergency management. Group work by thematic areas was carried out, followed by restitution in large group. The results of this after action review show many shortcomings: i) A long diagnostic delay (34 hours for the transport of samples to the hemorrhagic fever reference laboratory, which only had outdated reagents and therefore could not be used, 146 hours to obtain the final results); ii) Chaotic management of the suspected case (more than 150 direct contacts, absence of an isolation room requiring hospitalization in the COVID19 resuscitation room, inadequate training of personnel in the surveillance of MVE: unarmed personnel not knowing what to do, insufficient sample-takers, absence of legal texts for the mobilization of EIRs for the management of health emergencies, absence of standard operating procedures for the notification of cases of MVE according to the one-health approach, absence of a crisis communication plan).Taking into account all these criteria, and a virus reproduction rate equal to 2, approximately we would 302 cases would be confirmed on the evening of August 28th 2022. In 6 days this epidemic could have reached all continents. The question is: if nothing is done, is the world prepared for the worst? It is urgent and imperative to strengthen the preparation of teams to manage public health emergencies in countries like Burkina Faso.

0078

USING OUTREACH TRAINING AND SUPPORTIVE SUPERVISION (OTSS) TO IMPROVE THE QUALITY OF INTEGRATED HEALTH SERVICES IN BENIN

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In Benin, improving maternal and child health services is a priority as 72% of people seeking care at a health facility are women and children under five. Routine supervision is key to improved quality service delivery. The outreach training and supportive supervision (OTSS) tool, developed to support quality improvement of malaria case management, was adapted by the Integrated Health Services Activity (IHSA) to be used for integrated supervision of health workers (HWs) in four departments: Alibori, Atacora, Oueme and Plateau. This tool allows health facility (HF) management teams to provide oversight and coaching for maternal and newborn health (MNH), family planning (FP), gender-based violence (GBV), infection control, and malaria services. These teams conduct quarterly OTSS visits to HFs, visiting each HF at least annually, providing advice and training to HWs on key technical elements of prevention, diagnostics, and treatment. Based on identified gaps, an action plan is developed and then monitored by the HF coordination doctor. Between Oct 2019-Sep 2021, the OTSS tool was used at 287 of the 298 HFs (96%) of the four IHSA-supported departments, at least once a year with more frequent follow-up at underperforming sites, enabling the supervision of 1,277 HWs on MNH, FP, malaria, and GBV. During the same period in those departments, the following results were obtained from the national health information system and were analyzed using a chi-square test. The proportion of fever cases tested for malaria increased from 82% to 92% ($p<0.001$). The proportion of HFs meeting the minimum standard (80%) of correct malaria testing and treatment increased from 70% to 79% ($p<0.05$). Pregnant women receiving at least three intermittent preventive treatment doses under direct observation increased from 7% to 30% ($p<0.01$). Women with obstetric complications who received appropriate care increased from 25% to 86% ($p<0.01$). Further investigation is required to determine if other factors pre- and post- intervention may have affected these results. However, systematic, integrated supervision may contribute to improved HW performance.

0079

ANALYSIS OF EBOLA VIRUS EPIDEMIC PREPAREDNESS AND ASSOCIATED CAPACITIES IN THE DEMOCRATIC REPUBLIC OF CONGO

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Several approaches and tools to assess country-level preparedness to public health emergencies exist. The World Health Organization's International Health Regulations (2005) and the Joint External Evaluations (JEE) were developed to inform National Action Plans for Health Security. However, these assessments and their associated recommendations tend to represent, at best, national aggregates that do not consider regional contexts, capabilities, and resources. The Democratic Republic of Congo (DRC) is the second largest and one of the poorest countries in Sub-Saharan Africa. Ebola Virus Disease (EVD) outbreaks are common in the DRC, where the 13th outbreak was recently declared over. Civil unrest, overlapping emergencies competing for political attention, intense poverty, and a fragmented health care system reduce DRC's capability to respond to public health emergencies. Under such conditions, the implementation of preparedness measures becomes an imperative for controlling EVD outbreaks before they reach an uncontrollable magnitude. We posit that low-income countries and fragile states would benefit from a scaled down version of the JEE to determine the most critical points of preparedness that need to be addressed. Because diagnostics are one of the most fundamental components of outbreak response, building and maintaining resilient laboratory capacity networks should be considered a priority when planning responses to outbreaks. This analysis looks at the preparedness of the DRC to respond to EVD outbreaks, and how to assess and incorporate subnational-specific barriers and facilitators when performing preparedness assessments and implementing standards. In addition, we look at how resilient laboratory capacity networks can be leveraged not only to specifically strengthen preparedness to EVD outbreaks, but also as an investment in strengthening DRC's overall health system.

0080

HOW FAMILIES REACT TO RECEIVING CAUSE OF DEATH INFORMATION OF CHILDREN ENROLLED IN CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) IN MOZAMBIQUE: RAPID QUALITATIVE ASSESSMENT

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A child death is a huge tragedy for parents and family members. Unfortunately, families in low and middle-income countries (LMIC) still face excess infant mortality. The Child Health and Mortality Prevention Surveillance (CHAMPS) uses minimally invasive tissue sampling (MITS) to determine causes of death (CoD) in children under-5 years. CoD results, in addition to being used to suggest health interventions to reduce child mortality, are delivered to the child's parents so that they know the specific CoD, which may help them to deal with the loss and to seek medical follow up when necessary. This study aims to explore the experiences of parents and relatives of deceased children on the procedure for delivering CoD results. A rapid qualitative assessment was carried out using semi-structured interviews with parents and relatives of deceased children and systematic observations during the delivery of CoD results. Data were independently coded by two researchers, summarized in an MS Excel matrix and submitted to content analysis. The delivery of CoD results is a symbolic moment marked by memories and a mixture of feelings such as sadness, pain, relief and satisfaction for the parents and relatives of deceased children. These results, although they bring memories and emotions, are important for the bereaveds' closure. They are useful for medical follow-up when necessary and to minimize family tension and conflicts due to accusations that the child died as a result of witchcraft. Delays in delivery of results cause anxiety and frustration, making some parents turn to traditional healers to consult them on the child's CoD and apply traditional therapies for the mother to become pregnant again and give birth to a healthy baby. Learning about the CoD is good and necessary for parents and relatives of deceased children who consented to the MITS procedure, but delays in delivering results cause anxiety and frustration to them. These findings suggest the importance of delivering CoD results promptly, and we recommend that after delivering of CoD results, a medical and psychological families follow-up, especially to the mothers of the deceased children.

0081

INVESTIGATION OF THE GASTROENTERITIS DISEASE OUTBREAK AT LUVEVE SUBURB IN BULAWAYO PROVINCE - ZIMBABWE, 2020

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On the 21st of May 2020, health department authorities were notified that residents in Luveve suburb at Emakhandeni District were reporting diarrheal incidences, turbid and foul-smelling water. To investigate, a study was conducted which probed into the cause and latent risk factors associated with the gastroenteritis disease outbreak at Luveve suburb. The study was an unmatched case-control study grounded on a structured questionnaire administered to 106 randomly sampled residents presenting with diarrhea (cases) and 106 neighbors of diarrheal patients (controls) as on May-June 2020. The minimum sample size was calculated on Epi Info version 7.2 software using the Fleiss method assuming a 95% confidence level, 80% power, 1:1 ratio of cases to control and odd ratio of 2.30. The cases were selected from a line-list generated at Luveve clinic. Univariate analysis and multivariate logistic regression were used to predict being a diarrheal case using Epi Info version 7.2 software. The stool samples results yielded *Shigella dysenteria, Salmonella typhi* and *Shigella sonnei.* From the univariate analysis the risk factors which emerged significant (p<0.05) were drinking municipal water and reporting sewage bursts. The significant protective factors were drinking stored water, reporting treating water and drinking one glass. However, in the multivariate logistic regression, drinking municipal water (aOR 5.0, 95% CI [1.2-14.1], p<0.003), reporting sewage bursts (aOR 4.5, 95% [1.4-14.1], p<0.010) and drinking five glasses of municipal water emerged as risk factors. The protective factors were drinking from water which was stored prior to the outbreak (aOR 0.3, 95% CI [0.1-0.7], p<0.003) and drinking treated water (aOR 0.3, 95% CI [0.1-0.8], p<0.012). The strategies to improve water quality should consider employing the use of aqua tablets to treat water and the issuance of a boil notice to the residents of the affected area. The emergent risk factors such as drinking municipal water and reporting sewage burst point to the need for provision of an alt.ernative water source and issuing of a water avoidance notice to the affected residents.

0082

INFECTIOUS BITES: A MULTIDISCIPLINARY APPROACH FOR BIOCONTAINMENT PREPAREDNESS

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In 2015, and in response to the Ebola Outbreak in West Africa, the U.S. Department of Health and Human Services designated ten health departments and associated partner hospitals to become regional treatment centers for patients with highly infectious diseases (RESPTC) and reinforce the nation's infectious disease response capability. Our institution carries the RESPTC denomination and our multidisciplinary High-risk Infections Team (HITeam), which encompasses a skillfully trained and engaged group of nurses, physicians, respiratory therapists, paramedics, pharmacists, infection control, research and laboratory specialists, emergency management, engineering and environmental services; works, learns, trains and thrives collectively with the aim of providing excellent clinical care to our patients while assuring safety of the team. We developed a collaborative, multidisciplinary didactic series on specific biocontainment topics showcasing the unique expertise of our team members. Our series thus far has reviewed topics such as South American Hemorrhagic Fevers, Nipah Virus, Crimean-Congo Hemorrhagic Fever, Lassa Fever, Hantavirus infections, Personal Protective Equipment and Ebola virus. Our sessions usually include a clinical presentation discussed by a physician, laboratory diagnostics by our laboratorians, bedside care and infection prevention by a nurse, and available and developing treatments by a pharmacist; if a clinical trial is available for a specific pathogen, our research nurse will provide a process overview. Although these series are planned by our HITeam members, they are available institution-wide. With the potential for an influx of highly infectious pathogens in the healthcare setting, identifying, training and engaging stakeholders uniquely equipped to provide excellent care is cardinal. Our Infectious Bites series can be used as a model for inter-professional work in Biocontainment preparedness and foster lasting partnerships at an institutional, regional and national level.

0083

COVID-19, BURIAL SITE SURVEILLANCE TO MEASURE EXCESS MORTALITY IN KARACHI, PAKISTAN

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In Pakistan, the government system for documenting fatalities and determining their causes is ineffective, leaving essential data on which to base health initiatives. In this regard we are collecting information to monitor unanticipated disparities in fatalities and their reasons, using burial ground surveillance and verbal autopsy methods, in order to measure the population-level impact of the COVID-19. This study is an observational surveillance consisting of retrospective data of 36 months and prospective data of 12 months within morgues and graveyards in Karachi, Pakistan. Ethnographic approach has been used in this study to collect data via IDIs, observations, formal and informal interview, with the community to facilitate the surveillance process. Surveillance process includes, data from graveyard registries, and verbal autopsy using the WHO verbal autopsy questionnaire. In addition e-questionnaires with geo-tagging and dashboard displaying mortality data against various variables consisting of graphs/ charts and scorecards have been created to visualize the real time data connected to a centralized system. At the conclusion of the study, this database and system, together with all records, will be handed over to a government body. The preliminary results show that out of the total deaths (N=22828), the highest number of deaths occurred in 2021 (n=12016), with a peak occurring in the month of August (n=2054), followed by 2019 (n=4021) and 2020 (n=3742). 556 deaths have been reported due to Covid-19. Males mortality prevalence was observed to be higher than females (males:56%, females:41%). Out of six districts of Karachi, Karachi West reported the highest proportion of mortalities (486.4/100,000). Themes obtained from qualitative data include (i) information about the graveyards, (ii) burial process (iii) record keeping system (manual/ computerized). The initial findings indicate the digitization of graveyard death registries to improve national mortality surveillance, which is required at every level of the health system in order to create the vital health intelligence needed for monitoring, policy, and planning.

0084

THE REMOTE EMERGING DISEASE INTELLIGENCE-NETWORK (REDI-NET): FROM CONCEPT TO ACTIVE SURVEILLANCE IN BELIZE

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The past decades have seen a dramatic increase of emerging and/or re-emerging infectious diseases worldwide, and more outbreaks will be foreseen in the future. Yet, proactive surveillance is still limited by the lack of expertise and capacity to provide reliable data in an actionable time frame across at-risk locations. The Remote Emerging Disease Intelligence-NETwork (REDI-NET) project was launched to enhance current surveillance efforts to detect, predict and contain potential emerging infectious disease threats in an efficient and timely manner. Specifically, consortium partners have established a complete set of robust standard operating procedures, including those for standardized field sample collection, storage and metagenomic next-generation sequencing (mNGS) to capture a broad spectrum of pathogens circulating in Kenya, Belize and Florida. In Belize, active surveillance was performed monthly from ten routine sampling sites within four of the six political districts, including Corozal, Orange Walk, Stann Creek and Toledo District, during November 2021 to March 2022. Field collections involved capturing four sample types including water, sediment, leeches and ticks to serve as sentinels for pathogens existing in water bodies (environmental biosurveillance) and/or blood meals of hematophagous invertebrates (invertebrate xenosurveillance). Here we report on viral and non-viral (e.g., bacterial, parasitic) pathogens detected using mNGS based on MinION/GridION sequencers (Oxford Nanopore Technologies) demonstrating the success of remote field and laboratory data acquisition by the REDI-NET program to validate an operational framework for reliable risk estimates on emerging pathogens.

0085

PERCEPTIONS AND LEVELS OF COMPLIANCE WITH ANTI-COVID-19 MEASURES IN SOUTHERN RURAL MOZAMBIQUE: THE CASE OF CONFINEMENT, SOCIAL DISTANCING, FREQUENT HAND WASHING, AND FACE MASK WEARING IN THE DISTRICT OF MANHICA

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This study assesses community perceptions and implementation of the measures recommended by the government of Mozambique to prevent COVID-19 in rural areas of southern Mozambique, taking immobility, quarantine, social distancing, frequent hand washing, and mask wearing as the key practices to measure; using data from a cross-sectional household survey that was conducted in the district of Manhica in 2020.

A total of 768 heads of households were interviewed - of which 98% said that they had heard of coronavirus, but this percentage drops to 92% when asked about COVID-19, which suggests that this disease was better known as coronavirus than COVID-19. Sixty-three (63.0%) of households did not have devices for hand washing or disinfection, and of those who had devices, 68.8% had no water and 68.8% had no soap in these devices. Almost all households (98.9%) had masks, but the ratio of masks per household member aged 6+ years) was only 1.0. Of those who said they had heard of coronavirus, 44.4% defined it fairly, but 45.1% said did not know how to define it. Perception of concepts - 37.0% of the respondents defined quarantine well, 29.2% said quarantine was staying at home, and 31.5% said did not know. Thirty-seven (37.0%) defined correctly social distancing, but 32.0% gave inconclusive answers such as "stay away from others". Immobility - 37.8% defined it fairly, but 40.9% said it was just staying at home, and 18% said did not know. The question "what do you mean by avoiding crowded places" gave the following responses: avoiding places with 10+ people (10.7%), with 20+ people (10.2%), with 50+ people (9.1%), don't know (8.5%), other definitions (39.8%). Participant's self-assessment of his/her degree of compliance with anti-Covid measures (on a scale of 0%, 25%, 50%, 75% and 100%) - 39.8% said cannot stay at home, 54.2% avoid travelling at 100%, 50% wear masks in crowded places at 100%. There is a need to react to these findings by increasing efforts to disseminate information and raise awareness at community level to improve compliance with the COVID-19 prevention measures.

0086

INSECT REPELLANT OR INSECTICIDE? EFFICACY, SAFETY, AND TOXICITY

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Insect repellants are chemical or organic agents that discourage insect contact by creating toxic atmospheres above applied skin to discourage insect bites and arthropod-borne infectious disease transmission. Unlike repellants, insecticides are chemicals that kill insects on contact. A convenience sample survey queried Internet search engines to identify case reports and series, entomological investigations, and toxicological studies on chemical and plant-based insecticides and repellants to determine their efficacy, safety, and toxicity. Citronella, IR3535, permethrin-treated clothing, and oil of lemon eucalyptus (p-menthane-3, 8-diol, or PMD) do not provide acceptable coverage over a broad enough range of insects. Picaridin is an effective alternative for N-diethyl-3-methylbenzamide (formerly N, N-diethyl-m-toluamide, or DEET). Unlike DEET, picaridin offers effective insect protection without toxicities in children and during pregnancy and does not damage plastics or clothing. Mite infections, including scabies, are best treated with topical or oral invermectin, an antiparasitic, rather than topical permethrin, an insecticide. Lice infections require physical removal of viable nits and treatment with oral or topical ivermectin rather than topical treatment with insecticides, such as lindane, malathion, or permethrin. Permethrin-impregnated clothing does provide contact-level insecticidal effects and offers better and longer duration protection against encephalitis and malaria-transmitting mosquitoes than topical DEET or picaridin alone. In special cases, where environmental exposures to disease-transmitting trombiculid mites, biting midges, sandflies, or blackflies occur, topical insect repellents containing IR3535, picaridin, or PMD offer better topical protection than DEET alone. Combinations of permethrin-impregnated clothing and either topical DEET or picaridin are recommended for the best protection from mosquitoes and ticks. Topical and oral ivermectin preparations are recommended over lindane and malathion for treating lice and mite infections, including scabies.

0087

CLOSE ENCOUNTERS OF THE ENVENOMATING KIND: MISSIONARIES, INSECTS, AND THE SCRAMBLE FOR AFRICA, 1885 - 1914

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Close Encounters of the Envenomating Kind: Missionaries, Insects, and the Scramble for Africa, 1885 – 1914 Encounters with envenomating insects of all kinds were, and remain, common in sub-Saharan regions throughout Africa. As Europeans, whether secular, military, or religious, pushed more deeply into these areas, these meetings grew increasingly likely. Missionaries who worked for the Church Missionary Society (CMS), an evangelical Anglican organisation founded in 1804, provide an excellent case in point. They provide vivid, sometimes humorous, and sometimes tragic, encounters with arthropods from ants to spiders. Naïve newcomers, blissfully ignorant of hazards that might await them in the bush, faced particular risk. Relying on published and archival contemporary accounts by CMS missionaries during the late 19th century Scramble for Africa, this presentation will highlight encounters, both comical and tragic, with envenomating insects in sub-Saharan Africa.

0088

MOLECULAR DETECTION OF CRIMEAN-CONGO HAEMORRHAGIC FEVER VIRUS IN ARTHROPOD VECTORS AND SEROLOGICAL EVIDENCE IN PASTORALISTS' LIVESTOCK IN NORTH CENTRAL NIGERIA

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Crimean - Congo haemorrhagic fever virus (CCHFV) is a tick-borne viral haemorrhagic disease that is highly pathogenic in humans with enzootic cycle between tick vectors and animal hosts. Human infection with CCHFV takes the clinical form of viral haemorhagic disease, a major health condition but with limited testing in Nigeria. This is the only recent work done since 1970 when it was first conducted to detect the circulation of the virus in ticks in Northern Nigeria and the role they play in the distribution of the virus. In this study, blood samples were collected from 333 pastoralists' cattle in North Central Nigeria and 1,470 ticks were picked from the animals. For serology, Enzyme Linked Immuno Sorbent Assay was performed using a double antigen multi species ELISA kit with sensitivity and specificity of 98.9% and 95% respectively both at 95% confidence interval to detect IgG antibody to CCHFV in plasma while RT-qPCR virological technique was used to identify viral antigen in ticks that were pooled based on location and genus followed by homogenization and RNA extraction from each tick pool. Four species of ticks were morphologically identified to parasitize cattle in the sampled location namely; *Boophilus decoloratus* (34.6%), *Hyalomma truncatum* (32.9%), *Amblyomma variegatum* (24.6%) and *Rhipicephalus sanguineus* (8%). Of the 41 pools of tick tested for CCHF, one (1) pool of 35 *Boophilus* ticks (2.4%) was positive for CCHF virus with qPCR cycle threshold of 33.3%. The seroprevalence of CCHFV was found to be 67%. In Kaduna state, 85 of 108 samples tested positive (78.7%) while in Plateau state 138 of 225 samples tested positive (61.3%). Although *Hyalomma spp*. is documented to be the main vector of CCHFV, in the present investigation, *Boophilus* species was identified to play a role as reservoir of CCHF. The high seroprevalence of CCHF in livestock underscores the public health risk associated with CCHFV at the human-animal interface in Nigeria.

0089

BACTERIAL PRODUCTS FROM MOSQUITO MIDGUT MICROBIOTA NEGATIVELY IMPACT PREVALENCE AND INFECTION INTENSITY OF *PLASMODIUM FALCIPARUM* IN *ANOPHELES GAMBIAE*

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Novel mosquito-borne disease control ideas include the use of bacterial symbionts to reduce transmission. Bacteria belonging to the family Enterobacteriaceae have shown promise in limiting *Plasmodium* intensity in the *Anopheles* vector. However, it remains unclear whether the interaction between bacteria and parasite is a direct cell-to-cell or indirect through secreted products. This study aimed at determining if naturally-occurring bacteria release substances that can disrupt mosquito stages of *P. falciparum* development. *Enterobacter cloacae* and *Serratia marcescens* bacterial species were isolated from field-caught *Anopheles gambiae* mosquitoes in Ghana. Media from liquid cultures of these bacteria were filtered, lyophilized and dissolved in sterile phosphate buffered saline (PBS). Their impact on the prevalence and intensity of infection with *Plasmodium falciparum* in the mosquito was assessed by introducing these bacterial products in a blood meal containing gametocytes grown *in vitro*, and feeding via membrane feeders to *An. gambiae* mosquitoes. Mosquitoes were dissected 10-11 days post-infection and oocysts were counted. Mosquitoes fed an infectious blood meal containing *S. marcescens* product had a significantly reduced prevalence of *P. falciparum* infection (P=0.00119) and infection intensity (P=7.85 x10^{-12}) compared to the control with lyophilized LB medium added. The addition of products from *E. cloacae* cultures however had no significant effect on prevalence of infection (P=0.306) or infection intensity (P=0.152). These products released by symbiotic bacteria can be used as potential transmission blocking agents to reduce the burden of malaria.

0090

ECO BIOTRAPS - AN INNOVATIVE ADJUNCT VECTOR CONTROL GREEN DEVICE FOR INTEGRATED VECTOR MANAGEMENT

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Vector-borne diseases are endemic in more than 100 countries and affect approximately half of the world's population. Mosquitoes are the deadliest animal in the world killing 1 million people annually. Malaria, Dengue, Chikungunya, Lymphatic Filariasis, Zika, Japanese Encephalitis, Yellow Fever are all transmitted by several species of mosquitoes. The existing methods of vector control need innovation. Eco Biotrap is one such tool that can be integrated under the integrated vector management. Eco Biotraps are inexpensive, just-add-water, biodegradable, easy to deploy in rural and urban settings that have been shown to be an mosquitocidal and larvicidal device.When filled with water, the Biotraps mimics the breeding sites of female mosquitoes, and once a mosquito approaches to lay eggs, a WHO approved mosquito insecticide embedded inside, ensures a 100% eggs do not turn into adults, thereby eliminating breeding.Eco Biotraps are easy to use, convenient to deploy, 100% biodegradable after 4-6 weeks with no recollection needed, affordable and the insecticide does not come in direct human contact. In addition, Eco Biotraps can be deployed very easily without training, so that a coordinated response could involve local stakeholders. We believe that Eco Biotraps would be an effective adjunct vector control device along with other vector control methods like long lasting insecticide treated nets (LLINs), and also indoor residual sprays (IRS) for control and elimination of mosquito borne diseases. Each Eco Biotrap holds 2-liter water and can be placed at different places in and around households and in neighborhoods. Preliminary studies indicated >95% larvae are eliminated using the traps. Details can be assessed at www.ecobiotraps.com.

0091

CDC BOTTLE BIOASSAY ASSESSING THE PATTERN OF THE INSECTICIDE SUSCEPTIBILITY OF *PHLEBOTOMUS ARGENTIPES* IN SRI LANKA

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Phlebotomus argentipes is the incriminated vector of *Leishmania donovani,* the causative organism of leishmaniasis. A proper understanding of the insecticide susceptibility pattern in the vector isimportant prior to planning and implementing a successful vector control program. Thus, the present study was conducted to assess the insecticide susceptibility levels of sand fly vectors in Sri Lanka. *P. argentipes* flies originated from those in the wild and were reared at the insectary of the Department of Parasitology, Faculty of Medicine, Colombo was exposed to malathion (0.005, 0.0075, 0.01, 0.05 µgml-1), propoxur (0.0125, 0.006875, 0.125 µgml-1) and lambdacyhalothrin (12.5 and 1.25 µgml-1) insecticides using standard guidelines of CDC bottle bioassay established for mosquitoes. Dead flies were counted every 2 minutes until all perished. Each concentration of insecticides was tested with four replicates. The total percentage mortality (Y-axis) against time (X-axis) was plotted in a graph with all replicates considered together using a linear scale. The results were validated with the control mortalities using Abbott's formula. Levels of resistance were calculated according to the WHO set standards. Resistant values obtained for the tested sandfly populations, were below 0.006875µgml-1 (25% mortality), 0.005µgml-1 (30% mortality) and 1.25µgml-1 (66% mortality) respectively for propoxur, malathion and lambdacyhalothrin. Overall, the Sri Lankan populations of *P. argentipes* can be considered susceptible to the tested insecticides, when compared to the discriminating dosages specified for either anopheline or aedine mosquitoes. However, the observed level of 80% mortality of flies when exposed to 0.0075µgml-1 of malathion suggests the possibility of resistance that needs to be confirmed with further experiments. Research is continuing to test further diagnostic dosages and study genetic markers such as kdr mutations associated with insecticide resistance in *P. argentipes* in Sri Lanka.

0092

METAGENOMIC STUDY OF BLOOD-MEAL HOSTS AND PARASITES OF TSETSE FLY IN TANZANIA

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Tsetse flies can transmit *Trypanosoma* spp. that cause trypanosomiasis in humans, wild animals, and domestic animals. Amplicon deep sequencing of the 12S rRNA gene can be used to detect mammalian tsetse hosts and the 18S rRNA gene can be used to screen eukaryotic pathogens, including *Trypanosoma* spp. Tsetse flies were collected from the Serengeti National Park (n=48), Maswa Game Reserve (n=42), and Tarangire National Park (n=49) in Tanzania. Amplicon deep sequencing targeting mammal-specific 12S rRNA and 18S rRNA genes was performed to screen the blood-feeding hosts of tsetse flies and eukaryotic parasites in tsetse flies, respectively. Various mammals were found to be blood feeding hosts of the tsetse flies, including humans, common warthogs, African buffalos, mice, giraffes, African elephants, waterbucks, and lions. African buffaloes were detected more frequently as a blood-feeding source (P=0.0010) in Serengeti. 18S rRNA gene deep sequencing showed that six tsetse samples harbored the *Trypanosoma* gene, which was identified as *T. godfreyi* and *T. simiae* in subsequent ITS1 gene sequencing. This study may provide essential data for formulating better strategies to control African trypanosomiasis.

0093

COMMUNITY-LED SKIN SURVEILLANCE TO ASSESS AND COMBAT THE BURDEN OF SKIN INFECTIONS SUCH AS SCABIES IN REMOTE AUSTRALIAN ABORIGINAL COMMUNITIES

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Reducing the burden of scabies is important to improve health and wellbeing for Australian Aboriginal children living in remote communities. Scabies infections are intensely itchy, and scratching can lead to secondary bacterial infections such as impetigo which in turn contribute to chronic diseases, including Rheumatic Heart Disease. We have been using school-based surveillance to assess the burden of skin infections such as scabies in nine remote Australian Aboriginal communities. Research like ours, and downstream service provision to tackle this burden, often relies on extensive travel by clinicians and researchers. This is time consuming, expensive, and frequent fly-in visitors may not always be in the best interests of a remote community (as has been the case during the COVID-19 pandemic). Therefore, in 2022 we are implementing and evaluating a co-designed virtual skin surveillance methodology with a focus on local capacity building and empowerment. In partnership with communities and schools, this program offers training opportunities for community-based individuals to conduct skin surveillance with virtual support from an experienced skin health researcher. Implementation concurrently with 'old way' (travel-reliant) surveillance in 2022 allows us to assess the comparative sensitivity of this approach, and extensive yarning with community members allows us to explore and learn from the experiences of those who participate, privileging community voices in our evaluation of this new approach to skin health research. If found to be effective and acceptable, this work will be translated to inform the development of a culturally sensitive remote schools training package, with the aim of empowering individuals to deliver genuinely community-led approaches to recognising and combatting the burden of skin infections such as scabies.

0094

RETROSPECTIVE AND LESSONS LEARNED FROM THE CONSTRUCTION AND COMMISSIONING OF AN ACL-3 INSECTARY

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Arthropods are vectors for many pathogens that significantly harm human and animal health globally, and research into vector-borne diseases is critical work of public health importance. The size, mobility, and life cycle of arthropods present unique risks for containment, and so, insectary laboratories are essential to the safe handling of arthropod-borne hazards. In 2018, the School of Life Sciences at Arizona State University (ASU) recognized the need for an insectary to support their expanding research mission and began the process to deliver a Level 3 arthropod containment (ACL-3) facility to investigators. Four years later, the insectary has yet to be commissioned. At the request of the ASU Environmental Health and Safety team (EHS), Gryphon Scientific, an independent team with biosafety and biological research expertise, studied the project lifecycle through the design, construction, and commissioning of the ACL-3 facility with the goal of identifying lessons learned from the delayed timeline. We interviewed involved personnel to glean in-depth insight from all perspectives. Here, we propose to present the synthesized findings that could benefit the biosafety of future insectary laboratories. The major themes include: the operational implementation of ACL requirements; gaps in available resources; prioritizing expertise over cost-savings; early involvement of safety personnel; and communication needs of a stratified team. The available guidance on construction of ACL laboratories was found not to be specific enough to address some risks inherent in the research, so several mitigations were designed by the ASU team that addressed the residual risk. These mitigations, which should be considered for wider implementation in ACL-3 facilities elsewhere, will be discussed. Completion of the ACL-3 insectary at ASU was delayed, but the team thoroughly assessed potential risks and enabled appropriate practices for the safe handling of arthropod vectors. By promoting these lessons learned, we hope to bolster the biosafety of forthcoming insectaries and to offer helpful guidance to EHS teams undertaking their construction.

0095

THE TICK CELL BIOBANK: TICK AND INSECT CELL LINES FOR STUDY OF TROPICAL DISEASE AGENTS AND VECTOR CONTROL

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Blood-feeding arthropods transmit numerous viral, bacterial, protozoan and helminth disease-causing agents, as well as causing irritation or direct damage to their vertebrate hosts. Arthropod cell lines are valuable tools for research on disease and vector control. The Tick Cell Biobank (TCB) is the world's only dedicated culture collection for generation, storage and distribution of cell lines derived from ticks and blood-feeding insects, and provision of training in arthropod cell line maintenance and application. The TCB hosts 70 cell lines derived from ixodid and argasid ticks (including tropical vector species of the genera *Amblyomma*, *Dermacentor*, *Hyalomma*, *Rhipicephalus* and *Ornithodoros)* and a growing panel of cell lines derived from mosquitoes (*Culex* and *Aedes*), biting midges (*Culicoides*), sand flies (*Lutzomyia* and *Phlebotomus*), triatomine bugs (*Rhodnius* and *Triatoma*) and tsetse flies (*Glossina*). TCB Outposts in Malaysia, Kenya and Brazil are facilitating uptake of arthropod cell line technologies in Asia, Africa and South America. Research in the TCB focuses on genotypic and phenotypic characterisation of selected tick and insect cell lines and determining their susceptibility to, and interaction with, a range of intracellular bacterial pathogens and symbionts including species and strains of *Anaplasma*, *Ehrlichia*, *Rickettsia*, *Spiroplasma* and *Wolbachia*. Recent in-house and collaborative research highlights include establishment of a *Phlebotomus papatasi* cell line naturally infected with *Wolbachia;* isolation in tick cells of *Wolbachia* from Malaysian cat fleas; and detection of short virus-derived DNA forms of the RNA orthonairovirus, Crimean-Congo hemorrhagic fever virus, that appear to play a role in maintenance of persistent infection in tick cells.

0096

COMPARISON OF DIFFERENT MOSQUITO TRAPS FOR ZOONOTIC ARBOVIRUS VECTORS IN PAPUA NEW GUINEA

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Little is known about zoonotic arboviruses and their vectors in Papua New Guinea (PNG). Vector surveillance is important to control mosquito-borne diseases. Incrimination and surveillance of zoonotic arbovirus vectors is important for the control of important diseases such as Japanese Encephalitis. In the present study, we compared the efficacies of three types of mosquito-trapping devices BG-Sentinel traps (BGS), CDC light traps with incandescent light (CDC_I) and CDC light traps with UV light (CDC_UV) to determine their suitability and cost-effective surveillance tool of key vectors of neglected zoonotic arboviral diseases in PNG. The study was conducted in various commercial chicken and pig farms in Central and Morobe provinces of PNG. All traps were used without lures.

Traps were placed outside animal houses for two periods of 5 consecutive days. The captured mosquitoes were identified by species, counted and species-specific capture rates were compared among trap types. A total of 13,788 mosquitoes were caught, including vectors belonging to the genera *Aedes, Anopheles and Culex*. Mosquito species captured included *Ae albopictus, Ae. aegypti, An. bancrofit, An. farauti, An. koliensis, An. longirostris, An. punctulatus, Cx annulirostris, Cx. gelidus, Cx. quinquefasciatus and Cx. Sitiens*. Of 13,788 mosquitoes, CDC_I trap caught 7.9%, BGS caught 14.5% and CDC_UV caught 77.6%. Median trapping rates showed significant difference among traps and ranging from species and farms. Culex was the most predominant genus caught in all the traps. BGS caught significantly more *Culex quinquefasciatus* than the two other two traps. CDC_UV captured the highest abundance, highest species richness and exhibited the highest overall *Culex* mosquito capture rates compared to BGS and CDC_I. This study represents the first assessment of mosquito trapping devices for zoonotic arbovirus vectors in PNG livestock farms. We recommend CDC_UV traps for future research and programmatic monitoring and surveillance of infectious arboviral vector programs in PNG.

0097

ENTOMOLOGICAL AND EPIDEMIOLOGICAL FACTORS OF VISCERAL AND CUTANEOUS LEISHMANIASIS OUTBREAK IN KAJIADO WEST, KENYA

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The Kajiado-West sub-county in Kenya, recently emerged as a new focus for visceral (VL) and cutaneous leishmaniasis (CL). We investigated entomological and epidemiological factors contributing to VL and CL occurrence to establish transmission hotspots and inform control strategies. We conducted a cross-sectional survey in four villages: Esonorua, Oldonyo Nyokie, Musenke and Shompole. Suspected VL and CL cases were screened using rK39 and microscopy. We did *Leishmania* parasite speciation by ITS1 PCR and sequencing. The entomological survey was conducted in November 2021 and February 2022 using CDC and Lumin-8 light traps. Regional taxonomic keys and *COX1* PCR were used for sandfly identification. 100 cases (males 56, females 44) were examined for VL infections. Overall, VL seroprevalence in the sub-county was 10%; the highest and lowest seroprevalences occurred in Esonorua (5%; n=5) and Shompole (1%; n= 1), respectively. 80% (n=8) of the VL patients were <15 years, with more infections in males (75%; n=6) than females (25%; n=2). There was no significant association between age group or gender and VL seropositivity. The overall CL prevalence in the sub-county was 36.4% (8/22), *L. tropica* was identified as the causative agent. We sampled 4,781 sandflies and identified 1,627 comprising four *Phlebotomus* spp. and eight *Sergentomyia* spp. The *Phlebotomus* spp. included *Ph. martini* (8.4%; n=136), *Ph. saevus* (2.3%; n= 38), *Ph. orientalis* (1.2%; n= 19), and *Ph. guggisbergi* (0.1%; n=1). We detected *L. tropica* DNA in *S. clydei* (n=3) and *Ph. saevus* (n= 1) while *L. donovani* was detected exclusively in *S. clydei* (n= 18). Overall, *L. donovani* and *L. tropica* infection rates in sandflies were 4% (18/450) and 0.7% (3/450), respectively. In conclusion, *L. donovani* and *L. tropica* are the main *Leishmania* spp circulating in the sub-county. Their presence in humans and sandflies indicates continuous transmission of the disease. *L. tropica* and *L. donovani* detection in *S. clydei* implicate the sandfly as a vector, however, requires further investigation. Factors behind the recent outbreak after long dormancy remain to be explored.

0098

AN UNUSUAL CASE OF HOME INFESTATION AND ALLERGIC REACTIONS ASSOCIATED WITH *ORNITHODOROS* SP. (IXODIDA: ARGASIDAE) IN COSTA RICA

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Infestation of homes with *Ornithodoros* spp. (Ixodida: Argasidae) and human biting depends on the particular species as well as nesting behavior and availability of hosts. Some species transmit pathogens like *Borrelia* spp. that cause tick-borne relapsing fever, and bites can cause toxicosis. Currently, there are only two such reports in Costa Rica: one includes two incidents associated with *O. kelleyi* (1979 and 1980), and the other cites a case by *Ornithodoros* sp. without dates. In February 2022, an infestation by argasid ticks was reported in a two-story mountain home in Heredia, Costa Rica. The owners, who visit occasionally, had been experiencing bites and allergic reactions for several months, including localized inflammation at the site, but also swelling, rashes, and itching in other parts of the body. They were treated with antihistamines. At the house, biting was concentrated in one room (second floor), where ticks were later found. There was no sign of recent animal activity, although pest control treatments were applied in the past 2 years for rodents, bats, and arthropods. Adults and nymphs (>60) were collected, as well as larvae (from aspirated material). Larvae were mounted in Hoyer's medium and identified as *O. kelleyi* according to taxonomic keys. However, larvae were smaller (body and scutum length= 0.8-0.86 and 0.305-0.325 mm, respectively, vs. 0.95-1.04 and 0.331-0.357 mm for *O. kelleyi*) and the apical 3/3 dentition comprised ~60% of the hypostome (distal third in *O. kelleyi*), with 8-9 denticles in the inner row (5-8 in *O. kelleyi*). Reports of bats and *O. kelleyi* in houses are not uncommon in North America, while human-biting seems less frequent. Interestingly, the only report of *O. kelleyi* south of Mexico is the one from Costa Rica, although *Ornithodoros puertoricensis, O. rudis*, and *O. talaje* are also known to bite humans in Central America. Given that these ticks may pose a risk to human health and that information on *Ornithodoros* spp. in Central America is scarce, further morphological and molecular analyses are being conducted to confirm the identity of the species associated with this case, as well as the main vertebrate host involved.

0099

ECO-FRIENDLY ALTERNATIVE MALARIA CONTROL STRATEGIES: INSECTICIDAL ACTIVITY OF *AEOLLANTHUS PUBESCENS* LEAF ESSENTIAL OIL AGAINST *ANOPHELES GAMBIAE*

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The excessive use of synthetic insecticides is responsible for many cases of resistance in insects. Therefore, the use of natural molecules of ecological interest with insecticidal properties turns out to be an alternative approach to the use of synthetic insecticides. This study aims at investigating the larvicidal, adulticidal activity and the chemical composition of the essential oil of *Aeollanthus pubescens* on the major malaria vector, *Anopheles gambiae*. Three reference strains of *Anopheles gambiae* sensu stricto (Kisumu, Kiskdr and Acerkis) were used in this study. The leaves of *A. pubescens* were collected in southern Benin. The standard WHO guidelines for larvicide evaluation were used and the chemical composition of

the essential oil was analysed by gas chromatography coupled to mass spectrometry. Adult mosquitoes were exposed to the net pieces coated with the essential oil for 3 min using the WHO cone bioassay method. Probit regression analysis was used to determine lethal concentrations (LC_{50}) and time to knockdown (KDT_{50}). The Log-rank test was performed to evaluate the difference in survival between the strains. Fourteen (14) components were identified representing 98.3% of the total of oil content. The major components were carvacrol (51.1%), thymyle acetate (14.0%) and ɣ-terpinene (10.6%). The essential oil has shown larvicidal properties with LC_{50} of 29.6, 22.9, and 28.4 ppm respectively on Kisumu, Acerkis and Kiskdr strains. With the net pieces treated at 165 µg/cm^2, the KDT_{50} of both Acerkis (1.71 s, Z =3.34, $p < 0.001$) and Kiskdr (2.67 s, Z =3.49, $p < 0.001$) individuals were significantly lower than that of Kisumu (3.8 s). The lifespan of the three mosquito strains decreased respectively to 1 day for Kisumu ($\chi2 = 99$, df = 1, $p < 0.001$), 2 days for Acerkis ($\chi2 = 117$, df = 1, $p < 0.001$) and 3 days for Kiskdr ($\chi2 = 96.9$, df = 1, $p < 0.001$). Our findings show that the *A. pubescens* essential oil has a larvicide and adulticide properties against the malaria vector *An. gambiae* s.s. This bio-insecticidal activity may be a promising discovery for the control of the resistant malaria-transmitting vectors.

0100

A FIELD BIOASSAY FOR ASSESSING IVERMECTIN BIO-EFFICACY IN MALARIA VECTORS

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Ivermectin (IVM) mass drug administration is currently under evaluation as a complementary malaria vector control tool. Mosquitoes ingesting blood from treated hosts suffer reduction in survival. Estimating bio-efficacy of IVM on wild-caught mosquitoes requires they ingest IVM in a bloodmeal either through a membrane or direct-feeding on a treated host. The latter, has ethical implications, the former results in very low feeding rates. Therefore, there is need to develop a safe and effective method for monitoring IVM bio-efficacy in wild mosquitoes. Our study exposed insectary-reared *Anopheles gambiae s.s* to five IVM doses: 85, 64, 43, 21, 11 and 0 ng/ml (control) in three different types of solutions: i) blood, ii) 10% glucose, and iii) blood in 10% glucose mixture in four ratios: 1:1, 1:2, 1:4, and 1:8 fed through a filter paper. Following treatments, mosquito survival was monitored for 28-days. Shortly after ingesting the meal, a pool of mosquitoes was sacrificed and weighed to determine mean weights of each meal type. Regardless of solution used, higher IVM doses resulted in significant reduction in survival. However, mortality rates for each IVM dose differed by solution. IVM was most lethal in a bloodmeal and least lethal in sugar solution, and when administered in sugar-blood mixture resulted in effects closer to bloodmeal. Larger blood meals was ingested compared to sugar or sugar-blood mixtures. However, meal sizes of mosquitoes fed on sugar and sugar-blood mixtures were similar despite pronounced difference in mortality rates. Ivermectin bio-efficacy differs depending on meal type used to deliver the drug. Meal volumes do not explain differences in lethality of IVM when comparing different meal types, further research is needed to understand the underlying mechanism. None of the solvents tested here performed better than blood but 1:4 sugar-blood mixture was comparable to blood. Given that the assay is sugar feeding based and wild-caught readily sugar feed, the mixture, is a good candidate for field-based bio-efficacy monitoring. To ascertain utility in the field, the mixture is currently being tested on field-collected mosquitoes.

0101

PHENOTYPIC, GENOTYPIC AND BIOCHEMICAL CHANGES DURING PYRETHROID RESISTANCE SELECTION IN *ANOPHELES GAMBIAE* MOSQUITOES

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The directional selection for insecticide resistance due to indiscriminate use of insecticides in public health and agricultural system favors an increase in the frequency of insecticide-resistant alleles in the natural populations. Similarly, removal of selection pressure generally leads to decay in resistance. Past investigations on the emergence of insecticide resistance in mosquitoes mostly relied on field survey of resistance in vector populations that typically had a complex history of exposure to various public health and agricultural pest control insecticides in nature, and thus the effect of specific insecticides on rate of resistance emergence or resistance decay rate is not known. This study examined the phenotypic, genotypic, and biochemical changes that had occurred during the process of selection for pyrethroid resistance in *Anopheles gambiae*, the most important malaria vector in Africa. In parallel, we also examined these changes in resistant populations when there is no selection pressure applied. Through repeated deltamethrin selection in adult mosquitoes from a field population collected in western Kenya for 12 generations, we obtained three independent and highly pyrethroid-resistant *An. gambiae* populations. Three susceptible populations from the same parental population were generated by removing selection pressure. These two lines of mosquito populations differed significantly in monooxygenase and beta-esterase activities, but not in *Vgsc* gene mutation frequency, suggesting metabolic detoxification mechanism plays a major role in generating moderate-intensity resistance or high-intensity resistance. Pre-exposure to the synergist piperonyl butoxide restored the susceptibility to insecticide among the highly resistant mosquitoes, confirming the role of monooxygenases in pyrethroid resistance. The rate of resistance decay to become fully susceptible from moderate-intensity resistance took 15 generations, supporting at least 2-years interval is needed when the rotational use of insecticides with different modes of action is considered for resistance management.

0102

INSECTICIDE RESISTANCE SURVEILLANCE OF MALARIA VECTORS IN PAPUA NEW GUINEA 2017 - 2022

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Anopheles farauti, An. koliensis and *An. punctulatus* are the 3 major malaria vectors in Papua New Guinea (PNG), and determining their distribution and susceptibility to insecticides is important for informing public health vector control strategies. Previous insecticide resistance (IR) data in 2018 reported these species to be susceptible to deltamethrin, lambdacyhalothrin and dichlorodiphenyltrichloroethane (DDT) across 4 provinces of PNG. This study presents an update of IR status of malaria vector populations in 9 provinces of PNG. IR monitoring was conducted between 2017 to 2022. Mosquitoes were collected as larvae from georeferenced natural habitats and reared to adults. 3-5 days old adults were tested against 4 insecticide classes (Carbamates, Organochlorines, Organophosphates, and Pyrethroids) using standard WHO tube bioassays to assess knockdown kinetics and 24-hour mortality. The samples

were then morphologically identified, and stored in ethanol for further laboratory analysis. A total of 12,972 female Anopheles mosquitoes were tested, controls included. All 3 species showed susceptibility to all 8 insecticides tested, except *An. koliensis*, which showed resistance to DDT, having 33.3% mortality, and lambdacyhalothrin, 83.3% mortality, in East Sepik province. Phenotypic resistance also shown in *An. punctulatus* population to DDT in Milne Bay, having 88.2% mortality, and lambdacyhalothrin in West Sepik, 87.5% mortality. Possible phenotypic resistance to DDT in the *An. farauti* population was also observed in Madang, Milne Bay and Western provinces (94.4-96.8% mortality), as well as to lambdacyhalothrin in the *An. punctulatus* population of East New Britain, East Sepik and Madang provinces (92.7-96.3% mortality). We now report evidence of phenotypic resistance in *An. koliensis* and *An. punctulatus* to DDT and lambdacyhalothrin in 3 provinces of PNG, as well as possible resistance in all 3 major Anopheles species to the same 2 insecticides, in several provinces. In particular, pyrethroid resistance is of concern given that the national malaria control program relies on pyrethroid treated long-lasting insecticidal nets.

0103

RESULTS OF THE 2021 ANNUAL VECTOR CONTROL REPORT IN MAINLAND TANZANIA

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Malaria is a leading cause of morbidity and mortality among children under 5 and pregnant women in Tanzania. The National Malaria Control Program (NMCP) must have readily available, digestible data to adjust their strategies and operations to maximize impact. The PMI-funded Tanzania Vector Control Activity (TVCA) worked with the NMCP to compile and synthesize the most current entomological, epidemiological, and other relevant data in addition to conducting an overview of the effectiveness of ongoing vector control interventions in mainland Tanzania. Council-level monthly malaria case data (confirmed positives) were pulled from the Tanzania DHIS2 from 2018 to 2021 and transformed to rates per 1,000 population. Slope equations from linear best fit lines and simple linear regression were used to determine if case data were steady, decreasing, or increasing. Nets per capita were derived from ITN distribution data and net decay rates, then converted to population ITN access at council level. Indoor residual spraying timing and insecticide resistance data were mined from reports covering 2011 to 2021. At the end of 2021, about one-third (n=62) of the councils had malaria incidence below 30 cases per 1,000 population, 16% were between 30 and 60, a quarter between 60 and 120 and another quarter above 120. Most councils (79 of 184; 42.9%) showed decreasing monthly malaria case incidence trends as well as at least 51-80% bed net population access with no evidence of insecticide resistance (even if driven by the overall lack of widespread resistance data). Even among the 39 mainland councils with evidence of pyrethroid resistance, ITN access was above 50% and malaria case incidence was either declining or holding steady in 36 (92.3%). A slight majority of councils fell into the 51-80% bed net access range and were noted as having a decreasing trend in monthly malaria case incidence (98 of 184; 53.3%). These results are being used to guide NMCP decision making for vector control activities including quantification of ITNs to be distributed.

0104

IVERMECTIN RESISTANCE MECHANISMS IN ECTOPARASITES: A SCOPING REVIEW

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Mono-therapeutic ivermectin mass drug administration (MDA) has been used for many years to control both human and veterinary parasites. This approach has provoked concern regarding its potential to increase selection pressure and accelerate the development of resistance in target and non-target organisms. Although widespread ivermectin resistance has been observed in veterinary parasite populations, until now there have been few and contended reports of resistance in human parasites. With ivermectin MDA now being investigated for efficacy and safety as a malaria control tool, it is important to consider potential resistance mechanisms that may develop in ectoparasites such as headlice and bed bugs, that may also inform our predictions of resistance mechanisms in mosquitoes. The aim of this scoping review was to map existing knowledge of resistance mechanisms in these organisms and to attempt to predict potential resistance mechanisms to ivermectin that may develop in the future. We searched databases including MEDLINE, PubMed and Web of Science using relevant search terms, and included studies that describe a validated mechanism of resistance in ectoparasites. We conducted a quality assessment for each of the included studies and results were summarised in terms of organism, resistance mechanism, degree of resistance, geographic location, and where possible, gene target. Predicting mechanisms of ivermectin resistance in mosquitoes will facilitate the development of molecular assays and enable preparedness of monitoring and evaluation strategies.

0105

WIND TUNNEL STUDIES ON THE IMPACT OF INSECTICIDE TREATED MATERIALS (ITMS) ON *AEDES AEGYPTI* HOST LOCATION BEHAVIOR

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Insecticide treated materials (ITMs) offer a simple yet effective method to reduce domestic infestations of disease vectors. However, their use against *Aedes aegypti* is complicated by the development of insecticide resistance. The study aimed to investigate whether resistant and susceptible *Ae. aegypti* strains exhibit behavioural differences during host-seeking at insecticide-treated netting and how they respond to host behind an ITM barrier containing holes.Two experimental assays were developed based on host seeking and final stage host feeding behaviours in three strains of *Ae. aegypti,* New Orleans (pyrethroid-susceptible), Jeddah and Makkah (pyrethroid-resistant). Individuals were exposed to Insecticide treated and untreated materials and their host feeding behaviour was assessed based on groups of 5 mosquitoes, attempting to reach and feed on human bait. Host seeking behaviour was assessed using a wind tunnel, with individuals flying upwind and allowed to pass through holed material. Behavioural events were recorded over 10 and 20 min respectively and logged manually. A significant reduction in time spent resting, probing or bouncing was seen with treated compared to untreated materials. However, no difference was observed between resistant and susceptible strains. After contact with treated nets, all strains of mosquito were seen to favour resting at a distance from the treated surface. In the wind tunnel, hole entry was seen to vary between mosquito strains, along with a significant reduction in the number of mosquitoes that passed through treated compared to untreated material (P<0.0005). This effect was significantly greater for the susceptible strain compared to the resistant strains(P<0.01) with this also being reflected in post-exposure knock-down and mortality.These results demonstrate how physiological resistance may

enable mosquitoes to more easily pass through holed treated materials due to increased resilience to the insecticide rather than through altered behaviour, with patterns of behaviour being similar or not varying consistently between strains.

0106

MULTIPLE MECHANISMS MEDIATING INSECTICIDE RESISTANCE IN *AEDES AEGYPTI* AND *AE. ALBOPICTUS* MOSQUITO POPULATIONS FROM CAMEROON

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Insecticide resistance is an increasing threat limiting the efficacy of vector control measures worldwide. Alongside Anopheline and *Culex* species, *Aedes* species including *Aedes aegypti* (Linnaeus, 1762) and *Ae. albopictus* (Skuse, 1894) from urban settings of Cameroon becoming resistant to pyrethroids and DDT. The F1 progeny of these *Aedes* species collected in Douala, Yaoundé and Dschang from August to December 2020 were tested using WHO tube assays with four insecticides : deltamethrin 0.05%, permethrin 0.75%, DDT 4% and bendiocarb 0.1%. TaqMan, qPCR, RT-qPCR assays and Cuticular Hydrocarbons (CHCs) identification and quantitation by GC-MS and GC-FID were used to detect kdr mutations, expression profiles of eight detoxification genes and implication of cuticle tickness respectively in insecticide resistance. *Ae. aegypti* mosquitoes from Douala were found resistant to DDT, permethrin and deltamethrin also three kdr mutations (F1534C, V1016G and V1016I) were detected in *Ae. aegypti* populations from Douala and Dschang. The kdr allele F1534C was predominant (90%) in *Ae. aegypti* ffrom Douala and was detected for the first time in *Ae. albopictus* (2.08%). P450s genes, Cyp9J28 (2.23-7.03 folds), Cyp9M6 (1.49-2.59 folds), Cyp9J32 (1.29-3.75 folds) and GSTD4 (1.34-55.3 folds) were found overexpressed in the Douala and Yaoundé *Ae. aegypti* populations. Furthermore, we found substantially higher CHC content in *Ae. aegypti* from Douala, compared to susceptible control mosquitoes (38% increase in mean CHC amounts). The large distribution of insecticide resistance in *Ae. aegypti* and *Ae. albopictus* populations calls for alternative strategies towards the control and prevention of arboviral diseases in Cameroon.

0107

RESPONSE OF *ANOPHELES FUNESTUS* S.L. AND *AN. GAMBIAE* S.L. TO DIFFERENT INSECTICIDES IN MALAWI

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Insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS) are the primary malaria vector control interventions in Malawi. *Anopheles funestus* s.l. and *An. gambiae* s.l. are the main malaria vectors targeted by these interventions. However, prolonged use of insecticides may lead to the emergence and spread of insecticide resistance in the target vectors. From July 2018 to December 2022, susceptibility of the two main malaria vector populations to different insecticides was monitored in Malawi. Larval and adult mosquitoes were sampled and reared from sentinel sites in Karonga, Nkhata Bay, Nkhotakota, Kasungu, Salima, and Chikwawa districts, and the resultant F1 progeny were tested for their susceptibility to different classes of insecticides. CDC bottle assays and WHO tube assays were used to determine the frequency of phenotypic resistance. Intensity of pyrethroid resistance was assessed. Both *An. funestus* s.l. and *An. gambiae* s.l. across the six sentinel sites were highly resistant to pyrethroids (permethrin, deltamethrin, and alpha-cypermethrin) even after increasing the diagnostic dose by 2 to 10-fold. However, pre-exposure of both species to piperonyl butoxide (PBO) restored their susceptibility status to the diagnostic dose of the pyrethroids. Both species were fully susceptible to pirimiphos-methyl (organophosphate), chlorfenapyr (pyrrole), and clothianidin (neonicotinoid). These data have led the National Malaria Control Programme to adjust its ITN distribution policy from using standard pyrethroid only treated nets to nets with PBO and/or other dual active ingredient ITNs. Further, pirimiphos-methyl and clothianidin are also being used in rotation for IRS as part of the insecticide resistance management strategy in Malawi. Continued monitoring of the insecticides used in IRS and ITNs is important for early detection and containment of insecticide resistance.

0108

THE TARGETED INDOOR RESIDUAL SPRAYING (TIRS) TRIAL. PROTOCOL AND PRELIMINARY ENTOMOLOGICAL FINDINGS OF A CLUSTER RANDOMIZED CONTROLLED TRIAL ASSESSING EFFICACY OF TARGETED INDOOR RESIDUAL SPRAYING TO PREVENT AEDES BORNE VIRAL ILLNESSES IN MERIDA MEXICO

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Current methods to control Aedes aegypti, the major vector of dengue, Zika, and chikungunya, have proven insufficient in preventing disease outbreaks. A promising new approach termed targeted indoor residual spraying (TIRS) consists of the selective application of residual insecticides on *Aedes aegypti* indoor resting sites, such as exposed lower sections of walls (< 1.5m), under furniture, and on dark surfaces. TIRS is a novel approach for *Ae. aegypti* control that has two major enhancements to existing practice; it exploits mosquito behavior to target insecticide applications and it is being applied preventively (before transmission season) rather than reactively (in response to reported cases). Here, we present the design and preliminary entomological findings of the TIRS trial, a two-arm, parallel, cluster randomized controlled trial quantifying the efficacy of TIRS in reducing the burden of laboratory-confirmed *Aedes*-borne viral clinical disease. Preliminary results after the first year of applying pirimiphos-methyl (Actellic 300CS, Syngenta) in ~8,000 houses were estimated by measuring indoor adult *Ae. aegypti* density through Prokopack aspirator collections in a sub-sample of 1,500 houses monitored monthly for 6 months covering the arbovirus transmission season. The overall effect across 6 months post-TIRS application showed a 77.4% reduction in positivity (calculated as the total number of houses positive for adult *Ae. aegypti*) in the TIRS arm compared to the control arm. Furthermore, we observed a waning in bioefficacy as the insecticide residual effect diminished over time. Results from a satisfaction and perceived effectiveness survey applied to 750 TIRS-treated households showed that 88% reported a reduction in the number of indoor mosquitoes and 96% would recommend the TIRS intervention to others. Our preliminary findings suggest a high and sustained effectiveness of TIRS for the control of indoor *Ae. aegypti* and high levels of satisfaction and uptake by the community. Epidemiological data collection is ongoing and will be analyzed for the primary endpoint when the predefined number of clinical endpoints is reached.

0109

PILOT TRIAL USING MASS FIELD-RELEASES OF STERILE MALES PRODUCED WITH THE INCOMPATIBLE AND STERILE INSECT TECHNIQUES AS PART OF INTEGRATED *AEDES AEGYPTI* CONTROL IN MEXICO

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The combination of *Wolbachia*-based incompatible insect technique (IIT) and radiation-based sterile insect technique (SIT) can be used for population suppression of *Aedes aegypti*. We implemented open-field mass-releases of *w*AlbB-infected *Ae. aegypti* males, as part of an Integrated Vector Management (IVM) plan lead by the Mexican Ministry of Health, to suppress natural populations of *Ae. aegypti* in a suburban setting in south Mexico. A controlled before-and-after quasi-experimental study was developed in two suburban localities of Yucatan (México): San Pedro Chimay (SPC), which received IIT-SIT, and San Antonio Tahdzibichen as control. Release of *w*AlbB *Ae. aegypti* males at SPC extended for 6 months (July-December 2019), covering the period of higher *Ae. aegypti* abundance. Entomological indicators included egg hatching rates and outdoor/indoor adult females collected at the release and control sites. Approximately 1,270,000 lab-produced *w*AlbB-infected *Ae. aegypti* males were released in a 50-ha area. The efficacy of IIT-SIT in suppressing indoor female *Ae. aegypti* density (quantified from a generalized linear mixed model showing a statistically significant reduction in treatment versus control areas) was 90.9% a month after initiation of the suppression phase, 47.7% two months after (when number of released males was reduced to match local abundance), 61.4% four months after (when normal 10:1 ratio of releases was re-established), 88.4% five months after and 89.4% at six months after the initiation of the suppression phase. Our study, the first open-field pilot implementation of Wolbachia IIT-SIT in Mexico and Latin-America, confirms that inundative male releases can significantly reduce natural populations of *Ae. aegypti* within a IVM plan implemented by Ministry of Health personnel.

0110

FIRST DETECTION OF THE KNOCKED DOWN RESISTANCE *(KDR)* MUTATION, L1014F, IN THE THREE MAJOR MALARIA VECTOR SPECIES IN PAPUA NEW GUINEA

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Malaria vector control in Papua New Guinea (PNG) is primarily pyrethroid treated long-lasting insecticide nets that are routinely distributed since 2005. Routine insecticide resistance monitoring reported that the three major malaria vector species, *Anopheles punctulatus, An. farauti* and *An. koliensis* are pyrethroid susceptible. Recent data suggest that these vector populations have developed phenotypic resistance to dichlorodiphenyltrichloroethane (DDT) and a possible cross-resistance to the pyrethroid insecticide, lambdacyhalothrin. In an effort to understand the underlying molecular mechanisms conferring this resistance, we conducted a molecular analysis of resistant and susceptible mosquito phenotypes tested against several pyrethroids and DDT from 2018 to 2021. All DDT, deltamethrin and lambdacyhalothrin resistant phenotypes and a subset of susceptible phenotypes in routine World Health Organization susceptibility bioassays were analyzed. Genomic DNA was extracted from these mosquitoes using standard methods. A PCR detecting the L1014F *kdr* mutation in *An. punctulatus* group was used to differentiate mutant alleles from the susceptible wild type alleles. A total of 25 resistant and 63 susceptible phenotypes were used in the preliminary analysis. We detected both the heterozygous and homozygous resistant alleles at a frequency of 0.30 and 0.01 respectively, and the homozygous wild type allele at 0.69. All resistant phenotypes had either the heterozygous (96%) or homozygous resistant allele (4%). Susceptible phenotypes had either the heterozygous allele (4.55%) or the wild type allele (95.45%). L1014F mutation was mostly detected in *An. punctulatus* (88%), 8% in *An. koliensis* and in a single *An. farauti* specimen (4%). We report for the first time the presence of the common *kdr* resistant mutation, L1014F, which confers pyrethroid and DDT resistance, in the three major malaria vector species in PNG. Further analysis to determine the magnitude of L1014F resistant mutation within the malaria vector population is ongoing and is crucial to inform the national malaria control program on effective control strategies.

0111

IMPACT OF DUAL ACTIVE INGREDIENT INSECTICIDE-TREATED NETS CONTAINING ALPHA-CYPERMETHRIN PLUS PYRIPROXYFEN ON THE MORTALITY, FERTILITY, AND FECUNDITY OF PYRETHROID-RESISTANT *ANOPHELES GAMBIAE* S.L. IN BENIN

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To mitigate the widespread resistance of malaria vectors to pyrethroids, new generation insecticide-treated nets (ITNs) have been developed. One of these new generation ITNs is the Royal Guard® net, which combines alpha-cypermethrin with a juvenile hormone analog, pyriproxyfen (PPF), which disrupts female reproduction and fertility of eggs. This study evaluated the impact of PPF ITNs on the mortality, fertility, and fecundity of *Anopheles gambiae* s.l. from Benin after exposure. Three populations of *An. gambiae* s.l. (Kisumu susceptible strain and two wild Benin resistant populations from Cotonou and Seme-Podji) were exposed for 3 minutes to either new PPF ITNs, standard alpha-cypermethrin ITNs (SAC; [Royal Sentry® net]), and an untreated net and evaluated using a protocol developed by Innovation-To-Impact (Liverpool, UK). Mosquito mortality was recorded 24, 48, and 72 hours after net exposure. Ovary dissections and identification of Christopher's stages in 75% of the surviving mosquitoes were used to determine the impact of PPF on ovary development and fertility rates. The abdomens of the remaining 25% of the surviving mosquitoes were dissected, and the number of eggs was counted to determine fecundity. Mortality rates of *An. gambiae* Kisumu exposed to PPF ITNs were 100% after exposure. Mortality rates of wild *An. gambiae* s.l. populations exposed to PPF ITNs from Cotonou and Seme were 29% and 13%, respectively, and 3% and 1% for those exposed to SAC ITNs, respectively, after 72 hours of observation. While the mortality rate of the wild resistant *An. gambiae* s.l. after exposure to the PPF ITNs was low, all surviving mosquitoes dissected were infertile (100%), and no eggs were observed in the abdomens of the remaining 25% of *An. gambiae* s.l. dissected for oviposition and fecundity measurements. The PPF ITN inhibited the reproduction of pyrethroid-resistant mosquitoes, suggesting that PPF ITNs may be an effective vector control tool in Benin.

0112

AGE GRADING OF *ANOPHELES GAMBIAE SENSU STRICTO* MOSQUITOES USING MALDI TOF MS PROTEIN PROFILING

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Malaria is transmitted by the bite of an infected female *Anopheles* mosquito. Transmission can only occur if a mosquito survives the extrinsic incubation period of 10 to 14 days. Assessing the age structure of mosquito populations could help in evaluating the impact of control methods. Traditional techniques are cumbersome and subjective. Malaria vectors have been shown to undergo proteomic changes as they age. MALDI-TOF is a mass spectrometry technique that uses laser technology for protein profiling and identification. This study aimed to determine if MALDI-TOF MS is capable of distinguishing different age groups of *Anopheles gambiae s.s.* mosquitoes based on their protein profiles. *Anopheles gambiae sensu stricto* mosquitoes (Kilifi strain) were reared in a laboratory controlled environment at KEMRI-Wellcome Trust insectary. Mosquito were reared to different physiological and chronological ages. The individual life history of each mosquito was recorded including mating, blood-feeding and oviposition. Approximately 100 mosquitoes per group of distinct physiological and chronological age were processed using MALDI TOF MS. Principal components analysis was used to explore differences in each group's spectrum profiles. Age-grading databases were created using ClinProTools and validated with spectra of unknown age. The study is ongoing. We expect to present the protein profiles of different ages of mosquitoes and database accuracy. We also aim discussing whether the method is worth exploring more widely in the field. The information will be used to validate the importance of MALDI-TOF MS as a new tool for entomological surveillance.

0113

ELECTRONIC MOSQUITO BARRIERS: A NON-CHEMICAL INSECT REPELLING TECHNOLOGY USING ELECTRIC FIELDS

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Decades of research have made great advances in controlling mosquitoes that transmit infectious diseases with insecticides. But our overreliance on insecticides raises concerns for our environment, our health and the development of insecticide resistance. As such, there is a critical need for novel non-chemical technologies to control insects. High voltage electric fields (EFs) provide great promise, but EF-insect science remains in its infancy. I will present the electric field concept, how insects respond to EFs, and preliminary data on how they prevent both host-seeking (feeding) and water-seeking (ovipositioning) mosquitoes from entering spaces. This first non-chemical insect repellent technology is safe and can be incorporated in window/door/eaves openings, larger fences, storm drains and water tanks to prevent mosquito from biting or laying eggs.

0114

INCREASE IN THE MALARIA ENTOMOLOGICAL INOCULATION RATE FOLLOWING THE WITHDRAWAL OF INDOOR RESIDUAL SPRAYING IN ATACORA, BENIN

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The National Malaria Control Program (NMCP) withdrew indoor residual spraying (IRS) from the Atacora department in northern Benin after six consecutive years (2011-2016) of implementation in the region, with the expectation that past IRS campaigns significantly reduced seasonal malaria transmission. An IRS withdrawal strategy, comprised of enhanced surveillance, reinforced case management, and availability of insecticide-treated bednets (ITNs) through continuous channels, was done to maintain the suppression of malaria. The entomological inoculation rate (EIR), a measure of exposure to infectious mosquitoes, was evaluated before and after IRS withdrawal to measure malaria rebound. Monthly mosquito collections by human landing captures (HLCs) were done in two Atacora districts (Natitingou and Toukountouna). Entomological monitoring occurred during the last IRS campaign year (2016) and two years after the IRS withdrawal (2018), both times from January to December. Technical constraints prevented entomological assessment in 2017. Two years after IRS withdrawal, the average EIR increased in the two survey districts. In 2016, the cumulative EIR was 17.2 infected bites/year in Natitingou and 24.8 infected bites/year in Toukountouna. In 2018, the EIR significantly increased ($p<0.0001$) from 94.9 infected bites/year in Natitingou to 129.2 infected bites/year in Toukountouna. While the EIR increased significantly after IRS withdrawal, it is not clear if mitigation measures were insufficient in this seasonal malaria transmission setting or if other factors, such as rainfall, ITN coverage, or insecticide resistance accounted for the increased EIR. The lack of control districts also limits the interpretation of the result.

While EIR is an accepted vector-based transmission indicator, human malaria cases are the definitive measure of impact. Thus, additional investigation with robust epidemiological and entomological monitoring may provide a better indication of whether IRS withdrawal led to malaria rebound.

0115

METABOLIC BASIS OF PYRETHROID RESISTANCE IN *AEDES AEGYPTI* FROM CENTRAL AMERICA AND THE DOMINICAN REPUBLIC

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Insecticide-based interventions have been central to the prevention and control of *Aedes*-borne diseases. However, resistance to DDT, permethrin and deltamethrin was documented during 2017-2018 in *Aedes aegypti* across Central America and the Dominican Republic. Molecular assays detected the presence of multiple *kdr* mutations (V410L, V1016I and F1534C) in the region, which partially explains the phenotypic resistance observed. However, metabolic mechanisms conferring pyrethroid resistance in *Ae. aegypti* remain poorly characterized. Thus, we aimed to elucidate the metabolic basis of pyrethroid resistance across the region. Mosquito eggs were collected across Central America and the Dominican Republic between 2021 and 2022. The insecticide susceptibility profiles, the intensity of resistance, and the potential role of detoxification enzymes were determined using CDC bottle bioassays. Expression levels of six cytochrome P450 genes (CYP6BB2, CYP6Z8, CYP9J10, CYP9J28, CYP9J32 and CYP9M6) were measured by RT-qPCR in pyrethroid-resistant populations. Bioassays confirmed resistance to DDT, permethrin and deltamethrin, and increased activity of detoxification enzymes (esterases, cytochrome P450s and glutathione-S-transferases) was associated with phenotypic resistance to permethrin and deltamethrin. Gene expression analyses revealed significant ($p<0.05$) overexpression of CYP9J10 and CYP9M6 in the pyrethroid-resistant populations. These findings are the first report of specific metabolic genes associated with pyrethroid resistance in Central America and the Dominican Republic. Moreover, the results highlight the urgent need to implement an integrated approach for insecticide resistance management using molecules without potential cross-resistance in the region or other non-chemical alternatives. Operational failure of the insecticide-based control interventions must be also measured to preserve the efficacy of the insecticides available in the future.

0116

STATUS OF INSECTICIDE RESISTANCE IN MALARIA VECTORS IN THREE PROVINCES IN ZAMBIA: INFORMING THE NATIONAL INSECTICIDE RESISTANCE MANAGEMENT PLAN

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The emergence of insecticide resistance (IR) is a threat to the effectiveness of indoor residual spraying (IRS) and insecticide-treated nets (ITNs). Zambia's National IR Management Plan recommends rotating IRS insecticides every two years; but, due to a lack of viable options, many districts in 2022 will use clothianidin (CN) for the 4th or 5th consecutive year. Pirimiphos-methyl (PM) was used widely for IRS from 2012 to 2018 but will not be reintroduced given its shorter than anticipated residual efficacy (3-5 months). DDT has been used from 2020 to 2021 in several districts where there is susceptibility. In addition, Zambia's National Malaria Elimination Program plans to shift its primary vector control strategy to universal coverage with PBO or dual active ingredient ITNs in 2023. Routine IR data collected by PMI in 2021 was reviewed to inform decision-making. Susceptibility testing of *Anopheles funestus* s.l. and *An. gambiae* s.l. to all WHO prequalified ITN pyrethroids and IRS insecticides (DDT, PM CN) was done in 3 provinces (Luapula, Eastern, Copperbelt) using WHO tube and CDC bottle assays. *An. funestus* s.l. and *An. gambiae* s.l. were fully susceptible to 2.0% CN, 100 µg chlorfenapyr, and 0.25% PM in all three provinces. A mix of susceptibility and resistance to 4.0% DDT was found in *An. funestus* s.l. in Luapula and Copperbelt (mortality 89-100%), while *An. gambiae* s.l. in Eastern Province were fully susceptible (mortality 100%). Both species were resistant to 0.05% deltamethrin, 0.75% permethrin, and 0.05% alpha-cypermethrin in Luapula and Copperbelt; a mix of resistance and susceptibility was noted for *An. gambiae* s.l. in Eastern Province. Alpha-cypermethrin had the lowest mortalities (44% for *An. funestus* s.l., 27% for *An. gambiae* s.l.). Susceptibility restoration by PBO pre-exposure in pyrethroid-resistant mosquitoes ranged from 85% to 100% from mortality levels as low as 32%. Despite the susceptibility of local vectors to clothianidin, its continued deployment raises concern for the emergence of resistance and should continue to be monitored. PMI's routine IR testing will continue to focus on current and emerging vector control insecticides.

0117

HETEROGENEITY OF INSECTICIDE SUSCEPTIBILITY FROM SIX ECOLOGICAL ZONES IN NIGERIA SUGGEST A HIGHLY EVOLVING *ANOPHELES GAMBIAE* S.L. POPULATION UNDER SELECTION PRESSURE

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Annual insecticide resistance monitoring is an essential tool to guide improved malaria vector control decisions. However, the value of collecting and analyzing this data over time and in several locations has not been justified. We investigated patterns of mosquito susceptibility to pyrethroid insecticides (permethrin, deltamethrin, and alpha-cypermethrin) based on data collected from 2016-2020 under the U.S. Presidents' Malaria Initiative VectorLink project in Nigeria. Mortality data were grouped into six ecological zones and subjected to one-way analysis of variance. Monitoring sites with at least four years of consecutive resistance data for all three pyrethroids were included. The range of mortality rates of *An. gambiae* s.l. mosquitoes exposed to permethrin, deltamethrin and alpha-cypermethrin were 5-100%, 33-100% and 16-100%, respectively. The proportion of local government areas (LGAs) that reported *An. gambiae* s.l. resistance to all three pyrethroids in a given year fluctuated over the period of interest—the percent of LGAs reporting resistance to permethrin, deltamethrin, alpha-cypermethrin ranged from 54.2-94.2%, 29.2-57.4%, and 15.9-29.2%, respectively. Significantly high variation ($p \leq 0.05$) in the mortality rates of *An. gambiae* s.l. mosquitoes exposed to the three pyrethroid insecticides was found in the mangrove, rainforest, transitional forest, Sudan savannah, and Guinea savannah ecozones, indicating ongoing insecticide selection pressure. In contrast, variation in the mortality of *An. gambiae* s.l. exposed to pyrethroids was not significant ($p \geq 0.05$) in the Sahel savannah ecozone, which suggests less intensive insecticide selection pressure in this ecozone. Outcomes from analyzing several years of data provide a clear and consistent distinction in the response of *An. gambiae* s.l. mosquitoes to pyrethroids. Such information may be used for evidence-based decision making, particularly given the need to consider scaling up new types of nets, such as PBO and dual active ingredient nets, for malaria vector control across the diverse ecozones and mosquito population resistance profiles of Nigeria.

0118

COMBINING MULTIPLE METHODS OF NEXT GENERATION SEQUENCING ENHANCES UNDERSTANDING OF INSECTICIDE RESISTANCE MECHANISMS IN PERMETHRIN RESISTANT *ANOPHELES COLUZZII* DISPLAYING REDUCED PBO-SYNERGY FROM MAFERINYAH, GUINEA

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Resistance to insecticides may severely threaten the long term efficacy of malaria vector control programmes. The synergist piperonyl butoxide (PBO) restores pyrethroid susceptibility by inhibiting mosquito detoxification enzymes and has been incorporated into some insecticidal nets. However, reduced PBO synergy has been reported in *Anopheles*. Next generation sequencing methods (NGS) enable detection of emerging resistance mechanisms, unlike targeted assays which are used in routine entomological surveillance and are rapidly outdated as mosquitoes evolve. This study uses NGS to characterise resistance mechanisms in an F1 population of field caught, permethrin resistant *Anopheles (An.) coluzzii* from Maferinyah, Guinea which displayed reduced PBO-synergy. We performed whole genome sequencing (WGS), whole transcriptome sequencing (RNA-Seq) and 16S rRNA sequencing on permethrin exposed *An. coluzzii* who did and did not experience PBO synergy. We developed a bioinformatics pipeline which can be used to identify single nucleotide polymorphisms (SNPs), insertions, deletions, copy number variants (CNVs) and chromosomal inversions from WGS data; expression of candidate genes from RNA-Seq data and abundance of microbes from 16S data. Preliminary data analysis revealed that microbial profiles vary with PBO exposure and resistance status, with PBO-exposed mosquitoes having significantly lower microbial diversity and mosquitoes with restored susceptibility having an increased abundance of *Staphylococcus spp.* and *Chromobacterium spp*. No SNPs were found to be significantly associated with PBO resistance suggesting that other genomic mutations such as CNVs may be driving resistance. Further analysis of WGS data will identify the impact of CNVs, which are thought to play a larger role in resistance but are more difficult to identify. RNA-Seq data will identify differentially expressed genes (including metabolic or cuticular) which may be contributing to reduction in synergy. Using NGS to identify population-specific markers of resistance will enable the development of up-to-date assays which can be widely used in the field.

0119

EARLY BIO-EFFICACY LOSS OF NETS MASS DISTRIBUTED FOR MALARIA VECTOR CONTROL IN MADAGASCAR: IMPLICATIONS FOR MALARIA PREVENTION STRATEGY

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In September 2018, the National Malaria Control Program and partners conducted a campaign to distribute insecticide-treated nets (ITNs) across Madagascar. Bio-efficacy of ITNs was tested upon arrival in Madagascar and after distribution. We conducted chemical analyses of insecticide residue on ITNs using HPLC and standard WHO cone bio-assays using a fully-susceptible strain of *Anopheles arabiensis*. Thirty DawaPlus® 2.0 and PermaNet® 2.0 ITNs were tested on arrival and 12, 24, and 36 months after distribution. DawaPlus® 2.0 nets were collected from three districts with differing climates: Bekily (semi-arid), Farafangana (humid), and Maintirano (tropical), while PermaNet® 2.0 nets were from sub-humid Taolagnaro district. On arrival, mosquito mortality rates observed from DawaPlus® 2.0 (86.4%) and PermaNet® 2.0 nets (83.6%) were above the WHO threshold of 80.0%. At 12, 24, and 36 months after distribution, mosquito mortalities induced by both DawaPlus® 2.0 and PermaNet® 2.0 were <56% for all districts. Moreover, knock-down effect was below the WHO threshold of 95.0% for both DawaPlus® 2.0 and PermaNet® 2.0 nets for all districts and time points. Finally, the deltamethrin residue on each ITN was also below the expected values of 80mg/m² for DawaPlus® 2.0 and 55mg/m² for PermaNet® 2.0; regardless of ITN age, the concentration of deltamethrin was <66mg/m² for DawaPlus® 2.0 and <36mg/m² for PermaNet® 2.0 ITNs. According to manufacturers, ITNs are effective for ≤36 months, thus, mass distribution campaigns are organized every three years. However, the DawaPlus® 2.0 and PermaNet® 2.0 ITNs showed a loss of bio-efficacy within one year of distribution. This bio-efficacy loss could be due to a manufacturing problem, to poor storage and transportation conditions, or to use and maintenance practices in Madagascar. Understanding and correcting the root causes is critical to guide corrective actions such as improving manufacturing, replacing ITNs more frequently, and increasing education on ITN care.

0120

COMPARATIVE TRANSCRIPTOMIC ANALYSIS OF INSECTICIDE RESISTANT *AEDES AEGYPTI* FROM PUERTO RICO REVEALS INSECTICIDE-SPECIFIC PATTERNS OF GENE EXPRESSION

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Aedes aegypti transmits major arboviruses of public health importance, including dengue, chikungunya, Zika, and yellow fever. The use of insecticide represents the cornerstone of vector control, and insecticide resistance (IR) in *Ae. aegypti* has become widespread. Here, we applied Illumina RNA-Seq to study the gene expression patterns in *Ae. aegypti* populations from 2 sites (Manati and Isabela) in Puerto Rico (PR). *Aedes aegypti* populations were phenotyped as either malathion, alpha-cypermethrin or lambda-cyhalothrin resistant, and transcriptomes of these phenotypes were compared against non-insecticide exposed individuals from the same populations as well as the insecticide susceptible Rockefeller reference strain. The analysis showed that cytochrome P450s were the predominant over-expressed detoxification genes across all resistant phenotypes, with CYP6Z7, CYP28A5, CYP9J2, CYP6Z6, CYP6BB2, CYP6M9, and two CYP9F2 orthologs commonly over-expressed in mosquitoes that survived exposure to all three insecticides (independent of geographical origin), suggesting their association with both pyrethroid and organophosphate resistance. Some detoxification genes were uniquely overexpressed in mosquitoes that survived exposure to malathion (CYP6BY1), alpha-cypermethrin (GSTD1), and lambda-cyhalothrin (CYP4H29, GSTE6), suggesting that their overexpression is associated with resistance to specific insecticides. For 4 out of 6 Resistant vs Susceptible comparisons, the gene ontology (GO) terms associated with monooxygenase, ironbinding, and passive transmembrane transporter activities were significantly enriched in the list of upregulated genes, indicating the potential contribution of these molecular activities to IR in this species. Interestingly, for all experiments, the downregulated genes that were significantly enriched were GO terms associated with chitin binding and chitinase activities. This RNA-Seq analysis presents a detailed picture of gene expression patterns and provides evidence for the molecular basis of pyrethroid and organophosphate resistance in *Ae aegypti* populations from PR.

0121

USING BAYESIAN STATE-SPACE MODELS TO UNDERSTAND THE POPULATION DYNAMICS OF THE DOMINANT MALARIA VECTOR, *ANOPHELES FUNESTUS* IN RURAL TANZANIA

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It is often assumed that the population dynamics of the malaria vector *Anopheles funestus*, its role in malaria transmission and the way it responds to interventions are similar to the more elaborately characterized *An. gambiae*. However, *An. funestus* has several unique ecological features that could generate distinct transmission dynamics and responsiveness to interventions. The objectives of this work were to develop a model which will; 1) reconstruct the population dynamics, survival, and fecundity of wild *An. funestus* populations in southern Tanzania, 2) quantify impacts of density dependence on the dynamics, and 3) assess seasonal fluctuations in *An. funestus* demography. A Bayesian State Space Model (SSM) based on mosquito life history was fit to time series data on the abundance of female *An. funestus* collected over 2 years in southern Tanzania. Prior values of fitness and demography were incorporated from laboratory-reared first generation progeny of wild *An. funestus*. The model was structured to allow larval and adult fitness traits to vary seasonally in response to environmental covariates, and for density dependency in larvae. The model accurately reconstructed the seasonal population dynamics of *An. funestus* and generated biologically-plausible values of their survival larval, development and fecundity in the wild. This model suggests that *An. funestus* survival and fecundity annual pattern was highly variable across the year, but did not show consistent seasonal trends either rainfall or temperature. While the model fit was somewhat improved by inclusion of density dependence, this was a relatively minor effect and suggests that this process is not as important for *An. funestus* as it is for *An. gambiae*. The model's ability to accurately reconstruct the dynamics and demography of *An. funestus* could potentially be useful in simulating the response of these populations to vector control techniques deployed separately or in combination. The observed and simulated dynamics also suggests that *An. funestus* could be playing a role in year-round malaria transmission, with any apparent seasonality attributed to other vector species.

0122

THE HUMAN-BAITED HOST DECOY TRAP (HDT) IS AN EFFICIENT SAMPLING DEVICE FOR EXOPHAGIC *ANOPHELES ARABIENSIS* WITHIN IRRIGATED LANDS IN SOUTHERN MALAWI

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Irrigation schemes provide an ideal habitat for *Anopheles* mosquitoes particularly during the dry season. Reliable estimates of outdoor host-seeking behaviour are needed to assess the impact of vector control options, and this is particularly the case for *Anopheles arabiensis* which displays a wide range of behaviours that circumvent traditional indoor-insecticide based control. In this study we compared the sampling efficiency of the host decoy trap (HDT) with the human landing catch (HLC) and Suna trap in a repeated Latin square design in two villages (Lengwe and Mwanza) on an irrigated sugar estate in southern Malawi. Over the course of 18 trapping nights, we caught 379 female *Anopheles*, the majority of which were identified as *An. arabiensis*. Across both villages, there was no detectable difference in *Anopheles* catch between the HDT compared with the HLC (RR = 0.85, $P = 0.508$). The overall sensitivity of the HLC was greater than the Suna trap regardless of mosquito density (Lengwe, $\alpha = 2.75$, 95% credible interval: 2.03–3.73; Mwanza, $\alpha = 3.38$, 95% credible interval: 1.50–9.30) whereas the sensitivity of the HDT was only greater than the Suna trap when mosquito numbers were high (Lengwe, $\alpha = 2.63$, 95% credible interval: 2.00–3.85). We conclude that the HDT is an effective sampling device for outdoor host seeking *An. arabiensis* in southern Malawi. The presence of *An. arabiensis* in irrigated lands during the dry season poses a challenge for ongoing indoor vector control efforts.

0123

SPATIO-TEMPORAL CLUSTERS AND PATTERNS OF SPREAD OF DENGUE, CHIKUNGUNYA, AND ZIKA IN COLOMBIA

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Colombia has one of the highest burdens of arboviruses in South America. The country was in a state of hyperendemicity between 2014 and 2016, with co-circulation of several *Aedes*-borne viruses, including a syndemic of dengue, chikungunya, and Zika in 2015. We analyzed the cases of dengue, chikungunya, and Zika notified in Colombia from January 2014 to December 2018 by municipality and week. The trajectory and velocity of spread was studied using trend surface analysis, and spatio-temporal high-risk clusters for each disease in separate and for the three diseases simultaneously (multivariate) were identified using Kulldorff's scan statistics. During the study period, there were 66,628, 77,345 and 74,793 cases of dengue, chikungunya, and Zika, respectively, in Colombia. The spread patterns for chikungunya and Zika were similar, although Zika's spread was accelerated. Both chikungunya and Zika mainly spread from the regions on the Atlantic coast and the south-west to the rest of the country. We identified 21, 16, and 13 spatio-temporal clusters of dengue, chikungunya and Zika, respectively, and, from the multivariate analysis, 20 spatio-temporal clusters, among which 7 were simultaneous for the three diseases. For all disease-specific analyses and the multivariate analysis, the most-likely cluster was identified in the south-western region of Colombia, including the Valle del Cauca department. The results further our understanding of emerging *Aedes*-borne diseases' trajectory in Colombia and provide useful information on the identified spatio-temporal disease-specific and multivariate clusters of dengue, chikungunya, and Zika, that can be used to target interventions. To our knowledge, this is the first time that the co-occurrence of all three diseases in Colombia was explored using multivariate scan statistics.

0124

APPLICATION OF A SPATIALLY EXPLICIT SAMPLING DESIGN TO IDENTIFY HETEROGENEITIES IN THE DISTRIBUTION OF MOSQUITOES

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The quality of data collected in any entomology study is heavily reliant upon the sampling design. In Kenya, the Division for National Malaria Program uses health facility data to select three sub-counties within the County that have high, medium, and low transmission, and the surveillance teams then perform convenience sampling within the selected sub-counties. This means that harder-to-reach areas may never be sampled and the surveillance is likely to be focused within a small geographical area within the sub-County. This study reports on the practical application of a stratified lattice and close pair sampling design for evaluating the spatial distribution of mosquito abundance. Sampling was conducted in Kilifi County in the coastal region of Kenya. Thirty sampling points were selected across 3 predefined ecotypes. CDC light trap collections were made at 4 households at each sampling point fortnightly over 2 months. A spatial negative binomial GLMM of the *Anopheles funestus sl*, *An. gambiae s.l.* and *Culex* spp. abundance was conducted using the sdmTMB package in R and predicted abundance mapped across the study area. *An. funestus s.l* was the dominant malaria vector in the region followed by *An. gambiae s.l.* Modelling indicates the presence of spatial correlation in the sampled mosquito abundance and a significant association for the Anopheles spp. with proximity to freshwater sources. This relationship was not mirrored in the Culex spp. which showed relative ubiquity throughout the study region. The environmental stratification was not significant. In conclusion**,** the stratified inhibitory lattice with close pairs sampling design established a clear relationship with the two primary vector species and the proximity to water. The ability of the design to isolate this relationship and produce spatial prediction maps with a balanced number of locations over the study region allows for the tailoring of vector control efforts in this area.

0125

CHECKMATE OR STALEMATE? MODELLING DENSITY-DEPENDENCE & ALLEE EFFECTS IN THE MALARIA VECTOR CONTROL ENDGAME

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Understanding the interplay between vector control and malaria mosquito population dynamics is critical to assess and improve vector control. Mosquito populations are regulated through a range of biotic and abiotic mechanisms, and among them, density-dependence is thought to be widespread. Density-dependence means per capita growth rate should be fastest when density is very low, for instance through competition for larval habitat that is alleviated as population size goes down. Although, an opposing scenario is also possible where small mosquito populations experience Allee effects*,* defined as positive density-dependence, in which per capita growth rate reduces as population declines. Here, we aim to identify the trade-offs between density-dependence and Allee effects, and how they might be impacted by interventions such as larvicides. Learning how to exploit this trade-off could make the difference between extinction or persistence (checkmate or stalemate). We developed a deterministic-stochastic simulation based on a stage-structured population model. The model follows a mosquito life cycle stages with life history traits such as adult and larval survival and fecundity defined as a function of density, larvicides and environmental variables. We included density-dependence as a predictor of larval stage and Allee effects as a predictor of adult mosquito fecundity rate. With density-dependence and Allee effects at levels that lead to a stable population, results indicate that there is at least 56% and 21% decline in average number of adult mosquitoes at a 100% and 50% coverage of larvicides respectively. However, if density-dependence increases by 50% and the intervention is short termed, the mosquito population bounces back to similar or higher levels than before. In contrast, if Allee effects are increased by only 36%, the population will decline 3 times faster. This indicates that density-dependence and Allee effects could be used to drive the population to extinction when used in combination to larvicides as an intervention.

0126

CHANGING SPECIES COMPOSITION OF POTENTIAL MALARIA VECTORS IN MEGHALAYA, NORTHEAST INDIA

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Malaria in India is declining, in part due to use of long lasting insecticide treated nets (LLINs) and vector control. The north-eastern (NE) region of India contributes ~10% of the nation's malaria burden, with Meghalaya state specifically continuing to experience low-level endemicity and occasional seasonal epidemics. The important mosquito vectors in NE India have long been considered to be *Anopheles baimaii* and *An. minimus*, both associated with forest habitats. Local deforestation and increased rice growing, along with widespread LLIN use, may be changing vector species composition. Understanding if and how vector species composition is changing is critical to successful malaria control. In a biodiverse setting like Meghalaya, where >24 *Anopheles* mosquito species have been recorded, accurate morphological identification of all species is logistically challenging. To accurately determine *Anopheles* species richness in the West Khasi Hills (WKH) and West Jaintia Hills (WJH) districts, adult and larval mosquitoes were collected and identified using molecular methods of allele-specific PCR and cytochrome oxidase I DNA barcoding. In 14 villages across both districts, we identified high species richness; 19 species in total. Molecular findings indicated that *An. minimus* and *An. baimaii* were rare, while five other species (*An. maculatus*, *An. pseudowillmori*, *An. jeyporiensis*, *An. nitidus* and *An. peditaeniatus*) were abundant. *An. maculatus* was highly prevalent in WKH (39% of light trap collections) and *An. pseudowillmori* in WJH (45%). Larvae of these five species were found in rice fields suggesting that land cover change is influencing species composition change. Our analysis investigates how changing land cover may affect malaria risk, including assessment of the spatial relationship between mosquito host-seeking, malaria cases, and land cover categories. Results suggest that rice fields are contributing to the observed abundance of *An. maculatus* and *An. pseudowillmori* which could be playing a role in malaria transmission, either independently due to their high abundance, or in combination with *An. baimaii* and/or *An. minimus*.

0127

ELECTROPENETROGRAPHY FOR THE STUDY OF PROBING BEHAVIORS OF A DISEASE VECTOR MOSQUITO *CULEX TARSALIS* COQUILLETT (DIPTERA: CULICIDAE)

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*Culex tarsalis*mosquitoes are capable of vectoring numerous pathogens affecting public andanimal health. Unfortunately, probing behaviors of mosquitoes are poorly understoodbecause they occur in opaque tissues. Electropenetrography (EPG) has thepotential to elucidate these behaviors by recording the electrical signalsgenerated during probing. We used an AC-DC EPG with variable input resistors(Ri levels) to construct a waveform library for *Cx. tarsalis* feeding onhuman hands. EPG waveforms representing different probe phases werecharacterized and defined by visual and video observations of biologicalactivities and analyzed for differences in appearance at four Ri levels and twocurrent types to identify electrical origins. The optimal settings for EPG recordingsof *Cx. tarsalis* probing on human hands was 150 millivolts of alternatingcurrent with 10^7 Ohms of resistance. Waveforms for *Cx. tarsalis*included those previously observed and associated with probing behaviors in *Aedesaegypti*: waveforms J (surface salivation), K (stylet penetration throughthe skin), L (type 1 and 2, search for a blood vessel/ingestion site), M (type1 and 2, ingestion) and N (an unknown behavior which may be a resting anddigestion phase before stylet withdrawal). However, we also observed additionalvariations in the waveforms that are not exhibited by *Ae. aegypti* thatwe named type 3 L waves, type 3 and 4 M waves, and type 1 and 2 N waves. Thisinvestigation enhances our understanding of mosquito probing behaviors. Weexpect it to facilitate future pathogen acquisition and transmission studiesand help identify new pest and disease management targets.

0128

MALARIA VECTOR MOSQUITOES LIVE LONGER AND LAY MORE EGGS AROUND IRRIGATION SCHEMES IN ETHIOPIA

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Water resource development projects like irrigated agriculture are key to ensuring economic growth and food security in Africa. However, such development projects cause environmental modification that could potentially favor vector-borne diseases transmission like malaria. This study aimed at assessing the effects of environmental modification due to irrigation practices on malaria vector mosquito development and survivorship in Ethiopia. The study was conducted in two agroecosystems, irrigated and non-irrigated areas, in western Ethiopia. Monthly larval surveys were conducted between 2017 and 2020. Life-table experiments were done to examine the effect of environmental modification on survivorship and development of both immature and adults *An. arabiensis.* Habitat diversity, larval abundance, pupation rate, development time of immatures, and adult longevity and fecundity were compared between the two agroecosystems. The irrigated agroecosystem was significantly associated with larval anopheline occurrence. The estimated mean survival time of female *Anopheles arabiensis* in the irrigated and non-irrigated areas was 37.9 and 31.3 days, respectively. The study found that fecundity of *An. arabienis*, was 96.2% higher in the irrigated agroecosystem than in the non-irrigated area. The findings of this study underscore that irrigation in semi-arid areas of Ethiopia increases the survival and fecundity of the major malaria vector, *An. arabiensis*.

0129

THE ORIGIN OF *AEDES ALBOPICTUS* INVADED MOZAMBIQUE

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Asian tiger mosquito, *Aedes albopictus*, is known as a main vector of various arboviruses. This species was originally described from Asia, but it has spread to several non-native geographical regions through the international movements of people and commodities. In Africa, although this mosquito has already established in West Africa, its established population had not been reported from the continental part of East Africa until it was confirmed in an urban neighbourhood of Maputo City in 2015. Since *Ae. albopictus* occurs in Madagascar, we hypothesized that the Mozambique population was introduced from the island. To confirm this, we identified the origin and invasion pathways with mitochondrial gene cytochrome c oxidase subunit 1 (CO1). The mosquito specimens were collected with ovitraps in Matola, a city adjacent to Maputo, Mozambique. We compared the CO1 gene sequences of the specimens with those from Madagascar and other countries that were available in GenBank. The genetic analysis revealed a total aligned length of 1,320 bp in which 7 variable sites were observed and 8 haplotypes were determined. One of the haplotypes was new and the other 7 haplotypes matched up with those reported from Malaysia. The population genetic structure was also similar to those found in Singapore and Hangzhou (a tropical region of China). These results indicate that the Mozambique population of *Ae. albopictus* was not originated in Madagascar, but in Southeast Asia.

0130

EFFECT OF CO-INFECTIONS ON THE TRANSMISSION OF CHIKUNGUNYA, MAYARO AND UNA VIRUSES BY *AEDES AEGYPTI* MOSQUITOES

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Chikungunya (CHIKV), Mayaro (MAYV) and Una (UNAV) are mosquito-borne alphaviruses that are currently co-circulating in Latin America. Each of these viruses shares its geographical and ecological niche with the mosquito vectors that can transmit it. CHIKV is mainly transmitted by the urban yellow fever mosquito *Aedes aegypti.* MAYV is mainly maintained in a sylvatic cycle between *Haemagogus* spp. mosquitoes and several vertebrates, but studies have shown that MAYV can also be transmitted by *Ae. aegypti*. UNAV is very closely related to MAYV and CHIKV, and although the vector species are unknown, it has been isolated from *Aedes* spp. Despite the potential challenge to public health, we fundamentally know little about co-infections in humans and mosquitoes. In particular, we do not know the impact of alphavirus co-infections on transmission by *Ae. aegypti*. We investigated the vector competence of *Ae. aegypti* co-infected with CHIKV, MAYV and UNAV. The mosquitoes were given an infectious bloodmeal in our BSL-3 facility and were incubated for 10 days at 28ºC, 70% relative humidity. After RNA extractions on collected mosquito bodies and saliva, the presence and relative RNA quantity of each of the viruses in co-infected mosquitoes was determined by qPCR. We show that UNAV can be experimentally transmitted by *Ae. aegypti*. Experiments exposing the mosquitoes to a single virus show a difference in infection rates (57-76%) but not in transmission rates (11-13%). Exposing the mosquitoes to all possible combinations of the three viruses with equal virus titers increased infection rates (67-97%). Co-infections do, however, not seem to affect transmission rates (12-20%). Further analysis of the qPCR results will elucidate if one of the viruses is more dominant than the others. Vector competence is only one of the factors that contributes to transmission potential. To determine how alphavirus infection can impact the mosquito's host-seeking behaviour, we will study the response of virus-infected *Ae. aegypti* to human odours in an olfactometer. Altogether our results contribute to our knowledge on the vectorial capacity of *Ae. aegypti* for alphavirus transmission.

0131

ECOLOGICAL DETERMINANTS AND RECORDED DISTRIBUTION OF *ANOPHELES STEPHENSI* IN ETHIOPIA

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Entomological surveillance conducted on *Anopheles stephensi* from August 2018 to December 2020 in Ethiopia enabled mapping of the extent of detection sites, data on sporozoite infections, blood meal sources & susceptibility to insecticides. In 2021, monitoring was expanded to previously uninspected sites to characterize breeding habitats & assess larval indices. These data serve as a baseline before a planned larviciding intervention. A site was considered positive whenever larvae were found, reared to adults & identified to the species. Larval density, container indices, relative breeding indices & adults' susceptibility to insecticides were determined. *Anopheles stephensi* was detected in 22 urban & 23 peri-urban/rural sites in Afar, Amhara, Dire Dawa, Oromia, & Somali regions. In these locations, *Anopheles stephensi* was found to breed in artificial containers such as cisterns, covered *birkas* (household water storage), water tanks & smaller vessels. Natural breeding habitats such as puddles, rain pools, rock pools & hoof prints were also found with *An. stephensi* larvae in Dire Dawa. In four towns in the eastern part of the country, concrete cisterns comprised 49-79% of all containers, whereas *birkas* were mostly found in the Somali region & comprised up to 77% of the breeding habitats. Adults were mainly caught in animal sheds. The water in breeding containers was stagnant, clean rain/tap water, sometimes with algal growth. The mean larval density ranged from 1.5 to 3.0 larvae/dip/day. The relative breeding index was 50-80%, while the relative habitat index was 0.8-1.0. *Aedes aegypti* larvae was found in 40% of containers positive for *An. stephensi*. Populations of *An. stephensi* were susceptible (> 98% mortality) to chlorfenapyr & clothianidin but resistant (<90% mortality) to deltamethrin, permethrin, alpha-cypermethrin, pirimiphos-methyl, propoxur, & bendiocarb. In conclusion, *An. stephensi* is widely distributed in Ethiopia, where it exists, prefers to breed in container habitats. Further surveillance should continue to elucidate the extent of distribution & if additional natural breeding habitats support larval development.

0132

HIGHER INFESTATION RATES OF THE VECTOR *AEDES AEGYPTI* IN RURAL AREAS THAN IN URBAN AREAS IN MANAGUA, NICARAGUA

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Surveillance and control of *Aedes aegypti*, primarily responsible for the transmission of dengue, chikungunya, and Zika viruses, continue to be a public health priority in many countries worldwide. We initiated a cohort study of 2,134 participants in Managua, Nicaragua, to investigate arboviral infections and disease across a gradient of urbanicity. To create a spatially representative sampling design, we used satellite imagery to define the sampling area in rural and urban areas in District III using impervious surfaces (man-made structural features) as a proxy for potentially inhabited sampling locations, which were then selected randomly, taking into account close-pair points and allowances for misclassification and inaccessibility. Two entomological surveys were conducted in the context of this A2CARES study. The first measured larval and pupal stages in 10% of the dwellings (167 households in rural and 470 in urban study areas) using a systematic sampling design. The second targeted 50% of the 1,000 cohort houses (250 households in rural and 250 in urban areas) selected with a random spatial distribution method. We measured multiple entomological indices including Breteau, pupae per 100 persons (PPP) or per 100 containers, and adult mosquito indices. The first survey yielded Breteau indices of 35.3 (95% Confidence Interval 26.9-45.6) in rural vs. 19.6 (15.8-24.2) in urban areas; p=0.0003, and PPP indices of 13.8 (11.1-16.8) in rural vs. 9.6 (8.4-11-0) in urban areas; p=0.0034; while in urban areas, the container productivity was significantly higher. In the second survey, the PPP index was 24.5 (21.7-27.6) in rural and 4.5 (3.4-5.8) in urban areas; p=0.0003. With respect to the mean numbers of adult *Ae. aegypti* captured per 100 homes, we found 32.0 (25.4-39.8) in rural vs. 16.0 (11.4-21.8) in urban areas (p<0.0001). Thus, contrary

to assumptions, we found higher infestation rates of *Ae. aegypti* in rural areas compared to urban areas using different sampling methodologies and multiple entomological indices.

0133

EVALUATION OF DIFFERENT TRAPPING METHODS FOR THE COLLECTION OF *ANOPHELES* MOSQUITOES IN WESTERN KENYA

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Entomological surveillance is essential for monitoring the impact of control tools and is mostly conducted using human landing catches (HLCS) or CDC-light traps (CDC-LT). HLCs may expose collectors to potentially infectious mosquito bites. To assess the optimal approach for mosquito surveillance for a large-scale trial of attractive targeted sugar baits, we compared five trapping methods indoors and outdoors in western Kenya. Five mosquito sampling methods—CDC-L), UV light traps (UV-LT), aspiration, HLC, and malaise trapping were evaluated in villages of Asembo, in Siaya County, western Kenya between July and September 2020. CDC-LTs, UV-LTs, and HLCs were conducted in three locations of the same compound (inside houses; outside 10 meters from the house; and outside 10 meters from the compound boundary). Collections were rotated through houses following a five-by-five Latin-square design. Mosquito densities, species abundance, and sporozoite infectivity rates were compared across all sampling methods. Data analysis was performed using R statistics software version 4.1.2. A total of 5483 *Anopheles* mosquitoes were sampled from 868 trapping efforts: 246 CDC-LTs, 237 UV-LTs, 223 aspirations, 148 HLCs, and 14 malaise traps. *Anopheles funestus* constituted 3824, (69.74%) of the sampled *Anopheles* mosquitoes. Compared to HLC, indoor aspiration captured highest number of *An. funestus,* mean=8.82 (RR =12.74, 95% CI 6.02-24.58, P <0.001) followed by indoor UV-LT, mean=4.26, (RR= 5.13, 95% CI 2.80-9.39, P <0.001) and indoor CDC-LT mean=2.30 (RR= 3.00, 95% CI 1.63-5.53, P <0.001). Similarly, outdoor UV-LT and CDC-LT collected a higher number of *Anopheles* mosquitoes across all species when compared to outdoor HLC. Hourly biting rates in UV-LT and CDC-LT indicated different peaks compared to HLC. *An. funestus* were primarily caught indoors. *An. arabiensis* and *An. coustani* were mostly collected outdoors with UV-LTs. The UV-LT and CDC-LT were superior to HLC both indoors and outdoors. Differences in hourly biting by different collection methods indicate the need to further investigate the behaviour of *An. funestus*.

0134

FACTORS ASSOCIATED WITH QUALITY OF LIFE IN CHRONIC CHIKUNGUNYA RHEUMATISM IN GUADELOUPE

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Chronic chikungunya disease is associated with a poor quality of life and symptoms not restricted to the musculoskeletal system. A cohort of patients with chronic chikungunya disease in Guadeloupe were evaluated in order to identify the main factors determining quality of life. Sixty-one patients were followed up a mean of 36 months after chikungunya infection. Patients underwent comprehensive examination for musculoskeletal involvement, assessment of subjective symptoms, and the impact on mood, physical activity and quality of life (SF12). Spearman correlations and multivariate regression analysis were performed using a multiple imputations technique, for handling missing data, followed by stepwise procedure to determine the main predictors of quality of life. Patients had extensive musculoskeletal involvement shown by high scores for the number of tender joints (9±4) and stiff joints (5±4). Patient symptom scales (% ±SD) revealed high scores for pain (62% ±24), stiffness (76% ±17) and fatigue (57% ±24), while SF12 physical and mental component scores showed a poor overall health-related quality of life. Measures of joint pain, stiffness impact and inflammation were found to contribute to impaired quality of life scores in 81%, 48% and 30% of the regression model iterations, respectively. In addition, fatigue and disturbed sleep appeared to be important predictors for physical aspects of quality of life, appearing in 39% and 100% of model iterations, respectively. The emergence of anxiodepressive syndromes post-chikungunya infection was also strongly associated with both physical and mental component scores of SF12. These data confirm that musculoskeletal symptoms are not the only determinants of quality of life in chronic chikungunya disease. Follow-up of patients should include assessment and management of fatigue, poor sleep quality and anxiodepressive syndromes.

0135

GENETIC DETERMINANTS OF A CHIKUNGUYNA VIRUS OUTBREAK IN NORTHEAST BRAZIL

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Chikungunya virus (CHIKV) is a virus transmitted by *Aedes* mosquitoes that causes significant morbidity in humans. The heterogenous transmission dynamics and epidemiology of CHIKV infections seen in different locations are thought to be associated with complex interactions of multiple genetic, ecological, and social determinants that are poorly understood. Understanding these determinants on a fine, local scale is critical to better predicting and controlling future CHIKV outbreaks. We aim to understand viral genetic determinants associated with transmission and human disease across a 1-year outbreak period in an urban area in northeast Brazil that has been a hotspot for arbovirus transmission. We sampled blood from chikungunya disease patients over the duration of this CHIKV outbreak from a 100 km^2-municipality within the Recife Metropolitan Region (RMR) that ultimately infected more than half of the city. From this cohort, we are in the process of sequencing CHIKV from 132 serum samples from well-characterized clinical cases. This data set offers us the opportunity to explore key unanswered questions regarding the underlying genetic factors that contributed to this intense and prolonged CHIKV outbreak in Brazil. We plan to identify the CHIKV genotypes circulating within the study population during the outbreak period and their prevalence over time. We will characterize the evolutionary dynamics of the genotype(s) as the virus first adapted to the region and as selective pressure from increasing population immunity to CHIKV occurred over time. We will also determine associations of viral genotypes or genetic variants with differential clinical symptoms of infected patients. We expect that more than one genotype was circulating during this outbreak, that we will see evidence of CHIKV evolution/adaptation over the span of the outbreak and that clinical symptoms of our cohort will associate with certain genotypes or virus variants. These data will contribute to a better understanding of CHIKV transmission dynamics and pathogenesis.

0136

SEROSURVEILLANCE OF CHIKUNGUNYA INFECTIONS AMONG U.S. MILITARY PERSONNEL DEPLOYING IN THE AMERICAS, 2013 - 2020

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Examining the risk and risk factors of chikungunya virus (CHIKV) infection during military deployment is important for CHIKV prevention efforts in any population. We leveraged the U.S. Department of Defense Serum Repository (DoDSR) to identify post-deployment CHIKV seropositivity in U.S. Military personnel deployed in the Americas during and after the CHIKV epidemic. The DoDSR comprises > 60 million sera from U.S. military members undergoing routine HIV screening . We selected DoDSR sera collected after n = 1500 deployments to Belize (n = 205), Colombia (n = 250), Curacao (n = 100), El Salvador (n = 225), Honduras (n = 250), Guatemala (n = 220), and Puerto Rico (n = 250) between 2013-2020. Post-deployment sera were screened for anti-CHIKV antibodies with a Vero cell-based microPRNT80, and confirmation using a CHIKV PRNT50 and a CHIKV/Mayaro Virus (MAYV) PRNT50 ratio ≥ 4. We analyzed 1500 deployments (including n = 13 individuals with > 1 deployment) with a median deployment duration of 0.5 years (IQR 0.25 - 0.75 years, range < 0.25 - to 4.5 years). Screening CHIKV microPRNT80 post-deployment sera positivity frequency was 25/1500 (1.7%). 18 (1.2%) met a CHIKV/MAYV PRNT50 ratio threshold to confirm CHIKV seropositivity. No sera met positivity criteria for MAYV infection, although n = 7 CHIKV screen-positive sera were equivocal for both MAYV and CHIKV. When constrained to deployments overlapping with the peak CHIKV Americas epidemic period (2014-2015), CHIKV seropositivity frequency remained low (0.9%). Post-deployment CHIKV seropositivity correlated with deployment length (p = 0.0001). Post-deployment seropositivity frequencies by country of deployment were: Belize (0/205, 0%), Colombia (0/250, 0%), Curacao (0/100, 0%), El Salvador (0/225, 0%), Guatemala (1/220, 0.5%), Honduras (3/250, 1.2%), and Puerto Rico (14/250, 5.6%). In conclusion**,** among those deploying to CHIKV endemic countries in the Americas between 2013-2020, post-deployment CHIKV seropositivity was low and correlated with deployment length. This may reflect effective vector avoidance or heterogeneity in CHIKV exposure in deployed personnel.

0137

ENDEMIC TRANSMISSION OF CHIKUNGUNYA VIRUS IN SOUTHERN THAILAND

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Chikungunya virus (CHIKV) infections are distributed across the globe, causing significant and, often, lasting morbidity. CHIKV vaccines are in development, but their evaluation is limited by the unpredictability of CHIKV transmission, which classically manifests as explosive epidemics separated by variable interepidemic periods. A passive surveillance study for undifferentiated febrile illness was established in southern Thailand in 2012 and is ongoing. Among 1473 individuals with paired acute and convalescent specimens, 391 (26.5%) had molecular or serological evidence of acute CHIKV infection. The proportions of participants confirmed to have CHIKV infection differed by year, being highest during epidemic periods (39.2% in 2018-2019, corresponding to a large regional CHIKV outbreak, compared to 18.9% in the inter-epidemic period 2012-2017). The highest burden of CHIKV infection was observed in younger adults, which may reflect age-related differences in exposure patterns and / or differences in the frequencies and manifestations of CHIKV-related disease. In phylogenetic analysis, the large epidemic of 2018-2019 in Thailand represented monophyletic expansion of a clade that was first identified in Africa, South Asia, and Singapore in 2015. Thai sequences from the inter-epidemic period were interspersed with those from other South and Southeast Asian CHIKV, suggesting frequent introductions and regional mixing. These data indicate possible stable endemicity of CHIKV in the study area, though additional studies are needed to confirm these findings and to discern whether this persistence reflects widespread, low-level transmission or migrating bursts of focal epidemic activity. For episodic pathogens such as CHIKV, intensified detection and study of endemic hot spots may hold the key to proactive preparation and countermeasure development, rather than reactive attempts at mitigation, for future epidemics.

0138

LONGITUDINAL AND TRANSVERSAL STUDIES OF CHIKV SEROPREVALENCE IN SOUTHEAST BRAZIL REVEALS A CRYPTIC CIRCULATION OF THE VIRUS

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Chikungunya vírus (CHIKV) and Mayaro vírus (MAYV) are arthropod-borne viroses of Alphaviruses genus transmitted by Aedes sp. genus mosquitões. In 2015 CHIKV was the first detected in São José do Rio Preto (SJdRP) and in the period between 2015-2020 the surveillance program notified a total 463 suspect cases and 41 confirmed cases in the city. The study aimed to investigate the presence of CHIKV antibodies in a cohort study participants (a 4 year follow-up of 341 subjects) and in the samples from a panel from the arboviruses surveillance program of the city during a dengue outbreak in 2019. We analyzed 341 serum paired samples of the cohort study (2015-2019), and 497 dengue-negative samples (2019) of a dengue outbreak using anti-CHIKV IgM/IgG by ELISA. After that, equivocal and positive samples in ELISA were confirmed by Plaque Reduction Neutralization Test (PRNT80), showing low cross reactivity with MAYV and a low prevalence of MAYV in southeast Brazil. Demographics data were associated with serological results and analyzed. A positive sample by Rt-qPCR to CHIKV was sequenced and subsequently submitted to a phylogenetic analysis. The total prevalence of anti-CHIKV IgM/IgG positive was 7.9% and 2.3% in the cohort study and 4.4% and 8.9% in samples from dengue-suspects subjects. During the cohort study (4 year), the incidence was 20.6/1,000 habitants and the attack rate was 2.1%. The phylogenetic analisys identified that the genotype CHIKV present in the municipally was the ECSA lineage, wich was associated with outbreaks in our country. Using both a longitudinal cohort and transversal studies the data showed a cryptic circulation of CHIKV the data showed a cryptic circulation of CHIKV in SJdRP, since no epidemic associated to this vírus since its introduction in 2015, as seen in most places in the world. This data reinforces the importance of arboviruses surveillance and especially in

the contexto of a new arboviruses introduction in a region wich can lead to na outbreak due to the know emerging and epidemic potential of the vírus.

0139

ALPHAVIRUS SEROPOSITIVITY IN ACUTE FEBRILE PATIENTS DURING A DENGUE OUTBREAK IN AN ARBOVIRUS ENDEMIC AREA IN PERU

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The Peruvian Amazon is endemic for different arthropod-borne viruses (arboviruses) mainly those transmitted by mosquitos. Yearly outbreaks and/or epidemics are reported for which the main etiological agent is dengue virus (DENV), followed by the flaviviruses Zika (ZIKV), and yellow fever, and the alphaviruses chikungunya (CHIKV) and mayaro (MAYV). Despite febrile patients (FPs) present with nonspecific symptoms early in the acute phase of the disease, the simultaneous screening of arboviruses is poorly evaluated, and then the co-infection or prevalence of less-frequent arboviruses is generally missed. CHIKV is currently the most prevalent alphavirus, however the circulation of the antigenically related virus MAYV pose a problem for serodiagnosis, similar to the one described for flaviviruses. In this study, we evaluated the presence of the antigenically-related alphaviruses CHIKV and MAYV in 148 acute serum samples from dengue-suspected cases during a DENV outbreak in Yurimaguas, an arboviral endemic city at the Peruvian Amazon, between 2018 and 2019. Viral RNA was evaluated using a multiplex RT-PCR for the detection of DENV, ZIKV and CHIKV, while IgM and IgG antibodies (Abs) were assessed using ELISA tests from Euroimmun for DENV, ZIKV, CHIKV and MAYV. By using RT-PCR, DENV was detected in 51.4% (76/148) of patients, while all samples were negative to ZIKV and CHIKV. The identification of MAYV by RT-PCR is under evaluation. Higher positivity rates were observed for IgG Abs in comparison to IgM in the ELISA assays, thus for DENV 79.1% vs 29.7%, for ZIKV 43.2% vs 2.7%, for CHIKV 24.3% vs 7.4% and for MAYV 29.1% vs 6.1% of patients were positive for IgG and IgM respectively. Three FPs were simultaneously positive to CHIKV and MAYV for IgM, while 29 were positive for CHIKV and MAYV for IgG. These findings highlight the need (i) to further investigate the presence of possible arboviral co-infections in FPs and also (ii) to assess the potential cross-reactivity of Abs raised against related alphaviruses such as CHIKV and MAYV in areas with reported co-circulation of different arboviruses and their implications in the diagnosis and management of FPs.

0140

THE CHIKUNGUNYA VIRUS: A REEMERGING CAUSE OF ACUTE FEBRILE ILLNESS IN THE HIGH JUNGLE OF NORTHERN PERU

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The Chikungunya virus (CHIKV) is an emerging arthropod-borne virus (arbovirus) that causes undifferentiated acute febrile illness in Peru. We performed a study to identify the prevalence of CHIKV in febrile patients. A cross sectional study was conducted in the province of Jaen, Cajamarca's state, located in the high jungle of northern Peru. Patients attending primary care health centers within Cajamarca's Regional Health Direction were enrolled between June 2020 through June 2021. Patients were included with a acute febrile illness (AFI). Serum sample collection was performed on all patients and the diagnosis of CHIKV was performed using real-time RT-PCR and detection of IgM antibodies by ELISA assay. A total of 1047 patients with AFI were enrolled between June 2020 and June 2021. Identification of CHIKV was carried out in 130 patients (12.42%), of which 84 (8.02%) were diagnosed by RT-PCR, 42 (4.01%) by IgM ELISA detection and 4 (0.38%). by both assays. Most of the patients with CHIKV infection corresponded to the 18-39 years old (46.92%), followed by the 40-59 years old (23.85%) and those with 60 years or older (12.31%). Also, a greater proportion of female patients was identified (53.07%). The most common clinical symptoms in the whole study population were headache (85.67%), myalgias (71.35%) and arthralgias (64.76%). In the case of patients with CHIKV the most common symptoms were headache (84.62%), myalgias (70.77%) and arthralgias (64.62%). Most positive cases for CHIKV occurred during the months of May (23.08%), March (20.00%) and February (13.85%) of 2021. In conclusion, we report a considerable frequency of CHIKV infections in patients with AFI from the high jungle in northern Peru. These findings should raise awareness that CHIKV is a pathogen with continuous transmission in different regions of Peru. Epidemiological surveillance should be strengthened with reliable diagnostic techniques, given that clinical symptoms may be nonspecific.

0141

DETECTION OF SARS-COV-2 ANTIBODIES IN FEBRILE PATIENTS FROM AN ENDEMIC REGION OF DENGUE AND CHIKUNGUNYA IN PERU

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The rapid expansion of the novel SARS-CoV-2 virus has raised serious public health concerns due to the possibility of misdiagnosis in regions where arboviral diseases are endemic. We performed the first study in northern Peru to describe the detection of SARS-CoV-2 IgM antibodies in febrile patients with a suspected diagnosis of dengue and chikungunya fever. A consecutive cross-sectional study was performed in febrile patients attending primary healthcare centers from April 2020 through March 2021. Patients enrolled underwent serum sample collection for the molecular and serological detection of DENV and CHIKV. Also, serological detection of IgM antibodies against SARS-CoV-2 was performed. 464 patients were included during the study period, of which (40.51%) were positive for one pathogen, meanwhile (6.90%) presented co-infections between 2 or more pathogens. Most patients with monoinfections were positive for SARS-CoV-2 IgM with (73.40%), followed by DENV 18.09% and CHIKV (8.51%). The most frequent co-infection was DENV + SARS-CoV-2 with (65.63%), followed by DENV + CHIKV and DENV + CHIKV + SARS-CoV-2, both with (12.50%). The presence of polyarthralgias in hands (43.75%, $p<0.01$) and feet (31.25%, $p=0.05$) were more frequently reported in patients with CHIKV monoinfection. Also, conjunctivitis was more common in patients positive for SARS-CoV-2 IgM (11.45%, $p<0.01$). The rest of the symptoms were similar among all the study groups. SARS-CoV-2 IgM antibodies were frequently detected in acute sera from febrile patients with a clinical suspicion of arboviral disease. The presence of polyarthralgias in hands and feet may be suggestive of CHIKV infection.

These results reaffirm the need to consider SARS-CoV-2 infection as a main differential diagnosis of acute febrile illness in arboviruses endemic areas, as well as to consider co-infections between these pathogens.

0142

LONGITUDINAL ANALYSIS OF PLATELET INDICES AND RED-CELL DISTRIBUTION WIDTH AND ITS CORRELATION WITH THROMBOCYTOPENIA IN DENGUE PATIENTS: A CASE-CONTROL STUDY

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Emerging evidence suggest association of certain platelet indices with degree of thrombocytopenia in dengue patients. However, there is paucity of longitudinal follow-up of these parameters with decline and recovery of platelet counts. The objectives were to determine the differences of red cell distribution width-standard deviation (RDW-SD), red blood cell distribution width-coefficient of variation (RDW-CV) and platelet indices including platelet distribution width (PDW), mean platelet volume (MPV), platelet-large cell ratio (P-LCR), and plateletcrit (PCT) among dengue and non-dengue patients. Analysis was done in dengue patients of longitudinal 7-days follow-up for correlation with platelet counts. This case-control study was conducted upon retrospectively collected data of admitted patients in a tertiary care hospital. Cell counts were collected from hospital's medical record of 131 dengue patients and 131 non-dengue patients via CELL-DYN Ruby automated Hematology Analyzer by Abbott (IL, USA). Mann-Whitney U test and Spearman's correlation coefficients were applied. The mean age was 35.25 ± 15.08 and 30.72 ± 13.63 in controls and cases respectively (p=0.106). Baseline characteristics including gender (p=0.247) and comorbidities were similar in both groups. Mean PDW, MPV and P-LCR were found higher in dengue patients while PCT was found lower (p<0.001). In non-dengue patients, only RDW-SD (r-0.236) and PCT (r+0.951) were found correlating with platelet counts, while RDW-SD (r+0.245), RDW-CV (r=0.371), P-LCR (r-0.400), MPV (r-0.252) and PCT (r+0.842) were found correlating in dengue cases. In longitudinal analysis of dengue cases, RDW-SD and RDW-CV remain decreasing with platelets till day 2, and then start increasing with rising platelets at day 7. PCT remained positively correlated till day 7. MPV became positively correlated on day 2. PDW became negatively correlated at day 6 with rising platelets. CIn conclusion, platelet indices and RDW on days 2, 6 and 7 of in-hospital stay were found predictive of dengue-related thrombocytopenia, hence they are useful parameters for dengue recovery.

0143

SOLUBLE SUPPRESSOR OF TUMORIGENICITY (SST2) PREDICTS SEVERE DENGUE AND CARDIAC DYSFUNCTION

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Dengue can be complicated by severe disease including cardiac dysfunction. The lack of reliable prognostic biomarker poses a challenge in managing dengue patients. We investigated the functionality of soluble suppressor of tumorigenicity (sST2) as a predictive marker of severe dengue. Plasma samples came from a longitudinal cohort (with study visits in the febrile, critical and recovery phaes) of slightly older adult dengue patients recruited between 2016-2019 in Singapore. Cardiac parameters: stroke index (SI), cardiac index (CI) and Granov-Goor Index (GGI) were measured with a bioimpedance device at the different phases for dengue participants and once for the controls. Plasma levels of sST2, Troponin T and NT-proBNP were measured via ELISA. A total of 120 subjects, 36 dengue fever (DF), 43 dengue with warning signs (DWS), 11 severe dengue (SD) and 30 controls were assayed. In the febrile, critical, and early recovery phases, sST2 levels were significantly elevated in dengue participants and with greater disease severities (P<0.001 for all). sST2 concentrations were negatively correlated with SI (r=-0.48; P<0.001), CI (r=-0.26; P=0.02) and GGI (r=-0.44; P<0.001) in the critical and phase. sST2 levels in the febrile and critical phases, were positively correlated to troponin-T (r=0.44, P<0.001; r=0.22, P=0.03 respectively) and NT-proBNP (r=0.21, P=0.03; r=0.35, P<0.001 respectively). Interestingly, ROC analysis demonstrated sST2 as a good biomarker of SD in the critical phase, (AUROC 0.79, P<0.001). In conclusion, sST2 levels were raised in dengue patients especially in SD. Furthermore, sST2 levels were associated with markers of cardiac impairment. sST2 may be a useful prognostic biomarker of severe dengue.

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A FATAL CASE OF DENGUE HEMORRHAGIC FEVER ASSOCIATED WITH DENGUE VIRUS 4 (DENV-4) IN BRAZIL GENOMIC AND HISTOPATHOLOGICAL FINDINGS

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Dengue infection is the most prevalent arthropod-borne viral disease in subtropical and tropical regions of the world, whose primary vector is *Aedes aegypti* mosquitoes. The mechanisms of dengue virus (DENV) pathogenesis are little understood because we have no animal models of disease; only humans develop symptoms and research has been limited to studies involving patients. DENV is very diverse: there are four antigenic groups (serotypes) and three to five genetic groups (genotypes) within each serotype. Thus, it has been difficult to evaluate the relative virulence or transmissibility of each DENV genotype as both of these factors are important determinants of epidemiology and their measurement is complex because the natural cycle of this disease involves human-mosquito-to-human transmission. Samples from serum, brain, cerebellum, heart, lungs, liver and kidneys from a 13-old male patient that died with hemorrhagic manifestations were sent for differential diagnosis at Adolfo Lutz using both classical virological methods (RT-qPCR, virus isolation, ELISA and hemagglutination inhibition test) and immunohistochemistry (IHQ). A DENV serotype 4 was detected by a DENV multiplex RT-qPCR, and a full genome was obtained from C6/36 cell supernatant using Minion. Lesions were described in heart, liver, lung and kidney with positive IHQ in endothelial cells of brain, cerebellum, heart and kidney, and also in Hepatocytes and Kuppfer cells. Sequencing revealed a DENV-4 genotype II showing an unique non synonymous mutation on position I759M (envelope protein - steam region), however, electrostatic changes in these protein were not significant. Here we report a whole genome of a fatal case caused by a DENV-4 genotype II showing hemorrhagic lesions in several organs in a DENV endemic area of Brazil, with a positive immunohistochemistry on several endothelial cells, liver and kidney, in a patient with no signs of previous DENV infection.

0145

DENGUE VIREMIA KINETICS AND ITS EFFECT ON CLINICAL OUTCOMES

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Dengue incidence has been increasing for the last four decades and has been identified as one of the top 10 threats to global health by the WHO.

Higher viremia levels in the early phase are associated with more severe dengue outcome, but data on overall viremia kinetics and its effect on clinical outcomes remain limited. We analysed a pooled dataset of 2340 laboratory-confirmed dengue patients from three prospective observational studies performed between 2000 and 2016 in Ho Chi Minh City, Vietnam. The studies enrolled both pediatric and adult patients presenting within three days after fever onset (illness day 1, 2 or 3). All had daily viremia data from enrolment. Viremia levels were measured by RT-PCR. Clinical endpoints included severe dengue (based on the WHO 2009 classification) and predefined moderate-severe plasma leakage. We investigated the trajectory of viremia over time and how it differed by age, sex, serotype and immune status using a mixed-effects model with zero-inflation to account for undetectable values. On each illness day we assessed the effect of viremia on clinical endpoints by logistic regression. We found that viremia rapidly decreased after symptom onset and was detectable in only one case after illness day 8. Viremia kinetics differed by serotype, immune status, and age ($p < 0.0001$): DENV-1, primary infection (for DENV-1 and 3) and older age had highest viremia and took the longest to become undetectable. The effect of viremia on the endpoints did not differ by age, sex, serotype, and host immune status. Higher viremia levels on any illness day increased the risk of developing severe dengue and plasma leakage but effect sizes were modest (ORs [95% CIs] were 1.27 [1.04; 1.56] and 1.24 [1.10; 1.41] per each 10-log increase) compared with the effects of a secondary immune response (ORs [95% CIs] were 73.1 [9.91; 540] and 2.31 [1.49; 3.04], respectively). The findings will be of use for planning antiviral therapeutic trials as well as for incorporation into electronic clinical decision support systems.

0146

AN UPDATED ASSESSMENT OF DENGUE ALGORITHMS INTEGRATED INTO FIVE SOUTHEAST ASIAN INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS (IMCI) GUIDELINES

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During the early stages of dengue fever, clinicians need to identify children who might develop severe disease course and need referral. The WHO Integrated Management of Childhood Illness (IMCI) algorithms currently, don't include dengue in the generic IMCI algorithm. However, the management of dengue has been incorporated into several IMCI country adaptations. We aimed to evaluate the dengue algorithms incorporated into IMCI guidelines in Southeast Asian countries. The study methodology comprised three components. First, we investigated dengue fever algorithms incorporated into five Southeast-Asian country IMCI guidelines through a desk-based analysis. Second, we conducted an expert survey to elicit opinions regarding the incorporation of dengue in IMCI. Third, we compared our findings with data from a multicentre study on dengue risk assessment, management and surveillance (IDAMS). There was considerable variation in the classification schemes across the guidelines investigated. Generally, the guidelines did not differentiate between a screening tool to identify dengue versus warning signs for progression to severe dengue. There was a consensus by expert to include dengue and to extend the age range for IMCI guidelines since dengue is relevant for children beyond 5 years of age. Using data from the IDAMS study, we found that the likelihood of virologically confirmed dengue increased after three days of persistent fever but nearly half of the patients (366 out of 910) who had fever for only one day had virologically confirmed dengue. This study supports the extension of the IMCI age range for dengue assessment beyond 5 years of age. Because of the challenge of distinguishing dengue from other febrile illnesses, conducting laboratory testing for dengue is important to do at an early stage during the course of the illness. Testing only children with persistent fever for 3 days may lead to an underdiagnosis of dengue among those with acute febrile illness but the cost-effectiveness and public health benefits of earlier testing needs further assessment.

0147

CHANGES IN THE TRANSMISSION INTENSITY OF DENGUE VIRUS ACROSS ECOLOGICALLY DIVERSE REGIONS OF ECUADOR AND ASSOCIATED RISK FACTORS

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In the 20th into the 21st century, viruses transmitted by *Aedes aegypti* mosquitoes have worsened in previously affected areas and expanded into new regions. Dengue is one of the few tropical diseases with an increasing global burden over the last 20 years. The ecological and demographic drivers of dengue virus (DENV) can be studied in Ecuador, a South American country with multiple distinct regions. Here, we used province-level age-stratified dengue incidence data from 2000-2019 and catalytic models to estimate the force of infection of DENV over decades and across geographically diverse provinces in Ecuador. We identify provinces at different stages of establishing endemic DENV transmission. Coastal provinces with the largest and most connected cities had the earliest and highest increase in DENV transmission intensity, starting around 1980 and continuing to the present. In contrast, remote and rural areas with reduced access, like the northern coast and the Amazon regions, experienced a rise in DENV transmission and endemicity only in the last 10 to 20 years. The newly introduced chikungunya and Zika viruses have distinct age-specific incidence distributions consistent with recent emergence across all provinces. We then evaluated factors associated with geographic differences in vector suitability and arbovirus disease in the last 10 years by modeling 11,693 *A aegypti* presence points and 73,550 cases. In total, 54% of the population of Ecuador lives in areas with high risk of *Ae. aegypti,* including in the provinces we identified as experiencing recent increases in DENV transmission intensity. Most suitable provinces had hotspots for arbovirus disease risk, with population size, elevation, sewage connection, trash collection, and access to water as important determinants. Our investigation serves as a case study of the changes driving the expansion of DENV and other arboviruses globally and provides an approach for identifying areas at early stages of establishing endemic transmission that should be targeted for intense preventative efforts to avert future epidemics.

0148

THE ROLE OF ANTIGENIC AND GENETIC DIVERSITY IN DRIVING THE INFECTION AND DISEASE RISKS OF DENGUE VIRUS

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Despite the substantial global burden, the infection and disease risks from dengue virus (DENV) remain not well understood. Co-circulation of four serotypes and resulting human multiple infections increase the complexity. DENV's infection and disease processes are driven by multiple competing factors, including the antigenic and genetic evolution of DENV and the effects of pre-existing immunity. These factors are often analyzed separately using different data sources. It remains unclear how heterogeneous data from case-based surveillance and viral surveillance could be combined together to assess DENV's infection and disease risks in the community. Here we analyzed 12,389 laboratory-confirmed secondary DENV cases collected from a children's hospital in Bangkok from 1994 to 2014. We used their information of infecting year, age, and serotype. To capture antigenic diversity within the population, we build a three-dimensional antigenic map using data from a large antigenic testing program that systematically tested the neutralization ability of 348 different DENV strains isolated in Thailand from 1994 to 2014 against a suite of reference sera. We further increased the resolution of the population antigenic profile in any year by placing an additional 2242 sequenced viruses onto the map, based on genetic similarity. Using Bayesian methods to incorporate year, age, serotype, and antigenic information, we jointly estimated the yearly serotype-specific force of infection, degree of cross-protection, and most importantly, the infection and disease risks over antigenic distance. We reconstructed the age- and serotype-specific distributions of incident cases per year. Our model selection suggests that the full model incorporating all available information has the highest predictive power. Our study provides a unified framework to integrate heterogeneous data from case-based surveillance and viral surveillance for assessing the infection and disease risks of DENV in the community.

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ESTIMATING PATHOGEN FITNESS FROM GENETIC DATA

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Subclinical infections and co-circulating lineages commonly hide the underlying dynamics of dengue fever from surveillance systems. Therefore, the role of different lineages in driving epidemics remains largely unknown. Models informed by pathogen sequences can help. Here we develop a light analytical framework that makes use of genetic data and quantifies the fitness of individual mutations in a population. We extend a recently developed isolate-specific, genetic distance-based measure of epidemic success. We derive an expected value of this index given the underlying level of transmission in the population. By fitting this index for each isolate, we estimate their effective reproduction number R(t). Through this framework, we are able to assess which genetic markers are significantly linked to dengue virus fitness, without specifically looking at known circulating genotypes. Using simulated data, we demonstrate the validity of our approach. We simulate an endemic transmission and generate sequences for each infected individual. We let some mutations be significantly more fit in the population than others. We then sample the sequences generated with a range of procedures, mimicking common surveillance system biases (e.g., uneven sampling by location and year). We show our method can efficiently and accurately recover isolate fitness, as well as decipher the contribution of the different variants to fitness. Next, we apply this method to dengue virus sequences from Thailand (n = 726 over 18 years). This novel method provides an exciting way to quickly assess pathogen fitness from phylogenetic trees, and is highly relevant for pathogen surveillance.

0150

PROFILE AND DYNAMICS OF THE ANTIGEN-SPECIFIC BINDING ANTIBODY RESPONSE AND ANTIBODY-DEPENDENT COMPLEMENT DEPOSITION ACTIVITY AFTER PRIMARY AND SECONDARY DENGUE VIRUS TYPE 1 AND TYPE 3 INFECTIONS

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Dengue is the most medically important mosquito-borne viral disease and a major public health concern worldwide, with the four dengue virus serotypes (DENV1-4) being responsible for 50-100 million cases annually. DENV immunity is complex, and antibodies generated after a primary infection with one serotype can cross-react with other serotypes, leading to either protection, increased risk of symptomatic infection or enhanced disease severity upon subsequent infection. In this study, we investigated the quality and dynamics of antibodies generated after DENV1 and DENV3 primary and secondary infections over time. We analyzed samples collected at 14-28 days, as well as 3, 6, and 18 months post-infection from a long-standing pediatric dengue hospital-based study in Managua, Nicaragua, using a newly developed multiplex Luminex assay and an antibody-dependent complement deposition (ADCD) assay. Here, we describe the binding and isotype profile of antibodies targeting the envelope protein (E), E domain III (EDIII), and non-structural protein 1 (NS1) of DENV1-4 and ZIKV, as well as the ADCD activity to each antigen. Notably, we found that antibodies generated after primary DENV1 infection bind and deposit complement on DENV3 EDIII but not on DENV3 NS1, whereas upon primary DENV3 infection, ADCD activity was observed on DENV1 NS1 but not on DENV1 EDIII. We also observed that ADCD activity mediated by anti-DENV3 NS1 antibodies wane faster after a secondary DENV3 infection compared to a secondary DENV1 infection. This study reveals that the binding profile and ADCD activity of the anti-DENV antibody response differ by infection history and infecting serotype, resulting in a fingerprint unique to each serotype.

0151

DETERMINANTS OF SYMPTOMATIC DENGUE VIRUS INFECTION IN A PEDIATRIC COHORT IN NICARAGUA

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Dengue is the most medically important arbovirus worldwide, affecting more than 140 countries, with 50-100 million cases each year. The determinants of symptomatic dengue virus (DENV) infections among individuals and communities are of public health importance and are relevant for vaccine development to create strategies to lessen the burden of dengue. Previous studies have reported varying DENV symptomatic-inapparent infection ratio (S:I ratio) year-by-year and varying predictors of the S:I ratio, including age, time since the last infection, prior DENV immunity, and spatial location. Here we evaluated 3,720 DENV infections in children 2-17 years old in the Pediatric Dengue Cohort Study (PDCS) in Managua, Nicaragua, from 2004 to 2020. We analyzed the S:I ratio of DENV infections by demographic factors, immune response, prior DENV antibody titer, predominant circulating serotype, and epidemic year. A

Least Absolute Shrinkage and Selection Operator (LASSO) regression was used for feature selection to capture the most important variables determining the S:I ratio. In addition, we performed a spatial analysis of the S:I ratio in the DENV2 epidemic in 2019 in the same cohort. The yearly S:I ratio ranged greatly, from 1:1 to 1:17, with the highest yearly S:I ratios coinciding with the largest DENV epidemics. In our analysis of determinants of the S:I ratio, we found older age, epidemic year, prior intermediate DENV titer, time since the last infection, prior DENV and ZIKV infection, and spatial household location as significant predictors of greater symptomatic infection. The feature selection analysis showed epidemic year as the most important variable for predicting the S:I ratio, followed by prior intermediate DENV titer and older age, which predicted a higher S:I ratio. In this study, we cover a broad range of individual and ecological factors over a long period of time, and our results suggest that the yearly size of the epidemic, changes in individual-level immunity, and key demographic characteristics shape the varying determinants of DENV S:I ratios.

0152

THE INFLAMMASOME IS ACTIVATED BY DENGUE VIRUS NONSTRUCTURAL PROTEIN 1 AND PLAYS A PROTECTIVE ROLE DURING VIRAL INFECTION

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Dengue virus (DENV), consisting of serotypes 1-4, is the most medically important flavivirus, causing an estimated 50-100 million dengue cases globally every year. Most symptomatic DENV infections present as an acute febrile illness that is self-limited though debilitating; however, some cases progress to severe and potentially fatal complications that include vascular leakage leading to hemorrhage and hypovolemic shock. DENV nonstructural protein 1 (NS1) is secreted from infected cells and has been implicated as a major driver of dengue pathogenesis, activating immune cells and acting directly on endothelial barriers, causing them to become pathologically hyperpermeable. While recent work has delved into the mechanisms behind the endothelial cell-intrinsic pathway of DENV NS1-induced vascular leak, much less is known about how DENV NS1 interacts with immune cells and what role this activation plays in DENV infection. We have discovered that DENV NS1 can trigger activation of the inflammasome, a family of cytosolic innate immune sensors that react to danger-associated molecular patterns. DENV NS1 induces the release of the pro-inflammatory cytokine IL-1β in human and murine monocytes in a caspase-1 dependent manner that is independent of the sensor NLRP3. Additionally, we found that caspase-1-deficient, but not NLRP3-deficient, mice are more susceptible to infection in a murine model of DENV infection. These results indicate that the inflammasome acts as a sensor of the DENV viral toxin NS1 and plays a protective role during DENV infection. Work is ongoing to identify the inflammasome that senses DENV NS1 and investigate the mechanisms by which inflammasome activation leads to host defense against DENV infections.

0153

CONSISTENCY OF ESTIMATES OF THE INTENSITY OF DENGUE VIRUS INFECTION FROM SEROLOGICAL AND PASSIVE CASE SURVEILLANCE STUDIES

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Force of infection (FOI) is an important metric when designing and implementing interventions. Ideally, FOI would be calculated using serologic data from highly powered prospective cohort studies, directly measuring rates at which naive individuals seroconvert to the pathogen of interest. However, because this approach is resource intensive, FOI is typically inferred from mathematical models applied to cross-sectional seroprevalence or passive surveillance case datasets. Consistency of FOI estimates from these different approaches remains poorly understood. Here, we use data from a series of cohort studies in Kamphaeng Phet, Thailand (1998-2016: total 10159 individuals, 59801 bleeds with hemagglutination inhibition antibody measurements to all four dengue serotypes) and case data from the provincial hospital (1994-2019, n=12222). We built a suite of models to estimate the annual FOI between 1998 and 2018, considering the cohorts as both longitudinal measures (multiple samples per individual) and cross-sectional data (single sample per individual). By comparing the consistency of the estimates and modifying models to reconcile the discrepancies, we gained insight into key drivers of dengue risk. We found broad concordance in the timing of peaks and troughs of FOI in the different approaches but with significant differences in their magnitude. It was only when incorporating two key extra components that we were able to reconcile these differences. Firstly, we allowed for differences in the risk for infection by age, highlighting how the risk of infection among susceptible individuals is highest for 12-15 year olds. Secondly, we allowed for serological responses to be 'lost' after a first infection (i.e., falling to levels below 1:40), which we estimate occurs in 65% of primary infections. Our findings suggest that all approaches including seroconversion rates will need to be interpreted with caution. Specifically, age structure differences between individuals under study and the general population and effects of antibody kinetics on observed seroconversions will need to be considered.

0154

DENGUE VIRUS DAILY DIARY (DENV-DD) - A NEW PATIENT-REPORTED OUTCOME (PRO) TOOL MEASURING DENGUE SYMPTOM INTENSITY: FINDINGS FROM A DEN-3 HUMAN CHALLENGE STUDY

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Dengue is the most common arboviral infection worldwide. Infection can result in a febrile illness with headache, abdominal, muscle/bone pain, rash or diarrhea. Understanding the patient's experience of dengue illness can provide insight on the unmet individual/public health burden of dengue. We describe frequency and intensity of self-report dengue signs/symptoms in a DEN-3 human challenge study using a novel PRO tool, the Dengue Virus Daily Diary (DENV-DD). Healthy adults were challenged with a single dose of DEN-3 ($1.4*10^3$ pfu/ml; CH53489) and asked to complete the DENV-DD daily for 28 days during follow-up. The DENV-DD uses a 4-point intensity scale for 24 symptoms ("not at all" to "a lot"), global symptom intensity ("good" to "very bad") and global impact ("not at all" to "very hard" to do usual activities). Treatments taken and temperature were also self-recorded. Clinical measures and viral RNA were collected routinely through day 28 follow-up. For each participant, a daily mean symptom rating was estimated by averaging individual symptom intensity. PRO completion, response distributions/patterns and relationships

with clinical/lab characteristics were explored. Nine volunteers (Mean age: 33; 5 female; 8 white) were challenged. Daily completion rate was high (90%). Most signs/symptoms occurred between Days 4-14 (86%). Tiredness, body hurting, back hurting and body weakness were the most common symptoms and had the highest intensity. We identified a positive relationship between fever intensity and temperature as well as between global impact and mean symptom ratings. We also observed a positive relationship between clinical and PRO-measured symptom intensity. Viral replication and mean symptom rating both peaked between Days 4-12. We demonstrated the use of the DENV-DD to capture a wide range of signs/symptoms associated with dengue illness in the context of a well-established human challenge model. Validation of this tool in a natural dengue infection setting is underway. Self-reported measures of dengue illness are helpful to assist with public health monitoring and vaccine clinical endpoint development.

0155

DENGUE IN US STATES AND TERRITORIES, 2018-2020

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Dengue virus (DENV) is an arbovirus associated with high morbidity that can result in severe disease or death. In the U.S., dengue cases are reported to ArboNET, the national arboviral surveillance system. This analysis describes trends and characteristics of dengue cases reported to ArboNET during 2018-2020. Dengue cases met the dengue clinical criteria definition with either (*i*) DENV nucleic acid detected by RT-PCR in a clinical specimen; or (*ii*) detection of anti-DENV IgM in serum. A total of 3,449 DENV cases were reported to ArboNET; 2,311 (67%) were travel associated and 1,138 (33%) were locally acquired. Locally acquired cases were reported from Puerto Rico (n=861; 76%), American Samoa (n=150; 13%), Florida (n=90; 8%), Guam and Texas (n=15 each; 1%), and the US Virgin Islands (n=3; 0.3%). Fifty-eight percent of travel-associated cases were submitted by four states: Florida (n=514; 22%), California (n=455; 20%), New York (n=223; 10%) and Texas (n=141; 6%). The largest number of DENV cases was reported in 2019 (n=1,593; 46%), followed by 2020 (1,217; 35%) and 2018 (n=639; 19%). A quarter of all dengue cases were from Puerto Rico (n=875; 25%), most of which occurred in 2020 (n=780; 89%). Half of all dengue cases occurred among males (n=1,725; 50%) and case-patients with known race were white (n=1,132; 56%), Asian (n=303; 15%), Native Hawaiian or Other Pacific Islander (n=176; 9%), Black or African American (n=120; 6%), and other (n=261; 13%). DENV case-patient median age was 34 (IQR 17-53) years. Approximately 40% (n=1,389) of DENV patients were hospitalized, and three fatal cases were reported. Of 585 cases with reported serotype, the majority were DENV-1 (n=461; 79%), followed by DENV-2 (n=67; 12%), DENV-3 (n=53; 9%), and DENV-4 (n=4; <1%). The proportion of DENV-1 cases increased by year (46%, 61%, and 89%). Dengue continues to be a public health threat in the U.S. both for travelers and people living in endemic areas. Disease monitoring through surveillance is critical to support effective control and prevention measures, including education to healthcare providers, travelers, and people living in areas with dengue transmission.

0156

INDIVIDUAL, HOUSEHOLD, AND COMMUNITY DRIVERS OF DENGUE VIRUS INFECTION RISK IN KAMPHAENG PHET PROVINCE, THAILAND

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Dengue is endemic in many tropical and subtropical regions. In settings with high levels of transmission, it remains unclear which are the main risk factors that alter individual infection risk. To explore the drivers of infection, we tested blood taken from individuals living in multigenerational households in Kamphaeng Phet province, Thailand, for DENV antibodies (N=2376, mean age 31y). Seropositivity ranged from 45.4% among those age 1-5y to 99.5% for those >30y. We explored the drivers of infection risk by fitting spatially explicit serocatalytic models. Using this regression framework, we incorporated individual and household characteristics from questionnaires as well as data from entomological surveys. We estimated that 11.8% of the susceptible population gets infected annually, with less than 2% of all infections detected by the passive surveillance systems. We estimated the average basic reproductive number (R0) to be 2.60 across the province. We found 37.5% of the variance in seropositivity was explained by unmeasured household-level effects with only 4.2% explained by spatial differences between households. Door screens appear to have a protective effect but the number of adult mosquitoes trapped in the households at random timepoints was not significantly linked to infection risk. The serostatus of individuals from the same household were significantly correlated with a 1.26 odds ratio of being seropositive if another individual in the household was seropositive rather than seronegative. This correlation remained significant when individuals were separated by up to 15 years in age. This correlation structure vanished when considering groups of households located within 500m from each other instead. These findings show that despite highly endemic transmission, persistent differences in infection risk exist across households, the reasons for which remain further investigation.

0157

MOSQUITO SALIVARY SECRETIONS DISRUPT ENDOTHELIAL CELL PERMEABILITY AND MAY FACILITATE FLOOD FEEDING AND PATHOGEN TRANSMISSION

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Mosquito blood feeding is an essential process for reproduction and the vehicle for pathogens transmission to vertebrate hosts. During blood feeding, the host's hemostatic system is activated resulting in platelet aggregation, vasoconstriction, coagulation, inflammation, and cell recruitment to the bite site. Mosquitoes have evolved an array of bioactive salivary compounds that counteract the hemostatic system of their hosts. These salivary molecules have also been implicated in pathogen transmission and establishment in their vertebrate hosts. Mosquito saliva increases the migration of neutrophils, macrophages, and monocytes to the bite site; the recruitment of these cells is accompanied by increased endothelial permeability. However, the role of mosquito saliva on endothelial permeability is not well understood. Here, we evaluated the

effect of salivary gland extracts (SGE) of three major disease vectors: *Culex quinquefasciatus, Anopheles gambiae*, and *Aedes aegypti* on endothelial permeability in vitro and in vivo. Our results show that SGE of *Ae. aegypti* and *Cu. quinquefasciatus* significantly increased the endothelial permeability in vivo while *An. gambiae* SGE showed a modest increase in permeability. Similar results were obtained in FITC-Dextran Trans-Epithelial in vitro assays. Human Primary Dermal Microvascular Endothelial Cells (HDMVECn) treated with SGE resulted in a higher leakage of Dextran. We measured the expression of 84 genes related to endothelial cells biology by qPCR. HDMVECn treated with *Ae. aegypti* SGE resulted in upregulation of Tissue factor, CCL2, KIT, PECAM-1, and Selectin-E genes. Leukocyte recruitment in vitro experiments also shows that mosquito SGE increases cell transmigration. These results demonstrate that mosquito SGEs have a profound effect on endothelial cell integrity and immune response leading to the upregulation of several pro-inflammatory genes. Identifying individual salivary proteins responsible for these activities may lead to a transmission-blocking approach to mosquito-borne diseases.

0158

LONGITUDINAL ASSESSMENT OF DENGUE NS1-SPECIFIC HUMORAL IMMUNE MEMORY IN HUMAN COHORTS FOLLOWING PRIMARY DENGUE INFECTION

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The four serotypes of dengue virus (DENV 1-4) are considered the most important vector-borne viral pathogens effecting humans worldwide. Following DENV infection, naïve host B-cells expand, produce, and secrete DENV-specific antibodies (Abs) that recognize viral antigens, specifically epitopes present on the surface of whole virus and secreted non-structural protein 1 (NS1). After viral clearance, some of these B-cells become long-lived plasma cells (LLPCs) which secrete Abs into the serum, while others become memory B cells (MBCs) that remain in circulation, quiescent, but poised to respond and expand on repeat infection. The humoral response against some antigens, such as measles, is long-lived (the lifetime of an individual), while against others is much shorter. The durability and breadth of DENV whole virus specific Abs has been widely interrogated, however the durability and breadth of NS1-specific Abs and memory B-cells remains largely uncharacterized. Here we quantify DENV NS1-specific Abs, both LLPC and MBC-derived, in humans following DENV infection in a longitudinal manner. Using peripheral blood mononuclear cells (PBMCs) and matched serum samples from DENV immune donors with times post-infection ranging from <1-43 years, we interrogated the durability and breadth of the NS1-specific antibody response. LLPC-derived Abs were quantified by ELISA against DENV (1-4) NS1 and endpoint titers were calculated. NS1-specific MBC frequencies were determined by limiting dilution assay wherein, PBMCs from human subjects with history of prior DENV infection were stimulated *in vitro* to become antibody-secreting cells and the resulting Abs were assessed for DENV (1-4) NS1 specificity by ELISA. Using this approach, we identified DENV (1-4) NS1 homotypic and cross-reactive Abs, both LLPC and MBC-derived, that remain in circulation years to decades after infection in subjects from both endemic and non-endemic transmission settings. To more rigorously interrogate the change in NS1-specific Abs and MBCs overtime we also determined measles-specific antibody titers and MBC frequencies in the same samples.

0159

INVESTIGATING THE TRANSCRIPTIONAL RESPONSE OF HUMAN ENDOTHELIAL CELLS UPON TREATMENT WITH WILDTYPE DENGUE VIRUS NONSTRUCTURAL PROTEIN 1 AND A GLYCOSYLATION MUTANT

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Members of the *Flaviviridae* family pose a major public health challenge; infection and case numbers have been steadily increasing in recent years. During flavivirus infection, the nonstructural protein 1 (NS1) is secreted from infected cells. The level of soluble NS1 in the bloodstream has been shown to correlate with flavivirus disease severity, and vaccination of mice with NS1 has been shown to be protective from lethal flavivirus challenge. Mechanistically, NS1 from different flaviviruses has been shown to specifically bind to human tissue-derived endothelial cells in a manner that reflects disease tropism. The interaction with the endothelium leads to the disruption of intercellular junctions and the endothelial glycocalyx, ultimately resulting in endothelial barrier dysfunction. Here, we investigate the transcriptional response of endothelial cells upon dengue virus (DENV) NS1 treatment and compare the gene expression changes induced by the wildtype protein and a mutant (N207Q) that was previously shown not to trigger endothelial hyperpermeability. To investigate both pathogenic barrier breakdown and its recovery, we determined differentially expressed genes 6 and 24 hours post-treatment of human pulmonary microvascular endothelial cells by RNA sequencing. We found 359 and 146 genes that were differentially regulated at 6 and 24 hours post-treatment, with an enrichment for factors associated with inflammatory and growth factor signaling. We validated these findings by quantitative reverse transcriptase-PCR and investigated the differential gene expression of several factors, including the putative NS1 receptor beta-2-adrenergic receptor, in endothelial cells derived from the lung, umbilical vein, dermis, brain and liver. Further, we are identifying genes whose regulation is conserved across flaviviruses (DENV, Zika virus, West Nile virus) and those that are regulated differentially. The insights provided by this study will help understand the pathogenic cascade triggered by NS1 and open avenues for the development of high-throughput assays for the evaluation of compounds inhibiting these processes.

0160

CHARACTERISING CLIMATE DEPENDENCIES IN VECTOR BIONOMICS AND MOSQUITO-PATHOGEN INTERACTIONS FOR GLOBAL DENGUE VIRUS TRANSMISSION

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Climatic relationships with *Aedes aegypti* life-traits and subsequently dengue virus transmission have been shown to be non-linear. The turning point values of these relationships (for example the optimum temperature for the extrinsic incubation period) are usually based on laboratory derived data. Previous work has demonstrated that laboratory and field derived estimates are substantially different, for example the additional *Aedes* mortality rate in the field is estimated to be 0.179 $days^{-1}$. A greater understanding of the mechanisms underlying the climatic relationships with dengue transmission in the field is essential, particularly given the likelihood that the spatiotemporal distribution of dengue will vary with the changing climate in the coming decades. The aim of this study is to reconstruct 'epidemiologically-derived' relationships between climate and mosquito life-traits using mechanistic epidemiological modelling. We use a Bayesian modelling approach to estimate the turning point values of several mosquito life-trait climate relationships determining

survival, feeding behaviour, development, and reproduction. We calibrate mechanistic models which explicitly incorporate temperature-, humidity- and rainfall-dependent mosquito compartments to the force of infection of dengue previously calculated using catalytic models applied to case notification and serology data in 349 global locations. In preliminary work we estimated a higher minimum and lower maximum threshold in the function describing the temperature-dependent mosquito mortality, compared to laboratory derived values, which suggests mosquitoes cannot survive at as a wide a range of temperatures in the field as is currently suggested from laboratory data. Subsequent work will refine our understanding of the quantitative relationships between multiple mosquito life-traits and climate in real-world settings, which should facilitate improved accuracy in future mechanistic dengue transmission models.

0161

LONG TERM HUMORAL IMMUNOGENICITY OF LIVE ATTENUATED AND PURIFIED INACTIVATED DENGUE VACCINES

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Dengue vaccine development is challenging due to concerns about waning immunity and the potential for vaccine induced disease enhancement. The Walter Reed Army Institute of Research has developed several potential dengue vaccine products including a tetravalent live attenuated vaccine platform (TDENV), a purified formalin-inactivated tetravalent vaccine (DPIV) and an alternative heterologous sequential prime boost utilizing both the DPIV and TDENV (ADVP). In this study, we called back volunteers who had previously participated in vaccine trials involving these vaccines 4-14 years prior, in order to evaluate long term immunogenicity. We recruited a total of 54 subjects from 4 different studies using these investigational products. 30 subjects recruited were from the ADVP prime boost study, 22 subjects from DPIV studies and 2 subjects from TDENV. Subjects underwent a single sera collection between 2019-2020. Neutralizing antibody titers were measured via a microneutralization assay. ADVP recipients demonstrated long term detectable tetravalent neutralizing antibody titers that varied significantly (p=0.008) by regimen received (DPIV-TDENV 66-83% and TDENV-DPIV 0-36%). DPIV with ASO3B adjuvant recipients from years 2015-2017 demonstrated 56-100% tetravalent seropositivity with those who received 3 doses maintaining 100% tetravalent seropositivity. None of three DPIV with Aluminum hydroxide adjuvant recipients who received vaccine between years 2011-2012 maintained tetravalent seropositivity. Both recipients of the 2 dose TDENV regimen given between years 2006-2008 maintained tetravalent seropositivity. Geometric mean neutralizing antibody titers per serotype were highest in the DPIV-TDENV 0, 6 month group (118-233) and recipients of three doses of DPIV (348-779). Overall these results demonstrate variable maintenance of durable neutralizing antibody titers for these vaccine platforms, with notably higher geometric mean titers and tetravalent seropositivity rates in the 0,6 month DPIV/TDENV and 3 dose DPIV cohorts and highlight that maintenance of humoral immunogenicity beyond 10 years is possible.

0162

REFINING EFFICACY ESTIMATES OF A SECOND-GENERATION DENGUE VACCINE

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It is an exciting time for dengue vaccine development, with one licenced vaccine candidate (Dengvaxia) and two second generation candidates currently in phase III clinical trials. Presently however, Dengvaxia is not in widespread use due to the absence of accurate diagnostics enabling the rapid detection of seropositive subjects ahead of vaccination. A second-generation vaccine developed by Takeda Pharmaceutical is currently in the fourth year of its phase III trial, and overall results thus far show that this new candidate is efficacious against symptomatic dengue. However, efficacy has also decayed with time and is thought to vary with the infecting dengue serotype, reflecting the difficulty of eliciting a balanced tetravalent immune response. The vaccine's efficacy may also vary by the baseline serostatus and age of the vaccine recipients, although small sample sizes limit interpretation. In this study, we assess the extent to which published clinical trial data can be used within Bayesian survival models to refine vaccine efficacy estimates by serotype, baseline serostatus, age and disease severity. These models are also being used to test different hypotheses about the vaccine's mechanism of action, which will be used to evaluate the potential population-level impact of vaccination. As licensure is currently being sought, refined characterisation of the vaccine's complex efficacy profile is vital.

0163

TAK-003 DRIVES SUSTAINED AFFINITY MATURATION OF POLYCLONAL ANTI-DENGUE ANTIBODY RESPONSES AGAINST ALL FOUR DENGUE SEROTYPES IN PARTICIPANTS ACROSS A WIDE AGE RANGE AND IRRESPECTIVE OF BASELINE SEROSTATUS

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Dengue is a mosquito-borne disease caused by four dengue virus serotypes (DENV-1-4) with half of the world's population at risk. Therefore, a safe and effective dengue vaccine is an unmet clinical need. Neutralizing antibody titers are a common measure of immunity to flavivirus vaccines. However there is increasing evidence that additional aspects of antiviral immune responses may contribute to vaccine-elicited immunity. The degree of antiviral antibody affinity maturation, driven by vaccination or natural infection is considered an important arm of protective antiviral immune response. Takeda's tetravalent dengue vaccine candidate (TAK-003) has been shown to trigger tetravalent seropositivity and neutralizing antibodies in children, adolescents, and adults during two Phase 3 clinical trials conducted in dengue-endemic and non-endemic regions (DEN-301, NCT02747927; DEN-304, NCT03423173, respectively). To assess the magnitude of avidity index, a measure of the degree of polyclonal antibody affinity maturation in response to vaccination with TAK-003, we utilized an anti-dengue IgG avidity assay employing bio-layer interferometry and dengue virus-like particles (VLPs). Avidity index was calculated as: antiviral IgG response/dissociation constant, k_{off}. The magnitude of affinity maturation was measured pre- and post-vaccination in samples from study participants from both phase 3 clinical trials. Vaccination with TAK-003 stimulated robust tetravalent polyclonal antibody affinity maturation against all DENV serotypes across a wide age range of vaccine recipients, irrespective of baseline serostatus. Additionally, vaccine-driven antibody affinity maturation evolved rapidly and was sustained over time post-vaccination in baseline seropositive and seronegative pediatric, adolescent and adult participants from both endemic and non-endemic countries. Further characterization is currently underway to assess the relationship between vaccine-driven anti-dengue antibody affinity maturation and outcome of subsequent dengue infection.

0164

PHYLOGENETICS AND EVOLUTIONARY ANALYSIS OF CAMEROON 2017-2018 DENGUE VIRUS SEROTYPES 1 OUTBREAK STRAINS

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Dengue fever continues to be one of the main public health threats globally and poses a health risk to U.S. military personnel deployed to dengue endemic areas. For the past few decades, Cameroon has continued to experience sporadic outbreaks of arboviral infections including dengue fever. Here, we describe for the first time, the phylogeny and origin of complete dengue viral genomes isolated from Cameroon. Samples collected between 2017-2018 during dengue virus (DENV) outbreaks in Cameroon were screened for DENV using reverse transcription polymerase chain reaction (RT-PCR), followed by whole genome sequencing of positive samples. Bayesian inference phylogenetic approach based on the Bayesian Markov chain Monte Carlo (MCMC) method was used to determine the time of the most recent common ancestor (TMRCA) and evolution rates of the Cameroon dengue virus strains. Sample analysis yielded six near-complete DENV-1 genomes. Phylogenetic analysis revealed that the strains from the current study belong to an emerging sub-lineage of DENV-1 genotype V and form a monophyletic taxon with a 2012 strain from Gabon. The TMRCA of the Cameroon strains was estimated to have existed around 2010 with a 95% highest posterior density (HPD) interval of 2008-2013. The strains appear to be evolving at 5.04 x 10^{-4} nucleotide substitutions per site per year (95% HPD interval of 4.12 x 10^{-4} and 5.97 x 10^{-4}). Our study showed that an emerging sub-lineage of the dengue DENV-1 genotype V was responsible for the 2017-2018 outbreaks in Cameroon. Our results highlight the need for constant genomic surveillance on DENV and other arboviruses to determine the viral origin and routes of propagation, and consequently aid in understanding their evolutionary dynamics to enhance preparedness for future outbreaks.

0165

MOLECULAR CHARACTERIZATION OF CIRCULATING VIRUSES IN AN OUTBREAK OF YELLOW FEVER FROM OCTOBER 2021 TO FEBRUARY 2022 IN COMMUNITIES IN GHANA

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Yellow fever is an acute viral hemorrhagic disease transmitted by infected *Aedes spp.* mosquitoes. Disease severity ranges from self-limited febrile illness to hemorrhagic syndrome with jaundice, multiple organ failure and death. During outbreaks, severe cases are more likely to be detected and reported. From October 2021 to February 2022, an outbreak of Yellow Fever in some communities in Ghana resulted in 70 confirmed cases with 35 deaths (case-fatality, 50%). In all, a total of 188 clinical specimens of human sera were collected within the period of the outbreak and submitted to the Noguchi Memorial Institute for Medical Research (NMIMR) for testing. Large proportions (65%) of the cases were sent from communities within the Savannah region where the outbreak started in a predominantly unvaccinated nomadic community. The recorded age range was from 4 months to 70 years, and they mostly presented with symptoms of body pain, fever, abdominal pain, vomiting, jaundice, and bleeding from the gums. Information from this genomic surveillance of YF during this recent outbreak will better inform US AFRICOM regarding the risks to Force Health Protection (FHP) when deployed in austere settings like Ghana. Molecular amplification methods were used on de-identified specimens collected during the outbreak and subsequently produced full-length sequences of three confirmed cases. Phylogenetic analysis characterized the three under the West African genotype II strains and they shared a close homology with sequences from Cote d'Ivoire and Senegal. The utility of the more sensitive advanced molecular diagnostic techniques deployed for the laboratory testing during this outbreak investigations made it distinctive from the serological assays previously used. It enabled us to characterize the circulating strains and for the first time deposited YF strains from Ghana at the GenBank. To change the trend of YF outbreaks in Ghana and elsewhere, public health authorities must increase efforts to ensure that individuals and groups in difficult-to-access areas and at highest risk of exposure are educated about the potential risk of YF infection and vaccinated.

0166

SEROPREVALENCE OF CHIKUNGUNYA, DENGUE AND WEST NILE VIRUS INFECTIONS AMONG PATIENTS WITH FEBRILE ILLNESS IN SOME HEALTHCARE FACILITIES IN GHANA

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The re-emergence of vector-borne diseases has highlighted arboviruses, which includes Chikungunya, Dengue and West Nile viruses, as a major public health concern globally. They are known to be endemic in many parts of the world, including Ghana, and affect military personnel deployed to these endemic regions. The non-specific clinical manifestations that are like other endemic diseases such as malaria, with fever being a major symptom, make the diagnosis of these infections very challenging. There is limited data on circulating arboviruses in Ghana; hence, this study sought to determine the seroprevalence of Chikungunya, Dengue and West Nile virus among febrile patients in select clinics in Ghana. This cross-sectional study was a hospital-based surveillance study which used questionnaires to collect demographic data from febrile patients. Case definition for enrolling patients (5 to 65 years) was fever and/ or history of fever. Serum samples were tested for IgM and IgG antibodies of selected arboviruses using commercially available ELISA kits. Of the 280 serum samples obtained from study participants, 132 (47.1%) demonstrated exposure to at least one or all three of the arboviruses tested. Ninety-nine (35.4%), 64 (22.9) and 50 (17.9%) were exposed to Dengue, Chikungunya and West Nile virus, respectively. Among the patients that were exposed, the most prevalent dual exposure observed was Dengue and West Nile virus 56 (20%). Adults were more likely to be exposed to Dengue (OR=6.7, 95%CI=3.3-3.8), Chikungunya (OR=2.8, 95%CI=1.3-6.3) and West Nile virus (OR=4.1, 95%CI=1.9-9.1) than children. Using the multinomial logistic regression model, adults were found to have a higher likelihood of being exposed to one or multiple arboviral infections. The predominant arboviral infection detected among febrile patients in Southern Ghana was Dengue fever. Some patients showed exposure to two or all three viruses tested. Adults were more exposed to any or all three arboviruses. These findings suggest the circulation of these arboviruses, which should be included during differential diagnosis of febrile patients in Ghana.

0167

DETERMINING THE VECTOR COMPETENCE OF JAPANESE MOSQUITOES FOR JAPANESE ENCEPHALITIS VIRUS

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The ability of a mosquito to be infected with and later transmit the arthropod-borne virus to susceptible hosts is called vector competence. Results from the vector competence studies have been used to incriminate mosquito species in arbovirus transmission cycles, in combination with virus detection in field-captured individuals and their vertebrate host feeding patterns. Despite being widely known as *Culex*-borne (mainly *Culex tritaeniorhynchus*), the Japanese encephalitis virus had been inferred by some studies to also be vectored by *Culex pipiens* and *Aedes*

albopictus. Here, we examined the two mosquito species, *Culex pipiens* form *molestus* (CPM) and *Aedes albopictus* (AAL) originating from Japan, to find out their level of susceptibility and to clarify whether both species could serve as a Japanese Encephalitis virus (JEV) vector in their respective area of distribution in Japan. Laboratory colonies of the two mosquito species were starved overnight and blood-fed the next day using a Hemotek membrane feeder in a dark or lighted room. At 7 and 14 days post-infection (dpi), the mosquitoes were harvested for their body parts and saliva to evaluate infection, dissemination, and transmission rates. Results showed infection rates of 28 and 25% across time points in CPM after exposure to JEV G-I and G-III, respectively. Whereas the transmission rates were observed in G-I (2.5%) but not in G-III exposed CPM. In AAL, as much as 53% of mosquitoes were infected after exposure to JEV G-III at 14dpi. We are currently assessing the infection, dissemination, and transmission rates in both colonies after the exposure to various JEV genotypes to determine the whole picture of their vector competencies. The JEV G-I presence in the saliva suggested the occurrence of virus transmission by CPM, along with the possibility of the mosquito species being refractory to JEV G-III. Nevertheless, this study adds up the knowledge pool of two mosquito species' roles in the JEV transmission cycle in Japan and highlights the information of species that should be included in mosquito control programs.

0168

CHARACTERIZATION OF UNIQUE POWASSAN VIRUS ISOLATES FROM NEW YORK STATE

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Powassan virus (POWV, family *Flaviviridae*), first isolated in Canada in 1958, is a reemerging tickborne virus endemic in the U.S., Canada, and Russia. In 1997, a POWV-like agent was isolated from *Ixodes scapularis* in New England and determined to be genetically distinct from the original POWV isolate. This revealed the existence of two lineages: lineage I, POWV (POWV-1) and lineage II, deer tick virus (DTV). It is suggested that POWV-1 is maintained between *I. cookei* and groundhogs and *I. marxi* and squirrels, while DTV is maintained in a cycle between *I. scapularis* and small mammal hosts. This distinction suggests an evolutionary progression of either POWV-1 or DTV into unique transmission cycles and subsequent evolution of divergent lineages. Tick, mammalian, and human case isolates from New York State (NYS) are typically identified as DTV, but for the first time in 45 years three POWV-1 isolates were detected, including the first known isolation of POWV-1 from *I. scapularis*. This study aimed to investigate genotypic and phenotypic characteristics of recent NYS isolates in distinct hosts through sequence analysis and replication kinetics *in vitro* and *in vivo*. Genetic data revealed distinctions between POWV-1 isolates from both *I. scapularis* and *I. cookei* compared to historic POWV-1 isolates. Of note, a DTV isolate from a recent NYS human case displayed POWV-1-like mutations that had not been previously identified in DTV. *In vivo* growth kinetics in *I. scapularis* revealed intermediate fitness for an *I. scapularis*-derived POWV-1 isolate and increased fitness in the NYS human isolate relative to isolates of both lineages. These data suggest a possible role of lineage-specific mutations in increased viral fitness that influence host-specific adaptations and continued emergence of POWV in the Northeast.

0169

ESCAPE OF ARBOVIRUSES FROM MOSQUITO SALIVARY GLANDS INTO SALIVA

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Arboviruses, such as Zika virus (ZIKV), West Nile virus (WNV) and chikungunya virus (CHIKV) are transmitted by mosquitoes, leading to millions of infections worldwide each year. When a mosquito feeds on an infected host, the virus must infect the midgut, escape the midgut, infect the salivary glands, escape the salivary glands and be present in the saliva at sufficient levels to infect a new host when the mosquito takes its next bloodmeal. Each of these steps present barriers to transmission, with escape from the salivary glands serving as the strongest barrier for many arboviruses. We sought to measure the role of escape from the salivary glands on transmission, and the relationship between level of virus in salivary glands and saliva in three mosquito-virus pairs; ZIKV and CHIKV in *Aedes aegypti* and WNV in *Culex quinquefasciatus*. For ZIKV, we found a strong salivary gland escape barrier. Within mosquitoes that had virus present in their saliva, there was a strong positive relationship between level of virus in the saliva and salivary glands. However, there were many mosquitoes with high levels of virus in the salivary glands, and no virus present in saliva. Within the salivary glands, virus must first pass through the basal lamina, then infect acinar cells and shed into apical cavities, before being transported to the saliva via the salivary duct. We will use fluorescent microscopy to determine if level of virus in the saliva correlates with localization and or/accumulation of virus in the proper compartments of the salivary glands. These experiments will further define virus-vector interactions, and identify additional barriers to transmission across arboviruses and their mosquito vectors.

0170

CCL3, CCL5, IL15, IL1RA, AND VEGF ARE USEFUL BIOMARKERS TO DISCRIMINATE CLASSES OF ADVERSE EVENTS FOLLOWING 17DD YF PRIMARY VACCINATION ACCORDING TO CAUSE SPECIFIC DEFINITIONS

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Yellow fever (YF) is a viral hemorrhagic vectorborne disease considered one of the most lethal viral infections. The largescale vaccination coverage is essential to controlling disease spread and the reemergence of the YF epidemic. The YF vaccine is well tolerated, and adverse events following YF immunization (YEL AEFI) are usually mild and occasionally reported. Several hypotheses have already been proposed to explain the basis of the YEL AEFI, but the precise mechanisms involved in the development of these events remain unknown. In the present study, a range of serum biomarkers was quantified in suspected cases of YEL AEFI to propose a reliable laboratory algorithm to discriminate confirmed YEL AEFI cases ("A1" class) from those with other illnesses ("C" class). The analysis of serum biomarkers, including chemokines, inflammatory and regulatory cytokines, and growth factors, was performed using the BioPlex Pro Human Cytokine 27plex Assay. Our findings demonstrated that increased levels of CXCL8, CCL2, CXCL10, IL1β, IL6, and TNFα were observed in YEL AEFI ("A1" and "C" classes) as compared to primary vaccines without YEL AEFI [PV(day

3-28)] and reference range (RR) controls. Notably, increased levels of CCL3, CCL4, CCL2, CCL5, IL1β, IL15, IL1Ra, and GCSF were found in "A1" as compared to "C" class. Venn diagrams analysis allowed the preselection of biomarkers for further investigation of performance indices. Data demonstrated that CCL3, CCL5, IL15, and IL1Ra presented high global accuracy (AUC = 1.00) to discriminate "A1" from "C". Decision tree was proposed with a reliable algorithm to distinguish YEL AEFI cases according to cause specific definitions with outstanding overall accuracy (91%). CCL3, CCL5, IL15, and IL1Ra appear as root attributes to identify "A1" followed by VEGF as branch nodes to discriminate Wild Type YFV infection ("C(WTYFV)") from cases with other illnesses ("C*"). Together, these results demonstrated the applicability of serum biomarker measurements as putative parameters toward establishing accurate laboratory tools for complementary differential diagnosis of YEL AEFI cases.

0171

MURINE MODELS OF POWASSAN VIRUS DISEASE REVEAL A ROLE FOR CD8+ T CELLS IN PROTECTION AND PATHOGENESIS

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Powassan virus (POWV) is a tick-borne flavivirus which causes fatal meningoencephalitis in 10-15% of reported human cases, but for which there are no approved vaccinations or therapeutics. Concomitant with this high fatality rate are predictions that incidence of POWV infection is expected to increase as the warming climate expands the range of *Ixodes* ticks capable of transmitting the virus to humans in North America. With the goal of establishing the correlates of protection for POWV to aid the development of efficacious POWV vaccines, we used C57BL/6 mice as a model of POWV infection. Using this model, we have identified two murine CD8 T cell epitopes and two CD4 T cell epitopes. We also provide evidence that CD8 T cells may potentiate immunopathogenesis during POWV-infection. Conversely, CD8 T cells also appear to be important for control of viral replication in the peripheral and central nervous system organs. Identification of beneficial and detrimental aspects of POWV-immune protection is significant as it will aid in the design of POWV vaccines.

0172

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF SOFOSBUVIR AND DACLATASVIR FOLLOWING A RESPONSE GUIDED TREATMENT OF HEPATITIS C

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Treatment of Heptatis C is of today still very expensive, which hinders potential elimination of the diseases. A contributing factor to the high cost is the long treatment regimen, for example, the standard treatment with sofosbuvir and daclatasvir is a twelve-week regimen. Shorter regimens have been evaluated but have shown low cure rates. However, a promising alternative would be response-guided therapy, in which the choice of treatment duration is guided by early virologic response. In the current study, Hepatitis C infected Vietnamese adults with mild liver disease received either a 4-week or an 8-week treatment with sofosbuvir and daclatasvir, based on their day 2 virologic response. Treatment failures were retreated with a standard 12-week regimen. A total of 52 patients were enrolled in the study and had bloods sample taken for pharmacokinetic analysis at baseline, day 14 and at the end of treatment. In addition, 40 of these patients participated in a pharmacokinetic sub-study in which 5 additional blood samples were taken after the first dose and at day 28. Drug levels of sofosbuvir, its metabolite GS-331007, and daclatasvir were quantified using liquid chromatography tandem mass-spectrometry. The pharmacokinetic properties were evaluated using a non-compartmental analysis as well as a modelling approach, and drug exposure were linked to therapeutic outcome. Treatment failures were only seen in the 4-week arm, showing that virologic response on day 2 is not enough to archive a successful treatment. The pharmacokinetic analysis was successfully performed and, using the non-compartmental analysis results, no significant correlation between drug exposure and therapeutic outcome were seen.

0173

A HUMAN SKIN MODEL OF ARBOVIRUS INFECTION FOR ASSESSING THE IMPACT OF MOSQUITO SALIVARY FACTORS AT THE MOSQUITO-VIRUS-HOST INTERFACE

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Mosquito-borne viruses inflict a significant burden on human health all over the world. Viruses such as Zika virus (ZIKV), West Nile virus (WNV), or Mayaro virus (MAYV) are transmitted at the mosquito-host interface during blood feeding. Not only do pathogen immune evasion strategies influence the initial infection and replication of pathogens delivered, but arthropod salivary factors also influence initial infection and replication. Single cell type in-vitro cultures provide limited ability to study the microenvironment of virus delivery and subsequent infection. To study complex interactions between viral, mosquito, and host factors, we describe a proof-of-concept model for arbovirus infection using adult human skin ex-vivo with ZIKV (flavivirus) and MAYV (alphavirus). Histological analysis showed viability of skin to 4 days post-surgical removal in culture. Arboviruses replicated in human skin up to 4 days post infection and shed into culture media. Proinflammatory cytokine and chemokine genes, such as IFN-β and CCL20, were elevated in infected skin relative to uninfected controls. Genes for intracellular pattern recognition receptor molecules RIG-I and MDA5 were increased after MAYV and ZIKV infection. Interferon-induced transmembrane proteins (IFITMs) were significantly upregulated during MAYV infection in skin. Immuno-histochemical detection of virus antigen in skin showed disseminated virus throughout skin tissue. This model brings physiological relevance to studying the impact of infection on skin cell populations and the influence of arthropod salivary molecules during virus delivery.

0174

A NS4A ZIKA VIRUS MUTANT DEMONSTRATES ENHANCED VIRULENCE IN MICE

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Zika virus (ZIKV) is now in a post-pandemic period, for which the potential for re-emergence and future spread is unknown. Adding to this

uncertainty is the unique capacity of ZIKV to directly transmit between human hosts via sexual transmission. Recently, we demonstrated that direct transmission of ZIKV between vertebrate hosts resulted in ZIKV strains with increased mortality in mice and increased transmission in mosquitoes, suggesting that human-only transmission chains could pose a threat for enabling the emergence of more virulent ZIKV strains. Coincident with this change in phenotype was the emergence of three amino acid substitutions (NS2A-A117V, NS2A-A117T, and NS4A-E19G) shared among all vertebrate-passaged lineages. To understand the contribution of these genetic changes to the virulence phenotype, we engineered these amino acid substitutions singly and in combination into a Zika virus infectious clone. Ifnar1-/- mice were then subcutaneously inoculated with 10^3 PFU of each of these viruses, or a wild-type infectious clone (WT-IC) control. Infection with the NS4A-E19G mutant resulted in significantly enhanced mortality and significantly higher viremia at 4 days post infection (dpi) compared to the NS2A-117 mutants or the WT-IC. The double mutant viruses (NS4A-E19G/NS2A-A117V and NS4A-E19G/NS2A-A117T) also caused enhanced mortality and similarly increased viremia at 4dpi compared to the NS2A single mutants or the WT-IC. These results suggest that the NS4A-E19G substitution contributes to the enhanced virulence phenotype observed in serially-passaged viruses. Data are forthcoming, but we are now performing experiments to understand the potential mechanisms by which the NS4A substitution aids in more effective viral evasion or regulation of the immune response in mice, and to assess the role of these substitutions in increased mosquito transmission potential. Defining the genetic determinants of enhanced ZIKV virulence and their underlying mechanisms could inform better surveillance for variants of concern and provide insights into future ZIKV evolution.

0175

INVESTIGATING THE ROLE OF TEMPERATURE IN THE TRANSMISSION DYNAMICS OF FLAVIVIRUSES IN COLOMBIA

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Previous studies have investigated fitting various *Aedes* spp. mosquito life traits to temperature-dependent functions. However, as the underlying studies are typically laboratory-based, they may not be indicative of field-settings. Here, we show analytically that small adjustments within the reported credible intervals of the parameterization of these thermal responses can yield markedly different transmission dynamics of *Aedes*-borne flaviviruses. We then demonstrated this mechanistically through a stochastic, temperature-dependent metapopulation model applied to Colombia. In doing so, we accounted for patch connectivity through a radiation model and calibrated mean mosquito carrying capacities across the spatial grid from previous maps of dengue force of infection estimates to allow for spatial variation in the baseline level of *Aedes* spp. environmental suitability. We then utilized fine-scale historical temperature data to investigate various combinations of previously proposed thermal responses, and scalings of them, for different entomological and epidemiological parameters, for both dengue and Zika. While accounting for under-reporting, model fits were assessed against municipality-level time series incidence data across Colombia through a Bayesian framework using a Dirichlet-multinomial likelihood function to account for overdispersion. When applied in an epidemic context, our model demonstrated high predictive accuracy of the timings of the 2015-16 Zika outbreak across different departments, even though the outbreak was relatively heterogenous across space. Our model also had strong predictive accuracy in an endemic context for dengue, where it accurately predicted the timing of the 2010 outbreak. However, it also predicted a dengue outbreak in 2015-16 that was not observed, which coincided with the Zika outbreak. This corroborates other studies that highlighted dengue incidence was atypically low in Latin America following the Zika outbreak, and highlights the need for an improved understanding of potential biological mechanisms that may suppress dengue incidence when Zika is co-circulating.

0176

ADAPTIVE IMMUNE RESPONSES TO WEST NILE VIRUS CROSS-REACT WITH USUTU VIRUS

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Usutu virus (USUV) is a mosquito transmitted flavivirus that originated in Africa. Since USUV emerged in Europe in 2001, it has caused numerous mass bird die-offs and >100 human infections, including several cases of encephalitis. USUV shares approximately 76% amino acid identity with West Nile virus (WNV), a closely related flavivirus. Previously, we showed WNV vaccination protects against lethal USUV infection of African (Uganda 2012) or European (Spain 2009) isolates and significantly reduces viremia in an immunodeficient mouse model. Protection was greater against Spain 2009. Here, we investigated whether WNV mediated cross-protection against USUV is antibody or T cell mediated. To determine whether WNV specific antibodies neutralize USUV, we performed plaque reduction neutralization tests on convalescent sera from humans who had symptomatic WNV infections against WNV or multiple USUV strains, including Uganda 2012 and Spain 2009. We found the geometric mean $PRNT_{50}$ titers of these sera samples against WNV was 1:300, while the titers against most USUV strains, including Uganda 2012, were approximately 1:60. The titer against Spain 2009 isolate was 1:265. These results indicate that natural WNV infection produces antibodies that can neutralize USUV *in vitro*. Passive transfer studies are ongoing to determine whether these titers can protect against USUV disease *in vivo*. To determine whether T cells from WNV exposed individuals can recognize USUV, we isolated splenocytes from WNV vaccinated mice and stimulated them with WNV or USUV. Splenocytes stimulated with WNV produced approximately 1650pg/mL of IFNγ, and splenocytes stimulated with two different USUV strains (Uganda 2012 or Spain 2009) produced 250-730pg/mL of IFNγ, indicating that WNV vaccinated T cells do respond to USUV virus. In the future, we will perform adoptive transfer studies to determine whether WNV specific T cells are protective against USUV infection *in vivo*. Understanding the mechanisms behind cross-protective immune responses between WNV and USUV will be crucial to assessing risk of USUV disease in WNV endemic areas and developing therapeutics against USUV.

0177

RETROSPECTIVE INVESTIGATION OF HORSES WITH ENCEPHALITIS REVEALS UNNOTICED CIRCULATIONS OF WEST NILE VIRUS IN NORTHEASTERN BRAZILIAN STATES

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Among the zoonotic arboviruses detected in Brazil, since 2004, several studies have provided serological evidence regarding the circulation of West Nile Fever Virus (WNV) in mammal and bird reservoirs. Recently genomic monitoring activities in horses, also revealed the circulation of WNV in several states located in southeastern and northeastern Brazilian regions. This highlights how pivotal it is investigating the unnoticed circulation of WNV in horses, as this host' infections may precede human cases of encephalitis. Here using a nanopore sequencing approach we obtain WNV complete genome sequences from two states located in northeast Brazil (Bahia and Ceará). A total of 54 suspicious WNV samples collected between 2017 to 2020 from horses with encephalitis were screened. Viral RNA was extracted from samples (brain and spinal cord) using Kit QIAamp Viral RNA Mini Kit (Qiagen). A multiplex PCR using a primer scheme based was then performed in order to amplify the entire coding region of WNV. Samples with DNA concentration >2ng/ul were then submitted to nanopore sequencing using the MinION. Basecalling of raw files and barcode demultiplexing were performed using Guppy, and the consensus sequences generated by de novo assembling using Genome Detective. Phylogenetic inferences were then performed. Our results revealed that genomes generated in this study belonged to Lineage 1a. The ML reconstruction revealed that our newly isolates were scattered through the tree highlighting that multiple introduction events have occurred trough time. Together, our results reinforce the necessity to improve the profile of epidemiological and genomics investigation towards zoonotic arbovirus in Brazil, increasing priority of WNV genomic surveillance in equines with encephalitis in order to follow the dispersion of WNV through the country.

0178

HARMONIZATION OF MULTIPLE SARS-COV-2 REFERENCE MATERIALS USING THE WHO IS (NIBSC 20/136). RESULTS AND IMPLICATIONS

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There is an urgent need for harmonization between SARS-CoV-2 serology platforms and assays prior to defining appropriate correlates of protection and as well inform the development of new rapid diagnostic tests that can be used for sero-surveillance as new variants of concern (VOC) emerge. We compared multiple SARS-CoV-2 serology reference materials to the WHO IS to determine their utility as secondary standards, using an international network of laboratories with high-throughput quantitative serology assays. This enabled the comparison of quantitative results between multiple serology platforms. Between April and December of 2020, thirteen well-characterized and validated SARS-CoV-2 serology reference materials were recruited from six different providers to qualify as secondary standards to the WHO International Standard. All samples were tested in parallel with NIBSC 20/136 and parallel line assays were used to compute the relevant potency and binding antibody units. All samples saw varying levels of concordance between diagnostic methods at specific antigen-antibody combinations. Seven of the 12 candidate materials had high concordance for the Spike-IgG analyte (%CV between 5% and 44%). In conclusions**,** despite some concordance between laboratories, qualification of secondary materials to a WHO IS using arbitrary IU or BAU/mL does not provide any benefit to the reference materials overall, due to the lack of consistent agreeable IU or BAU/mL conversions between labs. Secondary standards should be qualified to well-characterized reference materials, such as the WHO IS, using serology assays that are similar to the ones used for the original characterization of the WHO IS.

0179

ZIKA VIRUS: INTERIM FINDINGS IN THE SINDH REGION OF PAKISTAN

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Globally, the Zika virus (ZIKV) has emerged as a cause of acute febrile illness in children and adults. In Pakistan, the detection of ZIKV antibodies has been reported. However, the validity of this data is questionable given the current understanding of flaviviral antigenic cross-reactivity. To confirm ZIKV circulation in the Sindh region of Pakistan, patients presenting to healthcare with a febrile illness were evaluated using ZIKV nucleic acid, IgM antibodies, and neutralization assay. Patients were recruited after taking formal consent from referral hospitals situated in 4 rural and one urban center in the Sindh region of Pakistan. All samples were tested for flaviviruses including Dengue, Zika, West Nile, and Japanese Encephalitis Virus using a commercial IgM capture ELISA kit and singleplex real-time PCR. For the confirmation of IgM positivity, the plaque reduction neutralization test (PRNT) was performed on selected Zika IgM positive samples to measure neutralizing antibodies. A total of 745 samples were collected from acute febrile patients admitted over a period of three years (2015-17), IgM ELISA and RT-PCR were for ZIKV and three other commonly circulating Flavivirus, DENV, WNV, and JEV. A total of 203 patients showed IgM positivity for the ZIKV. Of these 19.59% (n=146) were also positive for either DENV, WNV, and JEV. 7.6% (n=57) samples were showed IgM positivity exclusively for ZIKV and no cross-reactivity was noticed. These were considered as presumptive ZIKV Positive samples. Twenty-two samples of the Zika presumptive positive samples were further tested for confirmation using PRNT, Vero cell lines were infected with ZIKV; plaques were counted at day 5 post-infection. Serum samples with 50% reduction of the number of plaques at titers ≥10 were recorded as positive according to the CDC. The study provides evidence that the ZIKV has been circulating in Pakistan during the time of global transmission of this virus. Serologic cross-reactivity is a significant barrier to diagnosis in endemic areas where multiple flaviviruses co-circulate, serological diagnostics should be run in parallel with related co-circulating viruses.

0180

DEVELOPMENT OF A RECOMBINANT VSV VECTORED VACCINE AGAINST NIPAH VIRUS DISEASE

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Nipah virus (NiV) is a bat-borne henipaviral zoonosis causing outbreaks of lethal encephalitis and pneumonia in South and Southeast Asia. Development of a vaccine is a high priority for WHO and for the Coalition

for Epidemic Preparedness Innovations (CEPI), which is funding this work. A recombinant vesicular stomatitis virus (rVSV) expressing the glycoprotein (GP) of Ebola virus (rVSV-EBOV GP) has been approved for preventive immunization against Ebola (Ervebo®, Merck & Co.). The rVSV-EBOV vector was modified through reverse genetics to express an additional glycoprotein (G) of NiV. The rVSV EBOV GP NiV G vaccine candidate (code name PHV02) is a chimeric virus with tropism and immunological properties derived from the wild-type VSV parent, the rVSV-EBOV vector and the NiV transgene donor. Here we describe the characteristics of the vector and vaccine candidate relevant to clinical and environmental safety, immunogenicity and efficacy. The PHV02 vaccine candidate was shown to be highly attenuated in hamsters, ferrets and nonhuman primates. Hamsters and African green monkeys inoculated with the vaccine developed NiV neutralizing antibodies and were solidly protected against lethal NiV challenge. PHV02 virus inoculated intracerebrally in cynomolgus macaques was not neurovirulent and induced significantly lower histopathological scores than yellow fever 17D vaccine used as an active control. A biodistribution study in ferrets inoculated IM showed no neuroinvasion. Robust manufacturing methods have been developed and clinical immunological tests qualified. Based on the promising profile in animal models, this novel PHV02 NiV vaccine candidate has now entered clinical trials under an US FDA Investigational New Drug Application (IND).

0181

SARS-COV-2 TRANSMISSION DYNAMICS IN SCHOOLS FROM A SMALL MUNICIPALITY OF BUENOS AIRES PROVINCE, ARGENTINA

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There has been a lot of controversy around the effect of school closing on the spread of SARS-CoV-2 in the population, especially during a time when vaccines were not available. Studies conducted in different regions of the world, exposed conflicting results; most of them were based on government collected data. To safely return to schools in a municipality from the Province of Buenos Aires (Argentina) when few vaccines were available and with Delta as the predominant variant of concern (VOC), a surveillance protocol for a safe return to schools was established in San Antonio de Areco (SAA) at the initial, primary and secondary level. The objective of this study was to analyze the transmission dynamics of SARS-CoV-2 between cases and contact in SAA, though monitoring of infection in suspected cases and contacts through RT-PCR from nasopharyngeal swabs using individual samples and pools. The protocol was applied from March 8th, 2021, one week after the beginning of the school year, until the 22nd of May 2021, in all the SAA schools. In total, 920 tests were performed to all suspected cases and contacts related to schools (students, teachers and staff). From the total number of enrolled students (n=5297), 172 cases were confirmed as positive (3.3%), with a greater proportion of positives at the high school level; while the prevalence in teachers and staff was 10% (87/876). The predominant epidemiological nexus, both in students as well as teachers and staff, was the home/family setting. When considering only those cases where transmission occurred in the educational context, the proportion of cases in student was reduced to 0.21% and to 1.1% in teachers and staff. Therefore, it appears that the school is not a driver of infection in the community and what seems to be important to consider is the presence of health measures in schools, the state of transmission in the rest of the population, and the VOC circulating.

0182

HUMORAL AND CELLULAR IMMUNE MEMORY TO FOUR COVID-19 VACCINES

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Multiple COVID-19 vaccines, representing diverse vaccine platforms, successfully protect against symptomatic COVID-19 cases and deaths. Head-to-head comparisons of T cell, B cell, and antibody responses to diverse vaccines in humans are likely to be informative for understanding protective immunity against COVID-19, with particular interest in immune memory. Here, SARS-CoV-2-spike—specific immune responses to Moderna mRNA-1273, Pfizer/BioNTech BNT162b2, Janssen Ad26.COV2.S and Novavax NVX-CoV2373 were examined longitudinally for 6 months. 100% of individuals made memory $CD4^+$ T cells, with cTfh and CD4-CTL highly represented after mRNA or NVX-CoV2373 vaccination. mRNA vaccines and Ad26.COV2.S induced comparable $CD8^+$ T cell frequencies, though memory $CD8^+$ T cells were only detectable in 60-67% of subjects at 6 months. Ad26.COV2.S was not the strongest immunogen by any measurement, though the Ad26.COV2.S T cell, B cell, and antibody responses were relatively stable over 6 months. A differentiating feature of Ad26.COV2.S immunization was a high frequency of $CXCR3^+$ memory B cells. mRNA vaccinees had substantial declines in neutralizing antibodies, while memory T cells and B cells were comparatively stable over 6 months. These results of these detailed immunological evaluations may also be relevant for vaccine design insights against other pathogens.

0183

CHADOX1-VACCINATED SARS-COV-1 SURVIVORS EXHIBIT A BROAD SPECTRUM OF PROTECTION AGAINST SARS-COV-2 VARIANTS

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The last outbreak of severe acute respiratory syndrome-coronavirus (SARS-CoV-1) disease had occurred between November 2002 and August 2003, and it led to 8,098 suspected SARS cases, 774 SARS-related deaths (case fatality rate: 9.6%) and spread to 32 different countries. To investigate whether there is an advantage in protection against SARS-CoV-2 infection after SARS-CoV-1 infection compared to uninfected people 19 years later. In this study, we collected the serum samples of individuals who had been infected with SARS-CoV-1 19 years ago and have received either one or two doses of the AstraZeneca (AZ) vaccine against coronavirus disease-2019 (COVID-19). To ensure accurate comparison and analysis, we investigated cases with similar intervals between AZ vaccination and blood draw from those who had never been infected with SARS-CoV-1. We observed that after AZ vaccination, the neutralizing antibody expressions were significantly higher in the SARS-CoV-1-infected group compared to those in the uninfe cted group. Incidentally, in Taiwan, approximately 78 and 30% of the people remained negative with respect to the neutralizing antibody expression after receiving the first and second dose of the AZ vaccine, respectively. The pseudovirus neutralization (NT) assay revealed that sera from the SARS-CoV-1 survivors completely (100%) neutralized the Wuhan, Alpha, Gamma, and Delta variants after the first AZ vaccination. However, only 66% of the cases could neutralize the Beta and Omicron variants. In contrast, for the uninfected group, only the Wuhan and Gamma variants could be 100% neutralized after the administration of the first AZ vaccine. Unfortunately, the neutralizing ability for the other variants was completely absent in this group. After the second AZ vaccination, the SARS-CoV-1 survivors could neutralize all COVID-19 variants, whereas 16% of the casess in the uninfected group still failed to

neutralize the Beta and Omicron variants. Therefore, the AZ-vaccinated SARS-CoV-1 survivors have a broad spectrum of protection against the SARS-CoV-2 variants compared to the uninfected group.

0184

INFLUENCE OF AGE ON MSK SEQUELAE IN EBOLA SURVIVORS IN EASTERN SIERRA LEONE

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Ebola virus disease (EVD) survivors have presented with specific post-Ebola sequelae, collectively termed post-Ebola syndrome. Musculoskeletal (MSK) complaints are some of the most common complaints in post-Ebola syndrome. Here, we explore the influence of age on MSK signs in EVD survivors. Data was collected as part of an ongoing cohort study in Eastern Sierra Leone. Survivors completed questionnaires and physical exams at baseline and follow-up visits. Survivors were grouped by reproductive age categories: < 15 years of age, female reproductive age (15-40 years), and > 40 years of age. Date of first visit ranged from March 2016 to September 2020 and occurred 2.63 years after discharge from Ebola treatment unit (ETU), on average. At first visit, more female than male EVD survivors had MSK signs on physical exam (24.9% vs 22.4%), however this difference was not significant. Survivors 15-40 years of age were significantly more likely to display MSK signs on physical exam at first visit than those < 15 years (p = .008). Survivors > 40 years of age were not significantly more likely to demonstrate MSK signs than those < 15 years (p=.250). When grouped by sex, women 15-40 years of age were significantly more likely to demonstrate MSK signs on exam than women < 15 years (p=.040). Women > 40 years of age were not significantly more likely to demonstrate MSK signs than those < 15 years (p=.419). Our finding that EVD survivors 15-40 years of age were significantly more likely to demonstrate MSK signs on physical exam was surprising, as we expected survivors > 40 years of age to present with more MSK signs. Age may play a role in the development of MSK signs in post-Ebola syndrome. Studies into the immune response to EVD by age group and sex could provide insight into the pathogenesis of MSK sequelae in EVD survivors.

0185

CROSS-REACTIVITY OF DENGUE ANTIBODY TO SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreaks continue to increase globally, including areas where dengue virus (DENV) in endemic. Accuracy and early diagnosis are important factors to control these SARS-CoV-2 outbreaks. Serological cross-reactivity between DENV and SARS-CoV-2 virus have been reported in the endemic areas of arbovirus infections, and this can lead to misdiagnosis for both diseases and misunderstanding about potential cross-protection. Here, we demonstrated the potential cross-reactivity of DENV antibodies with SARS-CoV-2 using well-characterized acute and convalescent samples collected before SARS-CoV-2 outbreak including normal human serum (n=6), Febrile illness (n=23), primary DENV (n=20) and secondary DENV (n=20). The majority of anti-SARS-CoV-2 antibodies-positive samples (using an in-house ELISA) would cross react and appear as secondary DENV infections (7.2% of positive rate). We found poor correlation between DENV IgM antibody and in-house spike-RBD ELISA. Among ELISA positive samples, none of them was positive against live SARS-CoV-2 microneutralization assay. These data indicates a potential of cross-reactivity of binding antibody but not neutralizing antibody.

0186

REACTIVITY OF SARS COV 2 SPIKE PROTEIN AND ITS RBD AND P3 DOMAINS TO SERA OF COVID 19 AND PRE COVID 19 PATIENTS IN MALI

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The SARS-CoV-2 Spike protein and its receptor binding domain (RBD) play an essential role in the invasion of the virus into the host cell. P3 is a segment representing 6% of the length of the S protein, located in the RBD domain, which is recognized by the ACE2 (Angiotensin-converting enzyme 2) protein. The aim of this study was to evaluate antibodies (IgG) specific for S, RBD, and P3 of SARS-CoV-2 in specimens from patients hospitalized for COVID-19 and from pre-COVID-19 donors collected prior to the outbreak of COVID-19 in Mali. Sera from COVID-19 patients (N=266) at the Bamako Dermatology Hospital (HDB) in 2020 and from donors collected in Dangassa, a rural endemic area (N=283) in 2018, were tested to S, RBD, and P3 antigens using ELISA. Seroprevalence was 80.5% for Spike antigen (Ag), 71.1% for RBD and 31.9% for P3 at HDB. In pre-COVID-19 samples from Dangassa, the seroprevalence was 21.9%, 6.7% and 8.8% respectively for the same antigens. The presence of antibodies against SARS-CoV-2 in pre-CoVID-19 samples suggests the existence of cross-reactivity with other SARS viruses and/or other pathogens in endemic areas like *Plasmodium*.

0187

ASSESSMENT OF LONG-TERM IMMUNE RESPONSE FOLLOWING VACCINATION WITH THE RVSVΔG-ZEBOV-GP EBOLA VACCINE IN HEALTHCARE WORKERS IN HIGH-RISK DISTRICTS IN UGANDA

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The rVSVΔG-ZEBOV-GP Ebola vaccine (rVSV-ZEBOV) is a live recombinant vesicular stomatitis virus (VSV) vaccine containing the Ebola virus (species *Zaire ebolavirus;* EBOV) glycoprotein (GP) in place of the VSV GP. Since August 2018, rVSV-ZEBOV has been used in response to four Ebola virus disease (EVD) outbreaks in the Democratic Republic of Congo and neighboring countries, including Uganda. Data on the immune response duration following rVSV-ZEBOV vaccination are critical to inform recommendations on future use, including booster doses, in high-risk areas to help curtail further epidemics and ensure healthcare workers (HCWs) are protected. This study aimed to assess knowledge, attitudes, and practices related to EBOV, vaccination, and infection prevention and control among vaccinated and unvaccinated HCWs in three high-risk districts in Uganda (Kasese, Kabarole, and Bundibugyo Districts). We also sought to determine the prevalence of anti-EBOV IgG and assess risk factors for EBOV seropositivity among participants. We administered surveys and collected blood samples to test for the presence of EBOV-specific IgG antibodies. Laboratory testing is ongoing; here we present a descriptive analysis of survey data. Overall, 565 HCWs were enrolled, of which 210 (37%) were vaccinated. Knowledge that rVSV-ZEBOV only protects against EBOV was low among vaccinated (32%; 62/192) and

unvaccinated (7%; 14/200) HCWs. Most vaccinated (91%; 192/210) and unvaccinated (92%; 326/355) HCWs indicated that they would want to receive a booster or initial dose of rVSV-ZEBOV, respectively. Safety concerns (e.g., vaccine-related adverse events) was the most reported reason (60%; 28/47) for hesitancy in receiving a dose of rVSV-ZEBOV. As Uganda has experienced outbreaks of *Sudan ebolavirus* and *Bundibugyo ebolavirus*, for which rVSV-ZEBOV does not protect against, our data underscore the importance and challenges of risk communication to HCWs, and the need for continued vigilant infection prevention and control practices when working with suspect EVD patients. The results of this study will also help characterize immune response following vaccination.

0188

HUMORAL RESPONSES ELICITED BY VARIOUS SARS-COV-2 VACCINES IN MOUSE MODELS OF DIABETES

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The COVID-19 pandemic has resulted in an unprecedented burden to health systems, caused economic and social disruption, and led to a staggering number of deaths. Individuals with Type 2 diabetes mellitus (T2DM) are more susceptible to severe COVID-19 disease, accounting for 33% of hospitalizations in the United States, while those with obesity and morbid obesity, account for over 60% of the COVID-19 hospitalizations. T2DM affects 6.28% of the world's population and roughly 30 million people in the United States. Additionally, previous literature suggests reduced vaccine efficacy in individuals with T2DM. Considering how T2DM is a risk factor for severe COVID-19, as well as drastic increases in health disparities, it is important to understand how this metabolic syndrome affects the immunity generated by SARS CoV-2 vaccines and to understand COVID-19 hospitalization prevention within these populations. It is hypothesized that humoral immune responses elicited by differing vaccine platforms, including mRNA and subunit protein vaccines, will be decreased in mice with altered metabolic states compared to healthy control counterparts. To address this objective, an optimized multiplex bead-based immunoassay was used to delineate the humoral immunogenicity to SARS CoV-2 vaccine platforms in diabetic mouse models as well as anti-SARS CoV-2 Spike binding, a partial correlate of protection for SARS CoV-2. Preliminary results suggest a decrease in humoral responses in T2DM and obese mouse models after completing 2-dose regimens of two adjuvanted subunit protein vaccines and the mRNA vaccine. However, the promising new protein subunit vaccine, adjuvanted with CoVaccine HT, elicits greater humoral responses compared to Alum adjuvanted and mRNA vaccines in mice with altered metabolic states. As a partial correlate of protection for SARS CoV-2, these humoral responses can be used to determine the efficacy of varied vaccines in diabetic mouse models and could also be used for future vaccine development or even in vaccine and prevention interventions within populations of those with T2DM and obesity.

0189

A NOVEL METHOD FOR ESTIMATING VACCINE EFFICACY AGAINST INFECTION AND DISEASE PROGRESSION: APPLICATION TO A COVID-19 VACCINE TRIAL

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Vaccines can impact multiple aspects of the natural history of an infectious disease, providing protection against different stages of disease progression. Vaccine efficacy (VE) is typically evaluated independently for each disease outcome, but this can cause biased estimates and misleading interpretation of VE against some outcomes. We propose an integrated analysis of all outcomes based on a Markov model of disease natural history that adjusts for these biases. The model is implemented as a hierarchical multivariate multivariable generalised regression in RStan. The number of infections and disease cases is a function of VE, test sensitivity and specificity, adherence to testing, force of infection (FOI) and the probability of progression to each stage of severity. We tested the model using simulated data and then applied it to data from COV002, a phase 3 trial of the ChAdOx1 nCoV-19 (AZD1222) vaccine against COVID-19. In this trial, symptomatic cases were detected through testing in response to symptom-reporting while asymptomatic/pre-symptomatic cases were detected with weekly testing regardless of symptom status. Accounting for imperfect test characteristics and differences in adherence to weekly testing, our model estimated ChAdOx1 nCoV-19 VE against infection (VE_{in}) at 48% (95% CI 38-57) and against progression to symptoms (VE_{pr}) at 45% (95% CI 31-71). This implies a VE against symptomatic infection of 71.4% (95% CI 63-78), consistent with published trial estimates. Adjusting for test specificity made negligible difference, while accounting for a lower probability of detecting asymptomatic relative to symptomatic infections decreased estimated VE_{in}, particularly in subgroups with poorer testing adherence. The FOI and probability of symptom development, p_s, were higher in participants aged <55 years (FOI 0.37/year [95% CI 0.33-0.41], p_s 0.54 [95% CI 0.48-0.59] than ≥55 years (FOI 0.26/year [95% CI 0.21-0.32], p_s 0.33 [95% CI 0.24-0.45]). Our model framework can be used to analyse vaccine trial data with multiple disease outcomes and demonstrates the robustness of the trial-reported estimates for ChAdOx-1 nCoV-19.

0190

SARS-COV-2 SEROPREVALENCE IN RURAL & URBAN POPULATIONS IN GHANA

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Ghana officially announced its first case of COVID-19 on March 12, 2020 after which a nationwide age-stratified cross-sectional study was conducted from February until December 2021 to assess the severity of COVID-19 transmission. Study sites were selected based on disease burden stratification high, medium, low and very low zones according to real-time disease reports gathered. Probability Proportional to Size was applied within each geographic zone and 20 households selected from 300 Enumeration Areas (geographic area covering an average of 180 households). Naso/oropharyngeal swabs and venous blood were collected from 5898 consented participants (one per household). Swabs were tested using quantitative reverse-transcription PCR (qRT-PCR), and serum was tested using the WANTAI ELISA total IgG/IgM assay. The overall seroprevalence was 67.9%, with the highest rate in Greater Accra (76.0%) a high burden zone. Seroprevalence was higher in the urban population (70%) compared to the rural population (62.7%). Seroprevalence was lowest in young children, highest in teens and young adults, and slightly decreased in older age groups (5-9 years, 52.2%; 10-14, 63.9%; 15-19, 72.6%; 30-39, 72.5%; 50-59, 70.0%; 60-69, 69.2%; and 70+, 69.0%). There were no significant differences by gender. A total of 5389 participants were unvaccinated, and 65% were seropositive in this group. Of the 4,003 seropositive individuals, 69.2%were asymptomatic and 26.4% did not adhere to infection prevention guidelines. Of the 2219 samples tested using qRT-PCR so far, 6.9% were positive for the *E* gene only, 58.7% were positive for the *N* gene only, and 9.6% were positive for both. Confirmatory testing with qRT-PCR showed an overall infection rate of 7.6%. (29.7% *E* gene only, 1.2% *N* gene only, and 42% *E+N* genes). These results indicate that more than half of the sampled population has been exposed to the SARS CoV-2 virus since it was first reported, putting Ghana in the medium to high COVID-19 burden category. Infection rate was quite low compared to seroprevalence during the sampling period.

0191

KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS SHEDDING IN SALIVA AND CERVICAL SECRETIONS IN TANZANIAN WOMEN

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In endemic areas, Kaposi's sarcoma-associated herpesvirus (KSHV) transmission occurs to a significant degree via saliva, typically during childhood. Factors leading to KSHV viral reactivation and salivary shedding remain poorly understood. Preliminary data suggest that *Schistosoma mansoni* infection, which has been associated with impaired viral control, may contribute to KSHV reactivation. However, in those studies clear evidence for this impact was limited due to a focus on seroprevalence or small sample size. We sought to determine the relationship between active *S. mansoni* or *S. haematobium* infection and KSHV shedding.We quantified KSHV DNA in stored saliva and cervical swab samples from two cohorts of women living in areas of Tanzania with endemic *S. mansoni* or *S. haematobium* by real-time polymerase chain reaction. Chi-squared and Fisher's Exact tests were used to determine differences in clinical and demographic factors between those who were and were not shedding KSHV. Among the 99 women from the *S. mansoni* area, 6 (6.1%) had detectable KSHV in saliva, of whom 3 had *S. mansoni* infection. There was no difference in frequency of KSHV salivary shedding between the *S. mansoni* infected (n=39) and uninfected (n=60) groups. Women with KSHV salivary shedding more frequently reported infertility than those not shedding KSHV (80% versus 19.5%, p=0.009). Among the 43 women from the *S. haematobium* area, 7 (15.9%) had detectable KSHV in saliva, of whom 4 had *S. haematobium* infection. There was no difference in frequency of KSHV salivary shedding between the *S. haematobium* infected (n=18) and uninfected (n=25) groups. No woman had KSHV detected in her cervical sample. In conclusion, in this population with high KSHV seroprevalence, we provide the first report that *S. haematobium* infection was not associated with KSHV salivary shedding, and provide additional evidence for the same in *S. mansoni* infection. Interestingly, KSHV salivary shedding was associated with infertility, a known effect of another herpesvirus, HHV-6. Our results contribute to knowledge about the epidemiology and transmission of KSHV infection in an East African population.

0192

A SARS-COV-2 ANTIBODY LATERAL FLOW ASSAY PROVIDES A SEMIQUANTITATIVE ASSESSMENT OF ANTI-SPIKE ANTIBODY RESPONSES AFTER SARS-COV-2 VACCINATION

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Inexpensive, simple SARS-CoV-2 diagnostic tests can be useful tools for responding to the COVID-19 pandemic, especially in outpatient or low resource settings. Prior studies have shown that some SARS-CoV-2 antibody lateral flow assays (LFA) are sensitive for detecting antibodies within weeks after infection. This study tested samples from immunocompetent adults and those with chronic inflammatory disease (CID) who were taking a variety of immunosuppressive agents, before and after SARS-CoV-2 vaccination. We used the LFA COVIBLOCK Covid-19 rapid test cassette to detect antibodies to the SAR-CoV-2 spike (S) protein receptor binding domain. These results were compared with results obtained by anti-S ELISA and a SARS-CoV-2 viral particle neutralization assays. The LFA detected anti-S antibodies in 31/31 (100%) of the immunocompetent and 119/137 (86.9%) of the CID participants. Furthermore, the LFA detected anti-S antibodies in 28/28 (100%) of the immunocompetent and 112/116 (96.6%) of the CID participants who had detectible anti-S antibodies by ELISA. Semiquantitative LFA scores were significantly lower in samples from participants with CID. Semiquantitative LFA scores were significantly correlated with anti-S antibody ELISA OD values (Spearman coefficient r=0.92) and were also correlated with SARS-CoV-2 viral particle neutralization results. This simple LFA test appears to be a practical alternative to laboratory-based assays for detecting anti-S antibodies in individuals or populations. This type of test may be most useful for testing people in outpatient or resource-limited settings.

0193

INTERFERENCE OF COXSACKIEVIRUSES ON AZD1222 VACCINATION

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 470 million patients while taking the lives of more than 6 million. Despite preventive measures, the number of patients has kept growing worldwide. Currently, it is assumed that the most effective way to fight the virus is by an effective vaccination. It has been shown in many pieces of research that vaccines could induce innate and adaptive immune responses and reduce disease severity. In Taiwan, the common vaccines are Pfizer-BioNTech (BNT), Moderna(mRNA-1273), Medigen, and Oxford-AstraZeneca COVID-19 vaccine (AZD1222). Our laboratory has been performing neutralizing antibody titer ELISA assays for vaccinated Taiwanese. Results have shown that Taiwanese vaccinated with the AZD1222 vaccine have a scattered range of antibody titer, with a lower seropositive rate than other vaccines. Because coxsackieviruses use the same CAR receptor as the AZD1222 vaccine, and coxsackievirus infection often occurs locally. Therefore, we speculate that neutralizing antibodies produced by coxsackievirus infection may interfere with AZD1222 induced antibody titer. We performed Neutralization Titer Assays with coxsackievirus B viruses (CVB) using vaccinated serum. Results showed a positive correlation between CVB neutralization antibody titers and AZD1222 vaccination titers. To exclude the influence of other factors in serum and different viral-associated pathways in cells, we used the characteristics of CHO cells that do not express any known receptor for AZD1222 to engineer a CHO cell that stably expresses the CAR receptor. Then we used purified CVB neutralizing antibodies to test whether the infectivity of adenovirus is affected. This study may give us a clue why antibody responses differ among vaccinees of AZD1222 in Taiwan.

0194

SURVEILLANCE FOR ARBOVIRUSES AND LEPTOSPIROSIS AMONG NON-MALARIAL OUTPATIENTS WITH ACUTE FEBRILE ILLNESS IN AREAS AFFECTED BY CYCLONES IDAI AND KENNETH IN MOZAMBIQUE

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The floods associated with the landfall of cyclones Idai and Kenneth in Mozambique between March and April 2019 had a major impact on the country's public health and placed the population at risk for vector- and rodent-borne diseases. Aiming to improve the diagnostic capacity, yield information to guide public health responses, and assess potential short-term effects of cyclones Idai and Kenneth on arboviruses (dengue,

Zika, and chikungunya) and leptospirosis, we established a clinical and laboratory surveillance for non-malarial acute febrile illness in six health units located in different districts within the two provinces (Sofala and Cabo Delgado) most affected by the cyclones. Patients were tested by real-time reverse transcriptase polymerase chain reaction (qRT-PCR) for dengue (DENV), Zika (ZIKV) and chikungunya (CHIKV) viruses and by enzyme immunoassay (ELISA) to detect nonstructural DENV protein 1 (NS1) and DENV, ZIKV, CHIKV, and Leptospira IgM antibodies. From April to September 2019, we enrolled 305 patients aged ≥15 years, of which 58.4% were women and the median age was 30 years (IQR: 23 - 41 years). All patients were qRT-PCR negative for arboviruses. Three (1.0%) patients were positive by DENV NS1 ELISA, of which one also had positive IgM against DENV and CHIVK. In addition, specific IgM antibodies against DENV, ZIKV, CHIKV or Leptospira were found in the serum of 104 (34.1%) patients. Of them, 73 (23.9%) had evidence of a recent single infection, 19 (6.2%) had evidence of a recent infection by more than one arbovirus, and 12 (3.9%) had dual recent infection by an arbovirus and Leptospira. Our results indicate that vector- and rodent-borne diseases happened in all districts under investigation on wake of cyclones Idai and Kenneth, including some regions of the country where cases had not been previously detected. Although the absence of baseline, long-term surveillance data hampered assessing the impact of cyclones Idai and Kenneth on vector- and rodent-borne transmission, the investigation provided useful information to respond to post-cyclone emergency purposes.

0195

HIGH SEROPREVALENCE RATES OF SARS-COV-2 SPECIFIC IGG ANTIBODY IN SITAKUNDA, CHATTOGRAM, BANGLADESH

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We report results from serial population representative SARS-CoV-2 serosurveys in the Sitakunda subdistrict in the South-West Bangladesh. We used digitized satellite imagery to select a random sample of the population, asked all individuals ≥1 years old from selected household to participate in the study and used the Wantai total Ab assay to measure total antibodies against the SARS-CoV-2 RBD. From March through June 2021, we surveyed 2,307 individuals and estimated an adjusted (for assay performance and household clustering) seroprevalence of 64% of whom very few (5.4%; n=125) were vaccinated. After this serosurvey, a large epidemic of the Delta variant hit the area and we revisited all enrolled households from September to October, 2021. We found that 68% of those seronegative in the first serosurvey seroconverted in the three-month period between rounds. 12% of these individuals who seroconverted were vaccinated with at least one dose of Covid-19 vaccine, and 28.3% of those who seroconverted reported having an onset of at least one covid-related symptom since the first serosurvey. We estimated an adjusted seroprevalence after the Delta wave of 83.6%. We then revisited households in Jan-Feb 2022 after the Omicron wave and are currently testing these samples with the same methods and plan to estimate seroprevalence, seroincidence and seroreversion rates over the full time period.

0196

ANTI-VIRAL ACTIVITY OF FDA-LICENSED DRUGS ON ARBOVIRAL INFECTION *IN VITRO*

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Chikungunya virus (CHIKV) and Zika virus (ZIKV) are mosquito-borne viruses. There is currently no licensed vaccine or specific treatment available for either viruses. In this study, we investigated anti-viral activity of FDA-approved drugs including Favipiravir, Arbidol, Ivermectin B1a, Milbemycin oxime, Niclosamide, and Telmisartan on arboviral infection. The concentrations of each drug were selected based-on toxicity assay results in *Aedes albopictus*-derived cell line, C6/36 cells, to investigate the effect on CHIKV 181 clone 25 (vaccine strain) and ZIKV (Puerto Rico strain, Asian genotype) infections at MOI of 0.1. The half-maximal inhibitory concentration (IC50) values against CHIKV infection were 59.2, 24.3, 3.5, 26.4, 20.1 and 1.0 µg/ml for Favipiravir, Arbidol, Ivermectin B1a, Milbemycin oxime, Niclosamide, and Telmisartan, respectively. Among all, we observed only two drugs had any inhibitory effect on ZIKV infection including Arbidol and Ivermectin B1a with IC50 values of 2.5 and 0.3 µg/ml, respectively. These data indicate a potential inhibitory effect of these drugs against CHIKV and ZIKV replications which and may be considered as candidates for testing in animal model and future clinical evaluation.

0197

DETECTION OF RESPIRATORY VIRUSES IN HEALTHY CHILDREN IN THE ERA OF THE COVID-19 PANDEMIC

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Respiratory viruses are known to be detected in children irrespective of their health status. Two or more of these viruses can be detected simultaneously for one person although this might not change the severity of infections. While some studies suggest that the Covid-19 pandemic has suppressed the presence of these respiratory viruses as a result of the strict regulations implemented, much is not known about Ghana where the pandemic was less prevalent, and regulations were not strictly adhered to. The main aim of this study was to determine the viruses in circulation among healthy children during the Covid-19 pandemic. Nasopharyngeal samples were collected from 382 children between the ages of one and twelve years. These were transported in a viral transport medium and stored in a -20°C freezer. The samples were analysed for the presence of five respiratory viruses using Multiplex PCR. A questionnaire was administered to collect the demographic characteristics of participants. After the analysis, 65 samples (17.0%) were positive for at least one respiratory virus. The prevalence of viruses detected are as follows: 8.9% for SARS-CoV-2, 4.4% for Influenza Virus (A and B), 3.1% for Respiratory Syncytial Virus, 2.8% for parainfluenza viruses (1, 2 and 3), and 1% for Adenovirus. Ten samples (2.6%) were positive for two or more of the viruses under investigation. None of these participants presented signs of respiratory infections at the time of sample collection. This data suggests the presence of respiratory viruses in healthy children in Ghana. These viruses are co-circulating with a high prevalence of Covid-19. This data shows that there is a potential threat to disease outbreaks.

0198

MODELLING LASSA FEVER IN NIGERIA AND INVESTIGATION OF THE ECOLOGICAL CHARACTERISTICS OF THE DISEASE RESERVOIR

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Lassa fever is a viral haemorrhagic disease caused by infection with *Lassa mammarenavirus* and is endemic to many regions within West Africa. During the first four months of 2018, Nigeria experienced an unprecedented epidemic of Lassa fever resulting in a total of 633 confirmed cases and 171 deaths. Annual epidemics occurring at the same time of year have since followed, and the main drivers of these annual outbreaks are yet to be fully identified. The rodent *Mastomys natalensis* serves as the primary reservoir of the virus, and their ecology and behaviour has been linked to the distinct spatial and seasonal patterns of Lassa fever incidence. In this presentation we show that the population dynamics of the rodents are a key driver of the observed seasonality in cases. Using a vector transmission model with a periodic birth rate in the rodent population, we are able to replicate the trends in

the confirmed case data from 2018-2020 supplied by the Nigeria Centre for Disease Control. Furthermore, we investigate how the choice of contact-density function describing the disease transmission rate between rats affects the overall epidemiological dynamics of Lassa fever in human hosts. When applying an Approximate Bayesian Computation method of model selection, we conclude that the system supports a sigmoidal shape function for the rodent-to-rodent transmission rate. The resulting posterior parameter distributions indicate that the rodent reservoir spikes in population before the increase in reported cases, therefore our research suggests disease management could be improved by focusing efforts on reducing the number of interactions between humans and rodents, particularly at the end of a calendar year.

0199

PROTEIN-PROTEIN CONJUGATION ENHANCES IMMUNOGENICITY OF SARS-COV-2 RECEPTOR BINDING DOMAIN VACCINES

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The emergence SARS-CoV-2 in late 2019 and the ensuing pandemic have propelled an unprecedented effort to develop vaccines to contain virus spread or prevent disease. This resulted in numerous effective vaccines that are currently deployed, and candidates currently being evaluated. While vaccines based on mRNA and adeno viral vector platforms were highly effective and faster to develop, protein subunit vaccines also showed success. Many of the vaccines currently approved for human use target the Spike protein of the corona virus isolate from the early stage of the pandemic. Nevertheless, they afford significant protection against serious illness from newer variants, albeit with reduced effectiveness. Despite the success of new vaccines, the need for effective and affordable vaccines persists, especially in the developing world. More recent efforts target the receptor binding domain (RBD) of the Spike protein to focus the immune response to this domain and enhance neutralizing antibody generation that interrupts the ACE2 interaction. We adapted our protein-protein conjugate vaccine technology to generate a vaccine based on RBD antigen. RBD was conjugated to a carrier protein, EcoCRM, to generate two types of conjugates: crosslinked and radial conjugates. In the crosslinked conjugate, antigen and carrier are chemically crosslinked while in the radial conjugate, antigen is conjugated to the carrier by site specific conjugation. These conjugates were tested in mouse immunogenicity studies with two different adjuvants used in human vaccines, Alhydrogel® and AS01. With AS01, both conjugates showed enhanced immunogenicity in mice compared to RBD. Antibody subclass analysis showed a Th1 biased antibody response. In hACE2 binding inhibition and pseudo-virus neutralization assays, sera from mice vaccinated with the radial conjugate demonstrated strong functional activity. Immune sera obtained with the radial conjugate yielded strong virus neutralization activity in different variants of SARS-CoV-2 including WA1, Delta and Omicron. Further studies are underway to evaluate this conjugate in non-human primates.

0200

IMPLEMENTATION OF DIRECT DETECTION BY NANOPORE SEQUENCING OF POLIOVIRUS IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Delayed detection of poliovirus transmission has been described as one of the greatest risks to polio eradication. Direct detection of poliovirus from stool by nested PCR and nanopore sequencing (DDNS) offers a real opportunity to reduce the delivery time of results for the response to polio epidemics. We tested samples in 2 stages in this study: a retrospective arm in which we tested stools from suspected subjects with polioviruses by cell culture; a prospective arm including all samples received during the 4 months of the study as part of the surveillance of acute flaccid paralysis in the Democratic Republic of the Congo (DRC). A total of 2552 chloroform-treated stools were collected and analyzed in the laboratory with DDNS following the protocol protocols.io (https://dx.doi.org/10.17 504/protocols.io.b5pyq5pw) in parallel with cell culture, intra typic differentiation (ITD), and Sanger sequencing. Our results showed non-inferior sensitivity and specificity of DDNS compared with cell culture for both Sabin and vaccine-derived polioviruses. The generated sequences are very consistent between DDNS and traditional Sanger sequencing of cell culture supernatant (average similarity of 99.9%). DDNS PV1 sequences were obtained at a shorter median of 7 days after sample receipt in comparison with 33 days for cell culture, ITD and Sanger sequencing. DDNS allowed early detection of the new emergence of circulating vaccine-derived poliovirus 2 (cVDPV2) in Maniema province. These data showed that DDNS is sensitive, specific, and accurate, and also enables early identification of important viruses, a key component of the GPEI strategy for 2022-2026.

0201

PHARMACOVIGILANCE OF COVID-19 VACCINES IN SUB-SAHARAN AFRICA - A COHORT EVENT MONITORING STUDY OF THE SAFETY OF THREE COVID-19 VACCINES IMPLEMENTED IN GABON IN ADULTS AGED 18 YEARS AND ABOVE

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Like all countries around the world, African countries have also suffered the Covid-19 pandemic with several waves. It was on this order that when the first vaccines became available, the countries of sub-Saharan Africa also considered vaccinating their populations against Covid-19. The monitoring of vaccines against COVID-19 is a major challenge, in particular to guarantee their effectiveness in the population as well as to identify any adverse effects that may not have been observed during clinical trials, in particular the rare (<1/1000) or delayed effects. The objective of this analysis is to assess the safety of the Covid-19 vaccines

deployed in Gabon during the national immunisation campaign. In Gabon, a national vaccination committee (COPIVAC) has been set up to coordinate the national anti-Covid-19 vaccination campaign, with a pharmacovigilance subcommittee responsible for evaluating the safety of use of vaccines. deployed in Gabon, ensuring continuous monitoring of foreseeable or unexpected adverse effects. A national database has been set up on RedCap with active and passive detection of minor and severe adverse events post-immunization (AEFI). The vaccination campaign began on March 25, 2021, targeting adults aged 18 and over who would have given informed consent after eligibility assessment. As of March 28, 2022, 450,722 injections of the Sinopharm/BBIBP, BionTech/Pfizer, Janssen and Moderna vaccines have been administered in a population with a proportion of 73% (326,497) men and around 94% (425,359) aged between 18 and 59 years. A total of 6863 AEFIs were recorded including deaths. Systemic events such as headache, fatigue, fever and local and general pain were the most common. Adverse manifestations were mostly minor and transient. The few deaths observed were either due to Covid-19 or to other conditions not related to the vaccines. In conclusion, a pharmacovigilance system for monitoring the safety of Covid-19 vaccines in Gabon has been set up and the it has shown that vaccines against Covid-19 were well tolerated with good safety.

0202

DETERMINANTS OF COVID-19 VACCINATIONS AMONG A STATE-WIDE YEAR-LONG SURVEILLANCE INITIATIVE IN A CONSERVATIVE SOUTHERN STATE

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More than 350 million cases and 5 million deaths from COVID-19 have been recorded worldwide. With growing concern, and therefore increased public health measures for controlling the pandemic, came increased skepticism by a growing subset of the United States' population. Vaccine hesitancy has become a leading barrier in COVID-19 control and prevention. Given the intricate nature of this important barrier, a single statistical analysis methodology fails to address all eventualities of this complex issue. This study utilized multiple distinct, analytical approaches to understand vaccine motivations and population-level trends. With 14,915 surveys from a year-long, state-wide surveillance initiative, we performed three robust statistical analyses to evaluate vaccine hesitancy: principal component analysis, survival analysis, and spatial-time series analysis. The analytic goal was to utilize complementary mathematical approaches to identify overlapping themes of vaccine hesitancy and vaccine trust in a highly conservative US state. Principal component analysis showed four components correlated within the variables: vaccine mistrust and information garnered through various forms of media, and trust in both the science and safety behind the COVID-19 vaccine and the government. Spatial time series showed that overall, there was an increased tendency in vaccination rates towards the end of the study, as well as more positive vaccination perception. Finally, emerging hotspot analysis for vaccination status showed most areas had oscillating hot spots throughout the past year, indicating heterogeneity of vaccination status among the local population. The results indicate information source, and the population's trust in the science and approval behind the vaccine research influences vaccine receipt. Findings coincide with previous research on predictors of vaccine hesitancy and receipt. This multifaceted statistical approach allowed for methodologically rigorous results that public health professionals and policy makers can directly use to improve vaccine interventions.

0203

LOWER SEVERITY OF DENGUE FEVER TO PEOPLE WITH COVID 19 VACCINE FULL DOSES

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Dengue fever is rising in the early 2022 at Samarinda City, East Borneo of Indonesia. The trend within the last 2 years of Covid19 Pandemic, Dengue fever is at minimal level of cases. These are the side effect of under reporting cases during pandemic. Within January 2022 to March 2022, there are 721 cases reported, with 10 deaths, 71 cases with high severity cases, 640 with mild symptoms. The age under 18 years old are the most cases, following 18 - 40 years old, and over 40 years old with the highest percentage of deaths. Indonesia start Covid19 Vaccine at January 2021, with the age over 60 years old as priority to get it. In the middle of 2021, the government increase the participant to age over 40 years old, and at the late 2021, the government expand the criteria to age over 18 years old. At the early 2022, the government introduce Covid19 vaccine for under 18 years old. Until the end of March 2022, the Coverage for under 18 years old is 78% for Samarinda City. As the dengue fever and dengue haemorrhagic fever risen, 52 cases with high severity cases are among age under 18 years old, and received only dose 1 at the time they were sick. 19 cases with high severity cases are among age 18 - 40 years old without any Covid19 Vaccine received. 7 deaths cases are among 18 - 40 years old without any vaccine received, 3 deaths are among age over 60 years old. In conclusion, people who has no Covid19 Vaccine are more statistically significant to be more severe illness when they got Dengue Fever infection.

0204

"KUTETEZA": IMPLEMENTATION OF A VILLAGE-LED COVID-19 PREVENTION INTERVENTION IN RURAL MALAWI

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The COVID-19 epidemic in Malawi started in April 2020, with 85,667 cases and 2,626 deaths recorded nationally to date. Data suggest that the Malawi epidemic has largely centred around urban settings, but the true extent of rural spread - exposing the elderly in these communities - is less clear. The likelihood of SARS-COV-2 remaining an endemic pathogen means an effective long-term response is vital. The "Kuteteza" project (meaning "to protect" in Chichewa) is a community-based intervention using shielding of the elderly and additional strategies to mitigate the impacts of COVID-19 in rural and peri-urban Malawi. We partnered with government and district-level staff in the Blantyre and Mangochi districts. After engagement with village leaders, local volunteers and community members identified elderly residents and rearranged living spaces, ensuring continued provision of basic needs. Masks, handwashing stations, and soap were provided to shielding households. Context-responsive community engagement reinforced COVID-19 prevention during peak risk periods. Government ministry collaboration allowed extra support to key vulnerable groups, with food packages for instance. The project involved 25 villages. Multi-level stakeholder engagement was pivotal in developing and establishing the work, and strong district health office support was integral to implementation. Team members contributed to national meetings, aligning the project with national guidance and stakeholder actions. Established partnerships with relevant ministries resulted in the incorporation of shielding in the Malawi COVID-19 response plan. In 'Kuteteza' villages, handwashing stations and soap were used, and there

was awareness of COVID-19 prevention measures. Further experiences and evaluation results will be presented, including learning points for future outbreak responses. Through effective stakeholder engagement and contribution to national response strategy, the Kuteteza project raised awareness and supported populations at a critical time in the pandemic. These approaches can be incorporated in future epidemic and emergency responses.

0205

SEROPREVALENCE AND FACTORS CORRELATED WITH SARS-COV-2 INFECTION IN KAMPHAENG PHET, THAILAND

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Thailand initially experienced a delayed onset of SARS-CoV-2 pandemic activity but has since accumulated over 3 million infections to date. Defining seroprevalence over time and risk factors for infection are important for understanding SARS-CoV-2 transmission dynamics and informing control strategies. We present early findings from an ongoing population-based, prospective serological study of SARS-CoV-2 in Kamphaeng Phet, Thailand, nested within an ongoing multigenerational family cohort study for dengue virus (DENV) infection that began in 2015. For this sub-study, 1199 individuals enrolled from 231 multigenerational families from July to November 2021. The median age was 26 (range 0 to 96 years) and 59.2% were female. Seropositivity was determined by using AFRIMS in-house IgA and IgG ELISA to the spike protein's receptor binding domain of SARS-CoV-2. During enrollment, 29.0% reported a history of prior SARS-CoV-2 vaccination. The primary vaccines in use for a first dose were Sinovac (22.6%), AstraZeneca (2.8%), Pfizer (2.2%), and Sinopharm (1.3%). The majority of vaccinated individuals were seropositive for SARS-CoV-2 (58.9%), with the lowest seropositivity identified among those vaccinated with a single dose of Sinovac (16.8%). 5.1% of enrollees without a history of vaccination were seropositive on enrollment. Seropositivity was highest in unvaccinated adults aged 19-59 years (8.7% versus 2.2% and 4.5% in children and the elderly, respectively, p<0.01). Among adults, those who had completed high school or college were more likely to be seropositive than lower levels of education (p=0.01). Unvaccinated individuals with SARS-CoV-2 Seropositivity were less likely to have had an acute DENV infection identified during the course of the DENV cohort study (OR = 0.38, p=0.09). In this ongoing study of SARS-CoV-2 transmission within households in Thailand, we report early evidence of heterogeneity in risk of infection and a potential inverse association between risks of DENV and SARS-CoV-2 infection. These findings could inform mitigation measures for both of these viruses and represent an important area for further study.

0206

INHIBITORY EFFECT OF CONCOMITANTLY ADMINISTERED RABIES IMMUNOGLOBULINS ON THE IMMUNOGENICITY OF COMMERCIAL AND CANDIDATE HUMAN RABIES VACCINES IN HAMSTERS

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The World Health Organization protocol for rabies post-exposure prophylaxis (PEP) recommends extensive wound washing, immediate vaccination, and administration of rabies immunoglobulin (RIG) in severe category III exposures. Some studies have shown that RIG can interfere with rabies vaccine immunogenicity to some extent. We investigated the interference of RIG on a next generation highly purified Vero cell rabies vaccine candidate (PVRV-NG) versus standard-of-care rabies vaccines in a previously described hamster model. The interference of either human (h) or equine (e) RIG on the immune response elicited by PVRV-NG, a commercial purified Vero cell rabies vaccine (PVRV), and a commercial human diploid cell rabies vaccine (HDCV) was evaluated using the 4-dose Essen PEP regimen (vaccine administered via intramuscular (IM) route at Days 0, 3, 7, 14; RIG administered at Day 0 at a distinct IM site). The anti-rabies seroneutralizing titers and specific serum IgM titers were measured by fluorescent antibody virus neutralization (FAVN) test and enzyme-linked immunosorbent assay (ELISA), respectively, for the vaccines administered with or without RIG. For both read-outs, the RIG interference on PVRV-NG, observed transiently at Day 7, was in the same range as that on PVRV and tended to be lower than that on HDCV. More precisely, antibody titers at D7 were statistically significantly decreased for PVRV-NG, PVRV and HDCV co-administered with hRIG compared to vaccine alone: 1) reduction of FAVN titers by 2.2-fold (p-value= 0.01), 3.6-fold (p-value<0.001) and 10.5-fold (p-value<0.001), respectively; 2) reduction of IgM ELISA titers by 1.9, 2.1 and 3.9-fold (p-values<0.001), respectively. Similar trends were observed with eRIG when tested with PVRV-NG and PVRV vaccines. In summary, the results generated in the hamster model showed that RIG induced similar or less interference on the immunogenicity of PVRV-NG than the standard-of-care vaccines.

0207

COMPARISON OF ONE SINGLE ANTIGEN ASSAY AND THREE SARS-COV-2 MULTI-ANTIGEN IGG ASSAYS IN NIGERIA

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Determining an accurate estimate of SARS-CoV-2 seroprevalence has been challenging in African countries where malaria and other pathogens are endemic. Single-antigen assays have shown cross-reactivity and may not provide accurate SARS-CoV-2 seroprevalence estimates in these countries. We assessed the performance of one single-antigen assay and three SARS-CoV-2 multi-antigen IgG assays in a Nigerian population endemic for malaria. De-identified NIMR plasma from SARS-CoV-2 RT-PCR positive and pre-pandemic negative panels were used to evaluate the performance of the four assays (RightSign™ COVID-19 IgG/IgM (RDT), Tetracore® FlexImmArray™ SARS-CoV-2 Human IgG Antibody Test, Luminex xMAP® SARS-CoV-2 multi-antigen IgG assay, and a CDC SARS-CoV-2 multi-antigen IgG bead assay). The 2018 NAIIS pre-pandemic plasma panels were used to assess potential cross-reactivity by testing specimens with known reactivity to malaria. Overall sensitivity with NIMR specimens was 64.0% (95% CI: 53.7-73.2), 80.5% (70.0-88.1), 84.8% (75.9-91.0), and 95.9% (89.3-98.7) for RightSign, FlexImmArray, Luminex xMAP, and CDC assay, respectively. Specificity with NIMR plasma specimens was 100% (95% CI: 95.4-100) for RightSign, 98.0% (92.3-99.7) for Luminex xMAP, and 100% (95.3-100) for FlexImmArray and CDC assay. When stratified by days post RT-PCR confirmation, sensitivity for <15 days was 58.3%% (44.9-70.7), 75% (60.1-85.9), 83.1% (70.6-91.1), and 93.1% (82.5-97.8), while ≥15 days was 72.5% (55.9-84.9), 88.2% (71.6-96.2), 87.5% (72.4-95.3), and 100% (89.1-100) for RightSign, FlexImmArray, Luminex xMAP, and CDC assay, respectively. Specificities using NAIIS panels were 100.0% (97.7-100.0), 97.5% (93.9-99.6), 99% (96.1-99.8) and 100% (97.6-100)

for RightSign, FlexImmArray, Luminex xMAP, and CDC assay, respectively. Results showed higher sensitivity with the multi-antigen versus the single-antigen SARS-CoV-2 assay. Multi-antigen assays performed well in Nigeria, even with samples with known malaria reactivity, and might provide more accurate measures of COVID-19 seroprevalence and vaccine efficacy than single antigen assays.

0208

CLINICAL AND EPIDEMIOLOGICAL RISK FACTORS FOR COVID19 AMONG CASES SEEKING CARE IN LIBERIA, A MULTI-CENTERED, RETROSPECTIVE, OBSERVATIONAL STUDY

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Identifying clinical and epidemiological risk factors for COVID-19 is crucial for informingmeasures to reduce the burden of the pandemic locally. In Liberia, limited research has been conducted to inform clinical management, facilitate targeted preventive messaging within communities, and forecast resource needs. This research seeks to identify the clinical and epidemiological risk factors for COVID-19 morbidity and mortality among cases seeking care in Liberia. Data on confirmed COVID-19 cases who sought care between March 2020 and September 2020 were extracted from medical charts at health facilities in Liberia. Due to data quality issues associated with paper charts, data required cleaning to remove duplicates per three sets of pre-specified assumptions. The statistical analysis was implemented on the resulting three datasets as a sensitivity analysis. Associations between epidemiological, clinical, and demographic variables and indicators of disease severity (management with breathing support and survival status) were assessed using simple and multivariable logistic regression. Data from 1591 confirmed cases across 14 counties were analyzed. The median age was 38 years (IQR: 27-50), and the majority were male (n=1050, 64.7%). Rates of CPAP use for breathing support and case fatality were 5.3% and 5.3%, respectively. In the multivariable analysis, comorbid diabetes and hypertension and increasing age were associated with increased odds of CPAP use. Recent travel history, increasing age, and need for breathing support were associated with increased odds of mortality. Nearly 48% of raw case entries in the database warranted cleaning due to identification as duplicates. We identified epidemiological and clinical patient characteristics associated with increased odds of need for breathing support and mortality due to COVID-19 in a resource-poor setting. We also highlighted enormous data collection and management challenges that warranted intense data cleaning and, importantly, affected the ability to do real-time analyses for informing clinical management at the peak of the outbreak.

0209

CHARACTERIZATION AND EVALUATION OF THE EFFICACY OF THERAPEUTIC ANTIBODIES FOR THE PREVENTION OF SARS-COV-2 (OMICRON) INFECTION AND DISEASE IN THE HAMSTER MODEL

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The emergence of multiple variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has challenged the utility of vaccines and several therapeutic antibodies, as specific mutations within the viral spike protein has led to a decrease or complete loss of potency. The omicron variant (B.1.1.529), currently an urgent global health concern, further limited therapeutic options. In the absence of clinical information, it's critical to characterize the hamster model of SARS-CoV-2 respiratory disease for potential countermeasures against omicron. Here, the authentic infectious omicron BA.1 and BA.1.1 isolates were evaluated in hamsters for lung infection, clinical disease, and pathology. We observed attenuated pathogenicity, compared to previous SARS-CoV-2 variants, with no clinical signs of disease, limited (or no) weight loss, and reduced lung disease when evaluated by histopathology. Despite the limited clinical burden, we observed a marked and significant viral burden in the upper and lower respiratory tracts, allowing us the ability to assess medical countermeasures using viral load reduction. The prophylactic efficacy of nine therapeutic antibodies that neutralized omicron *in vitro* was evaluated against BA.1 or BA.1.1 infection in hamsters. We found that most of the monoclonal antibodies restricted viral infection in the upper and lower respiratory tract and limited the lung pathology of hamsters exposed with BA.1 or BA.1.1. These findings demonstrate that the attenuated replication and pathogenicity of BA.1 and BA.1.1 in the hamster model parallels human clinical data and most of the therapeutic monoclonal antibodies tested here maintain potency against omicron BA.1 and BA.1.1.

0210

COVID-19 VACCINE HESITANCY AMONG ADULTS AGED 18 YEARS AND ABOVE RESIDING IN THE LARGEST TOWNSHIP IN SOUTH AFRICA

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South Africa has experienced severe Covid-19 pandemic, with 2 waves prior to and 2 waves post Covid-19 vaccine availability. Despite vaccines being the most promising covid-19 prevention strategy, vaccine uptake in South Africa has been low, with 43.5% of adults aged 18 years and above fully vaccinated as of 25 March 2022, similar to other African countries. Vaccine hesitancy threatens the success of Covid-19 vaccine programs more so in countries like South Africa where vaccines are readily available free of charge. The objective of this study is to examine the level and determinants of Covid 19 vaccine hesitancy among adults (18 years and above) residing within the CHAMPS Soweto/Thembelihle Health and Demographic Surveillance (CHAMPS-SaT HDSS), Johannesburg, South Africa. The study includes 72766 adults from the surveillance total population of ~120 000 individuals. Descriptive statistics were used to examine proportion of people not vaccinated, and multivariate logistic regression modeling identified factors associated with non-vaccination. Further, we explored reasons given for non-vaccination to determine vaccine hesitancy. Seventy-nine percent (57 875) of the study sample was not vaccinated. Among those who were not vaccinated, 38% were undecided, 25% did not want the vaccine and 37% cited other reasons. The odds of not being vaccinated were lower among those with secondary (OR 0.60 CI 0.64 - 0.75) and higher education (OR 0.38 CI 0.34 - 0.43) compared to those with primary or less education. Those aged 35-49 years (OR 0.36 CI 0.34 - 0.38), 50-64 years (OR 0.15 CI 0.14 - 0.15) and 65+ years (OR 0.11 CI 0.10 - 0.12) were less likely to be unvaccinated compared those aged 18-34 years. Being employed (OR 0.65 CI 0.56 - 0.76) was associated with lower odds of not being vaccinated compared to being unemployed. There is evidence of vaccine hesitancy among adults who are not vaccinated within the CHAMPS-SaT HDSS site with significant socio-economic and demographic differences. There is need for more campaigns in townships like Soweto and Thembelihle to increase vaccine uptake and demystify myths that exist around Covid 19 vaccines.

0211

DIVERGENT RHABDOVIRUS DISCOVERED IN A PATIENT WITH NEW ONSET NODDING SYNDROME

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A divergent rhabdovirus was discovered in the bloodstream of a 15-year-old girl with Nodding syndrome from Mundri West County in South Sudan. Nodding syndrome is a progressive degenerative neuropathy of unknown cause affecting thousands of individuals in Sub-Saharan Africa. The index case was previously healthy until she developed head-nodding seizures four months prior to presentation. Virus discovery by VIDISCA-NGS on the patient's plasma detected multiple sequence reads belonging to a divergent rhabdovirus. The viral load was 3.85 × 103 copies/mL in the patient's plasma and undetectable in her cerebrospinal fluid. Further genome walking allowed for the characterization of full coding sequences of all the viral proteins (N, P, M, U1, U2, G, U3, and L). We tentatively named the virus "Mundri virus" (MUNV) and classified it as a novel virus species based on the high divergence from other known viruses (all proteins had less than 43% amino acid identity). Phylogenetic analysis revealed that MUNV forms a monophyletic clade with several human-infecting tibroviruses prevalent in Central Africa. A bioinformatic machine-learning algorithm predicted MUNV to be an arbovirus (bagged prediction strength (BPS) of 0.9) transmitted by midges (BPS 0.4) with an artiodactyl host reservoir (BPS 0.9). An association between MUNV infection and Nodding syndrome was evaluated in a case–control study of 72 patients with Nodding syndrome (including the index case) matched to 65 healthy households and 48 community controls. No subject, besides the index case, was positive for MUNV RNA in their plasma. A serological assay detecting MUNV anti-nucleocapsid found, respectively, in 28%, 22%, and 16% of cases, household controls and community controls to be seropositive with no significant differences between cases and either control group. This suggests that MUNV commonly infects children in South Sudan yet may not be causally associated with Nodding syndrome.

0212

HUMANIZED SCFV ANTIBODIES FOR COVID-19 THERAPY

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Effective therapies are urgently needed for COVID-19. Due to structurally analogous regions of the Ebola virus glycoprotein (GP) and SARS-CoV-2 spike (S) protein, we rapidly identified two murine anti-EBOV scFv antibodies generated from ribosomal display by re-testing against the receptor binding domain (RBD) variants of the SARS-CoV-2 spike (S) glycoprotein that prevents SARS-CoV-2 from infecting cultured cells. Murine scFv antibodies are relatively easy to produce but are severely restricted for therapeutic use by their immunogenicity in humans. Production of human antibodies has been problematic. Humanized antibodies can be generated by introducing the six hypervariable regions from the heavy and light chains of a murine antibody into a human framework sequence and combining it with human constant regions. We humanized, with the aid of computer modeling, a murine scFv antibody against the S RBD variants. The binding, virus neutralization, and cell protection results all indicate that humanized antibodies (HC2-LC1 and HC3-LC3) have retained the binding activities and the biological properties of the murine scFv antibodies.

0213

AEDES-BORNE ARBOVIRUS SEROPREVALENCE IN A COHORT OF CHILDREN FROM MERIDA, MEXICO: A BASELINE ANALYSIS OF THE TARGETED INDOOR RESIDUAL SPRAYING (TIRS) TRIAL

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Aedes borne viruses (ABVs) place a significant strain on public health resources globally. Vector control is an important public health strategy to control and prevent ABV infections. The Targeted Indoor Residual Spraying (TIRS) project is a cluster-randomized controlled trial to study the epidemiologic impact of novel vector control techniques in preventing illness due to ABVs in the city of Merida, Yucatan, Mexico. We selected 50 geographical neighborhood clusters that were randomly allocated to either the control or intervention arms of the trial and enrolled a cohort of 4,600 children aged 2-15 living in these clusters. We collected socio-economic and demographic data and serum samples during enrollment in 2021. Baseline seroprevalence of IgG antibodies against dengue, Zika, and chikungunya viruses was determined for n=1400 (~30%) enrolled participants. We found that 44.2% of children were seropositive for antibodies against dengue viruses, 21.5% against Zika virus, and 24.1% against chikungunya virus. No significant differences in ABV-seroprevalences between the control and intervention arms were detected, confirming balance between the arms at baseline. Our data indicated that a significant number of children were exposed to Zika virus, most likely during the pandemic of 2015-2016, and nearly half were previously exposed to one or more dengue serotypes. A subset of 225 randomly selected TIRS participants was tested by focus reduction neutralization tests (FRNTs) to determine dengue serotype specificity. Interestingly, compared to FRNT data collected from a similar (by age and location) population in 2016, the TIRS cohort showed a significantly lower frequency of dengue reactivity to any serotype (90% vs 37%). The results from these studies suggest low levels of recent exposure to dengue viruses and may be informative to predicting the susceptibility of the population of Merida to future outbreaks.

0214

COMPREHENSIVE MUTAGENESIS OF SARS-COV-2 S PROTEIN TO MAP ANTIBODY EPITOPES AND IDENTIFY RESIDES ESSENTIAL FOR FUNCTION

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To characterize the immune response to SARS-CoV-2 infection, we created a comprehensive Ala-scan mutation library (>1240 mutations) of the SARS-CoV-2 S protein. We use this library to epitope map anti-SARS-CoV-2 monoclonal antibodies (MAbs) by high-throughput, rapid screens of MAb binding to each mutant S protein. Individual mutant expression plasmids transfected into human cells achieve native protein expression and folding, immunoreactivity of MAbs to each mutant S protein is

quantified by high-throughput flow cytometry, allowing us to identify the S protein epitope residues with the highest energetic contributions to MAb binding. We have mapped over 100 MAbs targeting the S protein, identifying conformational epitopes in the S1 receptor binding domain (RBD) and N-terminal domain (NTD), and in S2, helping characterize MAbs that neutralize and protect in animal models of disease. To provide critical reagents for analyses of MAb or serum immune responses to SARS-CoV-2 infection, we developed a pseudotyped lentiviral reporter virus system for SARS-CoV-2, with reporter virus particles (RVPs) displaying S protein. These replication-incompetent RVPs perform one round of infectivity and enable safe (BSL-2) and reproducible virus neutralization assays with luminescent or fluorescent readout. We have produced over 60 SARS-CoV-2 RVP types incorporating variant S proteins. We also used our MPS antibody isolation platform to obtain MAbs against S protein, some of which neutralize the major Omicron variants. We used RVP technology to screen the S protein mutant library for infectivity, to identify residues critical for virus infectivity whose mutation eliminates virus infectivity but does not impact S protein expression, antigenicity, or reporter virus budding. To identify uncharacterized SARS-CoV-2 cellular binding factors we are assaying wild-type SARS-CoV-2 RVP infectivity in non-permissive cells expressing our membrane proteome array (MPA) of 6,000 unique human membrane proteins. Similar experiments with other viruses have yielded previously unidentified candidate membrane proteins that enable virus infectivity.

0215

RELATIONSHIP BETWEEN THE VACCINATION AGAINST COVID19 AND THE INCIDENCE OF IMPORTED CASES AND HOSPITALISATIONS IN THE CAPITAL CITY OF GABON, CENTRAL AFRICA

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Several reports showed that Sinopharm, Pfizer BioNtech and Janssen vaccines are safe and effective for preventing COVID-19-related serious illness, hospitalization, and death. Data on vaccine effectiveness are scarce in Central Africa. This incidence rate of COVID-19 imported cases and hospitalised case was compared between vaccinated and non vaccinated individuals. Results. Using national data, from October to December 2021 ; the incidence rate of hospitalizations significantly decreased among the vaccinated individuals although that of laboratory-confirmed cases remained high during epidemic peaks. Although less vaccinated, younger children were not a higher risk of being infected. Data on each vaccine specific effectiveness are being analyzed. The number of vaccinated individuals with a positive PCR test significantly decreased among the group of vaccinated individuals.

0216

SUSCEPTIBILITY OF *PLASMODIUM FALCIPARUM* ISOLATES FROM EASTERN UGANDA TO ANTIMALARIAL COMPOUNDS UNDER DEVELOPMENT

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Malaria, especially *Plasmodium falciparum* infection, remains an enormous problem, and its treatment and control are seriously challenged by drug resistance. New antimalarial drugs are needed. To characterize the pipeline of lead antimalarials under development, we assessed *ex vivo* drug susceptibilities to compounds targeting *P. falciparum* cytochrome b (PfCYTb), dihydroorotate dehydrogenase (PfDHODH), elongation factor 2 (PfEF2), phenylalanine t-RNA sythetase (PfPheRS) and phosphatidylinositol 4-kinase (PfPI4K) for 688 fresh *P. falciparum* clinical isolates collected in eastern Uganda from 2015-2021. Drug susceptibilities were assessed with 72 h growth inhibition (IC_{50}) assays using SYBR green. In general, field isolates were highly susceptible, with median IC_{50}s in the low nM range for compounds targeting PfCYTb (ELQ300, 13 nM); PfDHODH (DSM265, 3.6 nM; DSM421, 20 nM; DSM632, 9.8 nM; DSM705, 11 nM; DSM1049, 22 nM; BRD1331 13 nM), PfEF2 (DDD498, 0.6 nM); PfPheRS (BRD5018, 1.6 nM); and PfPI4K (MMV048, 60 nM; UCT943, 11 nM). Median IC_{50} values were near those reported previously for laboratory strains, but outliers with decreased susceptibilities were identified. Positive correlations between IC_{50} results were seen for compounds with shared targets. We also sequenced potential resistance mediators to search for polymorphisms previously selected *in vitro* and to determine genotype-phenotype associations. We identified many polymorphisms in target genes, generally in <10% of samples, but except for those in PfPI4K, none were previously selected *in vitro* with drug pressure or associated with decreased *ex vivo* drug susceptibility. Three mutations (N957H, I876V and Y883H) in PfPI4K were associated with slightly decreased susceptibility to MMV048 (median IC_{50} WT vs mutant: 55 nM vs 74 nM for N957H, 61 nM vs 75 nM for I876V, and 60 nM vs 77 nM for Y883H). Overall, Ugandan *P. falciparum* isolates were highly susceptible to 11 compounds under development as next-generation antimalarials, consistent with a lack of pre-existing or novel resistance-conferring mutations in circulating Ugandan parasites.

0217

ASSESSMENT OF *PLASMODIUM FALCIPARUM* ARTEMISININ RESISTANCE INDEPENDENT OF *KELCH13* POLYMORPHISMS AND WITH ESCALATING MALARIA IN BANGLADESH

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Emerging resistance to artemisinin drugs threatens the elimination of malaria. Resistance is widespread in South East Asia (SEA) and Myanmar. Neighboring Bangladesh, where 90% of infections occur in the Chittagong Hill Tracts (CHTs), lacks recent assessment. We undertook a prospective study in the sole district-level hospital in Bandarban, a CHT district with low population densities but 60% of reported malaria cases. Thirty patients presented with malaria in 2018. An increase to 68 patients in 2019 correlated with the district-level rise in malaria, rainfall, humidity, and temperature. Twenty-four patients (7 in 2018 and 17 in 2019) with uncomplicated *Plasmodium falciparum* mono-infection were assessed for clearing parasites after starting artemisinin combination therapy (ACT). The median (range) time to clear half of the initial parasites was 5.6 (1.5 to 9.6) h, with 20% of patients showing a median of 8 h. There was no correlation between parasite clearance and initial parasitemia, blood cell counts, or mutations of *P. falciparum* gene *Pfkelch13* (the molecular marker of artemisinin resistance [AR]). The *in vitro* ring-stage survival assay (RSA) revealed one (of four) culture- adapted strains with a quantifiable resistance of 2.01% ± 0.1% (mean ± standard error of the mean [SEM]). Regression analyses of *in vivo* and *in vitro* measurements of the four CHT strains and WHO-validated K13 resistance mutations yielded good correlation (R^2=0.7; ρ =0.9, $P < 0.005$), strengthening

evaluation of emerging AR with small sample sizes, a challenge in many low/moderate-prevalence sites. There is an urgent need to deploy multiple, complementary approaches to understand the evolutionary dynamics of the emergence of *P. falciparum* resistant to artemisinin derivatives in countries where malaria is endemic. DOI: 10.1128/mbio.03444-21

0218

EFFECTIVENESS OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY WITH SULFADOXINE-PYRIMETHAMINE IN IMPROVING PARASITOLOGICAL AND CLINICAL OUTCOMES IN SOUTHERN MOZAMBIQUE

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In 2014 Mozambique adopted the WHO intermittent preventive treatment in pregnancy (IPTp) policy, which recommends the use of IPTp with sulfadoxine-pyrimethamine **(**SP) for all HIV negative (HIV^-) pregnant women attending antenatal care (ANC). However, the effectiveness of IPTp-SP is threatened by the spread of SP resistance, and a continuous monitoring of IPTp-SP effectiveness is necessary to inform programmatic decisions. We conducted a three-year prospective observational study beginning two years after the policy implementation in Mozambique, at heath facilities in Magude (low malaria transmission area), Manhiça (low to moderate transmission) and Ilha Josina (high transmission). A form including the number of IPTp-SP doses registered from the woman's antenatal booklet was filled out. Finger-prick peripheral blood samples onto filter papers collected at delivery visits were analyzed by real-time quantitative polymerase chain reaction (qPCR) to assess the presence of *Plasmodium falciparum* (*Pf*), as well as by quantitative suspension array technology for antimalarial antibodies. Especially in Ilha Josina, *Pf* positivity rate by qPCR at delivery was lower in the group receiving the recommended three or more IPTp-SP doses (6.2%) than in the group receiving less than three doses (14.3%; p=0.019). The seroprevalence of pregnancy-specific antibodies was higher in the group not receiving the recommended number of doses than in the full IPTp-SP group in the three study areas. This probably reflects the higher *Pf* positivity rate in this group. An association between anemia and receiving less than three doses was found in Manhica and Magude. Similarly, receiving fewer than three doses was associated with low birth weight in Manhica and Ilha Josina. Our findings indicate that three or more doses of IPTp-SP is effective in reducing *Pf* positivity rate in high transmission settings, although pregnancy-specific seroprevalence also suggests an impact in low transmission settings. Following the IPTp-SP policy improves the health of the women and their infant even in contexts of high prevalence of molecular markers of SP resistance.

0219

PLASMODIUM FALCIPARUM MULTIDRUG RESISTANCE 1 GENE POLYMORPHISMS INFLUENCE OUTCOMES AFTER ANTIMALARIAL TREATMENT

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The *Plasmodium falciparum multidrug resistance transporter 1* gene (*pfmdr1*) is associated with altered response to artemisinin-based combination therapies (ACTs), particularly those containing the partner drugs lumefantrine and amodiaquine (i.e., artemether-lumefantrine (AL) and artesunate-amodiaquine (ASAQ)). Past studies of *pfmdr1* single nucleotide polymorphisms (SNPs) at codons 86, 184, and 1246 have shown different treatment responses to AL and ASAQ. To determine whether patients infected with parasites carrying specific *pfmdr1* SNPs are at increased risk of recurrent parasitemia or treatment failure, patient data on molecular markers of *P. falciparum* from 16 therapeutic efficacy studies in 13 African countries from 2013 to 2019 were analyzed. The Mantel-Haenszel (MH) method was used to create forest plots displaying the common effect odds ratio by treatment arm for each specific study and the pooled MH odds ratio by treatment arm when the data from all studies were compiled. This odds ratio represented the odds of recurrent infections with a specific allele compared to the odds of successfully treated infections with that same allele in pre-treatment samples. For patients treated with AL, the odds of the N86 allele in recurrent infections was 5.24 (95% CI 2.69, 10.20) times higher than the odds of the N86 allele in pre-treatment infections successfully cleared. For those treated with ASAQ, the odds of the 86Y allele in recurrent infections was 2.65 (95% CI 1.21, 5.79) times higher than the odds of the 86Y allele in pre-treatment infections successfully cleared. There were no statistically significant associations detected between recurrent infections and *pfmdr1* codons 184 and 1246. These results support prior studies that suggested: 1) patients given AL infected with parasites carrying N86 were at a significantly greater risk of recurrent infection; 2) patients given ASAQ infected with parasites carrying 86Y were at a significantly greater risk of recurrent infection. These findings suggest that ACT choice and *pfmdr1* genotype may influence treatment outcome after *P. falciparum* infection.

0220

MOLECULAR MARKERS ASSOCIATED WITH *PLASMODIUM FALCIPARUM* RESISTANCE TO ANTI-MALARIAL DRUGS IN MOZAMBIQUE, 2015 AND 2018

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Surveillance of molecular markers of antimalarial resistance in *Plasmodium falciparum* is an effective strategy to detect emerging resistance to current treatments. This study aimed to analyze the profile of the mutations associated with *Plasmodium falciparum* resistance to anti-malarial drugs in Mozambique in 2015 and 2018. A total of 1877 dried blood spots were collected in Maputo, Gaza, Inhambane, Sofala, Tete, Zambézia and Cabo Delgado provinces in the context of therapeutic efficacy studies, cross-sectionals in the community and pregnant women at health facilities in 2015 (543 samples) and 2018 (1334 samples). Whole genome sequencing of these samples was performed for detection of drug resistance mutations in Kelch type protein 13 (*pfkelch13*), multidrug resistance gene 1 (*pfmdr1*), dihydrofolate reductase (*pfdhfr),* dihydropteroate synthase (*pfdhps*) and chloroquine transporter gene (*pfcrt*) genes. No mutations related to artemisinin resistance were detected in the *pfkelch13* gene. Mutations on codons 74-76 in *pfcrt* gene were only observed in 2015 in Maputo (2%) and Gaza (9%) provinces. Mutation in codon 86 of *pfmdr1* gene was only found in Gaza province (8%) in 2015. Mutation in codon 184 of *pfmdr1* gene was common in all provinces (ranging from 54-61% in 2015 and 50-65% in 2018). Prevalence of quintuple mutants in *pfdhfr/pfdhps* was 70% in 2015 and 80% in 2018, and was highest in Maputo province and lowest in Cabo Delgado province. Mutation in the codon 436 of *pfdhps* gene was only observed in Cabo-Delgado, suggesting local selection of this mutation in Northern Mozambique. This data, the most comprehensive in the country, provides key information for the rationale use of antimalarials for malaria control and elimination.

0221

GENETIC DIVERSITY OF DRUG RESISTANCE GENES IN *PLASMODIUM MALARIAE* AND *P. OVALE*

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Although malaria remains a public health concern in sub-Saharan Africa, recent global concerted anti-malarial efforts have significantly reduced the burden. Unfortunately, the efforts are *Plasmodium falciparum*-focussed with the neglect of *P. malariae* and *P. ovale.* If malaria is to be eliminated and eradicated, there is the need to target all forms of human malaria-causing *Plasmodium* species. The true contribution of *P. malariae* and *P. ovale* to malaria worldwide is unknown mainly because they are frequently misdiagnosed; due to their characteristic low parasitemias, frequent mixed-species infection, and the subpar performance of malaria gold standard diagnostic tool. With antimalarial drug resistance posing a threat to the no malaria agenda, there is the need to periodically surveil and assess the genetic effect of drug pressure on the circulating *Plasmodium* species. Hence, this study seeks to analyse the genetic diversity of P. *malariae* and *P. ovale* drug resistance genes (multidrug resistance gene and Kelch-13 propeller gene) using Sanger sequencing. The resulting data will be instrumental in the development of future antimalarial drugs.

0222

EX-VIVO SUSCEPTIBILITY OF *PLASMODIUM FALCIPARUM* ISOLATES TO STANDARD ANTIMALARIALS IN BOBO-DIOULASSO, BURKINA FASO

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Malaria remains the leading cause of morbidity and mortality in Burkina Faso. The country utilizes artemether-lumefantrine, artesunate-amodiaquine, and recently dihydroartemisinin-piperaquine as first line therapies for uncomplicated malaria. Seasonal malaria chemoprevention (SMC) with amodiaquine plus sulfadoxine-pyrimethamine is implemented country-wide in children 5 years and under during the transmission season. With concerns regarding potential resistance to many classes of antimalarials, monitoring the efficacy of available antimalarial drugs is a high priority. To assess susceptibilities of malaria parasites to standard antimalarials, we measured ex vivo IC_{50}s for 11 compounds utilizing 79 isolates collected from patients presenting with uncomplicated *Plasmodium falciparum* malaria in Bobo Dioulasso from July to December, 2021. Assays utilized a standard 72 h growth inhibition microplate assay with SYBR Green detection, with results compared to those with laboratory-adapted control parasite strains. Isolates (median IC_{50} [range], nM) were generally highly sensitive to: chloroquine (10 [3.7 – 423]), monodesethylamodiaquine (24 [0.6 – 206]), piperaquine (4.4 [1.2 – 47]), lumefantrine (6.5 [0.5 – 38]), mefloquine (4.7 [0.3 – 30]), atovaquone (0.2 [0.01 – 1.0]), dihydroartemisinin (4.1 [1.1 – 25]), cycloguanil (774 [3.6 – 8265]), pyronaridine (4.5 [0.4 –15]) and quinine (40 [1.5 – 166]). With a few exceptions, parasites were highly resistant to pyrimethamine (29,845 [33 – 116,400]). These IC_{50} values were similar to those reported from our recent ex vivo studies in eastern Uganda, and suggested good antimalarial efficacy of all tested drugs except pyrimethamine. However, it is noteworthy that the median IC_{50} for monodesethylamodiaquine was greater than that recently reported in Uganda (7.1 [1.1 - 202]; $p < 0.0001$), possibly related to widespread use of amodiaquine as part of SMC in Burkina Faso. Genotyping of isolates from Burkina Faso to characterize key mutations associated with antimalarial drug resistance is currently underway.

0223

DIHYDROARTEMISININ PIPERAQUINE IS EFFECTIVE AS SEASONAL MALARIA CHEMOPROPHYLAXIS IN UNDER FIVE CHILDREN WITH MALARIA INFECTION IN EXTENDED SEASONAL TRANSMISSION SETTINGS OF TANZANIA: AN OPEN CLUSTER RANDOMIZED CLINICAL TRIAL

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In Tanzania, the Ministry of Health is planning to introduce seasonal malaria chemoprevention (SMC) in malaria endemic areas with very strong seasonal transmission pattern as a measure to decrease burden of infection in children. This study assessed the effectiveness of dihydroartemisinin-piperaquine (DP) as SMC for control of malaria in two districts of Masasi and Nanyumbu Mtwara region, southern Tanzania. Between March and June 2021 children aged 3-59 months in selected wards were enrolled in an open cluster randomized (intervention and control) study. Children in the interventional clusters were administered monthly with a full course of DP for three consecutive months regardless of the malaria infection status, whereas those in the control clusters were treated according to the national treatment guidelines once they got infected. The primary outcome was malaria prevalence as assessed by using malaria rapid diagnostic tests (mRDT) at the end of transmission season. The drug was well tolerated with no serious adverse events. Before intervention: malaria prevalence by mRDT was 23.69% (167/705) in Nanyumbu district and 12.60% (206/1635) in Masasi district. Following the intervention, malaria prevalence in Nanyumbu district declined to 9.20% (55/598), ($x2$=48.07, p<0.001), whereas in Masasi it declined to 6.80 (101/1486) ($x2$=29.55, p<0.001). Also, following the intervention there was significant decline in anaemia prevalence in the interventional clusters, whereas in the control clusters it increased. The SMC using dihydroartemisinin-piperaquine was safe and effective for seasonal malaria chemoprevention in Masasi and Nanyumbu districts.

0224

SEASONAL MALARIA CHEMOPREVENTION IN BURKINA FASO: IMPACT ON *PLASMODIUM FALCIPARUM* GENETIC DIVERSITY AND RESISTANCE PROFILE

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In Burkina Faso, the implementation of seasonal malaria chemoprevention (SMC) as a malaria prevention strategy started in 2014 and is now being implemented countrywide since 2019. Unfortunately, there is no routine malaria molecular surveillance to measure the impact of SMC on the genetic diversity of malaria parasites including resistance profiling, some characteristics of which are strongly correlated with the dynamics of the level of transmission and resistance.The present study was thus designed to measure the effect of SMC on malaria prevalence, complexity and polyclonality of infection, and the dynamic of resistance markers during the four months of the SMC in children in Saponé Health District located in the South-Central Region of Burkina Faso.This was a cohort study of 220 children aged from 3 to 59 months followed up during the 4 months (July-October 2020) of the SMC. Demographic, clinical and biological data were collected. Blood samples were taken before each of the 4 round visits for microscopic diagnosis and molecular typing by PCR.The mean age was 32,7 months. A gain of hemoglobin rate was effective from 10.2 g/dl to 10.8 g/dl respectively from July to October. The geometry mean of *P. falciparum* density statistically (p<0.05) increased from July (3390tf/ul) to October (5170tf/ul). We observed an increase in the parasite prevalence by PCR from July to October, 6% to 34% respectively. While there is trend of reduction in the prevalence of FC27 *msp2* alleles the results showed an increase of the RO33 *msp1* alleles from July to October. However, there was no significant difference in the complexity of the infection between the 1st and 4th round passages (p>0,05). Interestingly, there is an increase in monoclonal infection prevalence. The analysis of the resistance profile showed a significant reduction of the prevalence of the *pfmdr1*_86Y mutation opposed to a high prevalence of the *pfcrt*76T mutation at the end of the rounds.The results show an impact of SMC on the parasite diversity but especially a different dynamic at the level of resistance markers which would be interesting to monitor.

0225

NEXT-GENERATION SEASONAL MALARIA CHEMOPREVENTION: MODELLING THE PUBLIC HEALTH IMPACT OF NEW MEDICAL INTERVENTIONS

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Seasonal malaria chemoprevention (SMC) is a cornerstone of malaria control in settings with intense malaria transmission, administered monthly to children throughout the malaria season. However, the spread of partial resistance to sulfadoxine-pyrimethamine, which in combination with amodiaquine is the standard of care for SMC, threatens SMC's effectiveness. Guidance for developing new or repurposing existing drugs for SMC is needed and, yet, little is known about how different product characteristics contribute to SMC's effectiveness. We combined an individual-based mathematical model of malaria transmission with pharmacokinetics/pharmacodynamics models and statistical analysis to estimate the public health impact of next-generation SMC. Global sensitivity analyses identified trade-offs between a next-generation intervention's efficacy, prophylaxis period, and program coverage, and optimisation identified minimum criteria to achieve target malaria morbidity reductions. With this approach, framed by expert engagement, we provide modelling evidence to inform the iterative process of selecting seasonal chemoprevention candidates. Our preliminary findings indicate that high SMC coverage and lasting protection between rounds are critical for morbidity reduction. When four SMC rounds are equally spaced over four months and deployed to children under five or ten years, a drug elimination half-life of more than 15 days is required to achieve target clinical incidence and severe disease reductions of 85% to 80% (measured over the intervention period in the target population) in low to very high malaria transmission settings, respectively. Over 40% of children should receive all SMC rounds and 90% at least one round to achieve these targets. As a result, minimum criteria for SMC duration of protection should be set to facilitate next-generation SMC's effectiveness, alongside increasing access and uptake. Drug developers and funders should support the generation of evidence on duration through studies of pharmacokinetic/pharmacodynamic properties and malaria challenge trials or early clinical studies.

0226

POST-DISCHARGE MALARIA CHEMOPREVENTION IN CHILDREN ADMITTED WITH SEVERE ANAEMIA IN MALARIA-ENDEMIC SETTINGS IN AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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After recovery from severe anaemia, preschool children recently discharged from hospital are at high risk of dying or being readmitted in the first six months after discharge. Monthly post-discharge malaria chemoprevention (PDMC) has been shown to reduce this risk substantially. We conducted a systematic review and meta-analysis to determine the efficacy of PDMC. Three double-blind, placebo-controlled trials from Malawi, Kenya, Uganda and the Gambia, involving 3,663 children with severe anaemia, met the eligibility criteria. PDMC consisted of either monthly sulfadoxine-pyrimethamine (SP) until the end of the malaria transmission season (average: 3.1 doses per child, Hb<7 g/dL) (N=1,200, the Gambia), monthly artemether-lumefantrine (AL) given at 4 and 8 weeks post-discharge (N=1,414, Malawi, Hb<5 g/dL), or monthly dihydroartemisinin-piperaquine given at the end of the 2nd, 6th, and 10th week post-discharge (N=1,049, Uganda and Kenya, Hb<5 g/dL). Fixed-effects meta-analysis was used to generate pooled effect estimates. PDMC was associated with a relative risk reduction of 77% (95% CI 30-92) in mortality during the intervention period ending 4 weeks after the last PDMC course (primary outcome) ($p=0.01$, $I^2=0\%$), 58% (48-66) in all-cause readmissions ($p<0.001$, $I^2=87\%$), 68% (54-78) in readmissions due to severe malaria ($p<0.001$, $I^2=93\%$), 62% (44-74) in readmissions due to severe anaemia ($p<0.001$, $I^2=69\%$), 24% (17-31) in non-severe all-cause out-patient visits ($p<0.001$, $I^2=10\%$), and 57% (50-64) in uncomplicated clinical malaria ($p<0.001$, $I^2=71\%$). The reduction was restricted to the intervention period and not sustained in the three months after protective drug levels had waned. In malaria-endemic Africa, PDMC reduces mortality and readmissions in recently discharged children who have recovered from severe anaemia and can be a valuable strategy for management of this high-risk group following discharge from hospital.

0227

METHYLENE BLUE ENHANCES THE *EX VIVO* ANTIMALARIAL BLOOD SCHIZONTOCIDAL ACTIVITY OF TAFENOQUINE IN PLASMA SAMPLES COLLECTED FROM HUMAN VOLUNTEERS

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Resistance of *Plasmodium falciparum* parasites to dihydroartemisinin-piperaquine (DHA-PPQ) has spread throughout the Greater Mekong Sub-Region. To address this threat to malaria control and elimination, new drug combinations, which, ideally, kill asexual blood stage parasites, block transmission, prevent reinfections and provide radical cure by eliminating *P. vivax* hypnozoites are urgently needed. In 2018, a new 8-aminoquinoline drug, tafenoquine (TQ) was approved by the U.S. FDA for chemoprophylaxis and radical cure. Although TQ has a poor blood stage activity, it possesses gametocytocidal and hypnozoitocidal activities. Methylene blue (MB) is an old antimalarial drug with potent blood stage and gametocytocidal activity, and may be a suitable partner drug for TQ. We therefore evaluated the antimalarial activity of TQ in combination with MB. When tested *in vitro* against *P. falciparum* lines, W2 (chloroquine and pyrimethamine-resistant) and VPA02 (a recent isolate from Vietnam, resistant to DHA, PPQ and mefloquine), MB synergised the antimalarial activity of TQ against blood stage parasites using fixed-ratio drug combinations with summary fractional inhibitory concentrations of 0.33±0.09 and 0.42±0.10, respectively. Exposure of parasites to concentrations of 1000 or 4000 nM of TQ alone for 72 h did not inhibit growth of either W2 or VPA02 line, respectively. However, addition of MB (range 1.6 - 800 nM) to fixed TQ concentrations (range 125 to 4000 nM), markedly enhanced TQ activity compared to those of MB or TQ alone. Furthermore, we conducted *ex vivo* assays using plasma samples collected from 11 human volunteers after single oral doses of TQ (200 mg to 600 mg) with TQ concentrations ranging from 233 to 870 nM. While plasma physiological TQ concentrations were not sufficient to fully inhibit parasite growth, addition of MB (≥25 nM) resulted in complete inhibition of W2 and VPA02 parasite growth. These findings demonstrate that addition of MB enhances the activity of TQ against asexual blood stages of *P. falciparum* parasites and provide the impetus for further clinical evaluation of TQ-MB combinations for malaria treatment and elimination.

0228

ANALYSIS OF THE PREVALENCE OF MOLECULAR MARKERS IN *PFCARL* ASSOCIATED WITH RESISTANCE TO GANAPLACIDE (KAF156) IN FIELD SAMPLES FROM AFRICA

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Malaria case management has been one of the major pillars for the disease's control and is strongly dependent on the efficacy of the developed antimalarials. For several years now the highly efficacious artemisinin-based combination therapies (ACTs) have been the first-line treatment for uncomplicated *Plasmodium falciparum* malaria. Recent evidence, though, exhibit an increase in the parasite's resistance towards several artemisinin derivatives and other antimalarial agents, including Artesunate-Mefloquine and Dihydroartemisinin (DHA)-Piperaquine combination therapies. This creates the need for new alternatives for the future of malaria's control and elimination. Currently, a novel therapy including KAF156 (Ganaplacide), an imidazolpiperazine, in combination with a new formulation of Lumefantrine, is being proposed for the replacement of ACTs in the treatment of uncomplicated *P. falciparum* malaria. However, recently, parasite resistance to KAF156 has been developed in vitro, involving point mutations in *pfcarl* (*P. falciparum* cyclic amine resistance locus gene), namely M81I, S1076I/N and I1139K. An important concern is whether these mutations are already naturally present in African parasite populations. In this work we have developed new PCR-RFLP protocols for the identification of these SNPs, and tested in a sizable (n=531) sample of infections from two different geographical locations, Bangamoyo, Tanzania and Bougoula-Hameau, Mali. In the former set of infections we have also preliminarily analysed the hypothesis of lumefantrine driven selection of *pfcarl* SNPs by genotyping the baseline (n=266) and the recurrent infections (n = 37) of an Artemether-Lumefantrine (AL) efficacy trial. We did not find evidence for the presence of any of the aforementioned mutations that have been associated with resistance to KAF156, leading to the conclusion that if present they should be at frequencies significantly below 1%.

0229

THERAPEUTIC EFFICACY OF DIHYDROARTEMISININ PIPERAQUINE COMBINATION IN THE TREATMENT OF UNCOMPLICATED MALARIA IN THREE MALARIA SENTINEL SITES IN GHANA

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In 2020, Dihydroartemisinin-Piperaquine (DHAP) was adopted as a second line antimalarial for uncomplicated malaria in Ghana, following a review of the country's antimalaria medicines policy. Available data obtained in 2007

had shown DHAP therapeutic efficacy of 93.3% using a 28-day follow-up schedule. In 2020, the standard 42-day follow-up schedule for DHAP was used to estimate current efficacy levels in three malaria sentinel sites representing the three main ecological zones of the country- savannah, forest, and coastal. PCR genotyping distinguished between recrudescence and re-infection using merozoite surface protein 2 (MSP2)-specific primers: FC27 and 3D7. Per protocol analysis showed day-28 efficacy of 100% in all three sentinel sites. Day-42 PCR-corrected efficacy ranged between 90.3% (95% CI: 80.1 - 96.4) in the savannah zone to 100% in the forest and coastal zones, yielding a national average of 97.0% (95% CI: 93.4 - 98.8). We conclude that DHAP is highly efficacious in the treatment of uncomplicated malaria in Ghana. This data will serve as baseline for subsequent DHAP efficacy studies in the country.

0230

MONITORING MOLECULAR MARKERS OF *PLASMODIUM FALCIPARUM* DRUG RESISTANCE TO EVALUATE DRUG-BASED MALARIA INTERVENTIONS IN SENEGAL FROM 2000 TO 2020

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Senegal is a malaria-endemic country that has implemented successive antimalarial drug-based strategies for two decades, with intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (SP) since 2003, treatment with artemisinin-based combination therapies including artesunate amodiaquine (AS-AQ) and artemether-lumefantrine (AL) since 2006, and seasonal malaria chemoprevention (SMC) with SP-AQ for children under age 10 since 2014. Drug pressure may select resistant alleles and risk loss of drug efficacy. Annual therapeutic efficacy studies (TES) and surveillance of molecular markers of drug resistance are done to monitor and guide drug interventions. We genotyped drug resistant alleles of *Pfcrt*, *Pfmdr1*, *Pfdhfr*, *Pfdhps*, *Pfk13* from 3,804 samples (collected 2000 – 2020) from febrile patients with malaria at health facilities in Kedougou and Kolda (high transmission; SMC started in 2014); Diourbel and Kaolack (moderate transmission; SMC started in 2019); and Thies and Pikine (low transmission, no SMC). The triple DHFR mutant haplotype (N51I/C59R/S108N) was >80% by 2020 for all sites, regardless of SMC use. In Kedougou, while the DHPS A581G allele was detected once in 2017, the prevalence of the DHPS A437G allele decreased from 86.8% to 48.1% from 2015 to 2020. No PfK13 mutations of concern were detected . PfMDR1 N86Y remains below 25% in all sites, while PfMDR1 Y184F is >50% in all sites. The most common PfMDR1 haplotype is $N_{86}F_{184}D_{1246}$, followed by $N_{86}Y_{184}D_{1246}$ (wildtype). While PfCRT K76T has remained low (< 20%) in Diourbel, Kaolack, and Kolda), it increased from 10% to 35% in Kedougou (2015 to 2020), and in Thies, it increased rapidly after 2014, reaching > 90% in 2020. The unexpected rise of PFCRT K76T in Thies and Kedougou, the increase in the triple DHFR, and decrease in the DHPS A437G mutant under increasing SP-AQ pressure in Kedougou may relate to modulation of resistance or the fitness costs of specific drug resistance alleles. Different drug-based interventions in different transmission contexts modulate increases or decreases in molecular markers of resistance and warrant ongoing surveillance.

0231

PLASMODIUM FALCIPARUM DRUG RESISTANCE MARKER SELECTION AFTER REPEATED DIHYDROARTEMISININ-PIPERAQUINE TREATMENT IN AFRICA: A CASE STUDY FOR THE ANALYSIS OF LONG HALF-LIFE ANTIMALARIALS IN HIGH TRANSMISSION SETTINGS

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In 2020 infections with the parasite *Plasmodium falciparum* accounted most of the 241 million malaria cases, majority of them in the African continent. Dihydroartemisinin-piperaquine (DHA-PPQ) is being incorporated in African national control programs and it has been proposed for mass drug administration strategies. Although PPQ resistance has been already reported in SouthEast Asia, in Africa high-transmission settings the selection of resistance markers remains unclear. We analysed data from 224 patients receiving DHA-PPQ enrolled in a randomized clinical trial performed in southern Mali from 2012 to 2014. The WANECAM project included an active follow-up of 63 days and a distinctive long passive follow-up of two years. In this unique trial, we monitor the spread of molecular markers of resistance in 675 malaria infections by genotyping *pfcrt*, *pfmdr1* along the recurrent episodes and by analysing copy number distribution of *pfmdr1, pfpm2* and *pfpm3* genes in the context of time-to-reinfection.Out of all genotyped Single Nucleotide Polymorphisms (SNPs), *pfcrt* 76T and 356T were associated with significantly decreased times to re-infection compared with the wildtype infections [means (days) wildtype *versus* mutant: 155.2 *vs* 109, $P<0.001$; 138.6 *vs* 113.8, $P<0.05$, respectively]. In addition, *pfpm2* multicopy infections, not present in the baseline but being selected in surprisingly early recurrent infections. Furthermore, there is a significant increased tendency in *pfpm3* copy number variation along the trial. All SNPs under analysis were associated with less than 100 days recurrent infections, suggesting this period as the window of selection for the mutations.The unique longer follow-up of the trial allowed to capture some potentially resistance parasite populations being selected in the background, under the partner drug prolonged pressure. Thereby, new approaches need to be followed when analysing long half-life partner drugs aiming to captured resistance parasites selection early on time, especially in the context large-scale preventive interventions.

0232

DNA CONTAMINATION DURING EXTRACTION OF DRIED BLOOD SPOTS FROM WHATMAN FILTER PAPER

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Dried blood spots (DBS) on filter paper (confetti) are one of the most common methods used to collect and extract DNA from field samples for molecular epidemiology of malaria studies. This DNA extraction step may be challenging, particularly in resource limited regions where scissors are used to cut the filter papers with the possibility of introducing contamination between samples due to poor scissor cleaning. Many methods use 70% ethanol to clean the scissors. However, there is limited evidence that ethanol or other solutions used to clean the scissors optimally reduce sample contamination. This work aimed to provide such evidence. DBS were prepared from 3 drops of blood from two *Plasmodium falciparum* cultures (20-0119-0 and 20-2091-0 isolates) spotted on filter paper. All samples were dried for 24 hours at room temperature. We examined three solutions (Water, Ethanol and DNase) to clean scissors between spots during the DNA extraction. For each cleaning solution, two blank confettis were used as negative controls. DBS were cut into small pieces with scissors and transferred into 1.5-mL

microtubes. Parasite DNA was extracted using QIAamp kit and eluted in water. Parasite-infected and negative control samples were analyzed by PCR-based genotyping of the merozoite surface proteins 1 & 2 (*msp-1* and *msp*-2), and the *P. falciparum* chloroquine resistance transporter *(Pfcrt)* genes. A total of 15 samples were analyzed. Based on *msp*1 and *msp*2 amplification (3 for each cleaning solution, n=9), *P. falciparum* was detected on the blank confetti when scissors were washed with Ethanol. Based on *Pfcrt* amplification (2 for each cleaning solution, n=6), DNA of *P. falciparum* was detected on the blank confetti when scissors were cleaned with Ethanol and Water. We did not detect any DNA of any genes on the negative control confettis when the scissors were cleaned with DNase. In conclusion, scissors cleaned with DNase prevented cross-contamination between samples during processing of dried blood spots. Ethanol cleaning of scissors, which is commonly used, fails to completely avert cross-contamination.

0233

CHARACTERIZATION OF GENES IN *PLASMODIUM FALCIPARUM* MUTANTS ASSOCIATED WITH ALTERED SENSITIVITY TO ARTEMISININ

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Artemisinin combination therapies have led to a significant decrease in *Plasmodium falciparum* malaria mortality, but emerging artemisinin resistance (ART-R) that has reached Sub-Saharan Africa threatens to reverse these gains. ART-R that originated in SE Asia was first linked to polymorphisms in the Kelch propeller protein (K13) and now appears fixed in parasites of this region. Subsequently, several other seemingly unrelated genetic mutations are being linked to altered ART sensitivity. In earlier studies, we identified *P. falciparum* mutants created by *piggyBac* mutagenesis with increased sensitivity to ART, including a mutant of K13 with a single transposon integrated near the putative transcription start site. In this study, we characterize a similar ART-sensitive mutant in a gene defined as a "*Plasmodium*-conserved gene of unknown function", now functionally linked to K13 as the Kelch13 Interacting Candidate 5 protein (KIC5). RNAseq analysis of the KIC5 mutant during intraerythrocytic asexual development identified transcriptional changes associated with DNA stress response and altered mitochondrial metabolism, linking dysregulation of the KIC5 gene to the parasite's ability to respond to ART exposure. Through characterization of the KIC5 transcriptome, we hypothesize that this gene may be essential under ART exposure to manage gene expression of the wild-type stress response at early ring stage, thereby providing a better understanding of the parasite's processes that can alter ART sensitivity and resistance.

0234

EVALUATE THE ROLE OF CYTOKINES AND CHEMOKINES IN THE DEVELOPMENT OF COMPLICATIONS IN MALARIA CAUSED BY *PLASMODIUM VIVAX*

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Plasmodium vivax can cause complicated manifestations, the mechanisms that lead to this situation are not entirely clear. The presence of parasite and parasite-derived components triggers the inflammatory response, which is characterized by the production of pro- and anti-inflammatory molecules. These molecules may be responsible for the damage observed in different affected organs in complicated malaria. Evaluate the role of cytokines and chemokines in the development of complications in malaria caused by. Thirteen cytokines and chemokines were quantified in 106 people with malaria (severe and not severe) and 50 controls, with bead-based multiplex assay. The study variables were analyzed by non-parametric tests were carried with Prima and R statistical software. Fitting models with interaction to study the complication probability, using Lasso Regression with readjustment of Gamlss models of binomial family. IL-10, IL-6 and IFNg had higher concentration in the severe malaria group (<0.0001) and lower concentration of TGF-b (<0.0001), compared with non-severe malaria group and control group. IL-10, IL-6, IFNg showed a negative correlation with platelet count in severe malaria, IL-6 and IFNg specifically with severe thrombocytopenia; and a positive correlation between IFNg and transaminases, and IL-2 and creatinine. Lasso regression model suggests that IL-4, IL-10, CCL2 and TGF-β might be developed as prognostic for severity in *P. vivax* malaria. The inflammatory response during *P. vivax* infection can mediate the development of hematological, renal, and hepatic complications. TGF-b to protect against the development of complicated forms of *P. vivax* malaria.

0235

K13-ASSOCIATED ENDOCYTIC STRUCTURES IN *TOXOPLASMA* ARE REQUIRED FOR PLASMA MEMBRANE HOMEOSTASIS RATHER THAN PARASITE GROWTH

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Toxoplasma gondii is an obligate intracellular parasite that belongs to the phylum Apicomplexa. These parasites include both *Plasmodium*, responsible for malaria, and *Toxoplasma,* responsible for toxoplasmosis, which has a mortality rate that has significantly increased in the past years in low and lower-middle-income countries. There has been increasingly widespread resistance to the frontline antimalarial, artemisinin, and the protein K13 has attracted much attention in *Plasmodium* research because it is associated with both artemisinin-resistance and the endocytic process by which the parasite feeds on red blood cells through the cytostome. We identified that K13 in *Toxoplasma* also which raised the questions: Is a cytostome-equivalent structure present in *Toxoplasma*, and is endocytosis required for this parasite's growth in *Toxoplasma*? We found that K13 co-locates with other endocytosis-related proteins (DrpC, EPS15, and AP2) as well as others not previously implicated in endocytosis but also associated with artemisinin-resistance (e.g., UBP1). This putative endocytic structure is present at the parasite's inner membrane complex (IMC) in both mother and forming daughter cells, indicating that it is formed early in the development of the IMC even before contact with the plasma membrane during daughter parasite maturation. Live-cell imaging shows that this structure and its constituent proteins are stable features of the IMC. Depleting most of these proteins results in strong growth phenotypes, manifesting as extra-parasitic cytosolic extensions within the parasitophorous vacuole, swollen parasites, and a failure of the ordered rosette organization of the vacuole. However, the replication rate was not significantly affected with K13 protein depletion. Our results show that while endocytosis is essential for *Toxoplasma's* intracellular survival, unlike in *Plasmodium*, its more significant role might be plasma membrane homeostasis rather than parasite nutrition. Further understanding of this endocytic structure and its contribution to endocytosis will bring insights into a novel mechanism to tackle toxoplasmosis.

0236

MODELS OF MALARIA-INDUCED ACUTE KIDNEY INJURY

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In 2020, there were an estimated 241 million cases of malaria and 627,000 deaths, of which most are in children. Until the most recent decade, the impact of malaria-induced acute kidney injury (MAKI), one of the complications of severe malaria (SM), was severely underestimated and research in this area has been neglected. However, it has been reported that 40-60% of SM patients present with MAKI and it is in fact, the strongest predictor of death in children with SM. Almost half of these cases result in renal failure and MAKI has been associated with chronic kidney disease and other long term complications. There are currently no specific therapies to treat this complication, as the molecular pathways implicated in this pathology remain unknown, and there are no suitable rodent models that replicate the condition in humans. The purpose of this study is to develop an *in vivo* model that resembles the pathology in MAKI patients, specifically exhibiting signs of acute tubular necrosis (ATN), the hallmark of MAKI. In this study, unilateral nephrectomies were performed on wild type mice prior to infection with *Plasmodium berghei NK65*, a rodent-infecting *Plasmodium* species. The removal of one kidney and subsequent infection has resulted in development of kidney injury in mice within 14 days, evident by elevated levels of acute kidney injury (AKI) biomarkers including urinary neutrophil gelatinase-associated lipocalin (NGAL), serum cystatin C, serum lactate dehydrogenase (LDH), and serum potassium ion concentrations. Expression of AKI-associated proteins kidney injury molecule 1 (KIM-1), caspase-3, matrix metalloproteinase-9 (MMP-9), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), and retinol-binding protein-4 (RBP4) was also increased in renal tissue. Establishment of this *in vivo* model of MAKI is critical to the scientific community as it can be used to elucidate the molecular pathways implicated in MAKI, delineate the development of the disease, identify biomarkers for early diagnosis and prognosis, and test potential adjunctive therapies.

0237

IMPACT OF *PLASMEPSIN II* COPY NUMBER ON THE FITNESS OF PIPERAQUINE-RESISTANT PFCRT MUTANT *PLASMODIUM FALCIPARUM* IN CAMBODIA

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Plasmodium falciparum resistance to piperaquine was reported in Cambodia within two years of the 2010 country-wide switch to dihydroartemisinin-piperaquine as the first line therapy. Initial genotype-phenotype association studies identified amplified *plasmepsin II* (*pfpm2*) gene copy number as a potential molecular marker of piperaquine resistance. Subsequent genome-wide studies identified associations between mutations within the *P. falciparum* chloroquine resistance transporter (*pfcrt*) gene and parasite piperaquine susceptibility. Gene-editing studies indicated that these PfCRT mutations could confer piperaquine resistance in the absence of amplified *pfpm2,* but often at a fitness cost, and hypothesized that amplified *pfpm2* may have a compensatory effect in piperaquine-resistant PfCRT mutant parasites. To test this hypothesis, we compared the fitness of Cambodian field isolates harboring piperaquine-resistance-conferring PfCRT mutations (i.e., F145I, G353V, H97Y, or I218F) with different *pfpm2* copy number (i.e., 1, 2, or >2 copies). Cryopreserved *P. falciparum* isolates collected from patients in Cambodia were culture adapted and their growth rates compared to an eGFP+ Dd2 line using flow cytometry, with assays performed in triplicate. We observed that the Dd2 line outcompeted all the PfCRT mutant strains, regardless of *pfpm2* copy number; however, some strains were outcompeted more rapidly than others. In particular, PfCRT mutant parasites with *pfpm2* copy number >2 were more rapidly outcompeted compared to parasites with 2 *pfpm2* copies, particularly in parasites harboring the G353V and I218F mutations, which have been shown to confer a lesser fitness cost to the parasite in isogenic lines. Although the genetic background of these field isolates may differ, our analysis suggests that, in the absence of drug, *pfpm2* copy number >2 imposes a significant fitness cost to the parasite, as opposed to a compensatory effect, potentially explaining the rapid decrease in high *pfpm2* copy number parasites with the removal of piperaquine pressure.

0238

CHARACTERISATION OF *PLASMODIUM YOELII* 17XL INFECTED MICE AS A TRANSLATIONALLY RELEVANT MODEL OF MALARIA INDUCED ENDOTHELIAL GLYCOCALYX DEGRADATION

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The endothelial glycocalyx is a mesh-like structure of glycoproteins and proteoglycans which covers the luminal surface of vascular endothelial cells and plays crucial roles in maintaining the function and integrity of the vascular endothelium. In malaria, multiple pathological processes converge on the vascular endothelium, including inflammatory activation, oxidative damage, activation of coagulation pathways, and sequestration of parasite infected red cells. Recent evidence indicates that glycocalyx degradation occurs in human malaria and the extent of glycocalyx degradation is associated with severity of disease. Thus, preserving and restoring the endothelial glycocalyx may be promising therapeutic approaches. We have recently used comparative transcriptomics to identify *Plasmodium yoelii* 17XL (Py17XL) infection in C57BL/6 mice as a translationally relevant model for the most severe manifestations of *P. falciparum* malaria in children. Here we show that endothelial glycocalyx degradation in Py17XL infection, indicated by plasma levels of syndecan-1, exceeds that in other commonly used mouse models (*Plasmodium yoelii* 17XNL, *Plasmodium berghei* ANKA). This was corroborated by extensive loss of glycocalyx immunofluorescence staining on the surface of vascular endothelial cells in tissue sections. Artesunate treatment of Py17XL infected mice attenuated glycocalyx degradation, suggesting that it is being driven by a process related to parasite load. Glycocalyx degradation in Py17XL was positively correlated with malaria severity markers of parasitemia and lactate and negatively correlated with haematocrit, consistent with human studies. Glycocalyx degradation was also accompanied by pathological changes in multiple organs including brain, lung, liver and kidneys. These findings suggest that the Py17XL mouse model is promising for translational studies of the mechanisms of glycocalyx degradation and potential adjunctive treatments to preserve or restore the glycocalyx layer.

0239

AN UNKNOWN TRANSMISSION BOTTLENECK FOR MALARIA? QUANTIFYING SPOROZOITE EXPELLING IN RELATION TO OOCYST LOADS IN MOSQUITOES INFECTED BY CULTURED GAMETOCYTES AND NATURAL GAMETOCYTE CARRIERS

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It is currently unknown whether all *Plasmodium falciparum* infected mosquitoes are equally infectious. We assessed sporogonic development using cultured gametocytes and natural infections in Burkina Faso and Uganda. We quantified the number of sporozoites expelled into artificial skin in relation to intact oocysts, ruptured oocysts, and (residual) salivary gland sporozoites. Sporozoites were quantified by highly sensitive qPCR; intact and ruptured oocysts by fluorescence microscopy following anti-circumsporozoite antibody staining. Overall, 62% (45/72) of *P. falciparum* N54 and 60.7% (34/56) of N135-infected *Anopheles stephensi* mosquitoes expelled sporozoites. The geometric means of expelled and residual salivary gland sporozoites were 184 (IQR 45.7-659) and 31,779 (IQR 15,740-99,790), respectively. There was a strong correlation between ruptured oocyst number and salivary gland sporozoite load (ρ=0.74; p<0.001), but no statistically significant correlation between salivary gland sporozoite load and the number of sporozoites ejected. In Burkina Faso we performed 56 membrane feedings with *Anopheles coluzzii* mosquitoes on natural gametocyte carriers. We found that among those mosquitoes that were salivary gland sporozoite positive, 97.2% (36/37) ejected sporozoites with a geometric mean of 420 sporozoites ejected (IQR 116-2779) and 35,149 of residual sporozoites (IQR 20,310-164,900). Experiments in Uganda with *Anopheles gambiae* mosquitoes yielded similar results. Although some mosquitoes carried high numbers of sporozoites in their salivary glands, a minority were expelled and the size of the sporozoite inoculum was highly heterogenous. We observed no clear threshold sporozoite density necessary for successful expelling suggesting that all *P. falciparum* infected mosquitoes are potentially infectious mosquitoes.

0240

CLOSING THE GAPS - DELAYED TREATMENT OF MALARIAL-FEVER IN CHILDREN UNDER 5 YEARS

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Infants and children under 5 years old remain at great risk of malaria and also bear over 80% of all malaria deaths. Based on malaria morbidity and mortality estimates, over half a million children died from malaria in 2020 alone. Malaria case management, particularly early diagnosis and prompt, effective treatment, remains a priority and vital component of malaria control and elimination strategies. Early diagnosis and treatment of malaria reduce disease, prevent deaths, and reduce transmission. Delaying effective treatment with antimalarials can cause infections to progress to severe illness and death, especially for *Plasmodium falciparum*. While WHO recommends that all suspected malaria cases be confirmed using parasite-based early diagnostic testing and receive effective treatment prompt (within 24-48hrs from the onset of malaria symptoms), no recent studies provide the current global state of prompt treatment. This study assessed the global malaria treatment delay across 110 malaria endemic countries utilizing data from demographic health surveys and malaria indicator surveys (DHS/MIS) between 2005 and 2021 on the "time to receipt of the 1st antimalarial". Results revealed that huge progress had been made both in and outside sub-Saharan Africa (SSA) during the study period. Prompt treatment was generally higher outside SSA. Nonetheless, the study detected country and region-specific disparities in treatment timings with 23.4% (global), 21% (outside), and 27.2% (within SSA) of children with fever delayed in receiving treatment, respectively. The WHO AFRO region had the highest treatment delay (27.2%) than SEARO with the lowest (17%). During the same period, country delays ranged between 5% (Maldives) to nearly 70% for Haiti. These findings imply that over 130 000 deaths among children may arise from potential treatment delays. With the much-desired acceleration of the malaria elimination agenda and meeting the GTS goal of reducing malaria mortality rates by ≥90% by 2030, the lenses of malaria control efforts should not ignore early diagnosis and prompt treatment to avoid preventable deaths and to decrease the risk of onward transmission.

0241

PLASMODIUM FALCIPARUM DDI1 IS AN ESSENTIAL RETROVIRAL ASPARTYL PROTEASE WHICH REPAIRS ARTEMISININ DAMAGES IN THE MALARIA PARASITE

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The human malaria parasite, *Plasmodium falciparum*, has a complex stage-specific biology in a wide spectrum of human host and mosquito vector environments. This diversity requires swift transformation mechanisms to maintain cellular and proteome homeostasis. To maintain the homeostasis, the parasite utilizes the ubiquitin-proteasome system (UPS) to degrade and recycle the proteins. Most of the UPS components have informed development of many clinical inhibitors, especially in the treatment of different types of cancer. It is feasible, therefore, to speculate that the human malaria parasite UPS presents great opportunities for development of rational antimalarial drugs. Here, we identified and characterized the proteasome shuttle proteins; *Pf*Ddi1, *Pf*Rad23 and *Pf*Dsk2 as potential targets for known and novel antimalarial drugs. Using *in silico* analysis, we showed that while the three proteins belong to the ubiquitin like (UBL)–ubiquitin associated (UBA) domain family, *Pf*Ddi1 has an additional domain with a typical D[S/T]G aspartyl triad signature. Our enzyme activity assays demonstrated that *Pf*Ddi1 is an active retroviral aspartyl (A2) protease that hydrolyzes polyubiquitin and retropepsin substrates, an activity that is blocked by artemisinin, the mainstay antimalaria drug. In addition, immunofluorescence assays (IFA) showed that while the *Pf*Ddi1 localizes predominantly in the parasite cytoplasm, *Pf*Rad23 and *Pf*Dsk2 oscilates between the nucleus and cytoplasm. Our TUNEL assays and Western blot analyses demonstrated that artemisinin leads to DNA fragmentation and increased polyubiquitination in the parasite, which enhances the recruitment of *Pf*Ddi1 into the nucleus. On the other hand, functional complementation studies in *Sacharomyces cerevisiae* cells demosntrated that the *Pf*Ddi1, *Pf*Rad23 and *Pf*Dsk2 proteins are functional homologs of the yeast proteins, and Ddi1-deficient yeast cells have increased excretion of proteins to the media, and are more susceptible to artemisinin pressure.

0242

BRAIN ALTERATIONS IN ADULT NONCEREBRAL FALCIPARUM MALARIA

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Cerebral malaria in adults is associated with brain hypoxic changes on magnetic resonance (MR) images and has a high fatality rate. Findings of neuroimaging studies suggest that brain involvement also occurs in patients with uncomplicated malaria (UM) or severe noncerebral malaria (SNCM) without coma, but such features were never rigorously characterized. UM and SNCM patients underwent MR imaging on admission and up to 72 hours later, as well as plasma analysis. Apparent diffusion coefficient (ADC) maps were generated, with values from 5 healthy individuals serving as controls. Patients with SNCM had a wide spectrum of cerebral ADC values, including both decreased and increased values compared with controls. Patients with low ADC values, indicating cytotoxic edema, showed hypoxic patterns similar to cerebral malaria despite the absence of deep coma. Conversely, high ADC values, indicative of mild vasogenic edema, were observed in both patients with SNCM and patients with UM. Brain involvement was confirmed by elevated circulating levels of S100B. Creatinine was negatively correlated with ADC in SNCM, suggesting an association between acute kidney injury and cytotoxic brain changes. Brain involvement is common in adults with SNCM and a subgroup of hospitalized patients with UM, which warrants closer neurological follow-up. Increased creatinine in SNCM may render the brain more susceptible to cytotoxic edema.

0243

DETERMINANTS OF BRAIN SWELLING IN PEDIATRIC AND ADULT CEREBRAL MALARIA: A CROSS-SITE COMPARISON BETWEEN INDIA AND MALAWI

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Cerebral malaria (CM) is a common presentation of severe *Plasmodium falciparum* infection and remains an important cause of death in the tropics. Key aspects of its pathogenesis are still incompletely understood, but severe brain swelling identified by magnetic resonance imaging (MRI) was associated with a fatal outcome in African children. In contrast, our MRI findings in Indian patients suggest distinct pathogenic patterns between pediatric and adult CM, with a stronger cytotoxic component in the latter groups. Using MRI and blood profiling databases, we investigated features associated with brain swelling in our cohort of pediatric and adult patients with CM in Rourkela, India, and compared them with an African pediatric CM cohort in Malawi. We determined that higher plasma *Plasmodium falciparum* histidine-rich protein 2 levels and elevated var transcripts that encode for binding to endothelial protein C receptor (EPCR) were linked to CM at both sites. Machine learning models trained on the African pediatric cohort could classify brain swelling in Indian children CM cases but showed a weaker performance for adult classification, due to overall lower parasite var transcript levels in this age group and more severe thrombocytopenia in Rourkela adults. Overall, these findings provide evidence that higher parasite biomass and a subset of Group A-EPCR binding variants are common features in children and adult CM cases, despite age-related differences in their degree of brain swelling.

0244

BREADTH AND ABUNDANCE OF *PLASMODIUM FALCIPARUM* RIFIN AND STEVOR EXPRESSION IS ASSOCIATED WITH CEREBRAL MALARIA IN MALIAN CHILDREN

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The *Plasmodium falciparum* RIFIN and STEVOR variant surface antigen families are displayed on the surface of infected erythrocytes, where they mediate adhesion to nearby uninfected erythrocytes, cellular invasion, and inactivation of immune cells. While these *in vitro* findings suggest a role in severe malaria pathogenesis, little is known about RIFIN and STEVOR expression in clinical malaria episodes. We hypothesized that severe infections have greater breadth and abundance of RIFIN and STEVOR expression compared to uncomplicated infections, defining breadth as the number of unique variants expressed in an infection. Using Illumina short-read RNA-sequencing, we measured RIFIN and STEVOR expression in blood samples from Malian children with three clinical malaria phenotypes, including 14 cases of cerebral malaria (CM), 10 cases of severe malarial anemia (SMA), and 24 uncomplicated malaria (UM) controls matched to cases on age, sex, ethnicity, and residence. We used a custom bioinformatics pipeline to assemble *de novo* RIFIN and STEVOR transcripts. We also aligned sequence reads to the 3D7 reference genome for differential expression analysis of thirteen "strain-transcendent" RIFINs and STEVORs that are uniquely conserved across *P. falciparum* strains. Within each sample, the breadth ($p<0.001$) and abundance ($p<0.001$) of RIFIN transcripts were significantly higher than that of STEVOR transcripts. CM cases expressed more unique RIFIN ($p=0.009$) and STEVOR ($p=0.01$) variants and had higher RIFIN ($p=0.001$) and STEVOR ($p=0.01$) expression abundance compared to UM infections. SMA cases did not differ from UM controls in terms of RIFIN or STEVOR expression levels. A subset of strain-transcendent RIFINs and STEVORs was significantly upregulated in severe infections, although none were differentially expressed in CM or SMA alone. These findings suggest that RIFINs and STEVORs may be important for CM pathophysiology and that certain conserved targets are promising candidates for vaccine development. Further study is needed to determine whether these antigens induce immune protection against severe disease.

0245

ACCURACY OF DIAGNOSIS AMONG CLINICAL MALARIA PATIENTS: COMPARING MICROSCOPY, RDT, AND A HIGHLY SENSITIVE QUANTITATIVE PCR AND THE IMPLICATIONS OF SUB-MICROSCOPIC INFECTIONS

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The World Health Organization recommends parasitological confirmation of all suspected malaria cases by microscopy or rapid diagnostic tests (RDTs) before treatment. These conventional tools are widely used for point-of-care diagnosis in spite of their poor sensitivity at low parasite density. Several studies have compared the diagnostic accuracy of microscopy and RDT using standard 18S rRNA PCR as reference with varying outcomes. Here, we present for the first time in Ghana, the accuracy of diagnosis of microscopy and RDT using highly sensitive *var*ATS qPCR as reference in a clinical setting. 1,040 febrile patients were recruited from two primary healthcare centers in the Ashanti Region of Ghana and tested for malaria by microscopy, RDT, and *var*ATS qPCR. The sensitivity, specificity, and predictive values were assessed using *var*ATS qPCR as gold standard. Kappa (κ) values were calculated to determine the level of agreement between the tests. Parasite prevalence was 17.5%, 24.5%, and 42.1% by microscopy, RDT, and *var*ATS qPCR respectively. Using qPCR as the standard, RDT was more sensitive (55.7% vs 39.3%), marginally less specific (98.2% vs 98.3%), and had higher positive (95.7% vs 94.5%) and negative predictive values (75.3% vs 69.0%) than microscopy. RDT showed better diagnostic agreement (κ=0.571) with *var*ATS qPCR than microscopy (κ=0.409). Parasite prevalence and density was significantly higher ($p<0.0001$) among the 5-14 age group than the <5, 15-30, and >30 age groups across all the tests. RDT outperformed microscopy for the diagnosis of *Plasmodium falciparum* malaria in the study area. However, both diagnostic methods missed over 40% of clinical cases that were detected by *var*ATS qPCR. Novel tools are needed to ensure prompt diagnosis of all clinical malaria cases.

0246

MOLECULAR CHARACTERIZATION OF RESIDUAL PARASITAEMIA ON DAYS-3 AND 14 AFTER ARTEMETHER-LUMEFANTRINE OR PYRONARIDINE-ARTESUNATE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN NIGERIA

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Microscopic evaluation of parasite clearance is widely utilised as the gold standard in antimalarial drug efficacy trials. However, sub-microscopic residual parasitaemia after artemisinin-based combination therapy (ACT) may signal reduced parasite responsiveness. PCR-determined residual parasitaemia was evaluated on days 3 and 14 post-treatment with artemether-lumefantrine (AL) or pyronaridine-artesunate (PA) in children aged 3 -144 months. One hundred and twenty (AL: n = 60, PA: n = 60) days 3 and 14 dried blood spots, negative by microscopy, were analysed for residual parasitaemia of *falciparum* species using nested PCR. The allelic similarity of parasite clones of the residual parasitaemia on days 3 and 14 were determined with the corresponding day-0 isolates using merozoite surface proteins1 (*msp1*) (K1, RO33, MAD20) and *msp2* (3D7, FC27) families and glutamate-rich protein (*glurp*). The enrollees' mean age (month) was 80 ± 38 and 81 ± 40 for AL and PA, respectively. In all, 45% (AL) and 35% (PA) of enrollees were febrile (≥ 39°C) at baseline. The geometric mean parasite densities were 28,380 (95% CI: 18,625-41,481) and 25,411 (95% CI: 16,949-38,836) for AL and PA. Parasite and fever clearance times were optimal for both treatment arms. However, persistent PCR-determined sub-microscopic residual parasitaemia at day three post ACT treatment was 83 and 88% for AL and PA, while 64% and 36% were parasitaemic on day 14 for AL and PA respectively. Microscopy-confirmed gametocytaemia persisted from days 0 -7 and 0 -21 for AL and PA. When the alleles of day three versus day 0 were compared according to base pairs sizes, 59% of the parasites shared identical alleles for *glurp*, 36% for 3D7 and FC27, while K1 was 77%, RO33 64% and MAD20 23%. Similarly, Day 14 versus day 0 was 36% (*glurp*), 64% (3D7), 32% (FC27), 73% (K1), 77% (RO33) and 41% (MAD20) respectively. PCR-determined sub-microscopic residual parasitaemia on days 3 and 14 following AL or PA treatment was detected with identical parasite clones, which may compromise ACTs efficacy. Further studies are needed to characterize the viability status of these PCR-confirmed residual parasites.

0247

IMPLEMENTATION OF COMMUNITY CASE MANAGEMENT OF MALARIA IN MALARIA ENDEMIC COUNTIES OF WESTERN KENYA, ARE COMMUNITY HEALTH VOLUNTEERS UP TO THE TASK IN DIAGNOSING MALARIA

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Community case management of malaria (CCMm) is an equity-focused strategy that complements and extends the reach of health services by providing timely and effective management of malaria to populations with limited access to facility-based healthcare. In Kenya, CCMm involves use of malaria rapid diagnostic tests (RDT) and treatment of confirmed uncomplicated malaria cases with artemether lumefantrine (AL) by community health volunteers (CHVs). Test positivity rate (TPR) from CCMm reports collected by Ministry of Health in 2018 was twofold compared to facility-based reports for the same period. This necessitated the need to evaluate the performance of CHVs in conducting malaria RDTs. The study was conducted in four counties within the malaria endemic lake zone in Kenya with a malaria prevalence in 2018 of 27%; the national prevalence of malaria was 8%. Multi-stage cluster sampling and random selection were used. Results from 200 malaria RDTs performed by CHVs were compared with test results obtained by experienced medical laboratory technicians (MLT) performing the same test under the same conditions. Blood slides prepared by the MLTs were examined microscopically later as a backup check of the results. A kappa score was calculated to assess level of agreement. Sensitivity, specificity, positive and negative predictive values were calculated to determine diagnostic accuracy. The median age of CHVs was 46 (IQR: 38, 52) with a range [26, 73] years. Females were 72% of the CHVs. Test positivity rates for MLTs was 42% and for CHVs was 41%. The kappa score was 0.89 indicating an almost perfect agreement in mRDT results between CHVs and MLTs. The overall sensitivity and specificity between the CHVs and MLTs were 95.0% (95% CI: (87.7, 98.6) and 94.0% (95% CI; 88.0, 97.5) respectively. Engaging CHVs to diagnose malaria cases under CCMm yielded results which compared well with the results of qualified experienced laboratory personnel. CHVs can reliably continue to offer malaria diagnosis in the community setting. The reported TPR difference between CHV and facility-based testing needs to be explored.

0248

REVISITING A NEGLECTED SYMPTOM: CLINICAL EXPERIENCE USING THE HYFE COUGH TRACKER IN MALARIA PATIENTS

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Malaria remains the most important human parasitic disease causing over 240 million cases and 600.000 deaths in 2020. Acute respiratory distress can be present in up to 40% of children with severe malaria and up to 50% of patients have a cough of new onset. In spite of these notable respiratory features, the diagnosis of malaria remains blood-based which fundamentally restricts diagnosis to individual interactions with a health care worker. The usage of devices that can monitor and analyze coughs with artificial intelligence software is an entirely new, low-cost, non-invasive tool. This can be leveraged for malaria screening and differential diagnosis with bacterial pneumonia and other key respiratory conditions possibly improving the use of antimicrobials in settings with limited resources. To assess the presence of cough as one of the symptoms of malaria, we used a smartphone-based App (Hyfe cough tracker) in our clinical practice in the community health center of Mopeia, Mozambique. We attended clinically 63 children (1months - 11 years) who consulted for malaria (33) or any respiratory symptoms (30). As part of the clinical examination, the children were monitored for 30 minutes with a smartphone running Hyfe placed in a shoulder pouch. Overall, 63% of children had at least one episode of cough, this was similar in both groups. Patients with a positive malaria test had a median of 4 episodes/30min and those consulting with respiratory complaints had a median of 2. Malaria patients had an almost two-fold probability to experience more than 10 episodes of cough/30min than patients with other respiratory diseases. These results stress the importance of respiratory symptoms in malaria patients and open the door to better quantify cough as a biomarker for this disease.

0249

MALARIA DIAGNOSIS IN SALIVA BY DROPLET DIGITAL PCR (DDPCR) TARGETING NON-RIBOSOMAL MULTICOPY TARGETS

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Accurate diagnosis of malaria is fundamental for the adequate treatment of patients, prevention of mortality and disease control. Light microscopy is the gold standard for diagnosis; however its low limit of dectection may lead to a misdiagnosis of mixed infections and loss of low-density infections of *Plasmodium*. By using multicopy targets and highly sensitive molecular techniques, it is possible to change this scenario. This study evaluated the performance of droplet digital PCR (ddPCR) to detect non-ribosomal multicopy targets of *P. vivax* (Pvr47) and *P. falciparum* (Pfr364) in saliva samples. A total of 471 samples of blood, whole saliva and buccal swab (157 samples of each) were collected of individuals from the Brazilian Amazon region between 2017 and 2020. The sensitivity of qPCR in saliva was 77%; however, it was only 47% in buccal swab. Parasite DNA was not detected in saliva samples in low-density infections (<1500 parasites/µL) compared with the detection in blood samples. ddPCR showed increased sensitivity for detecting *Plasmodium* in the blood and swabs (99% in blood, 73% in saliva, and 59% in swabs). Noticeably, ddPCR detected a higher proportion of mixed infections in the blood (15%), saliva (9%) and swabs (18%) than qPCR. Our data showed that the differences between ddPCR and qPCR were the result of a higher number of *P. falciparum* infections detected by ddPCR. There was a moderate correlation between parasite densities estimated by the different methods in blood. Whereas a significant correlation was observed for all analysis performed for *P. vivax*, only density estimates obtained by qPCR and LM correlate to each other for *P. falciparum*. Our findings highlight the possibility of using non-invasive sample collection methods for malaria diagnosis by targeting multicopy sequences combined with highly sensitive molecular methods.

0250

PERFORMANCE AND USABILITY EVALUATION OF POINT-OF-CARE TESTS FOR GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY IN MAE SOT, THAILAND

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Radical cure of *Plasmodium vivax* malaria requires elimination of liver-stage parasites through treatment with 8-aminoquinolines. However, individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency—a commonly inherited enzyme disorder—are at increased risk of hemolysis following exposure to these drugs. Point-of-care (POC) diagnostics for G6PD deficiency are critical to expand access to safe treatment options for *P. vivax*. Several POC G6PD diagnostics have been developed, and data on test performance and usability are needed to inform further product development and facilitate uptake. Between November 2021 and March 2022, a study was conducted in Mae Sot, Thailand, to evaluate the performance and usability of three POC G6PD tests: two versions of a quantitative biosensor test and one qualitative rapid test. Healthy adults were recruited for the diagnostic accuracy study at clinics and through an enriched sample of participants with known G6PD status. Venous blood was collected and transferred to the central hematology laboratory where G6PD and hemoglobin measurements were obtained from the index tests, Fluorescent Spot Test, HemoCue® 301+, and a quantitative G6PD spectrophotometric reference assay. Index tests were run in duplicate in temperature-controlled and uncontrolled settings. To assess usability, intended users of POC G6PD tests were trained on test procedures and surveyed on key product features. Three-hundred participants were enrolled in the diagnostic accuracy study, including 35 G6PD deficient males and females (11.7%), 20 G6PD intermediate females (6.7%), and 245 G6PD normal males and females (81.7%). Diagnostic performance of the index tests in terms of sensitivity and specificity for G6PD deficients and intermediates will be reported. 15 health care workers participated in the usability assessment. Scores from the assessments, alongside qualitative user perceptions and experiences with the tests will also be presented. These data provide insights into key performance and usability considerations to inform product development of POC diagnostics for G6PD and expand access to radical cure.

0251

GENETIC DIVERSITY OF HISTIDINE-RICH PROTEIN 2 AND 3 GENES IN *PLASMODIUM FALCIPARUM* POPULATIONS IN GHANA AND ITS IMPLICATIONS FOR THE USE RAPID DIAGNOSTIC TESTS FOR MALARIA INFECTIONS

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Plasmodium falciparum histidine-rich protein 2 (*Pfhrp2)* based rapid diagnostic tests (RDTs) are extensively used to diagnose malaria worldwide. RDTs targeting *Pfhrp2* antigen cross react with *Pfhrp3* because they share structural similarities and this complements the detection of the parasites. However, the use of the test is being compromised by reports indicating the occurrence of deletions of the *Pfhrp2* and *Pfhrp3* genes in some parasites and the consequent false negative test results. We therefore, sought to detect reported deletions and genetic diversity of *Pfhrp2* and *Pfhrp3* genes (exon 2) using the parasite isolates from children ≤9 years with uncomplicated malaria from 10 sentinel sites during 2016 to 2020 transmission seasons. Both genes were amplified using nested PCR and repeated runs with no amplification indicated the presence of the deletion in the genes. Successfully amplified genes were sequenced using the Sanger method. Deletions were observed in 32.6% (569/1745) and 21.2% (402/1894) of the samples for *Pfhrp2* and *Pfhrp3* genes respectively. Sequencing was done for 1152 *Pfhrp2* and 1248 *Pfhrp3* amplicons however analysis was done with 824 and 901 good sequences. *Pfhrp2* repeat polymorphisms were dominantly of types 2 (AHHAHHAAD) and 7 (AHHAAD). Variant repeat polymorphisms were also observed in types 1, 2, 3, 7, 10, 12, 13, however 2 and 7 had most variants of 31 and 18 respectively. For the *pfhrp3* repeat types, 16 (AHHAAN), 17 (AHHDG) and 18 (AHHDD) were the dominant types observed. Number of variants of these three types were 32, 22 and 20 respectively. *Pfhrp2* polymorphisms showed more diversity than *pfhrp3* in Ghanaian isolates. The implication of our findings of the high frequencies of the *Pfhrp2* and *Pfhrp3* gene deletions as well as the variants of main epitopes of the monoclonal antibodies for the RDT (types 2 and 7) in our isolates could be suggestive of decreasing sensitivity of the tests in diagnosing malaria infections in Ghana and this is further discussed.

0252

REDUCTION OF CLINICAL MALARIA CASES FROM 2014 TO 2021 IN MAINLAND TANZANIA: A COMPARISON OF TRENDS BY HEALTH FACILITY OWNERSHIP

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Malaria remains a public health problem in Tanzania and a leading cause of morbidity and mortality with pregnant women and children under five years being the most vulnerable. There has been a gradual decrease in clinical malaria cases (presumptive without testing) largely due to implementation of policies and guidelines on malaria diagnosis and treatment of only malaria confirmed cases with artemisinin-combination therapy (ACT). This study aimed to investigate trends of clinical malaria cases reported by health facilities from 2014 to 2021. Monthly health facilities data were downloaded from the district health information system (DHIS2) and analyzed using Stata software. Descriptive statistics were used to explore the time trends and compare data by health facility type (Public, Defense, Private, Parastatal and Faith-based). Differences across health facility types were compared using test of proportions. The number of clinical malaria cases reported from 2014 to 2021 decreased by 99.7% (2,591,519/2,599,990) in OPD while clinical malaria admissions decreased by 97.9% (119,095/121,635). The proportion of clinical malaria cases decreased from 36.3% (2,599,990/7,156,298) in 2014 to 0.2% (8,471/4,279,835) in 2021 for OPD, and from 35.6% (121,635/341,978) in 2014 to 1.3% (2,540/193,148) in 2021 for IPD. Compared to other facility types, Public Health facilities consistently reported a significantly lower proportion of clinical cases (p=<0.001). There were differences in the proportion of clinical cases across other facility types; however, the difference was not statistically significant. The findings suggest that public health facilities adhere consistently to the National Guidelines for Diagnosis and Treatment of Malaria. This might be attributed to investments and improvements in training, supervision, commodities, and other malaria supplies to public health facilities. Further efforts are needed to improve malaria diagnosis and treatment practices in Defense, Parastatal, Private and Faith-based facilities.

0253

SUPPLY AND DEMAND SIDE FACTORS INFLUENCING UPTAKE OF MALARIA TESTING SERVICES IN THE COMMUNITY; LESSONS FOR SCALE-UP FROM A CLUSTER-RANDOMIZED, COMMUNITY BASED TRIAL

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Maximizing the impact of community-based programs requires understanding how the supply of, and demand for, the intervention interact at the point of delivery. We present results from a large-scale community health worker study designed to increase the availability of and demand for malaria diagnostic testing in a rural, malaria-endemic region in western Kenya between 2015 and 2017. Community Health Workers (CHWs) provided free malaria Rapid Diagnostic Test(mRDT) in the community. Those with a positive malaria test were provided with a discounted first-line antimalarial over-the-counter. We conducted a community-based survey of household members with fever in the last four weeks to collect individual study outcomes at 12- and 18-months post-implementation. In addition, we collected monthly testing data from the 244 participating CHWs and also conducted semi-structured interviews with a random sample of 70 CHWs. From the survey, 55% (n=948/1738) reported having a malaria test for their recent illness with 38% having been tested by a CHW. Being aware of a local CHW (Adj. OR=1.50, 95% CI:1.10-2.04) and belonging to a wealthy household (Adj. OR=1.53, 95% CI:1.14-2.06) were associated with higher malaria testing uptake from any source. Poorer households were more likely to receive a test from a CHW. School-aged children between 5-17 years were more than twice as likely to be tested by a CHW (Adj. OR=2.39 95% CI:1.43-4.01). Both confidence in AL treatment (Adj. OR=2.75, 95% CI:1.54-4.92) and perceived accuracy of an RDT performed by a CHW (Adj. OR =2.43, 95% CI:1.12-5.27) were strongly and positively associated. Scale-up of community-based malaria testing intervention through CHWs is feasible and effective at reaching the poorest households. In order to maximize the impact of such interventions, it is important to recognize factors that may restrict both delivery and demand for such services.

0254

PLASMODIUM 18S RRNA BIOMARKER CLEARANCE AFTER FDA-APPROVED ANTIMALARIAL TREATMENT IN CONTROLLED HUMAN MALARIA INFECTION TRIALS

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Controlled human malaria infection (CHMI) studies at non-endemic sites are now widely used to evaluate candidate anti-malaria drugs and vaccines prior to larger field studies in endemic regions. Historically, thick blood smears (TBS) were used in CHMI studies to detect infection after challenge and to confirm the clearance of parasites after treatment. In the past several years, more sensitive molecular biomarkers, such as Plasmodium 18S rRNA, have been qualified by the US FDA for detection of infection after challenge and have supplanted TBS for this purpose. However, the FDA has not formally qualified such biomarkers for confirming clearance of parasites after treatment. We compiled and analyzed post-treatment TBS and 18S rRNA quantitative reverse transcription PCR (qRT-PCR) data acquired from 142 P. falciparum infected participants across 7 CHMI studies conducted at our center over the past decade. For studies where infections were protocol-defined by TBS positivity (treatment densities of 5,000 to 200,000 estimated parasites/mL(p/mL)), the 18S rRNA biomarker cleared from peripheral blood in an average of 3.5 ± 0.2 days, which was significantly longer than the mean time to a negative TBS (1.8 ± 0.2 days). In studies where infections were protocol-defined by qRT-PCR positivity (treatment densities between 20 to 40,000 p/mL), biomarker clearance averaged 3.3 ± 0.1 days, which was not significantly different from TBS-defined studies. However, across all studies, the time to 18S rRNA biomarker negativity after treatment was directly correlated to the parasite density at the time of treatment, with significantly longer clearance times for participants with higher densities at treatment ($p = 0.001$). Thus, initiating treatment earlier leads to faster biomarker clearance. The data defines the expected clearance kinetics in treated CHMI study participants and will help identify conditions that deviate from this normal clearance to further increase the safety of such studies. Overall, the Plasmodium 18S rRNA can be relied upon to confirm the adequacy of treatment in CHMI studies at non-endemic sites.

0255

IMPLEMENTATION OF PROFICIENCY TESTING IN ZANZIBAR SUPPORTS QUALITY IMPROVEMENT FOR MALARIA MICROSCOPY AT FACILITY LEVEL

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Quality assured malaria microscopy remains the 'gold standard' for diagnosing malaria. However, in limited resource settings like Tanzania, the accuracy of microscopy results remains a great challenge. To build microscopists' competence and improve the accuracy of test results, refresher trainings and provision of external quality assessment, which includes proficiency testing, onsite supportive supervision, and blind rechecking, are essential. During 2021, the Zanzibar Malaria Elimination Programme with support from U.S. President's Malaria Initiative Impact Malaria project provided basic Malaria Diagnostic Refresher Training (bMDRT) to 60 laboratory technologists from the two Zanzibar islands of Unguja and Pemba and distributed malaria proficiency testing (PT) panels to 44 health facilities. The aim of the PT was to evaluate the performance of laboratory technicians in public and private laboratories at health facilities in Zanzibar. Two rounds of PT panels were distributed between June and December 2021. The laboratory technicians were assessed on their competence for parasite detection (PD) and species identification (ID). The results were compared with validated results at the central laboratory and feedback was given to the facility. The results show an improving trend of PD and ID competencies for consecutive rounds. On average, PD improved from 74% to 90% and ID from 28% to 50% from Round 1 to 2. The next steps are to expand the number of microscopists trained and to continue doing further rounds of PT.

0256

DISTINGUISHING MALARIA-CAUSED COMA FROM NON-MALARIA CAUSED COMA: THE CONTRIBUTION OF MALARIAL RETINOPATHY

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The World Health Organization (WHO) defines a child as suffering from cerebral malaria (CM) if they are in coma, have malaria parasites in their blood, and have no alternative cause of the coma. In malaria endemic areas there is often a large proportion of children with asymptomatic parasitemia. When comatose, this group confounds the CM definition as it mis-classifies children with asymptomatic parasitemia and other causes of coma as having CM. An autopsy study showed that approximately 25% of the children who died of WHO-defined cerebral malaria did not have malaria parasites in their brain and had evidence of another coma-inducing etiology that was not appreciated prior to death. If it could be determined prior to death whether a child's coma is caused by malaria parasites or another pathology, treatment might be improved. Prior studies justified the discriminative power of platelet and white blood cell counts in diagnosing severe malaria. One important biomarker of CM is CM-specific retinopathy consisting of a set of malarial-specific retinal changes. CM can be classified as retinopathy-positive and retinopathy negative. This study aimed to quantify the power of malarial retinopathy in discriminating malarial- from non-malarial coma. Our study cohort consists of 1228 patients. We assume there are two latent classes among these patients, corresponding to malarial- and non-malarial coma, and that the parasite protein *Plasmodium falciparum* histidine-rich protein-2 (*Pf*HRP2) follows a log-normal distribution in each latent class. We implemented a Gaussian mixture model based on the $\log_{10}$-scale *Pf*HRP2, and find that 10% of patients had non-malarial coma. We then explored the diagnostic power of retinopathy by building logistic regression classifiers using a combination of patients' platelet counts, white blood cell counts, peripheral parasitemia, and retinopathy. We found that the platelets plus retinopathy model significantly improved the discriminative power of the platelets plus white blood cell model (AUROC: 0.830 vs. 0.752, p-value = 0.038).

0257

THE COMMCARE MOBILE APPLICATION IMPROVES THE QUALITY OF MALARIA CARE IN CHILDREN UNDER FIVE YEARS OLD AT THE COMMUNITY LEVEL IN MADAGASCAR

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Community health volunteers (CHVs) in Madagascar serve as first-line health care providers for many communities located more than five kilometers from a basic health center. The USAID-funded Accessible Continuum of Care and Essential Services Sustained (ACCESS) Program, led by Management Sciences for Health and in partnership with Dimagi, supports the Ministry of Public Health of Madagascar to introduce the use of the CommCare mobile application to improve the quality of care provided by CHVs. With the help of built-in algorithms, the application provides step-by-step instructions to the CHVs on case management, including malaria testing and treatment for children under five years of age (CU5); collects individual case management data; and automatically generates monthly activity reports. ACCESS compared monthly community activity report data from October 2020 to September 2021 within the 12 districts covered by CommCare in the four target regions of Atsinanana, Atsimo Andrefana, Fitovinany, and Vatovavy. The malaria testing and treatment rate for CU5 among 1,891 CommCare users was measured and compared with that of the 2,530 other CHVs in the same regions and districts and for the same period using a chi-squared test. Data from October 2020 to September 2021 was extracted from CommCare and ACCESS District Health Information Software II platforms. The rate of fever cases tested by rapid diagnostic test (RDT) was significantly higher among CHVs using CommCare (96% [7212/7499)]) compared to all other CHVs in the four regions (69% [44,367/64,023]) (p=0.001). Similarly, the treatment rate of positive cases with artemisinin-based combination therapy (ACT) is higher among CHVs using CommCare (86% [3541/4231]), compared to CHVs not using CommCare in the same area (81% [23,753/29178]) (p<0.001). No differences in RDT and ACT supplies between users and non-users were noted. These data therefore suggest that CommCare users have a higher rate of compliance with testing and treatment guidelines than non-users, improving the quality of uncomplicated malaria management in CU5.

0258

DELETIONS OF *PLASMODIUM FALCIPARUM PFHRP2* AND *PFHRP3* GENES FROM PARTICIPANTS IN ANTIMALARIAL EFFICACY TRIALS IN ANGOLA, GUINEA, AND UGANDA 2017-2020

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HRP2-based rapid diagnostic tests (RDTs) are widely used across sub-Saharan Africa to diagnose *P. falciparum* malaria, but the emergence of *pfhrp2* and *pfhrp3* (*pfhrp2/3)* gene deletions threatens their utility. In response to this threat, the WHO set a local prevalence of 5% *pfhrp2* deletions as the threshold for switching away from HRP2-only RDTs. In this study, dried blood spots (DBS) were collected from children under 12 years of age with *P. falciparum* mono-infection during enrollment in an antimalarial efficacy study. All children had symptoms of malaria and microscopically-confirmed *P. falciparum* infection of at least 1000 parasites/ul blood. A multiplex bead-based antigen detection assay screened these samples to identify low levels of HRP2/3 antigen expression relative to pan-*Plasmodium* lactate dehydrogenase and aldolase. Samples with low HRP2/3 expression in relation to pan-*Plasmodium* antigens were selected for *pfhrp2/3* genotyping. Before *pfhrp2/3* genotyping, a *Plasmodium* PCR speciation assay and *pfmsp1* and *pfmsp2* PCRs were used to assess DNA quantity and quality. A total of 610 DBS from three sites in Angola, 846 from four sites in Guinea, and 589 from three sites in Uganda were screened. Genotyping samples with low HRP2/3 antigen profile revealed two *pfhrp2*-single deletions (0.3%) and two *pfhrp3*-single deletions (0.3%) in Angola. Analysis of HRP2/3-low samples from Guinea revealed one *pfhrp2/3* dual deletion (0.1%), one *pfhrp2*-single deletion (0.1%), and one *pfhrp3*-single deletion (0.1%). In Uganda, one *pfhrp2*-single deletion (0.2%) and four *pfhrp3*-single deletions (0.7%) were observed. Of the samples included in this study, *pfhrp2/3* dual-deletions were only observed in one sample from Guinea. While not able to provide *pfhrp2/3* deletion prevalence estimates for an entire country, this report provides evidence that symptomatic *P. falciparum* infections from the study sites in these three countries show high levels of HRP2 and HRP3 expression, supporting the utility of HRP2-based RDTs in the study sites.

0259

DEVELOPMENT AND VALIDATION OF AN AFFORDABLE AND FULLY AUTOMATED MICROSCOPE SYSTEM FOR MALARIA DIAGNOSIS AND RESEARCH

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Despite the widespread use of RDT and the accelerated adoption of molecular tests, malaria microscopy remains an indispensable tool for malaria diagnosis, case management, treatment efficacy studies, vaccine trials and epidemiological research. The role microscopy needs to play is even more important with the rise of pfHRP2/3 deletion and the spread of drug resistant mutations. However, manual microscopy is labor intensive and error-prone - while the detection limit of manual microscopy is thought to be around 10-100 parasites/microliter, a 2019 work that surveyed 10 studies reported sensitivity ranging from 40% to 80% at 1000 parasites/ul. To address this challenge, we have developed a fully motorized, computer-vision based system for automated detection of malaria parasites in both asextual and gametocyte stages. The solution uses DAPI staining, which costs less than $0.02/test reagent-wise and stains rapidly (in 2 minutes). Use of fluorescence allows sensitive and specific detection with 10x-20x objectives that have 25-100 times larger field of views compared to traditionally used 100x oil immersion objectives. With both transmitted light and fluorescent contrast, the system is capable of screening 500,000 - 2,000,000 red blood cells per minute, with expected detection limit below 10 parasites/ul. Results from ongoing validation studies in India and Uganda will be shared.

0260

CLINIC-BASED ASSESSMENT OF QUANTITATIVE POINT-OF-CARE G6PD ACTIVITY ASSAY—KAMPONG SPEU, CAMBODIA, 2020-2021

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As countries push toward elimination of *Plasmodium vivax*, treatment of liver stage parasites with primaquine or tafenoquine is increasingly important. Both drugs are associated with hemolytic anemia (HA) in individuals with decreased glucose-6-phosphate dehydrogenase (GP6D) activity levels, a genetically determined trait commonly found throughout the Mekong Subregion. To mitigate this risk, several countries, including Cambodia, require *P. vivax* infected individuals be screened for G6PD deficiency before receiving primaquine. The gold standard assay for G6PD activity requires spectrophotometry which is not universally accessible in many malaria-endemic areas. Point-of-care (POC) testing provides an alternative, but several methods in use do not reliably detect individuals with intermediate levels of G6PD activity who may be at risk for primaquine-induced HA. Quantitative POC assays have been developed to address this gap. We enrolled 966 individuals seeking care for febrile illness from November 2020 to September 2021 in seven health facilities located in Kampong Speu Province, Cambodia, to determine the performance of the quantitative STANDARD™ G6PD (SD Biosensor) POC assay when used by local clinic staff. G6PD activity and hemoglobin concentration in capillary blood were measured on-site using the POC assay. Reference values for each participant were obtained by spectrophotometry and hematology analysis of a corresponding venous specimen. Using the manufacturer-recommended thresholds for G6PD deficiency, the sensitivity of the POC assay was 92.8% (95% confidence interval (CI): 88.8-96.8%) among men and 93.5% (CI 80.7-100%) among women. The negative predictive value for men was estimated to be 98.3% (CI 97.3-99.2%) and 99.3% (CI 98.0-100%) for women. Receiver operator curves for men and women had areas under the curve of 0.97 (CI 0.946-0.995) and 0.945 (CI 0.915-0.974), respectively. These results add to a growing body of literature that suggests this POC assay is capable of quickly and accurately identifying those at increased risk of primaquine-induced HA, potentially increasing access to *P. vivax* radical cure.

0261

QUANTITATIVE PCR ASSAY FOR DIAGNOSIS OF *PLASMODIUM FALCIPARUM* INFECTIONS TO MONITOR SEASONAL MALARIA CHEMOPREVENTION (SMC) EFFECTIVENESS IN MALI

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Malaria diagnosis relies on Giemsa-stained blood smears using microscopy and the Rapid diagnostic tests (RDTs) for detecting *Plasmodium* antigens in endemic setting. However, the sensitivity of these methods decreases as parasitemia falls below the detection threshold of 100 parasites/µL for microscopy, and 50 parasites/µL for RDTs. In addition, false positives are observed, particularly after treatment, as parasite antigens detected can remain in the circulation following parasite clearance. This study aimed to assess the molecular prevalence of malaria infection after provision of Seasonal Malaria Chemoprevention among school aged children in Koulikoro, Mali. DNA was extracted from blood spots on filter paper and stored at –20°C until used. For quantification by qPCR, we used an assay targeting the 18s rRNA gene. Serial dilution of cloned *P. falciparum* 18sRNA from 10^5 copies/µl to 5 copies/µl were prepared and use as positive control and to derive a standard curve for quantification of parasite copy number. Based on the optimized qPCR, 54.5% (364/667) of blood samples were positive for *P. falciparum*. More than half of the positive samples (56%, 167/298) presented with low parasite density (below 5 copies /µL). High disagreement rates between the two diagnostic methods with regard to positive parasitemia was observed with 61/667 samples positive at microscopy but negative by qPCR, and 134/667 samples positive at *P. falciparum* by qPCR but negative by microscopy. A sensitivity and specificity were 45% and 79% respectively in microscopy compared to qPCR. Kappa statistics showed poor agreement between the two diagnostic techniques (Kappa=0.24). The ability of microscopy to detect true positives was estimated at 69% compared to qPCR with statistical significance (P<0.0001). This study demonstrates the importance to implement molecular monitoring for *Plasmodium* infections for better characterization of epidemiologic strata and to detect possible resistance to treatment.

0262

EFFICACY AND SAFETY OF IVERMECTIN FOR THE TREATMENT OF *PLASMODIUM FALCIPARUM* INFECTIONS IN ASYMPTOMATIC GABONESE ADULTS - A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL

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New antimalarials are needed to improve malaria control and elimination. Mosquitoes feeding on ivermectin-treated hosts die and it has *in vitro* anti plasmodial activity. Ivermectin's *in vivo* efficacy against blood stage infection is unknown. We assessed the efficacy and tolerability of ivermectin for the treatment of *Plasmodium falciparum* infections in asymptomatic Gabonese adults. We conducted a phase 2a monocentric clinical trial. It consisted of a safety dose-escalation phase followed by a randomized, double-blind, placebo-controlled trial. Asymptomatic adults with *P. falciparum* parasitemia of 200-5000 parasites/µl residing in Lambaréné, Gabon, were enrolled. In the dose-escalation phase, groups of 5 participants received 200 µg/kg ivermectin q.d. for 1, 2 or 3 days. Subsequently, 34 participants were randomized to 300 µg/kg ivermectin or placebo q.d. for three days. Primary efficacy outcome was the time to 90 % parasite reduction for at least 8 hours by microscopy. Safety outcomes were the number of drug-related serious adverse events and grade 3 adverse events (trial registration: PACTR201908520097051). Out of 49 participants who received at least one dose of placebo or ivermectin, 39 completed the trial as per protocol. At baseline, the median age (IQR) was 25 (20-40) years, there was more male than female participants (63% vs 37%). The median *P. falciparum* parasite load was 599 (314-1102) Pf/µL. No severe or serious adverse events were observed. 3d-300µg/kg IVM showed no significant activity against blood stage parasites compared to placebo-control one-week post-treatment (RD = 0·04, 95% CI -0·18 - 0·27). In this trial, ivermectin did not reduce *P. falciparum* parasitaemia in asymptomatic individuals. Due to its mosquitocidal effects, ivermectin is still an effective altruistic therapy for the protection of other community members by reducing transmission. A dose-dependent effect of ivermectin on *plasmodium* cannot be ruled out.

0263

IVERMECTIN AND PREGNANCY, SAFETY EVIDENCE FROM THE BOHEMIA CLUSTER RANDOMIZED TRIAL IN MOZAMBIQUE

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Ivermectin has been used for over 35 years in mass drug administration campaigns for neglected tropical diseases. In this context, women of reproductive age are screened and excluded based on self-reported pregnancy status. This approach is justified based on the known risk of blindness and disability related to onchocerciasis and lymphatic filariasis. Despite uncertainty on the safety of ivermectin during pregnancy, the documented experience of more than 900 pregnant women inadvertently exposed and the biological basis of active xenobiotic pumps in the placenta suggest that administration during pregnancy may not entail an increased risk of adverse pregnancy outcome. As ivermectin is under evaluation as a potential novel tool for malaria vector control, the risk benefit for pregnant women must be reassessed in the context of this potential new indication, which would have a personal benefit but obtained indirectly through a community effect as it works by reducing the vector population at community level. The BOHEMIA project, funded by Unitaid, includes a large-scale cluster-randomized trial in the highly malaria endemic district of Mopeia, Zambezia province, Mozambique. The primary objective of the trial is to assess the efficacy and safety of three rounds of mass drug administration with ivermectin with a single dose of 400 mcg/kg, monthly during the rainy season. Women of child bearing age are only included for treatment after a negative pregnancy test. Nonetheless, it remains possible for women to become pregnant while the drug is still circulating at physiologically relevant concentrations. All women found pregnant within four weeks of dosing are followed until pregnancy outcome. Here we present key relevant data obtained during the first six months of the trial including: acceptability of pregnancy testing in the context of malaria-aimed MDA, appropriateness of self-reported pregnancy status as a screening method, and early safety results in women dosed peri-conception.

0264

IMPACT OF MASS DRUG ADMINISTRATION OF IVERMECTIN ON MALARIA TRANSMISSION IN RURAL MOZAMBIQUE, EFFICACY RESULTS FROM THE BOHEMIA CLUSTER RANDOMIZED TRIAL

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Mass drug administration with ivermectin has been proposed as a complementary strategy to reduce malaria transmission. The BOHEMIA project, funded by Unitaid, includes a large-scale cluster-randomized trial in the highly endemic district of Mopeia, Zambezia province, Mozambique. The local malaria prevalence in children under five years of age is 75% by RDT and the dominant vectors are *Anopheles arabiensis* and *Anopheles funestus*. The rainy season spans from December to May and transmission occurs year-round with a peak in May. The primary objective of the trial is to assess the efficacy and safety of three rounds of ivermectin mass drug administration with a single monthly dose of 400 mcg/kg for three months during the rainy season. The target population is all above 15 kg of weight, key exclusion criteria are pregnancy, current use of medications with potential drug-drug interactions, and severe illness. The primary efficacy outcome measure is malaria incidence in children under five years of age as determined by active case detection at community level. There are three intervention groups: (A) ivermectin is administered to eligible humans only, (B) ivermectin is administered to eligible humans and livestock, and (C) albendazole is administered to eligible humans as control group. The clinical trial was launched on March 14, 2022. The target enrollment is 35,000 participants for treatment and 3,000 children for the active case detection cohort divided in 159 clusters. The differential incidence between intervention and control clusters will be compared with a regression model using generalized estimating equations with exchangeable correlation structure that considers the cluster design effect. We present data on enrollment, acceptability, and efficacy obtained during the first six months of the trial.

0265

SAFETY OF MASS DRUG ADMINISTRATION OF IVERMECTIN TO DECREASE MALARIA TRANSMISSION IN MOZAMBIQUE, RESULTS FROM THE BOHEMIA CLUSTER RANDOMIZED TRIAL

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Ivermectin has an outstanding safety profile at the recommended doses for the current approved indications. For neglected tropical diseases, ivermectin is usually administered once a year at doses around 150-200 mcg/kg. For the intended use case of reducing malaria transmission, pharmacokinetic and epidemiologic modelling predict the need for higher doses in order to have an impact of public health value. Recently-finished or ongoing field trials have mostly centered around monthly administration during three months of the rainy season with treatment schemes ranging from a single dose of 400 mcg/kg once a month to three consecutive daily doses of 300 mcg/kg once a month. The BOHEMIA project, funded by Unitaid, includes a large-scale cluster-randomized trial in the highly endemic district of Mopeia, Zambezia province, Mozambique. The target population is all above 15 kg of weight, key exclusion criteria are pregnancy, current use of medications with potential drug-drug interactions, and severe illness. There are three intervention groups: in group (A) ivermectin is administered to eligible humans only, in group (B) ivermectin is administered to eligible humans and livestock, and in group (C) albendazole is administered to eligible humans as control. The primary safety outcome measure is the differential incidence of adverse and severe adverse events between the ivermectin and albendazole groups. This is captured by active follow up of all treated participants who keep a diary for the six days after treatment and are visited monthly by a field worker.

Robustness is added by passive detection of adverse events at all health facilities in the district and a toll-free number available throughout the study period. The trial was launched on March 14, 2022 and aims at recruiting 35,000 participants for treatment. Here we present safety data obtained during mass drug administration.

0266

EVALUATION OF IVERMECTIN AS AN ANTIMALARIAL THERAPY AGAINST *PLASMODIUM FALCIPARUM* LIVER STAGE

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Malaria remains a major global public health threat due to prevalence of drug-resistances and failure to frontline antimalarial therapy, hindering the global efforts to control and eliminate the disease. Almost none of the available antimalarial drugs are efficacious against the liver stage of *Plasmodium falciparum*, which is the initial stage of infection that leads to disease causing blood stage infection. The only currently FDA-approved class of drug capable of eliminating *Plasmodium* liver stage parasites are the 8-aminoquinolines and this drug class has its own limitations due to potential hemolytic activity in people with favism and therefore not suitable for mass drug administration (MDA). Due to these limitations, there is a critical need for safer and more efficacious drugs that can prevent liver stage development of malaria parasites. Ivermectin is an approved broad spectrum antiparasitic drug that has been proposed as a novel malaria transmission control tool to kill mosquito vectors that transmit malaria and aid malaria elimination. Recent studies have revealed ivermectin inhibit liver-stage development of *P. berghei*, a rodent malaria laboratory model, suggesting this drug may be an effective antimalarial drug. However, ivermectin is known to be metabolized by cytochrome 3A4, which exhibits polymorphism among different individuals to potentially alter efficacy against *Plasmodium*, emphasizing the importance of understanding the metabolism of ivermectin and its metabolites. We have established a robust invitro liver assay to study the liver stage development of human malaria parasites in primary human hepatocytes that can be used to evaluate the potential impact of these metabolic differences on ivermectin's anti-liver stage efficacy. This model can be used to evaluate the metabolism of ivermectin in hepatocytes from different donors and its efficacy against *P. falciparum* liver stages.

0267

REGULATORY PATHWAY FOR REPURPOSING IVERMECTIN FOR MALARIA: CHALLENGES AND SOLUTIONS

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Repurposing an "antique" drug for a novel malaria indication - as a complementary vector control tool- involves challenges in terms of regulatory and technical review. Regulation of drug and vector control tools are traditionally done by separate groups. However, ivermectin for malaria requires regulatory review as a drug for product quality, as well as an anti-vector product for efficacy. Ivermectin, although used broadly in Africa for several NTDs, has not been licensed, as it has been provided as a donated product for those campaigns for about 30 years. The BOHEMIA project, designed to evaluate the efficacy of ivermectin MDA in two countries, has challenged both global and national regulatory agencies to integrate and address several unique issues including the regulatory pathway for industry and key issues such as the need for pregnancy testing, dose optimization and generic supply for the potential new indication. We will describe the pathway that has evolved, the key issues identified, and propose options to resolution as the clinical trials are completed.

0268

EFFECT OF PRIMAQUINE DOSE ON THE RISK OF RECURRENCE IN PATIENTS WITH UNCOMPLICATED *PLASMODIUM VIVAX*: A SYSTEMATIC REVIEW AND INDIVIDUAL PATIENT DATA META-ANALYSIS

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Despite clinical use for over 60 years, the optimal dose of primaquine for *Plasmodium vivax* radical cure is unknown. Most endemic countries recommend a total primaquine dose of 3.5 mg/kg administered over 14 days. To directly inform global and national malaria treatment guidelines, we investigated the effect of the total dose of primaquine mg/kg on the risk of *P. vivax* recurrence. Efficacy studies of uncomplicated *P. vivax* including a treatment arm with daily primaquine, published between January 2000 and March 2021, were identified and individual patient data from eligible studies pooled using standardised methodology. The effect of receiving primaquine and primaquine mg/kg dose on the incidence risk of *P. vivax* recurrence between days 7 and 180 were derived using Cox regression analyses. Of 60 eligible studies, 23 studies enrolling 6,879 patients from 16 countries were available for analysis: 1,470 (21.4%) patients were not treated with primaquine, 29 (0.4%) received very low dose (<2 mg/kg) primaquine, 2,567 (37.3%) low dose (2 to <5 mg/kg) primaquine and 2,813 (40.9%) high total dose primaquine (>=5 mg/kg). The risk of recurrence by day 180 was 50.8% [95%CI 48.0-53.7] without primaquine, 19.3% [17.0-21.8] following low dose primaquine and 8.2% [7.1-9.4] following high dose primaquine. After controlling for confounders, the rate of first recurrence was greater in patients treated with low versus high dose primaquine (Adjusted Hazard Ratio (AHR)=2.2 [1.6-2.9]) and this was observed for both low (AHR for low versus high dose primaquine =2.3 [1.5-3.4]) and high relapse periodicity regions (AHR=1.9 [1.1-3.3]). In patients treated with primaquine, a 1 mg/kg increase in primaquine total dose was associated with an AHR of 0.8 [0.7-0.9], although the benefit of increasing primaquine dose reduced for total doses greater than 6 to 7 mg/kg. The widely recommended low total dose primaquine regimen (3.5 mg/kg) provides suboptimal anti-relapse efficacy and this is apparent in most vivax-endemic regions.

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AGE-DOSED SINGLE LOW DOSE PRIMAQUINE IN FALCIPARUM-INFECTED AFRICAN CHILDREN WITH G6PD DEFICIENCY IS WELL TOLERATED AND SAFE

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In 2012, the WHO i recommended the use of single low dose primaquine (SLDPQ) for blocking *Plasmodium falciparum* transmission. Most treatment guidelines in Sub Saharan Africa have not included SLDPQ for

the management of uncomplicated malaria. This is partly because of a paucity of data appraising the safety and efficacy of SLDPQ in glucose-6-phosphate dehydrogenase deficiency (G6PDd). We, therefore, investigated SLDPQ safety in G6PDd falciparum-infected children. We conducted a randomised, double blind, placebo-controlled, trial in Ugandan and Congolese children aged 6m–11y with baseline haemoglobin concentrations ≥ 6 g/dL, treated with artemether-lumefantrine or dihydroartemisinin-piperaquine and age-dosed SLDPQ/placebo. The primary endpoint was the development of profound (Hb < 4 g/dL) or severe anemia (Hb < 5 g/dL) with clinical features of severe malaria by Day 21; the non-inferiority margin in genotypically-confirmed G6PDd patients was 3%, assuming a 1.5% rate in the placebo arm. 1137 children were recruited: 239 A^- G6PDd hemizygous males & 45 A^- homozygous females (G6PDd group), 119 A^- heterozygous females, 418 normal males, 299 normal females, and 17 of unknown genotypic status. Median age was 5 years. Three patients met the primary end point: G6PDd group 0/133 (placebo) vs. 1/151 (0.67%): Δ= -0.66 [(-1.96–0.63)%, p=0.347] and nonG6PDd group: 1/430 (0.23%, placebo) vs. 1/407 (0.25%, SLDPQ): Δ= -0.014 [(-0.68 –0.65)%, p=0.958]. Nine patients (5 placebo) were transfused in the first week; four had G6PDd. Placebo-SLDPQ early vomiting rates were 49 (1.58%)/3103 treatments vs. 43 (1.38%)/3103 treatments (p=0.599). Although too few events of the stringently-defined safety endpoint precluded demonstrating non-inferiority of SLDPQ, age-dosed SLDPQ was safe with a similar blood transfusion rate as placebo. This study adds substantial evidence for drug policy and should serve as a paradigm across Sub Sharan Africa.

0270

THE TOLERABILITY OF ASCENDING DOSE PRIMAQUINE IN HEALTHY VOLUNTEERS WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY IN THAILAND

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Plasmodium vivax represents some 2% of the global malaria burden and is the most common species outside of subSaharan Africa. *P. vivax* elimination rests on eliminating the hypnozoite reservoir that is the source of recurrent blood stage infections called relapses. Primaquine and tafenoquine are recommended for treating liver hypnozoites but both cause dose dependent acute haemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency (G6PDd), necessitating pretreatment G6PDd testing. A primaquine regimen that could be used without G6PDd testing would be a substantial advance. Exploiting the primaquine dose haemolysis relationship, we conducted an adaptive challenge study of ascending dose primaquine (ADPQ) to determine whether we could produce a gradual, well tolerated haemolysis in healthy G6PDd males. Starting with a 20-day regimen of 7.5, 15, 22.5 & 30 mg/d, each for 5 days, subsequent changes to the PQ dose and number of days of a given dose within each cycle depended on the results of daily haemoglobin (Hb) concentrations and predefined rules for continuing or stopping PQ. We recruited 23 G6PDd males aged 18–55 (median 32) years with G6PD Viangchan (*n*=12 subjects), Canton (4), Mahidol (3), Orissa (1), Chinese-5 (1), Aures (1), and Union (1). 5 ADPQ regimens were tested: 3 x 20 days (*n*=9 subjects), 16 days (4), 15 days (10). Median (range) Day 0 Hb was 14.3 (11.4–15.8) g/dL. All subjects had Hb declines that nadired at the end of dosing. The 15 & 16d regimens produced a significantly (0=0.018) greater median fractional fall vs. 20d regimens: 26.7 (14.5–34.1)% vs. 19.6 (14.1–27.1)% for respective median nadir Hbs of 10.5 (9.2–11.70) and 11.7 (10.8–12.2) g/dL. Reticulocyte responses were rapid, peaking at 14.9 and 6.8% on Days 11 and 16 for the 15-16 and 20-day regimens, respectively. PQ was well tolerated. One subject stopped early because of fatigue and another for unexplained rises in ALT (445 IU/L) and AST (AST 220 IU/L). ADPQ induced a tolerated haemolysis. Data modelling is ongoing to suggest a regimen for testing in the field.

0271

EFFECT OF PRIMAQUINE DAILY DOSE ON TOLERABILITY AND SAFETY IN PATIENTS WITH UNCOMPLICATED *PLASMODIUM VIVAX*: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

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Despite greater efficacy, the use of high doses of primaquine (PQ) for radical cure of *Plasmodium vivax* is confounded by poor gastrointestinal (GI) tolerance and concerns of haematological safety. We investigated the relationship between the daily dose of PQ on GI tolerability and haematological safety. Individual patient data were pooled from clinical efficacy studies of patients with uncomplicated *P. vivax* including a treatment arm with PQ, published between January 2000 and March 2021. GI intolerance was defined as the presence of vomiting, diarrhoea, or anorexia between days 2 and 14. Haematological safety was defined as maximum absolute reduction in haemoglobin (Hb) levels on days 2-14 vs. day 0 and fractional fall in Hb ≥25% to less than 7g/dl. Data were available from 33 studies in which 1470 patients received no PQ, 2242 received low daily dose PQ (<0.375 mg/kg/day), 2880 received intermediate daily dose (≥0.375 to <0.75 mg/kg/day) and 1554 received high daily dose (≥0.75 mg/kg/day). Compared to no PQ, patients treated with low, intermediate and high daily doses had higher odds of GI intolerance (OR 1.39 [95%CI: 0.92,2.09], 1.57[1.19,2.08] and 2.29[1.72,3.05] respectively). The risk of Hb falling by ≥25% to <7 g/dL was 0.1% (1/1218) in patients not treated with PQ, 0.0% (0/1260) in patients treated with low daily dose PQ , 0.3% (5/1771) after intermediate dose and 0.7% (10/1461) after high dose PQ. After controlling for baseline Hb and other covariates there was no association between PQ daily dose and maximum absolute reduction in Hb between days 2 and 14 (high dose vs no PQ: 0.08 g/dL [-0.03, 0.18]). Higher daily doses of PQ were associated with more frequent GI symptoms, though further analyses including individual-level data on food co-administration are warranted. In patients not known to be G6PD deficient (<30% activity), there was no direct association between high daily PQ doses and adverse haematological outcomes.

0272

DEVELOPING PRIMAQUINE FOR MALARIA ELIMINATION WITH A HOLISTIC APPROACH

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Primaquine is an old drug which has a key role in malaria elimination as radical cure and transmission blocking. It is a WHO essential drug and has been recommended for decades by the WHO for the control and, more recently, elimination of *Plasmodium vivax* and *P. falciparum*. Despite this, its deployment at global level is low. Reasons for this gap between policy and practice are complex; the main challenges include the: i) absence of quality-assured, child friendly, PQ dosage forms, ii) limited interest from pharma, iii) fear of haemolysis in G6PD deficient patients, iv) paucity of evidence to inform safe and efficacious regimens, and v) lack of a supply chain plan to ensure optimal and sustainable

global distribution. To overcome these challenges and engage directly with pharma, we set up the Developing Paediatric Primaquine (DDP) consortium with European Union funding, that integrates multidisciplinary expertise from pharmaceutical development to field implementation. The key aim is to prequalify child-friendly and adult primaquine, followed by registration in malaria endemic countries. DPP core activities include: i) a bioequivalence study vs. Sanofi reference 15mg primaquine, ii) showing pharmaceutical equivalence of the paediatric line extension (7.5, 5, 3.75, 2.5 mg), iii) formulation work to mask primaquine's bitterness using a sensory approach, iv) initiating granule development as the optimal dosage form for better palatability, acceptability and marketing, iv) two field trials (radical cure & infectivity) to validate the safety, efficacy and acceptability of the paediatric line, and v) evaluate packaging designs. We will present and discuss our activities to date, including the challenges we have faced in a niche area of malaria elimination. As a small academia-NGO led consortium, we believe that our holistic strategy to see primaquine used for malaria elimination is timely and brings an important dynamic and new activities that complements the activities of bigger actors in malaria elimination.

0273

PRIMAQUINE TREATMENT IN LACTATING WOMEN IS SAFE FOR THE BREASTFED INFANT

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Primaquine and tafenoquine are the only available drugs providing radical cure of *Plasmodium vivax* malaria. However, these drugs are contraindicated in breastfeeding women as they cause acute hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals, and the excretion into breast milk and thus infant exposure are unknown. Healthy G6PD normal breastfeeding women with previous *P.vivax* infection and their healthy G6PD normal infants were enrolled in this trial. Mothers received primaquine 0.5 mg/kg/day for 14 days. Drug concentrations of primaquine and carboxyprimaquine were measured in maternal venous, capillary and breast milk samples as well as in infant capillary samples. Population pharmacokinetic-pharmacodynamic modelling and simulation were used to evaluate the drug exposure in mothers and breastfeeding infants. Venous and capillary concentration-time data in lactating mothers were modelled simultaneously by a drug-metabolite model with a flexible first-pass metabolism of primaquine into carboxyprimaquine. Drug concentration data in breast milk was characterized by estimating the distribution of drugs from blood to a separate breastmilk compartment. A mechanistic breastfeeding model was constructed based on the average breastmilk volume consumed during a feed and the feeding pattern in this population. Drug exposures were then simulated in all infants and compared to measured drug concentration-time data. Simulated and measured primaquine and carboxyprimaquine concentrations were negligibly low in breastfeeding infants. The estimated primaquine dose received by infants, based on breast milk levels, was <1% of the standard dose of 0.5 mg/kg. Primaquine should not be withheld from breastfeeding mothers due to safety concerns of G6PD-deficient infants or young children.

0274

PRIMAQUINE PHARMACOKINETICS AS TRANSMISSION BLOCKING IN FALCIPARUM-INFECTED AFRICAN CHILDREN

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Single low dose primaquine (SLDPQ) is recommended for transmission blocking but few pharmacokinetic (PK) data exist in acute paediatric *Plasmodium falciparum*. Rich blood sampling [baseline, +1, 1.5, 2, 4, 8, 12, 24 hours] was performed in Congolese and Ugandan children 6 months—11 years with acute uncomplicated *P. falciparum*, diagnosed by malaria slide or rapid diagnostic test, who were treated with 3-day dihydroartemisinin-piperaquine or 3-day artemether-lumefantrine. SLDPQ was dosed by age, using 2.5, 5 and 7.5 mg tablets, on Day 0: 6m—<1y: 1.25 mg, 1—5y: 2.5 mg, 6—9y: 5 mg, 10—11y: 7.5 mg. PQ and carboxyPQ PK were determined by noncompartmental analysis. Of 1,137 recruited patients, 258 of median age 5 [interquartile range (IQR) 3—7] years underwent PK analysis: 14 were aged 6m—<1y, 129 1—5y, 83 6—9y and 32 10—11y. Administered mg/kg PQ doses ranged from 0.10—0.40, IQR 0.16—0.25, median 0.21. SLDPQ was well tolerated; early vomiting occurred in 30/1137 (2.64%) and the 7-day transfusion rate was 0.88% in the SLDPQ (5/569) and placebo (5/568) recipients (p=1.0). Overall median maximum concentration (Cmax) was 103.0 (IQR 71.7—139.0, range 2.3—447) ng/mL, reached (Tmax) at median 2 (range 1.0—8.0) hours. Median (range) PQ—carboxyPQ exposures ($AUC_{0\text{-last}}$) were 713.2—3,157.7 (6m—<1y), 577.3—2,428.3 (1—5y), 893.4—4,273.8 (6—9y), and 931.0—4,522.9 (10—11y) ng*h/mL; respective median half-lives were 4.7 (2.4—75.4) and 17.5 (4.5—180.2) hours. Primaquine clearance increased with increasing age but was highest in the youngest children when adjusted by body weight. This well tolerated age-dosed SLDPQ regimen was characterised by wide interindividual variability in Cmax but less variability in $AUC_{0\text{-last}}$. The median dose of 0.21 mg/kg leaves scope for an increase in dose. More PK data in the youngest children would add weight to dosing recommendation in this group, which experiences higher clearance/kg. Our data will be included in pharmacokinetic pharmacodynamic models of haemoglobin changes and gametocyte carriage to define dose response relationships and inform optimal age and weight-based dosing.

0275

MOLECULAR MECHANISM OF ANTIMALARIAL INHIBITION FOR PLASMEPSIN IX AND X

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The emergence and spread of antimalarial drug resistance pose a threat to global efforts to control and eliminate malaria, and the discovery and development of new antimalarials with novel mode of action is an urgent priority. We have discovered a novel class of drug-like inhibitors of *Plasmodium falciparum* growth that blocked parasite egress from infected erythrocytes and subsequent invasion of released merozoites. These new compounds are potent inhibitors of the essential *Plasmodium* aspartic proteases plasmepsin IX and X (PMIX and PMX) and block multiple stages of the parasites lifecycle. The discovery of PMX-specific (WM4) and PMIX/X (WM382) dual inhibitors has also provided tools to investigate the function of these aspartic proteases to show that PMIX and PMX are master modulators of merozoite invasion and direct maturation of proteins required for invasion, parasite development and egress. Enzyme kinetic and determination of the 3-dimensional structure of protease-drug complexes have identified the molecular interactions responsible for specificity involved in the inhibition of these proteases by WM382 and WM4. In addition, attempts to select resistant *P. falciparum in vitro,* demonstrated a high barrier for the development of resistance against these compounds.This new class of PMIX- and PMX-inhibitors with dual-targeting activity, novel mode of action, ability to disrupt multi-lifecycle stages of *Plasmodium* parasites both *in vitro* and *in vivo,* and high resistance threshold, provides promising drug candidates for treatment and prevention of malaria infections.

0276

MALARIA BURDEN IN AREA WITH HIGH BED NET OWNERSHIP IN NORTH EASTERN TANZANIA

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Several interventions have been made to eliminate Malaria in Tanzania including use of insecticide-impregnated bed nets and artemisinin combination therapy. Nevertheless, malaria is still high in some parts of the country. We assessed the burden of malaria in terms of prevalence as well explored about bed net ownership and utilization.Three cross sectional surveys were conducted in June 2021, September 2021 and January 2022. A total of 457 participants were recruited. The study included children aged between 2-10 years and adolescents/adults aged 11-70 years. The study was conducted in Bondo site which comprises of Bondo, Kwadoya, Ngojoro and Kwamgwe villages in Handeni Tanga Tanzania.A face-to-face interview were conducted. A pre-tested questionnaire was used to collect demographic information, bed net use, bed net ownership and factors for malaria exposure. The developed questionnaire was uploaded in the system and data was collected electronically using Open Data Kit application. The blood sample from the finger-prick was used to test malaria parasites using malaria rapid diagnostic test.The prevalence of malaria was 32.8% (150), 21.7% (99), and 22.1% (101) in cross-sectional 1,2 and 3 respectively. Seventy percent (106), 66.7% (66) and 68.3% (69) who were malaria positive (by MRDT) used a Insecticide-treated bed nets in cross-sectional 1,2 and 3 respectively, less than 0.05.This study highlight that Insecticide-treated bed nets usage were signifcantly associated with malaria positivity. In order to achieve malaria elimination, we advocate malaria campaigns targeting proper usage of Insecticide treated bed nets.

0277

MODELLING THE OPTIMAL ALLOCATION OF GLOBAL MALARIA FUNDING FOR ERADICATION

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Large reductions in the global malaria burden have been achieved in the last decades, but plateauing funding poses a challenge for progressing towards eradication. We aimed to determine the optimal strategy to allocate global resources to achieve the ultimate aim of malaria eradication whilst minimising clinical burden. Using existing mathematical models of *Plasmodium falciparum* and *Plasmodium vivax* transmission, we determined the funding allocation for the distribution of insecticide-treated nets (ITNs) across countries that maximised the long-term reduction in global malaria cases from a baseline of no ITN coverage as an indicator of the eradication goal. We compared the impact of this optimal strategy on clinical case incidence and the population at risk of malaria at alternative global budgets and with different allocation strategies - including prioritising settings of high or low transmission intensity or allocating funding proportional to the malaria burden at the baseline (year 2000). The optimal strategy was closely aligned with an allocation framework that prioritises funding for high-transmission settings, resulting in case reductions of 79% (optimal strategy) and 71% (prioritising high-transmission settings) at intermediate budget levels. Allocation strategies that have the greatest impact on cases were associated with lesser near-term impact on the global population at risk, highlighting a trade-off between reducing burden and "shrinking the map" through a focus on malaria elimination. The optimal funding distribution prioritised high ITN coverage in high-transmission settings endemic for only *P. falciparum*, whilst maintaining lower levels in low-transmission settings. However, at high budgets, almost 75% of funding was targeted at low-transmission settings co-endemic for *P. falciparum* and *P. vivax*. These results support current global strategies to prioritise funding to the high-burden *P. falciparum*-endemic settings in sub-Saharan Africa to minimise clinical malaria burden but illustrate the trade-off against competing goals of advancing elimination and addressing the burden of *P. vivax*.

0278

EFFECTIVENESS OF REACTIVE STRATEGIES FOR MALARIA TRANSMISSION: SYSTEMATIC REVIEWS AND META-ANALYSES OF REACTIVE CASE DETECTION AND TREATMENT, REACTIVE DRUG ADMINISTRATION, AND REACTIVE INDOOR RESIDUAL SPRAYING

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Many countries pursuing malaria elimination implement 'reactive' strategies targeting household members and neighbors of index cases to reduce transmission. These strategies include reactive case detection and treatment (RACDT, testing and treating those positive), reactive drug administration (RDA, providing antimalarials without testing), and reactive indoor residual spraying (RIRS, spraying insecticide in/near index case houses). We conducted systematic reviews of RACDT, RDA, and RIRS. Two reviewers screened titles/abstracts and full-text records using defined criteria (**P**atient=those in malaria-endemic/receptive areas; **I**ntervention= RACDT, RDA, or RIRS; **C**omparison=standard of care; **O**utcome=malaria incidence/prevalence) and abstracted data for meta-analyses. The GRADE approach was used to rate certainty of evidence (CoE) for each outcome. For RACDT and RDA, 1,339 records yielded 5 RACDT studies (3 cluster-randomized controlled trials [cRCTs] and 2 non-randomized studies [NRS]) and 7 RDA studies (6 cRCTs and 1 NRS); 3 cRCTs comparing RDA to RACDT were included in both reviews. For RIRS, 457 records yielded 2 cRCTs. Compared to RDA, RACDT was associated with non-significantly (NS) higher parasite prevalence (odds ratio [OR]=1.85; 95% confidence interval [CI]: 0.96-3.57; 1 study) and malaria incidence (rate ratio [RR]=1.30; 95% CI: 0.94-1.79; 3 studies); both very low CoE. Compared to control or RACDT, RDA was associated with NS lower parasite incidence (RR=0.73; 95% CI: 0.36-1.47; 2 studies, moderate CoE), prevalence (OR=0.78; 95% CI: 0.52-1.17; 4 studies, low CoE), and malaria incidence (RR=0.93; 95% CI: 0.82-1.05; 6 studies, moderate CoE). Compared to no RIRS, RIRS showed lower parasite prevalence (RR=0.32; 95% CI: 0.13-0.80; 1 study, high CoE) and NS lower malaria incidence (RR=0.65; 95% CI: 0.38-1.11; 1 study, moderate CoE); compared to proactive IRS, RIRS was not inferior for malaria incidence (mean difference=0.10; 95% CI: -0.38-0.58; 1 study, moderate CoE). Evidence for reactive strategies' impact on malaria transmission is limited, especially for RACDT, but suggests RDA and RIRS might be more effective.

0279

ADHERENCE OF TREATMENT PRESCRIPTIONS TO GUIDELINE RECOMMENDATIONS IN PATIENTS WITH MALARIA IN REAL-WORLD SETTING: INSIGHTS FROM A PROSPECTIVE, MULTICENTRE OBSERVATIONAL STUDY IN SUB-SAHARAN AFRICA

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To understand the gap between guidelines and local clinical practice for diagnosis and treatment of malaria, the patient characteristics, diagnostic approach, treatment, and adherence to standard guideline recommendations were assessed in an observational study (October 2020 to March 2021). A total of 1001 patients, with symptoms suggestive of malaria, visiting a health care facility were prospectively enrolled across 11 sites in six countries in sub-Saharan Africa. The median age of patients was 11 years (range: 2 weeks to 91 years) with more patients coming from rural (44.9%) than urban (30.6%) or suburban areas (24.5%). Overall, 735 (73.4%) patients had confirmed malaria (based on local practice) at baseline (uncomplicated malaria: 598 [81.4%] and severe malaria: 137 [18.6%]); of whom 533 (72.5%) were administered a rapid malaria diagnostic test. At the community level, 57% of patients sought advice or received treatment for malaria and 56.1% of patients took one or more drugs for their illness before coming to the study site. In terms of early access to care, 44% of patients travelled to the site 48 hours or more after symptom onset. In patients with uncomplicated malaria, the most prescribed treatments were artemisinin-based combination therapies (ACTs; n=564 [94.3%]), primarily artemether-lumefantrine (82.3%), in line with the WHO treatment guidelines. In addition, these patients also received antipyretics (85.6%) and antibiotics (42.0%). However, in those with severe malaria, only 66 (48.2%) patients received parenteral treatment followed by an oral ACT as per WHO guidelines whereas 62 (45.3%) received parenteral treatment only. The present study's findings suggest that the prescribed treatment in most patients with uncomplicated malaria, but not of those with severe malaria, was in alignment with the WHO recommended guidelines in sub-Saharan Africa.

0280

MALARIA KNOWLEDGE, PREVENTION PRACTICES, AND CARE-SEEKING BEHAVIOR AMONG FOREST-GOERS IN CAMBODIA: A MIXED-METHODS FORMATIVE ASSESSMENT

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Consistent use of long-lasting insecticide treated nets/hammocks (LLIN/LLIHN), early diagnosis, and treatment are central to reducing malaria burden. As malaria cases decrease in Cambodia, forest-goers are most at risk of malaria due to their proximity to the forest, working during peak biting times, frequent mobility, and distance from health services. The study aimed to understand forest-goers' knowledge, attitudes, and practices related to malaria prevention and care-seeking and to identify key behavioral determinants of LLIN/LLIHN use and care-seeking within 24 hours of fever onset. A mixed-methods study design consisting of a cross-sectional survey and qualitative in-depth interviews was implemented in Kampong Chhnang and Pursat provinces. Survey participants (N=654) were recruited using respondent driven sampling. Findings were analyzed using univariate and bivariate analysis and multivariate weighted logistic regression. Interviews (N=28) were coded and analyzed using thematic content analysis. All study participants had heard of malaria and 98% knew that malaria was transmitted by mosquitoes. Although LLIN/LLIHN ownership was high (94%) and 99% of participants perceived LLIN/LLIHN use as an important malaria prevention measure, only 76% reported using one during their last visit to the forest. Only 57% of participants sought care within the recommended 24 hours of fever onset during their last febrile illness. In controlled regression models, perceived community social norms were significantly associated with LLIN/LLIHN use (OR: 2.7, 96%CI:1.99-2.64) and care-seeking within 24 hours of fever onset (OR: 1.7, 95%CI:1.00-2.88). Social support from other forest-goers was significantly associated with LLIN/LLIHN use (OR: 4.9, 95%CI: 1.32-18.12). The study identified rates of LLIN/LLIHN use and delayed care-seeking behaviors as concerns to address to meet malaria elimination goals. Social and behavior change activities may consider incorporating social norms and social support as mechanisms for behavior change given the identified positive correlations with LLIN/LLIHN use and prompt care-seeking behavior.

0281

TRIALS OF IMPROVED PRACTICES TO ASSESS COMMUNITIES' INITIAL REACTION TO A SPATIAL REPELLENT PRODUCT IN BUSIA, WESTERN KENYA

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Spatial Repellents (SR), a potential complementary malaria prevention tool, are designed to protect a space from mosquitoes. Trials of Improved Practices (TIPs) is being implemented to complement an ongoing cluster randomized trial testing the efficacy of an SR product in Busia, western Kenya. TIPs captures end-user experiences, perceived efficacy, acceptability, and recommendations over time. One week after installation, semi-structured double-blinded interviews were conducted with 30 purposively selected participants from 12 intervention clusters (SR and placebo) to capture participants' first reaction to the intervention applied in their home. Two months after installation, a second interview was completed to capture blinded perceptions of the product after two cycles of product replacement. During the first visit, most participants mentioned a perception that the product was effective, reporting fewer mosquitos. As a result, some households reported stopping use of other mosquito control tools. During the second visit, some reported mosquitoes had started to return due to perceived differences in intervention effectiveness from the beginning of the 28-day installation period to the end. Participants had positive views of the intervention, noting benefits of protection outside of sleeping hours, when nets provide protection, and not requiring daily action. Most liked the product appearance and some suggested increasing what they perceived as an active ingredient to make it last longer and installing products in additional locations such as bathrooms. Participants also requested biodegradable products, rather than plastic. Initial TIPS interviews provided an in-depth understanding of end users' initial preferences and can inform communication to study communities to promote continued use of core interventions. To capture participants' reaction over time, participants will be interviewed again at 6, 12, 18 and 24 months. These interviews will provide important data for comparing perceptions of SR product feasibility, effectiveness, and acceptability to actual household allocation following trial unblinding.

0282

DYNAMICS OF *PLASMODIUM FALCIPARUM* AFEBRILE MALARIA IN SOUTHERN MOZAMBIQUE

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Peaceful coexistence with the infected host is a common but poorly understood phenomenon for many human pathogens, including *Plasmodium falciparum* (*Pf*). The persistence of *Pf* afebrile infections and the continuous production of gametocytes may constitute a primordial source for ongoing transmission that may compromise the success of elimination initiatives. To date, few data are available regarding the progression of afebrile *Pf* infections in order to design effective interventions that can successfully detect and tackle this parasite reservoir. In this study, healthy individuals aged 5 - 60 years residing in Manhiça District were screened at the household level using a Histidine Rich Protein-2 based rapid diagnostic test (RDT) from SD Bioline. All RDT positive cases were also microscopically confirmed and closely followed for 28 days with daily visits during the first 4 days and weekly until day 28 during the rainy season (October-April) in 2020-21 and 2021-22. Antimalarial treatment was only provided at the end of follow-up or if clinical symptoms appeared before day 28. The average age of participants at enrollment was 18 years. The median body temperature was 36.4°C, and the average body weight was 41.3 kg. The geometric mean parasite density on day 0 was 1944 parasites/µL measured by microscopy. This analysis used data from 107 of the 146 individuals enrolled and excluded individuals with >2 missed follow-up visits. Parasite densities in 52 of the 107 participants (48.6%) decreased to microscopically undetectable levels. In 19 participants (17.8%), parasite densities drastically reduced and stabilized at low-density levels (below 100 parasites/µL). In 26 participants (24.3%), parasite densities were maintained at densities above 100 parasites/ µL. Ten participants (9.3%) developed a fever during the first week of follow-up. Therefore, approximately one-quarter of the afebrile RDT-detectable infections maintain densities with a high potential for transmission. The ongoing molecular characterization will provide further insights into the spontaneous clearance of afebrile infections in areas of low malaria transmission.

0283

REACHING POPULATIONS AT RISK OF MALARIA EQUITABLY: CHALLENGES AND PROSPECTS TO MALARIA ELIMINATION IN NEPAL

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Nepal is among six countries in the Asia Pacific that have made significant progress in policy milestones and its made tremendous progress in malaria elimination from over 42,000 reported cases in 1985 to only 390 cases in 2021. However, significant challenges persist to achieving a *"malaria free Nepal by 2025"*. We aim to outline the challenges and prospects for equitably achieving malaria elimination in Nepal, which can be applied to other countries. Firstly, the high proportion of vivax malaria (~80%), calls for innovative tools to address low-density infections and community mobilization to support drug adherence. Secondly, the importation of cases from India, which along with improved transport networks, leads to outbreaks and re-introduction of malaria in previously malaria-free areas. Additionally, malaria vectors are prevalent in many areas, and climatic and cultural factors promote human-vector contact, breeding, and transmission. Low private-sector engagement has resulted in limited involvement in malaria treatment and surveillance of PHFs and little ownership at provincial/local levels. To address these challenges, the National Program is focusing on the 1-3-7 surveillance strategy, improved cross border collaboration with India (including origin, travel, destination, and return interventions), LLIN/IRS coverage in areas with high receptivity and vulnerability, private sector involvement and community management of malaria. Prospects for malaria elimination include implementation of radical cure for *Plasmodium vivax*, including G6PD testing, and community transmission blocking interventions for *P. falciparu*m. Nepal established a national malaria elimination task force at the central level and is in the process of planning a provincial level task force to track, monitor, and resolve issues related to elimination efforts. If the current trends continue, epidemiological models project that there will be zero indigenous cases by 2023. Nepal needs to re-evaluate its current surveillance strategy, focusing on targeted community management of malaria and on targeted interventions to address imported malaria.

0284

DEFINING MALARIA OPERATIONAL RESEARCH AND PROGRAM EVALUATION PRIORITIES FOR SUB-SAHARAN AFRICA: RESULTS FROM A BROAD STAKEHOLDER CONSULTATION PROCESS

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Policy, strategy, and operational decisions should be grounded in evidence to reignite gains and accelerate progress toward improved malaria control and elimination. The U.S. President's Malaria Initiative (PMI) Insights Project, together with the Université Cheikh Anta Diop of Dakar, conducted a broad stakeholder consultation to identify pressing evidence gaps in malaria control and elimination policy, strategy, and guidelines across sub-Saharan Africa (SSA), and develop a priority list of country-driven malaria operational research (OR) and program evaluation (PE) topics to address the gaps. Five key stakeholder groups were engaged in the process: national malaria programs (NMPs), research institutions in SSA, funding agencies, WHO representatives in SSA, and global technical partners supporting malaria program implementation and research. Stakeholders were engaged through individual or small group interviews and an online survey, and asked about key operational challenges faced by NMPs, pressing evidence gaps in current strategy and implementation guidance, and priority OR and PE questions to address the challenges and gaps. Altogether, 47 interviews were conducted with 82 individuals and 46 global technical partners providing input through the online survey. A total of 33 emergent OR and PE topics were identified through the consultation process, and then evaluated and prioritized by an external evaluation committee made up of experts from NMPs, research institutions, and WHO across SSA. The resulting prioritized OR and PE topics predominantly focus on generating evidence needed to close gaps in malaria control and elimination intervention coverage, address persistent challenges faced by NMPs in the implementation of core strategic interventions, and inform the effective deployment of new tools. The prioritized research list is intended to serve as a key resource for informing OR and PE investments, thereby ensuring future investments focus on generating the evidence needed to strengthen national strategies and program implementation and facilitating a more coordinated and impactful approach to malaria OR and PE.

0285

COMMUNITY HEALTH WORKER RESILIENCE IN THE FIGHT AGAINST MALARIA AMIDST COVID-19: A CASE STUDY FROM EASTERN PROVINCE, ZAMBIA

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Zambia's Ministry of Health (MOH) has deployed 16,500 community health workers (CHWs) nationwide since 2011, of which 2,932 are providing malaria community case management (CCM) in Eastern Province. In 2019, the COVID-19 (COVID) pandemic spread throughout the world with Zambia recording its first case in March 2020. Between May 2020 and March 2022, Eastern Province recorded 36.3 COVID cases per 1,000 population, the third highest province in Zambia. The health system shifted its focus to pandemic control, and supply chains were disrupted, resulting in a considerable disruption to delivery of national health services, threatening the CHW program. This case study assesses CHW resilience amidst COVID by reviewing CHW malaria service provision data and commodity availability in Eastern Province from 2019 (prior to COVID) to 2021. Data describing passive number tested, positive, and treated cases were extracted from the health management information system. Changes in annual malaria test positivity rate of 39% (pre-COVID) vs 55% and 45% (2020 and 2021) in Eastern Province suggest potential changes in malaria treatment seeking during the pandemic. However, during this time CHWs increased the number of people tested for malaria—423,944 in 2019 (pre-COVID), 744,531 in 2020, and 834,505 in 2021. CHWs also maintained high annual treatment rates among confirmed cases—97%, 98%, and 97%, respectively—referring untreated cases onward to health facilities. Despite challenges posed by COVID, the CHW program remained resilient and maintained malaria service coverage. This could be attributed to the availability of commodities, COVID sensitization, continuity of program support by the national malaria program and cooperating partners, prioritization of CCM of malaria by the MOH, interest expressed by CHWs to serve their communities, and the trust communities have in the CHWs. Where the districts are adequately stocked and malaria commodities made available to CHWs, CHWs can continue to provide life-saving health services amidst a pandemic, and potentially shore up declines in treatment seeking at health facilities.

0286

EVALUATING THE 1-3-7 SURVEILLANCE FOR MALARIA ELIMINATION STRATEGY IN LAO PDR

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Between 2000 and 2020, the annual number of probable and confirmed cases of malaria in Lao People's Democratic Republic (PDR) fell by 99 percent, from 279,903 to 3,537. The National Strategic Plan for Malaria Control and Elimination (2021-2025) calls for malaria elimination by 2030. To reinforce efforts towards malaria elimination, Lao PDR adopted a 1-3-7 approach in 2020 under which cases are reported within 1 day, investigated within 3 days, and foci are responded to within 7 days. Health workers in 125 malaria elimination districts (out of a total of 148 districts) were trained by the national program on the approach throughout 2020. In 2021, U.S. President's Malaria Initiative (PMI) Impact Malaria Laos assessed the implementation of the 1-3-7 approach by evaluating the technical, programmatic, and human resource feasibility and appropriateness of the strategy. The assessment determined the type and level of human, material, and financial resources required for effective implementation, and identified factors and barriers to the successful implementation at each level of the health system. In total, 68 semi-structured key informant interviews were conducted with health workers at the provincial, district, and health facility levels. Findings suggest that streamlining the case notification and classification processes could reduce travel and workload on overburdened staff. Innovative mechanisms leveraging digital tools could ease and improve case notification, investigation, and response where geographical access is difficult. Readily available financial resources at the lowest health level could support field activities related to case investigation and response. The availability of training and resources were identified as areas where targeted response packages could be developed. In conclusion, the assessment found that implementation of the 1-3-7 strategy in Lao PDR is appropriate and feasible but can be further optimized with some modest adaptations.

0287

MALARIA BURDEN AND MALNUTRITION WITHIN MANANJARY DISTRICT, MADAGASCAR: AN ANALYSIS OF SPATIO-TEMPORAL PATTERNS AND THE POTENTIAL IMPACT OF IMPROVED MULTISECTORAL PROGRAMMING

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Little is known about the interactions between food security, moderate acute malnutrition (MAM), and malaria prevalence. In Madagascar, undernurishment is among the highest in sub-Saharan Africa (42%) and malaria incidence is high (71.6 per 1000). In the peri-costal district of Manjaray, malnutrition and malaria incidence are higher than the national average. To better understand this complex interaction, a prospective study of 10 cohorts (n = 2485, all ages, 171-292 individuals per site) was launched in 2021. Mobile clinical teams conduct monthly visits to cohort communities collecting malaria prevalence, anthropomorphic, micronutrient, and household level questionnaire data related to nutritional status, food access, malaria infection status, and use of prevention measures. Baseline malaria and nutrition prevalence showed spatial differences between nearby communities. MAM prevalence was 5.48% overall (range between sites: 2.14% to 12.45%, n = 2301). Indicating food insecurity is common, a large proportion of households reported reducing the number of meals (37.72%, n = 517) or portion size at mealtime (29.98%, n = 517) in the past week. Disruptive but not uncommon, two cyclones hit Manajary consecutively within four weeks in February 2022 creating widespread damage, population displacement, and geographical changes. Routine temporal changes coupled with severe weather events have created difficulties in food security and access to malaria treatment and prevention resources. Our growing understanding of the shared drivers between malaria and nutritional outcomes suggests the need for better coordination among community-based nutrition and health systems. Using the mobile and community coordination approaches outlined here will enable better multisectoral policy at the national level to be developed and help reduce food insecurity and malaria prevalence.

0288

IMPROVING MALARIA SURVEILLANCE DATA AS MALARIA INTERVENTION IN CENTRAL UGANDA

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Surveillance data collected from health facilities is critical for early outbreak detection, planning and decision making for effective malaria control and programming. The quality of this data, more so in developing countries is however often limited to allow use for the intended purposes. Reporting rates are often so low to make meaningful deductions from the data. The USAID's Malaria Action for Districts in mid-central Uganda operated in Kyotera, Sembabule, Lwengo, Rakai, Lyantodde, Bukomansibi, Kalangala, Kalungu and Masaka dsitricts implemented a package of interventions to improve surveillance data quality and its use in this area. The package included on-site mentorships, performance review meetings, support supervision as well as regular data review and cleaning exercises. Presented here is analysis of the quality of weekly malaria surveillance data submitted into District Health Information System (DHIS2) from health facilities in the focus area during implementation of these interventions from July 2017 to September 2020. The study assessed completeness data using the indicator: proportion of health facilities reporting weekly malaria surveillance data into DHIS2. In the focus area.Results showed that a total of 400 facilities reported into the DHIS2 in the study period. The proportion of facilities reporting weekly malaria surveillance data increased from 68.5% in Jul - Sep 2017 to 84.7% in Jul - Sep 2018 to 92.3% in Jul-Sep 2019 and 89.2% in Jul-Sep 2020. The slight reduction in Jul-Sep 2020 might be due to the lock-down instituted in the country to fight against the corona pandemic. With this data at least three malaria upsurges in the region were detected early to enable timely response.Malaria control in developing countries like Uganda has suffered from low reporting rates of weekly surveillance data yet it is a cornerstone for saving of lives through early detection. This study suggest that, with interventions as described, health facilities can be empowered to provide quality weekly data.

0289

PLASMODIUM FALCIPARUM MSP1 AND *MSP2* GENETIC DIVERSITY IN *P. FALCIPARUM* SINGLE AND MIXED INFECTION WITH *P. MALARIAE* AMONG THE ASYMPTOMATIC POPULATION IN SOUTHERN BENIN

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Plasmodium falciparum and *P. malariae* infections are very common in malaria-endemic countries. However, very little is known about their interactions especially the effect of *P. malariae* on *P. falciparum* genetic diversity. This study aimed to assess *P. falciparum* genetic diversity in *P. falciparum* and mixed infection *P. falciparum/ P. malariae* isolates among the asymptomatic populations in Southern Benin. Two hundred and fifty blood samples (125 of *P. falciparum* and 125 *P. falciparum/ P. malariae* isolates) were analyzed by a nested PCR amplification of *msp1* and *msp2* genes. The R033 allelic family was the most represented for the *msp1* gene in mono and mixed infection isolates (99.2% vs 86.4%) while the K1 family had the lowest frequency (38.3% vs 20.4%). However, with the *msp2* gene, the two allelic families displayed similar frequencies in *P. falciparum* isolates while the 3D7 allelic family was more represented *in P. falciparum/P. malariae* isolates (88.7%). Polyclonal infections were also observed to be lower (62.9%) in *P. falciparum/P. malariae* isolates ($p < 0.05$). Overall, a total of 96 individual alleles were identified (47 for *msp1* and 49 for *msp2*) in *P. falciparum* isolates while a total of 50 individual alleles were identified (23 for *msp1* and 27 for *msp2*) in *P. falciparum/ P. malariae* isolates. The Multiplicity of Infection (MOI) was lower in *P. falciparum/ P. malariae* isolates ($p < 0.05$). This study revealed a lower genetic diversity of *P. falciparum* in *P. falciparum/ P. malariae* isolates using *msp1* and *msp2* genes among the asymptomatic population in Southern Benin.

0290

NATIONWIDE FACILITY-LEVEL MALARIA INCIDENCE USING AVAILABLE ROUTINE DATA, MALAWI, 2018—2021

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Increasingly, sub-national data are pursued to inform decisions about allocating limited resources for geographically specific malaria control interventions. In some countries, routine data are unavailable, and acquiring these data requires collection of non-routine data through resource-intensive strategies. To calculate facility-level malaria incidence in Malawi, malaria case reports and facility-level catchment population estimates from the national DHIS2 were used. Facilities were included if they reported a catchment population estimate and submitted 100% of monthly reports for any year from 2018 to 2021. To obtain incidence denominators, facility population counts were summed by district and compared to 2021-adjusted National Statistics Office (NSO) district estimates to determine their accuracy (acceptable if variation ≤5%). To obtain facility-level incidence, mean case counts were divided by the adjusted facility-level population estimate. Of 1,008 facilities listed in DHIS2, 647 (64%) met the criteria for inclusion; 67 were excluded due to lack of population data, and 294 for lacking monthly reports. A mean of 3.5 years of data were included per facility. Estimated facility population data for 24/28 districts (86%) summed to within 5% of the 2021-adjusted NSO district population estimates, and the national population coverage for the facilities included was 96%. 27 million total confirmed malaria cases were included (90% of all cases reported during the analysis period). Four-year mean facility-level malaria incidence ranged from 12/1,000 to 3,329/1,000 population (median value: 381/1,000; 25th/75th percentile: 208/650). Facility-level standard deviation by district ranged from 136-583/1,000. Available facility-level population estimates were accurate compared to a standard, and data availability permitted the systematic calculation of incidence for most facilities. If these results accurately represent geographic incidence variation, these data could be mapped and higher risk areas identified. Monitoring routine data may help identify local trends and inform targeted control strategies.

0291

THE POSITIVE EXTERNALITIES FOLLOWING INDOOR RESIDUAL SPRAYING (IRS) IN NGOMA DISTRICT, RWANDA

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Positive externality occurs when an unrelated activity causes a benefit to a third party. Ngoma district, located in Eastern province of Rwanda, received the first round of indoor residual spraying (IRS) in April 2019 with the support of the Government of Rwanda and The Global Funds and a coverage rate of 98.9%. The district has fifteen health centers (HCs) and 1,419 Community Health Workers (CHWs) providing malaria case management. Comparative data analysis from the Routine Health Management Information System, twelve months before and after the first round of IRS, showed a decrease from 510,881 to 348,078 in the average outpatient's department (OPD) malaria case consultations (a 46%

decrease). The average daily OPD cases was 95 per HC before IRS and 64 after IRS (a 33% decrease). Assuming the time spent for OPD consultation of 10 minutes per patients, each HC gained approximately 5 hours per day, equivalent to 62% of an 8-hour working day of a nurse. Similarly at community level, the yearly number of consultations dropped from 1,023,644 to 222,995 cases (a 78% decline), with an average monthly number of consultations per CHWs estimated at 60 cases before and 14 after IRS (a 77% decrease). Discussions with community members suggested an economic effect due to averted malaria cases (direct and opportunity costs of seeking care such as travel, waiting time and loss of productivity due to illness). In addition, based on discussions with health workers at the HCs and communities, this subsequently led to reduced workload. Therefore, IRS not only reduced malaria incidence, saving lives, but also had a positive effect of reducing workload of health workers who are already overburdened with other health related activities. This may increase patient satisfaction by reducing the waiting time of consultation and increase quality of services.

0292

MONITORING MALARIA OUTCOMES IN REMOTE RAINFOREST REGIONS OF GUYANA

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Malaria is endemic in the hinterlands of Guyana, especially in remote gold mining regions. The Ministry of Health (MoH), Breakthrough ACTION Guyana, and the Pan American Health Organization (PAHO) trained volunteers near remote mining areas to provide rapid malaria testing and treatment to miners. Key programmatic indicators included the use of insecticide treated nets (ITN), prompt care-seeking, self-medication, and treatment adherence rates among miners. A new monitoring system was created to fill a critical information gap between local and regional services and management. It used exit interviews with miners who sought malaria services and field visits to volunteer testers by MOH supervisors who used a standardized monitoring tool, co-designed with MoH, PAHO, and mining camps. Regional Ministry teams were trained to analyze the monitoring data to inform restocking of test kits, treatment drugs, and counseling aids during quarterly field visits and provide needed feedback. This monitoring revealed challenges including lack of data entry/analysis capacity in regional offices, limited funds for transportation/logistics, and hesitancy of miners to be interviewed. These challenges were overcome with training of the MOH staff/volunteer testers and adjusting timelines to address logistic barriers. Monitoring data revealed improved outcomes. Of miners who accessed testing services, 43% had sought care promptly, 88% did not self-medicate, 73% adhered to treatment and 24% slept under an ITN, compared to 37%, 44%, 44% and 33% miners respectively before the scale up of the program. The decline in ITN use is presumably due to MOH challenges in ITN acquisition and distribution. Use of systematic monitoring enabled timely decisions for mid-course corrections and strategic prioritization of local capacity needs to ensure sustainability.

0293

ACCEPTABILITY OF WOMEN ATTENDING ANTENATAL CARE AS A SENTINEL SURVEILLANCE POPULATION FOR MALARIA IN GEITA REGION, TANZANIA

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Measurement of malaria prevalence in communities is conventionally estimated through infrequent cross-sectional household surveys that do not provide continuous information regarding longitudinal malaria parasitemia in the community. Recent studies have suggested that malaria parasitemia prevalence among women attending antenatal care (ANC) correlates with prevalence among children under 5 years old and that pregnant women could be a sentinel population for tracking malaria prevalence over time. However, acceptability of collecting malaria risk factor data during ANC visits is unknown. A tablet-based questionnaire was introduced at 40 healthcare facilities in Geita Region, Tanzania, which included 15 questions on insecticide-treated net ownership and use and care-seeking for febrile children. Facilities were chosen that had 15 to 120 first ANC visits per month. To assess perspectives regarding wider introduction of the questionnaire, 21 semi-structured interviews were held with health care workers (HCWs) and managers at 12 facilities. Thirty pregnant and recently delivered women participated in focus group discussions at 7 facilities to assess the acceptability of spending additional time answering questions about malaria risk. All pregnant women felt that introduction of ANC surveillance and spending 10 more minutes with HCWs answering questions about their health would be neutral or beneficial. They perceived being asked about their health as standard of care. HCWs and managers felt that introduction of ANC surveillance was within the scope of practice of HCWs. Nine of 21 perceived that it could potentially benefit the health of women. Six HCWs expressed concern about staffing shortages and need for reimbursement for extra time and noted that management of data and records occurs after hours when patients have departed. Pregnant women and HCWs generally perceived ANC surveillance for malaria as acceptable and mostly positive. To be seen as a part of standard practice, and not an additional activity, efforts will be needed to ensure HCWs perceive a benefit for ANC clients and that concerns regarding staffing are addressed.

0294

A NOVEL APPROACH FOR DETECTING MALARIA HOTSPOTS IN AREAS OF VERY LOW TRANSMISSION AND ITS APPLICABILITY FOR IMPROVING SURVEILLANCE AND RESPONSE ACTIVITIES IN MOZAMBIQUE

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Identifying malaria hotspots in time and space allows us to detect malaria reservoirs in elimination settings and key areas for targeted interventions. The commonly used SatScan hotspot detector identifies circular or elliptical areas with higher malaria prevalence than statistically expected, but it is limited by the irregular distribution of human populations. Methods that account for population distribution while maintaining operational feasibility are needed to improve the effectiveness of targeted interventions. We present a new method to detect hotspots that accounts for population density by linking Plasmodium falciparum positive cases between them when they are closer than a given distance

of programmatic relevance, identifying structures of any shapes and sizes. The cases closest to the hotspot members are used to estimate the statistical significance of the hotspot. The method can identify persistent hotspots that also evolve in time. We compared this method with SatScan, showing a better capacity to adapt to the population distribution and the specifics of the programmatic focus. We applied the method to two different scenarios in southern Mozambique. First, hotspots were identified from clinical cases passively detected at health facilities in a low transmission setting where reactive surveillance was conducted between 2018 and 2020 (Magude District). Most of the hotspots persisted for less than two weeks, but we identified a hotspot that persisted for two months. Secondly, we applied the method to data from community-based cross-sectional surveys and pregnant women attending antenatal care (ANC) visits from two districts between 2016 and 2019 (Magude and Manhiça Districts). We identified hotspots from ANC data missed by cross-sectional surveys. This suggests that ANC data may improve the hotspot detection with respect to cross-sectional surveys, showing the potential of pregnant women as a sentinel group for malaria surveillance. The method can be easily applied to reactive surveillance in low transmission settings and integrated in surveillance systems to quickly detect outbreaks for rapid responses.

0295

MAPPING MALARIA PREVALENCE IN SUB-SAHARAN AFRICA WITH DEEP LEARNING AND SATELLITE IMAGERY

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Maps of an infectious disease are integral to guiding public health policy. For vector-borne diseases such as malaria, statistical methods and location-specific information on the environment can be fitted to prevalence data. Typically prevalence data is collected through time-consuming and resource-intensive household surveys, which cannot be as regular as routinely collected data from health facilities. Statistical models are therefore critical to fill in the data gaps. Recent advances in computation and machine learning theory combined with publicly available satellite imagery can help address this problem. Although the use of satellite imagery has been a long-standing topic in epidemiological studies, practitioners rely on manually extracting the predictors such as temperature from the image and rarely consider very high resolutions (pixel sizes &lt 1km). Here we present a new approach, based on using raw satellite images as input data. In this work, we used Deep Learning models to predict the prevalence of malaria across the whole of sub-Saharan Africa. The model was trained using Demographic and Health Survey (DHS) prevalence data and corresponding satellite images covering approx. 6x6km areas for each of the DHS locations. We applied Convolutional Neural Networks to unprocessed images taken as the model input to automatically detect different malaria predictors, such as forests, water bodies or settlements. The model was able to estimate the malaria prevalence with a mean absolute error of around 13%, systematically achieving better performance than the benchmark linear model with the regular suite of environmental covariates. We tested various sources of openly available satellite data, as well as combining the image input with numeric socioeconomic and environmental covariates. We show that using raw satellite images can aid the mapping of infectious diseases while avoiding the subjective step of manual predictor extraction. This can help to quantify the prevalence of malaria in locations that are difficult to survey in traditional ways and thus to provide more targeted interventions in places which need it the most.

0296

OPTIMIZING THE DELIVERY OF ROUTINE MALARIA DATA QUALITY ASSESSMENTS: A MULTI-LEVEL LOGISTIC REGRESSION MODEL TO INFORM INSTITUTIONALIZED APPROACH IN MOZAMBIQUE

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While quality of surveillance data is essential for malaria programmes, the accuracy of reported data remains low. Many countries now strive to institutionalize routine data quality assessments (DQAs) as a key approach to improve data accuracy. Mozambique has been implementing this since 2019 with a selection of health facilities (HFs) receiving DQAs with differing frequencies. These are aimed at improving the accuracy of monthly malaria reports at HFs - containing aggregated data from register books - before being entered into the national health information system. Despite this being a resource-intensive exercise, the influence of different operational factors on the impact of DQAs including baseline accuracy, location and size of HFs, frequency of and lag between DQAs has never been systematically investigated. This is the first analysis aiming to inform an optimized operational delivery of routine DQAs. A 2-level logistic regression model of 650 DQAs, delivered from 10/2019 to 12/2021 and clustered within 175 HFs across 13 districts, was fitted in relation to operational factors outlined above. A binary outcome was used where in an 'accurate' monthly report >90% of confirmed malaria cases matched the number of cases reported in the register book. Controlling for operational factors, each DQA doubled the odds of an accurate report (OR 1.74 [1.38-2.20]). While most factors had no significant influence, the impact of each DQA was significantly higher if baseline accuracy was low: for baseline accuracies of 80-90%, each DQA tripled the odds of an accurate report; for baseline accuracies of <80%, each DQA quadrupled the odds. If baseline accuracy was ≤90%, the probability of an accurate report at the next visit was sustainably over 80% after the 2nd follow-up DQA. This is the first time the impact of routine DQAs was quantified in relation to various operational factors. This approach showed that after establishment of baseline accuracy, resources in Mozambique should focus on 2 follow-up DQAs to HFs where baseline accuracy is ≤90% to sustain data quality. Similar approaches will help to optimize the delivery of routine DQAs in other countries.

0297

MALNUTRITION AND RISK OF MALARIA IN CHILDREN UNDER 5 YEARS IN BURKINA FASO: A LONGITUDINAL STUDY

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The association between malaria and malnutrition is complex. Using data from a randomized controlled trial of 450 children 0-5 years of age in Burkina Faso, we examined the effect of malaria on anthropometric measures at 2 weeks and six months, the effect of malnutrition at baseline on incidence of malaria among those with no malaria at baseline, and whether age of child modifies the effect of malnutrition on risk of malaria. Malaria status (based on parasitemia on a smear), weight, height, mid-upper arm circumference (MUAC), Height-for-Age Z Score (HAZ), Weight-for-Age Z Score (WAZ), and Weight-for-Height Z score (WHZ) of children were measured at baseline, 2 weeks and 6 months. We used generalized estimating equations (GEE) adjusted for sex, age, breastfeeding, maternal

education, and study treatment (Azithromycin vs. placebo) for both analyses. We used GEE models that include the interaction term to assess effect modification by age on the multiplicative scale and relative excess risk due to interaction (RERI) on the additive scale. There were 51 kids (13.8%) with incident malaria among those with no malaria at baseline. There were no statistically significant differences in anthropometric measures between those with and without malaria. Among those with no malaria at baseline, there were no statistically significant differences in risk of malaria by baseline anthropometric measures. Age (0-30 months and 30-60 months) modified the effect of baseline weight and height on incidence of malaria on multiplicative scale and the effect of baseline weight, height, HAZ, WAZ, and WHZ on the additive scale. Among those 0-30 months, for each kg increase in weight, the risk of malaria increased by 19% (RR: 1.19 95% CI (1.05 to 1.36)); and for each cm increase in height, it increased by 7% (RR: 1.07 95% CI (1.03 to 1.12)) but did not increase for those 30-60 months. The effect of malnutrition on incidence of malaria may vary by age. The risk of malaria increased with increasing anthropometric measures among kids 0-30 months while it slightly decreased for kids aged 30-60 months. Underweight, stunted or wasted kids 30-60 months had the highest risk of malaria.

0298

MAPPING HOUSE LOCATION WITH REMOTE SENSING AND DEEPING LEARNING METHODS IN RURAL KENYA AND ETHIOPIA

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The human population represents one of the most critical variables in assessing exposure to vector-borne pathogens in rural African countries. Accurate information on the house location and house roof materials can improve modeling disease transmission risk and help plan interventions for malaria diseases. However, obtaining precise information in vast rural areas of Africa with no prior detailed mapping effort is labor-intensive, expensive, and time-consuming. High-resolution remote sensed images are helpful, but the traditional imagery analysis or manually identify methods need skilled technicians and are prone to human errors due to the morphological resemblance in visual of ground objects to human dwellings. Therefore, we utilized remote sensing and deep learning methods to detect the human house locations and roof materials in multiple study sites in western Kenya and Ethiopia. Using high resolution, multi-band pan-sharpened Pléiades satellite images with labeled dwellings from the ground survey, the Mask R-CNN, a deep convolutional neural network for object detection, was used to generate low-level features and high-level features. In addition, bounded box regression and classification were conducted. The model was trained on a 0.1° x 0.1° satellite image for each site with a total of 25,000 labeled houses and validated on the other adjacent 0.1° x 0.1° areas. The model yielded an overall accuracy of 85% in the area and 95% on the corrugated iron sheet roof-type houses. A combination of remote sensing and deep learning methods is valuable for detecting house location and roof materials, estimating population density, and the population under risk in rural Africa.

0299

CAREGIVERS' PERCEPTION OF RISK FOR MALARIA, HELMINTH INFECTION AND MALARIA-HELMINTH CO-INFECTION AMONG CHILDREN LIVING IN URBAN AND RURAL SETTINGS OF SENEGAL: A QUALITATIVE STUDY

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Malaria parasites and worms frequently co-exist in children living in low- and middle-income countries where existing vertical control programmes for the control of these two conditions are not operating at optimal levels. This gap necessitates the development and implementation of strategic interventions to achieve effective control and eventual elimination of these co-infections. Central to the successful implementation of any intervention is its acceptance and uptake by caregivers whose perception about the risk for malaria-helminth co-infection has been little documented. Therefore, we conducted a qualitative study to understand the caregivers' perspectives about the risk as well as the behavioural and social risk factors promoting malaria-helminth co-infection among pre-school and school-aged children living in endemic rural and urban communities in Senegal. In June and December 2021, we conducted individual and group interviews, and participant observations, among 100 primary caregivers of children recruited from Saraya villages in southeast Senegal and among leaders and teachers of Koranic schools in Diourbel, western Senegal. Our findings showed that a majority of the study participants in the two settings demonstrated a high level of perception of risk for malaria and acceptable awareness about handwashing practices, but had misconceptions that malaria-helminth co-infection was due to a combination of excessive consumption of sugary food and mosquito bites. Our observations revealed many factors in the house structures, toilet practices and handwashing with ashes and sands, which the caregivers did not consider as risks for malaria-helminth co-infections. These findings underscore the need to promote caregivers' awareness about the existence and risk of malaria-helminth co-infection in children. This approach would assist in addressing the caregivers' misconceptions about the occurrence of the co-infection and could enhance their uptake of the strategic interventions targeted at achieving control and subsequent elimination of malaria and helminth co-infection.

0300

SEVERE ILLNESS DANGER SIGNS AMONG MALARIA POSITIVE CHILDREN: AN ANALYSIS OF HOUSEHOLD SURVEY DATA FROM 21 MALARIA ENDEMIC COUNTRIES IN SUB-SAHARAN AFRICA BETWEEN 2011-2020

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Diagnosing a child with severe malaria or another illness is difficult since symptoms of severe malaria can be clinically indistinguishable from other illnesses. In areas of high malaria transmission, where asymptomatic parasitemia is common, malaria may be incidental to other severe illnesses. An accurate diagnosis of severe illness among malaria positive children is critical to the treatment of sick children. Most data about severe illness come from children presenting to the formal healthcare system, there is little data about children who have not yet sought care. This analysis examined data from 42 Demographic and Health Surveys (DHS) and Malaria Indicator Surveys (MIS) across 21 countries in sub-Saharan Africa between 2011 and 2020. The outcome of interest is the presence of severe illness. This is defined as children age 6-59 months who were RDT-positive for malaria with at least one caregiver-reported severe illness sign/symptom, including extreme weakness, loss of consciousness, difficult breathing, seizures, abnormal bleeding, jaundice, heart problems, dark urine, or severe anemia (hemoglobin levels <7.0 g/dL, via a HemoCue device). The study includes a weighted descriptive country-level analysis and a multilevel mixed-effects logistic regression model to assess the determinants of severe illness. In examining all children tested for malaria (n=209,405), 24.8% were positive by RDT. Among children RDT-positive for malaria, 17.1% (95% CI: 16.4-17.8) had at least one severe illness sign/symptom, with variations between surveys. Severe illness symptoms were significantly associated with gender, age, and wealth quintiles. Children surveyed between 2016 and 2020 were significantly less likely to report at least one severe illness sign/symptom than those surveyed between 2011 and 2015 (AOR: 0.83; 95% CI: 0.78-0.88). In examining caregiver-reported severe illness danger signs and presence of severe

anemia, this analysis provides additional insights to the level of severe illness among malaria positive children at the population level. This estimate can help guide referral and management of severe illness in children.

0301

PREVALENCE OF ASYMPTOMATIC *PLASMODIUM FALCIPARUM* INFECTION IN SCHOOLS IN THREE DISTRICTS IN SENEGAL (2021)

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Malaria is endemic in Senegal, with a reported incidence of 31.2 per 1000 residents in 2021. Malaria transmission is highly seasonal, peaking in October and November, and is highest in southeast Senegal. The three southeastern regions recorded 79% of all cases and 44% of deaths in 2021. Seasonal malaria chemoprevention (SMC) has been implemented in Senegal for children up to ten years since 2014, necessitating evaluation of parasite prevalence among school-aged children and children under five years to monitor SMC impact. In low and moderate transmission contexts, school-aged children have higher parasite prevalence than children under five years but may be symptomatic less often and may constitute the majority of the parasite reservoir. In November 2021, we conducted a cross-sectional survey of school-aged children in two conventional and three residential, religious schools in Diourbel region (low-moderate transmission), five schools in Tambacounda region (moderate transmission), and, four schools in Kedougou region (high transmission), all of which are targeted for SMC. Data on demographics and preventive measures were collected, along with rapid diagnostic test (RDT) and dried blood spots (DBS) for molecular analyses. We enrolled 3,748 children 6-14 years old, including 920 children from residential, religious schools and 979 pupils from conventional schools in Diourbel, 852 in Tambacounda, and 982 in Kedougou. Of these, 40.8% were female, 46.9% were aged 5-9 years, and 53.1% were aged 10 or more years. Among children aged 5-9 years, 95% reported having received SMC. RDT positivity rates were 4.5% and 1.5%, respectively, in residential religious schools and conventional schools in Diourbel; 5.2% in Tambacounda schools, and 17.2% in Kedougou schools. Parasite prevalence was comparable among children 5-9 years (7.0%) and children aged 10 or more years (7.4%). School surveys are an important tool to monitor parasite prevalence among school-aged children. Results from molecular analysis will also be presented. Data from the school surveys will be compared with health facility and household data collected from the same study sites.

0302

THE EFFECTS OF METEOROLOGICAL FACTORS AND GEOGRAPHICAL ELEVATION ON MALARIA INCIDENCE IN ELIMINATION TARGETED DISTRICT OF ETHIOPIA

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Ethiopia has made significant strides in the fight against malaria. The country has now adopted & is implementing the global malaria elimination program, which is expected to be completed by 2030. The success of the elimination attempt, on the other hand, can be influenced by multiple factors. Climate & environmental conditions can be one of the most significant factors affecting the progress of elimination. As a result, the study aimed to investigate the burden & transmission drivers of malaria in one of the country's elimination targeted districts. From 2010 to 2017, all febrile patients in the district's health facilities were diagnosed for malaria using a microscope & Rapid Diagnostic Test. The malaria data were collected from the malaria registers, the meteorological data from the country's National Meteorological Agency, & the geographic coordinates of each village. The data were entered using EpiData 3.1, & analyzed by R version 4.0.0. During the study period, a total of 135,607 patients were diagnosed, with 29,554 (21.8%) of them being confirmed malaria cases. Only two species, *Plasmodium falciparum* & *Plasmodium vivax*, were identified, with 56.3 % & 38.4 %, respectively. The rest 5.2 % was a mixed infection. A time series plot revealed a significant reduction in malaria, with a clear downward trend in case numbers. In a Negative Binomial Regression, the transmission season, rainfall, temperature, elevation, & the patient's sex & age were found to be predictors of disease incidence & spatial distribution. An ARIMA (2, 1, 2), the best fit model for point prediction of potential malaria incidence in 2030, the target year for elimination, projected that the monthly incidence will fluctuate around 88 cases. Finally, the results showed a significant reduction in malaria morbidity in the district. The results of the predictive model, on the other hand, raised doubts about whether the elimination goal will be reached within the time frame. Thus, achieving the elimination goal would necessitate an equitable distribution & efficient use of current interventions, as well as the development of evidence-based interventions.

0303

POTENTIAL MALARIA IMPACT OF THE GRAND ETHIOPIAN RENAISSANCE DAM ON MALARIA TRANSMISSION IN ETHIOPIA

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Ethiopia is building a mega dam, called the Grand Ethiopian Renaissance Dam (GERD), on the Nile River. The effect of this dam on malaria risk of the population around the impoundment has not been well explored. Better understanding of the potential malaria risk helps design proper malaria control measures to safeguard public health. In this view, this study assessed malaria incidence and its correlation with environmental factors in western Ethiopia and demonstrated how GERD might impact malaria dynamics in the area. Multiple data sources were used including District Health Information Software 2 (DHIS2) malaria case data of three districts covered by GERD reservoir (2018 to 2021), district population data, Remote sensed environmental data, climate data, and published articles on the impact of dams on malaria epidemiology. Malaria incidence rates and trends in the setting were summarized; the non-parametric Spearman rank test was used to test the correlation of malaria incidence with environmental factors, and Mann-Kendall Trend and Sen's Slope tests to estimate the impact of dams on local climate (the example of Gibe dam in Ethiopia), and finally, the impact of GERD on malaria was demonstrated. The annual malaria incidence in GERD-covered districts ranged from 103

to 780 per 1,000 populations at risk with a fluctuating trend between 2018 and 2021. The environmental factors associated with increased malaria incidence were normalized difference vegetation index (ρ=0.64, P<0.001), rainfall (ρ=0.547, P<0.001) and enhanced vegetation index (ρ=0.68, P<0.000). Twenty years of data (10 years before and 10 after the Gibe dam) shows that it significantly increased rainfall and temperature in the area. Malaria remains high in the GERD districts. The Dam could create a favourable environment for mosquito breeding if proper vector control is not placed. Hence, incorporating malaria control measures in reservoir management such as suppressing shoreline breeding habitats and creating a buffer zone for population settlement should be prioritized to prevent unprecedented malaria epidemics in the dam area.

0304

PLASMODIUM FALCIPARUM NEUTRAL MICROSATELLITES TO INFORM MOLECULAR CORRECTION IN THERAPEUTIC EFFICACY STUDIES IN AFRICA

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The differentiation of recurrent malaria infections as a reinfection or recrudescence during a therapeutic efficacy study (TES) in high malaria transmission areas has implications for the periodic monitoring of antimalarial efficacy. Various *Plasmodium falciparum* molecular markers have been used to achieve this, including genotyping of polymorphic surface antigen coding genes (*msp1*, *msp2*, and *glurp*) and highly polymorphic neutral microsatellites. Recently, WHO updated the recommended TES genotyping methods to include a combination of *msp1*, *msp2*, and 1-3 neutral microsatellites. However, the optimal neutral microsatellites have not been specified and will be dependent on the malaria transmission level of a country or region. To address this, a database of seven neutral microsatellite markers (Poly-α, PfPK2, TA1, TA109, C3M69, C2M34, and 2490) from multiple TESs was compiled and analyzed to determine the sensitivity and diversity of each microsatellite marker. This included data from 41 collection sites in ten African countries (Angola, Benin, DRC, Ethiopia, Guinea, Madagascar, Mozambique, Rwanda, Tanzania, and Uganda) with 1283 pretreatment samples collected between 2016 and 2020. Sensitivity was assessed by calculating the locus-specific multiplicity of infection. Genetic diversity at each locus was estimated by Shannon's diversity index (H). Among the seven markers genotyped collectively as part of these studies, the most discriminant marker was Poly-α, followed by PfPK2 and TA1, based on both high sensitivity and diversity. C2M34 had higher diversity but was less sensitive than TA1. The TA109, C3M69, and 2490 loci had the lowest sensitivity and diversity scores. This study provides scientific evidence for the selection of Poly-α, PfPK2, and TA1 as the most sensitive and diverse microsatellite markers in the classification of reinfections versus recrudescent infections, an analysis integral to TESs.

0305

A PROSPECTIVE STUDY OF *PLASMODIUM FALCIPARUM* GENOMIC INTELLIGENCE IN MOZAMBIQUE

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The integration of genomic data into routine surveillance activities has the potential to increase actionable intelligence for making programmatic decisions on the optimal mix of control and elimination measures. With the aim of informing Mozambique's national malaria control and elimination strategy, we are conducting a prospective genomic surveillance study targeting different settings and populations. The specific objectives are to: 1) monitor molecular markers of drug and diagnostic resistance; 2) characterize transmission sources in low transmission areas; 3) estimate transmission levels and the effectiveness of antimalarial interventions; and 4) assess the value of pregnant women as sentinel population. Sampling will take place in households and health facilities in 19 districts across 9 provinces, representing different transmission strata and geographical areas. Dried blood spots and rapid diagnostic tests will be collected during the rainy and dry seasons from consenting patients of all ages (low transmission areas) or 2-10 year-old children (medium-to-high transmission settings) seeking care for malaria symptoms and from pregnant women attending their first antenatal clinic visit. Samples will also be collected in the context of interventions such as mass drug administration, seasonal malaria chemoprevention, indoor residual spraying, and intermittent preventive treatment in infants, to assess the impact of these on the *Plasmodium falciparum* molecular epidemiology. We will use a multiplex amplicon-based next generation sequencing approach targeting informative single nucleotide polymorphisms, structural variants and microhaplotypes. Genetic data will be incorporated into epidemiological and transmission models to identify the most informative relationship between genetic features and malaria epidemiology such as sources of transmission and programmatic effectiveness of interventions. Strategic genomic information will be ultimately integrated into the national malaria information and surveillance system to improve the use of the genetic information for programmatic decision-making.

0306

SPATIOTEMPORAL MAPPING OF MALARIA INCIDENCE IN SUDAN USING ROUTINE SURVEILLANCE DATA

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Malaria is a serious threat to global health, with over 95% of the cases reported in 2020 by the World Health Organization in African countries, including Sudan. Sudan is a low-income country with a limited healthcare system and a substantial burden of malaria. The epidemiology of malaria in Sudan is rapidly changing due to factors including the rapidly developing resistance to drugs and insecticides among the parasites and vectors, respectively; the growing population living in humanitarian settings due to political instability; and the recent emergence of *Anopheles stephensi* in the country. These factors contribute to changes in the distribution of the parasites species as well as malaria vectors in Sudan, and the shifting patterns of malaria epidemiology underscore the need for investment in improved situational awareness, early preparedness, and a national prevention and control strategy that is updated, evidence-based, and proactive. A key component of this strategy is accurate, high-resolution endemicity maps of species-specific malaria. Here, we present a spatiotemporal Bayesian model, developed in collaboration with the Sudanese Ministry of Health, that predicts a fine-scale (1km X 1km) clinical incidence and seasonality profiles for *Plasmodium falciparum* and *Plasmodium vivax* across the country. We use monthly malaria case counts for both species collected via routine surveillance between January 2017 and December 2019, as well as a suite of high-resolution environmental covariates to inform our predictions. These epidemiological maps provide a useful resource for strategic planning and cost-effective implementation of malaria interventions, thus informing policymakers in Sudan to achieve success in malaria control and elimination.

0307

IMPLEMENTING A SIMPLIFIED, AUTOMATED ALGORITHM TO CLASSIFY MALARIA CASES IN SOUTHERN LAOS AND IDENTIFY HOTSPOTS OF TRANSMISSION

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Malaria in Laos has decreased by 86% over the last twenty years and has become increasingly focalized in hotspots, particularly in southern Laos. Laos has adopted the 1-3-7 approach for malaria elimination in low burden districts, including case notification by day 1, case investigation and classification (CICC) by day 3 and response by day 7. CICC is completed by the health facility, not necessarily the point of care (POC), which can slow down the process and increase the work burden, making it difficult to expand to areas with a higher number of cases. We conducted a pilot to demonstrate the feasibility of CICC, without the target of within 3 days, at POCs in high burden districts by adding two questions on infection and travel history to the existing malaria case register form (CRF). Data were entered every month at the district level into a pilot DHIS2 module to classify cases using an automated algorithm. After the pilot, we examined the CICC rates, surveyed staff, and conducted a sink-source analysis. The pilot ran from April to September 2021, alongside routine surveillance activities, in 24 POC in high burden provinces of Salavan, Savannakhet, and Attapu. Out of 114 cases reported on the national malaria information system in the pilot sites, 101 (89%) cases were investigated and classified on DHIS2, exceeding the 85% target. On a scale of 1 to 5, the survey showed that most POC and district staff agreed that the components of the pilot were comprehensive (4.4), easy to implement (4.1), received adequate support (4.8), and acceptable given their workload (5.0). Attapu had the highest number of cases overall (46/101), and the highest number of local cases, 36 (84%), with 5 (12%) imported and 2 (5%) relapse cases. 3 of 5 imported cases were from a different district within the province. Meanwhile, Salavan reported the most imported cases (18/101), with 13 of the cases being imported from Sekong, a province not included in the pilot. Overall, these results suggest that it is feasible to conduct CICC at the POC and scale up to high burden districts. This would provide a greater understanding of transmission patterns allowing for better targeting of interventions.

0308

EXPOSURE PATTERNS OF HUMANS TO MALARIA VECTORS IN WESTERN KENYA AND IMPLICATIONS FOR MALARIA CONTROL

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Despite sustained implementation of insecticide-treated nets (ITNs), malaria remains a leading cause of morbidity and mortality in western Kenya. Night-time entomological and human behavioral data were collected as part of a cluster-randomized clinical trial evaluating the efficacy of a spatial repellent to correlate exposure patterns of household residents to malaria vectors and potential gaps in bite prevention. Human landing collections and direct observation of household member behavior, related to indoor or outdoor location and ITN use, were conducted in 48 households in Busia County western Kenya from May to August 2021, prior to SR distribution. Data was collected hourly, between 1700 and 0700 hours, indoors and outdoors. Captured mosquitoes were assessed for species determination, sporozoite infection and parity status. Entomological and human behavioral data were layered to estimate exposure to anopheline bites. *Anopheles gambiae s.l*. species complex and *An. funestus* comprised the majority of anophelines collected. Indoor biting rates were 59% and 71%, respectively. However, when accounting for overlayed indoor and outdoor resident location, an estimated 97% of bites occurred indoors. Using an ITN while sleeping was estimated to prevent 80% of bites for *An. gambiae s.l.* and 83% of bites for *An. funestus*. Remaining exposure for ITN users occurred largely indoors in the evening and early morning hours. For both ITN users and non-users, most exposure to malaria vectors within the household space was estimated to occur indoors, suggesting the added value of complementary indoor-oriented interventions such as spatial repellents. Additional research is needed to better understand potential gaps in protection away from home. Differences between unadjusted anopheline vector biting rates and human behavior-adjusted indicators highlight the importance of integrating entomological and human behavioral data for a comprehensive understanding of malaria risk including how exposure patterns may change by time, cultural contexts, and in response to new malaria control interventions.

0309

IMPROVING ROUTINE MALARIA DATA QUALITY THROUGH DATA REVIEW MEETINGS IN THE FAR NORTH AND NORTH REGIONS OF CAMEROON FROM 2019

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In the North and Far North regions of Cameroon, malaria burden remains high compared to other regions. In the 2019-2023 National Malaria Strategic Plan, surveillance is considered as a specific intervention aimed at

producing quality data for decision making. However, the collection and use of quality malaria data remains a challenge. To address this issue, the NMCP and partners have been conducting regular data review meetings to improve routine data quality in the North and Far North regions since 2019. These meetings consist of checking data consistency between District Health Information Software 2 (DHIS2) and source documents, making corrections and visualizing keys malaria indicators. We assessed the contribution of these data reviews to the change in quality of malaria data in these regions. We extracted DHIS2 data Jan 2011 - Dec 2021 on two malaria indicators: number of suspected malaria cases (SM) and number of suspected malaria cases tested with rapid diagnostic test or microscopy (SMt). We performed an interrupted time series analysis comparing data consistency before and after the introduction of data review meetings in january 2019. To measure change, we calculated the change in mean inconsistency per report submitted after data review meetings were introduced using a Bayesian negative binomial model adjusted for secular trend and seasonality. Data review meetings were associated with 71% (incidence rate ratio [IRR]: 0.29 [95% CI: 0.067–1.253]) reduction of mean data inconsistency of SM and SMt in Far North region and 78% (IRR: 0.22, [95% CI: 0.042–1.234]) reduction in North region. Adding data review meetings at the district level further reduced data inconsistency by 91% (IRR: 0.09 [95% CI: 0.019–0.438]) for both indicators in Far North region and 69% (IRR: 0.31 [95% CI: 0.047–2.283]) in North region. Holding these meetings at the district level only was associated with an 83% and 68% reduction of mean data inconsistency in Far North and North regions respectively. Regular data review meetings at regional and district levels likely contributed to improving malaria data quality and should be maintained and institutionalized.

0310

THE IMPACT OF THREE YEARS OF INDOOR RESIDUAL SPRAYING (IRS) INTERVENTION ON CONTROLLING MALARIA DISEASE IN KAMONYI DISTRICT, RWANDA

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Following the upsurge of malaria occurred earlier in the last decade, the Government of Rwanda and its Partners have been combining efforts based on local evidences and increasing the coverage of interventions for effective malaria control countrywide. The primary vector-control interventions deployed in Rwanda for the management of insecticide resistance are Indoor Residual Spraying (IRS) with non-pyrethroid insecticides and Long Lasting Insecticidal Nets (LLINs). The IRS intervention targets the districts with high burden of malaria transmission with a rotation of insecticide every two years. The Kamonyi district is bordering with Kigali-City, in West, and benefited the IRS intervention with annual round from 2019. The insecticide used was Fludora Fusion WP-SB 56.25 in 2019 and 2020 and Actellic 300 CS in 2021 with an annual coverage of more than 98.50% of the targeted structures. This abstract assesses the impact of IRS in malaria control in Kamonyi district for the three consecutive years of its implementation. A comparative analysis of data extracted from the Routine Health Management Information System (RHMIS) of the Ministry of Health was performed on the average of outpatients and inpatients malaria cases or deaths for the three years before IRS (2016-2018) and the three years during the IRS intervention (2019-2021) in Kamonyi district. The analysis showed that in the last three years before spraying, simple malaria cases were 625,149 while the number of severe malaria was 1,464 cases and 37 malaria deaths. After the implementation of IRS in the three years (2019-2021), malaria decreased respectively to 528,786 (15%) for simple malaria cases, 501 (66%) for severe malaria and 10 cases (73%) of malaria deaths. The malaria incidence was dropped down from 599 (z-score: 0.87) in 2019 to 229 (z-score: -1.83) in 2021. The IRS using new generation of insecticides with high coverage contributed to reduce simple malaria incidence and importantly severe malaria cases and related death in Kamonyi district.

0311

APPLYING A STANDARDIZED, MOLECULAR ENTOMOLOGY DATA LABELING SYSTEM IN GHANA TO EFFECTIVELY INTEGRATE INTO CENTRAL DHIS2 DATABASE

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To reverse the rising trend in malaria cases, the U.S. President's Malaria Initiative's (PMI) flagship vector control program—the VectorLink project—uses entomological data to identify the mosquito vector, characterize its behavior, monitor susceptibility to insecticides, and measure the quality and impact of vector control interventions. By integrating molecular analysis as part of entomological monitoring, the project possesses a more granular understanding of species diversity, parasitic infection rates, and distribution of genetic markers for insecticide resistance towards more targeted vector control measures. However, molecular data management is complex, often fragmented, inconsistently used, and rarely integrated into existing information systems. To combat this, the PMI VectorLink project piloted a mosquito labelling system for molecular data in Ghana that tracks mosquito samples from the field to the laboratory, linking the entomological field and bioassay data set to the molecular data set through a central DHIS2 database to increase data utility. In mid-2022, a dual code system with scannable labels, unique identifiers, and central registration was implemented along with an archival system to account for previously collected mosquitoes from each month in 2022. A subset of collected mosquitoes were labelled with a piloted unique identifier and sent to the laboratory for molecular analysis. This pilot allowed for identification of system and workstream implementation weaknesses, including monitoring the integrity of pooled samples to ensure downstream use, and the roll-out established new roles and responsibilities for molecular data management. Based on the success of the pilot, by the end of the year, the labeling system will expand to include all insecticide resistance samples in Ghana. With this progress, all field and laboratory entomology data collected in 2022 for Ghana will be managed within the central database, VectorLink Collect, which facilitates transfer to the Ghana DHIS2 national health information system.

0312

A NON-PARAMETRIC APPROACH TO ESTIMATE MULTIPLICITY OF INFECTION AND PATHOGEN HAPLOTYPE FREQUENCIES

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Global efforts to monitor the spread of infectious diseases, particularly by molecular surveillance, led to tremendously reduced morbidity and mortality. However, there are still many confounding factors in molecular surveillance. Observing the presence of multiple genetically-distinct variants (lineages) within an infection (often referred to as multiplicity of infection - MOI) is common in many infectious diseases such as malaria. MOI is an epidemiologically and clinically relevant quantity as it scales with transmission intensity and might impact the clinical pathogenesis of the disease. In malaria, MOI is considered an important quantity, and a variety of methods to estimate it exists. A limitation of many statistical methods is the underlying assumption that MOI follows a Poisson distribution. For diseases like malaria, this assumption has been questioned because mosquito biting rates follow a negative binomial distribution, which better captures heterogeneity in biting rates in the vector population. We could show that maximum-likelihood estimation under this more general distribution leads to the same estimates as the Poisson model. To resolve this structural limitation, we provide a nonparametric approach to estimate haplotype frequencies and the multiplicity of infection (MOI). The unique characteristic of this approach is that it allows capturing overdispersion in

the distribution of MOI. E.g., in the case of malaria, overdispersion arises from seasonal fluctuation in transmission intensities or heterogeneous mosquito biting rates. In particular, we outline the underlying statistical model and show how the maximum-likelihood estimate of haplotype frequencies and the distribution of MOI can be obtained using the Expectation-Maximization (EM) algorithm. We report on the accuracy and precision of the proposed method (i.e., bias and variance of the estimator) based on a simulation study. Finally, we apply the method to estimate the distribution of MOI from malaria molecular data from endemic areas in Cameroon and Kenya.

0313

INVESTIGATION OF INCREASED MALARIA CASES IN SOLWEZI AND KALUMBILA DISTRICTS, NORTH-WESTERN PROVINCE OF ZAMBIA, SEPTEMBER, 2021

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North western province has been receiving financial and material support from First Quantum Minerals (FQM) alongside with government towards malaria control and elimination in Kalumbila and Solwezi districts since 2014. Despite the yearly support, malaria morbidity remains high. We conducted an investigation to establish the existence of an outbreak and the possible risk factors. Purposively, we sampled six health facilities from each district based on proximity to FQM mining sites, high malaria burden, past issues with data quality and at least one FQM owned facility from each district. We conducted data quality audits (DQA) for first and second quarter, 2020 to determine that there are no data quality errors and that the incidence is significantly abnormally high. We calculated epidemic thresholds from the third quartile of 5-year historic data. We collected qualitative data on malaria interventions and environmental factors using key informant interviews. We used RStudio to run spearman's correlation to compare trends in malaria incidence with rainfall pattern. The DQA revealed low overall data accuracy below 70%. Malaria case incidence in 2020 surpassed epidemic thresholds in both districts. A statistically significant positive monotonic relationship was found between rainfall and malaria incidence per 1000 population (rho=0.524, p-value < 0.001). A malaria outbreak was observed in Solwezi and Kalumbila districts in 2020. Poor data quality and reporting limits the ability of district health offices to detect and timely respond to outbreaks, so we encouraged health facilities to hold regular data audits to improve data entry, storage, and reporting. We recommended the sites rely also on patterns of rainfall as an early warning system and strengthen malaria epidemic preparedness and response at district level.

0314

THE RELATIONSHIP BETWEEN HOUSING, OCCUPATION, AND EDUCATION AND MALARIA RISK IN RURAL MOZAMBIQUE

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Housing construction is a known risk factor for *Plasmodium falciparum* infection. The hypothesized mechanism for this risk is that poor construction materials provide access for infectious mosquitos. However, different parts of the house structure (walls, roof, windows, eaves, and floors) have shown varying associations with malaria risk across different settings. It has been hypothesized that housing structure mediates the true association between income and malaria infection. This study investigated the complex relationships between housing construction, occupation, and education. We conducted a community-based, cross-sectional study of malaria prevalence and risk in Sussundenga Village, Mozambique from December 2020-February 2021. Ninety-eight (98) households with 302 residents completed the study. The overall malaria prevalence by rapid diagnostic test (RDT) was 31%. Rudimentary floor construction [OR: 2.1 (1.3-3.5)] and open windows [OR: 1.95 (1.2-3.3)] were independently associated with malaria infection. When adjusted for individual level confounders (age, insecticide treated net use, and number of residents per household) rudimentary roof [OR: 2.5 (1.1-5.5)], wall [OR: 1.8 (1.0-3.0)], floor [OR: 1.9 (1.2-3.3)] construction and open windows [OR: 2.0 (1.2-3.5)] were all associated with malaria infection. When education level (primary, secondary, tertiary) of the head of household and occupation (full-time, part-time) was added to the model, all associations between household structure were nullified except for rudimentary roof structure, suggesting the association between education and occupation is partially mediated by housing structure. While not statistically significant, the association between education and malaria infection was most strongly mediated by housing structure (18%: roof type, 28%: wall type, 44%: roof type, and 16%: windows). These results show that both education and occupation play an important role in household-level protection against malaria infection. This is partially mediated through housing structure, which is the primary risk factor for infection at the household level.

0315

TRANSITIONING MALARIA SURVEILLANCE IN ZANZIBAR FROM MALARIA EARLY EPIDEMIC DETECTION SYSTEM (MEEDS) TO INTEGRATED DISEASE SURVEILLANCE AND RESPONSE (IDSR) SYSTEM: AN ON-GOING SYSTEM EVALUATION

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A timely, complete, and actionable malaria surveillance system is critical to Zanzibar's success in malaria elimination. Zanzibar currently has two parallel weekly facility-based, passive surveillance systems that capture similar key malaria indicators: Malaria Early Epidemic Detection System (MEEDS) and Integrated Disease Surveillance and Response (IDSR). Zanzibar is in the process of streamlining malaria surveillance by discontinuing MEEDS and transitioning solely to IDSR in mid-2022. We assessed the performance of the IDSR and compared its performance to MEEDS to identify strengths, weaknesses, and lessons learned that stakeholders can leverage to support the successful transition from MEEDS to IDSR. We analyzed malaria indicators reported through the MEEDS and IDSR systems during January - August 2021 to estimate the number of reporting facilities, completeness, and timeliness (submitted by specified weekday), and describe data quality. We conducted key interviews with national and district-level staff, and health workers from 74 randomly selected health facilities from Unguja and Pemba islands, on knowledge of malaria case management and the strengths, challenges, and available resources to support malaria surveillance. Preliminary quantitative findings indicate lower data timeliness (77.2%) and completeness (93.4%) in IDSR when compared to the well-established MEEDS (81.4% and 99.2%, respectively). Initial qualitative findings suggest that most respondents are aware of malaria case management and have the key resources needed for IDSR and MEEDS reporting. However, there are gaps in the processes used for compiling weekly reports (e.g., lack of standardization for tallying complex IDSR indicators for aggregate data, numerous data sources from which patient information must be abstracted, including manually created laboratory books). These gaps have made it difficult to reproduce weekly reports during the data quality assessment. The final analysis will guide recommendations to strengthen the IDSR to improve long-term success as Zanzibar transitions surveillance systems for malaria elimination.

0316

GOLD MINERS SHOOT UP MALARIA TRANSMISSION IN INDIGENOUS AREAS OF RORAIMA, BRAZIL

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This descriptive study, based on secondary data, was carried out with the objective of knowing when, where, and who falls ill with malaria in Roraima, a Brazilian state, from 2010 to 2019. During this period, 113,326 autochthonous cases, 3,409 hospitalizations, and 54 deaths from malaria were reported. The annual parasitic incidence and the number of hospitalizations showed significant changes over the period, but without significantly affecting the number of deaths. The increase in the proportion of *P. falciparum* infections was significant throughout the study but did not influence hospitalization and death figures. Cases imported from Venezuela had increased significantly since 2016 and those with transmission in rural, urban, and settlement areas have decreased between 2010 and 2014. But, malaria prevalence in indigenous and mining areas has been increasing since 2014. The way gold miners cause dramatic changes in the environment, where mining wells produce a multitude of breeding sites, added to the behavior of miners who work with little clothes, at times of greater vector activity, together with the presence of asymptomatic carriers of the disease, contribute to the high incidence of malaria in mining sites. Besides that, the great mobility of miners facilitates the renewal of the susceptible population by the constant entry and exit of infected or not infected people. We conclude that the presence of miners in Yanomami indigenous areas is a reality that has been contributing to the increase of malaria cases in Roraima. In this way, the need to implement health policies that also meet this contingent is reinforced, and it is necessary to include other government bodies in the discussion on mining in indigenous lands which, like any other economic activity, must take into account the principles of sustainability, preservation of biodiversity and guaranteeing the cultural and social rights of indigenous peoples to ensure the social well-being and health of the entire indigenous and non-indigenous population.

0317

ASYMPTOMATIC *PLASMODIUM* PREVALENCE IN HIGH-RISK POPULATIONS IN MONDULKIRI, CAMBODIA

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Though malaria remains one of the most serious public health issues globally and is a leading cause of mortality in many developing countries, many areas are moving towards local elimination. Knowledge of both symptomatic and asymptomatic malaria point prevalence on a subnational scale allows the estimation of the number of parasites present in the transmission system enabling the targeting and tailoring of resources towards greater impact and better use of available capacity - especially in lower transmission areas. Malaria incidence or prevalence is typically based on symptomatic reporting of patients in conjunction with a positive malaria diagnostic - conventionally RDTs or microscopy. Asymptomatic malaria parasites carriers usually do not report for malaria diagnosis, resulting in this proportion of infections not being reported, even though they may serve as a significant reservoir of parasites. *Plasmodium* detection by PCR is much more sensitive than RDT or microscopy, particularly in low density or mixed infection cases, and it is valuable for the accurate collection of malaria epidemiological data. This study aimed to determine the PCR-based point prevalence of malaria infection by parasite species in forest rangers, forest dwellers, and forest goer populations, which are at high risk of malaria infection. A cross-sectional survey was performed during the high transmission season in November and December 2021, in Mondulkiri province, Cambodia. Blood samples collected on filter papers from participants were screened for *Plasmodium spp.* using PCR. The primary outcome measure of estimated mean malaria infection prevalence (by parasite species) per target population was determined. This result will allow the estimation of the amount of the reservoir in the high-risk populations and help implement an effective malaria control program toward achieving malaria elimination.

0318

INFORMING STRATIFIED MALARIA CONTROL FOR HIGHEST IMPACT: A SEMI-MECHANISTIC, MULTI-METRIC, BAYESIAN GEOSTATISTICAL MODELLING FRAMEWORK TO SUPPORT MALARIA CONTROL PLANNING IN MOZAMBIQUE

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The burden of malaria is disproportionately felt in a small number of high-burden countries, with ten African nations accounting for ~66% of global cases in 2017. Following large reductions in burden early this century, since 2015 progress has stalled, leading WHO and RBMP to coordinate the High Burden to High Impact initiative - a country-led program centred around a new paradigm in malaria control: intervention mixes which are efficiently targeted using a deep understanding of human, vector, and parasite ecologies. For such an approach to be feasible, programs require timely and accurate estimates of spatio-temporal variance in risk. The traditional data used in malaria risk estimation - cross-sectional parasite rate surveys - are spatially rich but infrequent. However, ongoing investment in strengthened routine health surveillance systems has resulted in an improved stream of robust, near-real-time, longitudinal information on the burden of malaria in health facilities. Synthesising these sources of data, each giving a partial but complementary view of the full picture, is key to producing these maximally accurate spatio-temporal estimates of malaria infection and morbidity. Here we present a new modelling framework to achieve this synthesis. We highlight Mozambique here thanks to its wide-reaching National Health Service and range of transmission settings. After adjusting incidence rates for variations in access to care and data quality, the framework jointly infers *Pf*PR and incidence, with a mechanistic model of fever aetiology determining a plausible mapping between community PR and observed cases in clinics. This extension of geostatistical techniques allows for the explicit inclusion of the prophylactic effect of antimalarials; and the role of non-malarial fevers prompting otherwise asymptomatic *Pf* infections to seek care. The outputs of this framework offer transformational improvements in risk stratification for malaria control planning: it provides detail on seasonal variation in burden, a country-specific *Pf*PR-incidence relationship; and a suite of spatio-temporally granular maps with principled uncertainty.

0319

CHARACTERIZING CASES OF FATAL SEVERE MALARIA IN THE CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) SITES OF MANHIÇA AND QUELIMANE, MOZAMBIQUE

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More than 5 million deaths occur annually in children <5 years of age globally, with malaria accounting for approximately 8% of these deaths. In 2020, there were 2-4M severe malaria cases and 627,000 malaria deaths worldwide, with 94% of these deaths occurring in Sub-Saharan Africa, mainly affecting children <5 years of age. Between December 2016 and December 2021, as part of the Child Health and Mortality Prevention Surveillance (CHAMPS) network, minimally invasive tissue sampling (MITS) were conducted postmortem in Manhiça and Quelimane district areas to ascertain the cause of death of 505 children <5 years of age and stillbirths, after written informed consent was obtained. Of those deaths, 43 (8,5%) were in infants and 73 (14,4%) were in children aged 12-<60 months. For each case, clinical, microbiological, molecular, histopathological and verbal autopsy data were reviewed by a multidisciplinary panel of local experts who determined the chain of events leading to death using the WHO ICD-10 coding system. Of 116 deaths in infants/children with a cause of death determined, malaria was in the causal chain leading to death in 20 (17%), being in 17 (15%) considered the underlying cause (2 infants and 15 children between 12 and 60 months). Of these malaria deaths 15 (75%) were specified as cerebral malaria and 10 children had more than one cause of death determined. Among these malaria deaths with multiple causes, 3 were HIV positive, 5 had also pneumonia (2 aspiration pneumonia, 1 pneumonia due to *H. influenzae*, 1 pneumonia due to gram-negative bacteria and 1 polymicrobial pneumonia (*S. pneumoniae, H. influenzae, M. catarrhalis*), 1 had polymicrobial sepsis (*S. pneumoniae, K. pneumoniae, Salmonella spp*), 1 had anemia and 1 had hypoglycemia. Considering other significant conditions contributing to death we found: anemia, acute gastroenteritis, aspiration pneumonia, acute malnutrition, hypoglycaemia and HIV exposure. Malaria remains a leading cause of death in children in Mozambique. Understanding the full chain of events leading to death and associated conditions could help to guide better strategies for research and mortality prevention.

0320

AN EVOLUTION FROM A PREDOMINANT K1 ALLELIC VARIANT TO MAD20 OF MSP1 GENE BETWEEN 2015 TO 2019 IN METEHARA, SOUTHEAST ETHIOPIA

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In this study, we try to investigate the temporal dynamics of genetic diversity and multiplicity as a result of evolutionary change in the genes that contribute to *Plasmodium falciparum* infection. We used a cross-sectional study design to carried out. From eighty-three dry blood spots from malaria patients who were screened for *P. falciparum* mono-infection by QPCR Eighty three confirmed P. falciparum were genotyping to merozoite surface protein 1,2 and glutamate-rich protein using nested PCR. Seventy (84.3%) of the isolates were successfully genotyped for all three target genes in In 2015 and 2019, the allelic distributions of the three genes differed significantly (P= 0.001). Overall, the most common allelic families for msp1 and msp2 were K1 and FC27 respectively. For glurp, eight distinct genotypes were identified. Genotyping of msp1, msp2 and glurp was 25 (86.2%), 25 (86.2%) and 24 (82.2%) respectively. K1, MAD20 and RO33 all have 19(65.5%), 3(10.3%) and 3(10.3%) msp1 allelic families respectively. Over all the multiplicity of infection was 1.67 (95 percent CI 1.54-1.74) and the heterozygosity index for msp1, msp2, and glurp was 0.48, 0.70, and 0.55 respectively. This study provides current information on the genetic diversity of P. falciparum populations in five-year intervals, The progression of the dominant K1 variant from 2015 to MAD20 variant in 2019 was observed in this study.

0321

USING TREE-BASED IDENTITY-BY-DESCENT SEGMENTS TO EVALUATE THE EFFECT OF DIRECTIONAL SELECTION ON THE ESTIMATION OF RECENT EFFECTIVE POPULATION SIZE AND POPULATION STRUCTURE IN *PLASMODIUM FALCIPARUM*

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Intensive malaria elimination efforts to counter the spread of multidrug-resistant *Plasmodium falciparum* (*Pf*) have led to a dramatic decrease in malaria cases in the Greater Mekong Subregion, with a corresponding reduced parasite effective population size (N_e) and more fragmented population structure. Estimates of parasite population demography are critical for monitoring sources and sinks of malaria transmission and the impact of targeted interventions in reducing malaria. Identity-by-descent (IBD) has been widely used in human studies to estimate N_e and population structure in recent time scales. However, strong positive selection related to antimalarial drug resistance in *Pf* can potentially cause inaccurate estimation of parasite demography. Here, we simulated positive selection using coalescent (msprime) and forward simulators (SLiM), implemented a tree-based true IBD-estimation algorithm, and directly evaluated how selection affects IBD-based demography estimation in *Pf*. With high-quality IBD as input, we found that selection strength, duration, and starting frequency of the selected allele all affect IBD coverage (enrichment by position) and length distribution, and thus estimation of parasite N_e (IBDNe). The effects are further aggravated when reductions in N_e occur in recent time frames. We found that removing IBD segments within the high-IBD region associated with selection can reduce selection-induced bias in N_e estimation. By simulating a multi-subpopulation model, we found that strong positive selection increases within and inter-population IBD sharing and blurs underlying structure; however, IBD filtration allows identification of finer-scale, more accurate population structure. We have jointly called variants from whole genome sequence data for >2300 Southeast Asian *Pf* isolates from MalariaGen *Pf* v6 and in-house data sets. We will evaluate the effects of drug resistance-related positive selection on the estimation of *Pf* demography by including and excluding regions predicted to be under selection and examine the necessity of selection-adjusted genomic analysis for low transmission settings.

0322

CHROMOSOME SPLITTING OF *PLASMODIUM BERGHEI* USING THE CRISPR/CAS9 SYSTEM

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Spatial arrangement of chromosomes is responsible for gene expression in *Plasmodium* parasites. However, methods for rearranging chromosomes have not been established, which makes it difficult to investigate its role in detail. Here, we report a method for splitting chromosome in rodent malaria parasite by CRISPR/Cas9 system using fragments in which a telomere and a centromere were incorporated. The resultant split chromosomes segregated accurately into daughter parasites by the centromere. In addition, elongation of de novo telomeres were observed, indicating its proper function. Furthermore, chromosome splitting had no effect on development of parasites. Splitting of the chromosome is expected to alter its spatial arrangement, and our method will thus be useful for investigating its biological role related with gene expression.

0323

MICROSATELLITE CHARACTERIZATION AND ANTIGENIC SEQUENCING OF KENYAN *PLASMODIUM FALCIPARUM* FIELD ISOLATES FOR DOWN SELECTION OF NEW STRAINS FOR USE IN CONTROLLED HUMAN MALARIA INFECTION (CHMI) STUDIES

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The development of an effective malaria vaccine would be monumental in helping control and eliminate malarial infections, which are a global risk to human health. Due to the low efficacy of the current malaria vaccines, it is essential that challenge strains used during vaccine and drug trials accurately reflect the genetic diversity of *Plasmodium falciparum* strains in the field. Currently, only four *Pf* strains are being used as challenge strains during Controlled Human Malaria Infection (CHMI) studies that test vaccine and drug efficacy. In order to identify additional strains for future use in CHMI studies that reflect the genetic diversity present in the field, we are receiving blood samples from subjects infected with *Pf* from clinical sites in Colombia, Ghana, Kenya, and Thailand with the intent to identify a strain that is genetically distinct from the current *Pf* challenge strains for use in CHMI studies. To date, eight isolates have been received from USAMRD-Africa in Kenya. *Pf* strains from these samples have been successfully culture adapted and genetically characterized by both microsatellite (MS) analysis of twelve loci and Sanger sequencing of the genes CSP, AMA1, MSP1, and MSP2. Two of the eight samples were found to be polyclonal and were subsequently cloned via limiting dilutions in an effort to isolate parasites into monoclonal cultures. The cloned cultures were reassessed via MS analysis to ensure they were singularly clonal before proceeding with antigenic sequencing. In total, twelve different strains have been identified, assayed via MS analysis, and sequenced. All twelve Kenyan strains were genetically distinct from 3D7 and 7G8, the current strains used for CHMI studies, based on targeted sequencing. In addition, they appear to cluster similarly with other East and West African *Pf* strains based on genetic distance matrices constructed from sequencing data. These strains will ultimately be compared against new isolates, tested for drug susceptibility and gametocyte formation, optimized for infection of mosquitos, assayed for liver cell infectivity, and considered for future *Pf* strains in CHMI trials.

0324

FROM SNPS TO MICROHAPLOTYPES - SEARCHING FOR GEOGRAPHIC SIGNALS IN *PLASMODIUM FALCIPARUM* DNA

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Modeling *Plasmodium falciparum* spatial population structure may contribute to strategies for malaria elimination by helping identify the origin and spread of infections. The wealth of next generation sequencing data that has been acquired from natural infections in endemic areas presents an opportunity to understand geographical patterns of parasite populations in great detail. Here, we use a machine learning algorithm to evaluate the spatial structure of *Plasmodium falciparum* infections in Mozambique. We used whole genome sequencing data from 832 samples from 7 provinces of Mozambique collected between 2015 -2019, and extracted allelic information from high quality SNPs and microhaplotypes with high diversity. We calculated genetic distances between pairs of samples using SNP genotypes, and performed Principal Coordinates analysis on the genetic distance matrix. We then applied the Random Forests machine learning algorithm on microhaplotype alleles to classify samples based on geographical location. We assessed allele contribution to geographic differentiation using the variable importance rank from the Random Forests classifier. Our results show that using either whole-genome level high quality SNPs or a selection of high-diversity microhaplotypes, samples can be classified at a regional level between Northern and Southern Mozambique. However, at the province level, the classifier fails to accurately predict sample location. While this regional structure may be sufficient to infer parasite importation in elimination settings in southern Mozambique, further analyses are ongoing to identify whether finer-scale population structure is reproducibly detectable at the province level among *Plasmodium falciparum* isolates in Mozambique, using existing and prospectively collected data.

0325

PLASMODIUM FALCIPARUM GENETIC DIVERSITY IN COINCIDENT HUMAN AND MOSQUITO HOSTS

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Population genetic diversity of *Plasmodium falciparum* antigenic loci is high despite large bottlenecks in population size during the parasite life cycle. The extent of this diversity in human blood-stage infections, following expansion from a small number of liver-stage schizonts, has been well described. However, little is known about parasite genetic diversity in the vector, where a similar bottleneck and expansion occurs following parasite mating and where parasite genotypes from several different human infections may accumulate. We assessed parasite genetic diversity within human and mosquito *P. falciparum* infections collected

from the same households during a 14-month longitudinal cohort study using amplicon deep-sequencing of two antigenic gene fragments (*ama1* and *csp*). To a prior set of infected humans (n = 1175/2813 with 86.2% sequencing success) and mosquito abdomens (n = 199/1448 with 95.5% sequencing success), we added *ama1* and *csp* haplotypes from infected mosquito heads (n = 134/1448 with 98.5% sequencing success). Across all sample types we observed 456 *ama1* and 289 *csp* unique haplotypes. Only 20.0% (*ama1*) and 21.5% (*csp*) of these haplotypes were shared between humans and mosquitoes, although these made up 89.4% (*ama1*) and 93.9% (*csp*) of the total set of sequenced haplotypes. While both hosts contained many rare haplotypes, population genetic metrics indicated that the overall and sample-level parasite populations were more diverse in mosquitoes than in humans, and infections were more likely to harbor a dominant haplotype in human than in mosquito infections (as determined by the proportion of sequenced reads). Finally, within a given mosquito there was little overlap in genetic composition of the abdomen and head, suggesting that infections may be cleared from the abdomen during the course of a mosquito's lifespan. Taken together, our observations provide evidence for the role of the mosquito vector in maintaining the diversity of malaria parasite populations.

0326

NOVEL MOLECULAR INVERSION PROBES FOR HIGH-THROUGHPUT GENOTYPING OF *PLASMODIUM VIVAX* POPULATIONS

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Over the last decade, genomic epidemiology of *Plasmodium falciparum* has become a useful tool for studying population movement, antimalarial resistance, importation, and other issues around elimination. Molecular inversion probes (MIPs) provide a highly multiplex and highly scalable genotyping approach that has provided valuable information about *P. falciparum* population genomics in Central Africa, East Africa, and the Horn of Africa. MIPs enable genome-wide coverage in an efficient and affordable fashion. *Plasmodium vivax* is the most widespread human malaria pathogen, with a global distribution, including in sub-Saharan Africa. In many areas where *P. falciparum* control is working, *P. vivax* has become an emerging malaria threat. As a result, there has been a recent proliferation in global *Plasmodium vivax* genomics studies, as well as a superior genome assembly from a Papua New Guinean isolate. Leveraging the success of MIPs in *P. falciparum*, we have developed MIP panels for the investigation of *P. vivax* populations. These four MIP panels include one containing 741 probes spanning multiple known genes of interest (e.g. reticulocyte binding proteins, Duffy binding proteins, potential vaccine targets, potential drug resistance genes, and diversity markers) and three MIP panels containing 1,625 probes designed using SNPs generated from all known published *P. vivax* genomes as well as newly generated genomes from Peru and the DRC. The SNP panels include a panel based on high F_{ST} SNPS that differentiate populations from different global geographic regions and two panels based on neutral SNPs. Using these panels, we have investigated the population structure from 689 Peruvian *P. vivax* samples collected by NAMRU in the region around Iquitos. We describe local connectivity between different populations of parasites as well as diversity in proteins involved in invasion, resistance, and vaccine candidates.

0327

STRONG FINE-SCALE SPATIAL AND TEMPORAL STRUCTURE OF RESIDUAL *PLASMODIUM FALCIPARUM* IN ZANZIBAR DETECTED THROUGH MULTIPLEXED AMPLICON SEQUENCING AND MINION SEQUENCING

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Over the past 15 years, Zanzibar has made great strides towards malaria elimination; yet progress has stalled despite access to efficacious antimalarials and good vector control coverage. Reactive case detection (RCD) using RDTs is routinely conducted by the Zanzibar Malaria Elimination Program (ZAMEP). To better understand residual *Plasmodium falciparum* transmission dynamics, we characterized the genetic diversity of parasites circulating within 5 districts covering both main islands. We sequenced 518 *P. falciparum* dried blood spot (DBS) samples at 35 loci using a novel, highly multiplexed droplet digital PCR (ddPCR)-based high-throughput amplicon deep sequencing method. Sequencing data was obtained at high coverage (median 98.6%) in DBS with ≥10 parasites/μL. The parasite population in Zanzibar was highly diverse (average H_E = 0.73) and 70% of infections were polyclonal. Infections in people with a recent travel history could not be distinguished from infections in individuals who had not traveled but had a significantly higher MOI. Strong fine-scale spatial and temporal structure in local parasite populations was observed, with two clearly separated clusters on Pemba Island. Relatedness analysis by identity-by-descent (IBD) revealed multiple near-clonal clusters in villages, linked to clinical cases. Travel history combined with genomic data revealed spread of these infections over the archipelago. No *kelch13* mutations were identified, but high prevalence of known resistance-associated mutations in *dhfr*, *dhps*, *mdr1*, and *mdr2* genes. No *hrp2/hrp3* deletions were found. A smaller panel of 6 highly informative microhaplotypes and 6 full-length drug-resistance markers was optimized for *MinION* sequencing and is currently being evaluated for in-country sequencing in Zanzibar. In conclusion, high-resolution *P. falciparum* genotyping identified pronounced population structure in Zanzibar. Closely related parasites within households point to clinical cases as important identifiers of transmission. Targeted interventions should be tested for the control of isolated parasite populations on the archipelago.

0328

RELATEDNESS OF *PLASMODIUM FALCIPARUM* WITH *PFHRP2* AND *PFHRP3* DELETIONS IN THE HORN OF AFRICA COMPARED TO OTHER GLOBAL ISOLATES

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Deletions of *pfhrp2 (*and paralogue *pfhrp3*, *pfhrp2/3*) genes threaten HRP2/3 antigen-based rapid diagnostic test (RDT) diagnosis of *Plasmodium falciparum.* Though *pfhrp2/3* deletions have been found in *P. falciparum* populations in different parts of the world, the high prevalence of deletions in the Horn of Africa (HoA) have provoked recommendations for alternate diagnostics for detecting *P. falciparum* infection in Ethiopia,

Eritrea, and Djibouti. It is unclear if deletions in the *pfhrp2/3* genes observed in different global settings are a result of parasite importation events or *de novo* gene deletions on endemic background lineages. Molecular data for a panel of seven *P. falciparum* neutral microsatellite (NMS) genomic markers was gathered for *P. falciparum* samples from three countries in the HoA and 11 other global locations for a total of 622 specimens. Relatedness among isolates was assessed by *pfhrp2/3* genotype through principal component analysis (PCA) and estimates for Hendrick Pairwise G_{ST}. Regardless of *pfhrp2/3* genotype, *P. falciparum* within the HoA was more related to other African isolates compared to Asian and New World parasites. For isolates showing *pfhrp2* deletions, Ethiopian, Djiboutian, and Eritrean parasites were all closely related (Pairwise G_{ST} <0.85) compared to *pfhrp2* deleted strains from Sudan, Peru, and Suriname (Pairwise G_{ST} >0.92), with similar findings in comparing strains with *pfhrp3* single deletions. Within the HoA, the relatedness of Ethiopian and Djiboutian gene deleted isolates was highest (Pairwise G_{ST}=0.68) compared with Eritrean and Djiboutian (Pairwise G_{ST}=0.77) or Eritrean and Ethiopian (Pairwise G_{ST}=0.84) isolates. *P. falciparum* with deletions in *pfhrp2/3* genes appear to have arisen *de novo* within background lineages in the HoA, and the evidence from this current study do not support the hypothesis that these parasites have been imported from other global sites. Ethiopian and Djiboutian deleted parasites within the HoA appear to have the most recent common ancestor.

0329

TARGETED NEXT GENERATION GENOMIC SURVEILLANCE APPROACHES TO CHARACTERIZE *PLASMODIUM VIVAX* RELATEDNESS

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Critical knowledge gaps remain in *Plasmodium vivax* epidemiology, largely due to the challenge of defining parasite relapse periodicity - this requires characterization of recurrent parasitemia that arise from either relapses from dormant hypnozoites, recrudescences, or reinfections. Molecular approaches in combination with relatedness inference and time-to-event analysis between the infective episodes offer great potential to resolve this. We have used microhaplotype markers to create a genotyping barcode for defining relatedness between recurrent infections. Using a global collection of 1,895 *P. vivax* genomes, we have selected 92 short (200 base pair) microhaplotype barcoding regions containing several high-diversity SNPs (single nucleotide polymorphisms) that overcome limitations of standard biallelic SNP barcodes (global mean diversity = 0.78), in addition to 4 putative drug resistance assay amplicon targets (PvMDR1, DHPS) and 2 mitochondrial amplicons that discriminate *Plasmodium* species. Our 98-assay Illumina panel successfully reconstructed relatedness relationships of 11 *P. vivax* recurrent pairs, and correctly classified geographical clustering of diverse populations from 17 different countries. In this presentation we will present evidence that the panel performs well in connectivity analyses with sufficient resolution to identify a major clonal outbreak in Malaysia, and subtle substructure in the region that were previously only possible with whole genome sequencing approaches. The assay panel is being refined and optimized to genotype parasite isolates from diverse geographical regions, which will be analyzed and contextualized using and end-to-end surveillance platform and will inform epidemiology and programmatic strategies for *P. vivax* control and elimination efforts.

0330

ESTIMATING MULTIPLICITY OF INFECTION FROM MULTIPLE GENETIC MARKERS

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Estimating multiplicity of infection (MOI)from multiple genetic markers The importance of estimating multiplicity of infection (MOI) as part of molecular surveillance of infectious diseases is well recognized, particularly in malaria. Here, MOI is defined as the number of super-infections due to the occurrence of multiple infectious events. Due to the lack of translational tools required for mainstream use by researchers with varying expertise, MOI estimates are often based on heuristic approximations, which are simple to use but biased. This is particularly true when estimating MOI based on molecular information from several genetic/ molecular markers (multi-locus data). Such data is often characterized by two problems: (i)missing data at one or more markers is common; (ii) the number of possible haplotypes (and hence parameters to be estimated) increases geometrically with the number of markers. In particular, although the availability of several markers increases the granularity for molecular surveillance, sample size is depleted due to missing information while the number of parameters increases. This problem is avoided when estimating MOI for each molecular marker separately. However, the estimates vary between the markers, and the variance for each marker can be substantial, leading to little confidence in the estimates. To overcome these drawbacks, we propose a maximum-likelihood method to estimate MOI from several markers, which disregards haplotype structure by treating the markers as independent. The method yields one estimate for the distribution of MOI and the marginal frequencies at each marker locus. The method avoids the problem of over parameterization and the depletion of sample size due to missing data. The maximum-likelihood estimate is readily obtained by the EM-algorithm, which is implemented in an easy-to-use R-script. Based on numerical simulations, we report the accuracy and precision of this method (i.e., bias and variance of the estimator). As examples we apply the method to malaria molecular data from Kenya and Cameroon to estimate the distributionof MOI and allele frequency spectra.

0331

A FORWARD GENETIC SCREEN REVEALS *PLASMODIUM FALCIPARUM* GENES LINKED TO SURVIVAL IN SICKLE-TRAIT CELLS

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Malaria causes over a half million deaths and >200 million cases of clinical disease annually, but sickle-trait cell (HbAS), representing individuals heterozygous for sickle hemoglobin, confers strong protection against lethal *Plasmodium falciparum* malaria, reducing the risk of severe, life-threatening malaria by over 90%. The mechanisms of this protection remain incompletely understood, but the redox imbalance of sickle-trait cells creates an intraerythrocytic oxidative stress microenvironment that limits parasite growth and virulence. A major protective role of HbAS arises from a cascade of events that starts with the redox imbalance and leads to aberrant intraerythrocytic actin remodeling in infected HbAS RBCs and reduced cytoadherence. Here, we applied a forward-genetic screen approach using *P. falciparum* mutants created by random *piggyBac (pB)* mutagenesis to elucidate genotype-phenotype associations of molecular mechanisms of parasite responses and survival in sickle-trait cells. We performed a sickle-trait *pB* screen by comparing survival in RBCs with HbAS and HbAA control of a 128-mutant *P. falciparum* library with broad genome-wide GO coverage. After cultivating *in vitro* over three and six parasite life cycles, we used Quantitative Insertion Site Sequencing counts of each *pB* insertion within the 128-*pB* library to score each

mutant's phenotype growth response in sickle-trait cells compared to that under ideal culture conditions. Our results revealed parasite sensitivity to sickle-trait cells is linked to cythoadhesion, redox response, exported protein, lipid metabolism, transcription, and translation. Notably, these adaptive response mechanisms in *P. falciparum* to survive in HbAS RBCs overlap with those we have previously observed as to oxidative stress sensitive phenotypes. This first small-scale screen of sickle-trait cells bring important insights to understand the host-parasite interactions and parasite survival mechanisms associated with HbAS that may help guide future development of therapies to treat or prevent severe, life-threatening falciparum malaria.

0332

EFFICACY OF ARTEMETHER-LUMEFANTRINE FOR THE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN DJOUGOU AND POBÈ IN THE REPUBLIC OF BENIN, 2020

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In Benin, malaria is the leading cause of childhood morbidity and mortality; early diagnosis and treatment with an effective antimalarial is a key strategy for malaria prevention and control. Artemether-lumefantrine (AL), an artemisinin-based combination therapy, was introduced in 2005 as the first-line treatment for uncomplicated *Plasmodium falciparum* malaria. In accordance with the World Health Organization (WHO) recommendation for regular monitoring of the efficacy of antimalarial treatments, a therapeutic efficacy study of AL was conducted. Between June and December of 2020, febrile patients aged 6-59 months with confirmed malaria (2,000-200,000 parasites/μL) were treated with AL for 3 days. Clinical and parasitological response was monitored in a 28-day in vivo efficacy trial in two sentinel sites in Benin: Djougou in the northwest and Pobè in the southeast. Polymerase chain reaction (PCR) using *msp1*, *msp2*, and *glurp* was used to distinguish recrudescence from reinfection in treatment failures to calculate PCR-corrected day 28 treatment efficacy. Molecular analysis of *K13* gene mutations at codon C580Y associated with artemisinin resistance was also performed. A total of 187 patients were included in the study, with zero lost to follow up. There were 7 clinical/parasitological failures (5 in Pobè and 2 in Djougou.) The day 28 uncorrected AL efficacy per site was 96.5% (111/115) in Pobè and 93.0% (67/72) in Djougou. PCR-corrected AL efficacy per site was 99.1% (114/115) in Pobè and 95.8% (69/72) in Djougou. The analysis of *K13* codon C580Y showed no evidence of mutations. Results from this study exceed the WHO's 90% acceptable treatment efficacy threshold, indicating that AL, the current first line treatment for malaria in Benin, remains effective. However, continued monitoring of clinical and parasitological efficacy of antimalarials and molecular resistance markers every two years is important to ensure treatments remain efficacious and to allow Benin's Ministry of Health to continue to make informed treatment policy decisions for malaria control.

0333

PLASMODIUM FALCIPARUM GENOMIC SURVEILLANCE REVEALS SPATIAL AND TEMPORAL TRENDS, ASSOCIATION OF GENETIC AND PHYSICAL DISTANCE, AND HOUSEHOLD CLUSTERING

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Genetic epidemiology can reveal parasite population structure, transmission intensity, and provide actionable data to assess malaria interventions. Coupled with geographic information, genomic data can further identify transmission hotspots, spatial connectivity, and parasite movement by humans or mosquitos over time and space. We carried out longitudinal genomic surveillance (8 visits over 2 years) in a cohort of 70 participants from across Thiès, Senegal—a region of very low malaria transmission (EIR <1). Genetic identity by state (IBS), was established using a 24-SNP molecular barcode, identity by descent (IBD) was calculated from whole genome sequence data, and a hierarchical Bayesian regression model was used to establish genetic and spatial relationships. Participants were living in "daaras" (religious boarding schools); only 16.9% participants reported bednet use; and 4 participants were re-infected over the follow-up period. Limited genetic diversity [nucleotide diversity (SNPϖ) = 0.274; He = 0.371 (0.341, 0.401); genotypic richness index R of 0.425], and a high frequency of monogenomic infections (90.5% (67/74)) were observed. Genomic haplotypes were shared within and persist across malaria transmission seasons (8 haplotypes shared between 40 patients). Genetically similar parasites were clustered within households and parasite genetic similarity declined with increasing distance. There was a significant positive association between physical and genetic distance by year with a 31% [95% credible interval, (11. 58)] per km increase in separation in 2015 and a 16% [95% credible interval, ((2.31)] per km increase in 2016. A similar trend was observed when the data were analyzed within a year with an increase of 4% [95% credible interval, (0.8)] per km increase in separation. IBD analysis of haplotypes persisting for multiple years showed that identical parasites (clonal by IBS) were generally identical across the

whole genome, sharing from 70 – 100% of their genome sequence. This works shows how genomic and epidemiologic data can be used for surveillance and detection of fine-scale malaria transmission patterns.

0334

ASSESSMENT OF THE IMPACT OF PREGNANCY AND MALARIA INFECTION ON THE VARIATION OF NEUTROPHIL LEVELS IN WOMEN FROM SAN, MALI

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Severely decreased neutrophils levels can have life-threatening implications. Probably due immunological and hormonal changes, pregnant women are more likely to get malaria than non-pregnant women. It is essential to understand whether pregnancy induces changes in neutrophil levels and thereby poses a threat to the health of gravidae. This is a cross-sectional analytical study assessing the impact of malaria in pregnancy on neutrophil level variation. The study was conducted in San Health District (Mali) and involved pregnant women infected or not by Plasmodium falciparum and non-pregnant healthy volunteers. Subjects were categorised as having neutropenia, normal neutrophil levels and neutrophilia. A linear regression model allowed to determine factors associated with neutrophil level variations in pregnant women. White blood cells mean count (4416.3, SD= 1313.8) while lower in healthy non-pregnant subjects, decreased from pregnant women without malaria infection (7673.8, SD= 10515.6) to pregnant women with malaria infection (5493.2, SD= 1528.6). Pregnant women in the malaria infected and non-infected groups had each 48.5% (98/ 202) cases of neutrophilia (48.5%). Surprisingly, 67 of the 71 cases of neutropenia (94.4%) observed in this study were in apparently healthy non-pregnant individuals. Categorising gestational age, the mean percentage of neutrophils level was significantly lower ($p<0.001$) in the first trimester (49.92%) compared to the second trimester of pregnancy (62.01%). A linear regression model showed that compared to early pregnancy, the second (OR= 3.301e+05, $p= 0.001$) and the third trimester (OR= 5.36e+05, $p< 0.001$) were strongly associated with an increase in neutrophil levels. The model also showed that each increase in malaria parasite density multiplies the neutrophil levels by 1.0001 times (OR= 1.0001, $p< 0.001$). In conclusion, data from Mali shows benign neutropenia in healthy non-pregnant people. This study suggests that, in absence of malaria infection, the second trimester of pregnancy is strongly associated with an increase in neutrophil levels.

0335

EVALUATION OF NATURALLY ACQUIRED IMMUNITY AGAINST NOVEL *PLASMODIUM VIVAX* PRE-ERYTHROCYTIC ANTIGENS IN HUMAN POPULATION FROM LOW ENDEMIC MALARIA REGION

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Plasmodium vivax (*Pv*) represents the most geographically widespread human malaria. Targeting the pre-erythrocytic (PE) stage of the parasite life cycle is especially appealing for *Pv* vaccines as even a partially-protective intervention could reduce the hypnozoite reserve responsible for disease and transmission. Here, we explore naturally acquired immunity to a panel of *Pv* PE antigens as a first step to enable vaccine development and to better understand naturally acquired PE immunity. To this end, we screened samples from *Pv* infected individuals from a low endemic malaria region in the Peruvian Amazon Basin for immunity to 12 *Pv* PE antigens by ELISA and ELISpot assays. In these samples, all PE antigens showed positive antibody reactivity with prevalence of 58-99%. The magnitude of the IgG antibody response against PE antigens was lower compared with blood stage antigens MSP-1 and DBP-II although in general, titers persisted better for PE antigens (average decrease of 6% for PE antigens and 43% for MSP1 over 6 months). A significant correlation between IgG antibodies levels and number of previous malaria episodes was observed only for blood stage antigens. Volunteers with high IgG responses to PE and Blood stage antigens showed a significantly lower parasitemia compared with low IgG responders (1921 vs 4663 par/µl, $p=0.014$). Analysis between antibody levels and parasitemia against 5 PE antigens showed a significant but low-medium negative correlation (Rho: 0.23-0.39,$p<0.05$). Our ELISpot analysis showed a positive T cell response in 35% vs 9-35% of total volunteers against blood stage antigen MSP1 and PE antigens, respectively, with no correlation with IgG responses. These results demonstrate clear humoral and T cell responses against *Pv* PE antigens in individuals naturally infected with *P. vivax*. In addition, these results provide data on some characteristics of antibodies to PE antigens (immunogenicity, durability, boosting after malaria episodes and correlations with parasitemia at time of disease) that should be further explored to inform selection of novel PE antigens for use in the development of new malaria vaccine candidates.

0336

INITIAL RTS,S/AS01 ANTIBODY RESPONSE AND EFFICACY ARE POSITIVELY ASSOCIATED WITH MALARIA TRANSMISSION INTENSITY

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RTS,S/AS01 has recently been recommended by WHO for widespread implementation in medium to high malaria transmission settings. Previous analyses have noted lower vaccine efficacies in higher transmission settings, potentially due to "rebound malaria," which occurs over multiple years due to the development of immunity due to natural infections in those not vaccinated with RTS,S/AS01. To investigate other potential mechanisms behind the lower efficacy in high transmission areas, we examine initial vaccine efficacy (against the first case of malaria so as to exclude the rebound effect) and vaccine antibody response using data from three study areas (Kintampo, Ghana; Lilongwe, Malawi; Lambarene, Gabon) from the 2009-2014 phase III trial. Our key exposures are parasitemia during vaccination, age at vaccination, and malaria transmission intensity computed using ecological variables from sixteen geospatial datasets, three surveys, and data from the phase III trial. We calculate vaccine efficacy (one minus hazard ratio) using a cox-proportional hazards model. We find that antibody response was highest in older children in high transmission settings and in children who had parasitemia during vaccination. We find that vaccine efficacy was lowest in children in low transmission settings (0.25 cases per person-year) with no parasitemia during vaccination: 30.77% (95% CI: 19.94%, 40.14%). Children in high transmission settings (but with no parasitemia during vaccination)

had increased efficacy against the first case of malaria: 51.13% (45.86%, 55.89%) and 59.95% (53.65%, 65.40%) in 2 and 3 cases per person-year settings, respectively. Among those with parasitemia during vaccination, efficacy varied little within levels of transmission intensity: 58.44% to 59.55%. These results suggest that vaccine efficacy may improve due to infections before and during vaccination, reinforcing that rebound malaria is the main reason for lower efficacy in high transmission settings. These results may be reassuring for implementation in high transmission settings and may build evidence for innovative vaccine dosing strategies.

0337

CROSS REACTIVITY OF *PLASMODIUM FALCIPARUM* ANTIGENS PF27, PF43, PF45 WITH THEIR ORTHOLOGS PV27, PV43, PV45 OF *P. VIVAX* TO SERA FROM DONORS LIVING IN KÉNIÉROBA, MALI

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Antigenic polymorphism of *Plasmodium falciparum* represents a major challenge for the development of an effective malaria vaccine. Bioinformatics tools remains a realistic approach to identify new antigens that can be used as potential vaccine candidates. In addition, the presence of homologies between *P. falciparum* (Pf) and *P. vivax* (Pv) proteins offers the prospect to develop multi-species and cross-protective vaccines. This study aimed to assess the cross-reactivity of *P. falciparum* Pf27, Pf43 and Pf45 antigens with their *P. vivax* orthologs Pv27, Pv43 and Pv45 to sera from donors living in Kéniéroba, a *P. falciparum* endemic area located at 55 km south-west of Bamako, Mali. Antigenic peptides covering the above orthologs Pf and Pv protein sequences were tested for IgG antibody levels by ELISA on sera samples from children (n = 41) and adults (n = 48). The seroprevalence for Pv27 was 42.7% vs. 29.2% for Pf27; 12.4% for Pf43 vs. 6.7% for Pv43, and 13.5% for Pv45 vs. 11.2% for Pf45. Seropositivity to Pf27 (56.1%, p = 0.0001), Pv27 (87.8%, p = 0.0001), Pv45 (29.3%, p = 0.0001) was significantly higher in children. A significant correlation was found between antibodies against *P. falciparum* antigens with their *P. vivax* orthologs in both children and adult sera ($p < 0.05$). The antibodies titers to Pf43 (p = 0.0001), Pv43 (p = 0.0002), Pf45 (p = 0.001) and Pv45 (p = 0.0001) were significantly higher in adults. Sera from children and adult donors reacted well to the couple Pf27/Pv27. The high seroprevalence suggests existence of cross-reactivity between *P. falciparum* antigens and their orthologs *P. vivax* that should be tested as potential vaccine candidates.

0338

TRANSCRIPTOME ANALYSIS OF ADAPTIVE IMMUNE RESPONSE TO CHAD63 MVA ME-TRAP VACCINE

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Malaria is still a major cause of mortality and morbidity in Africa despite various efforts to control it. This bottleneck has mainly been attributed to the complex life cycle of *Plasmodium* parasite and the high level of genetic diversity which allows it evade host immune system[1,2]. While a significant amount of effort is currently being directed towards the development of antimalarial vaccines, those so far developed including RTS,S at phase III trials have registered low efficacy levels[3]. There is therefore an urgent need for development of a high-efficacious malaria vaccine. Previous results have reported promising immunogenicity with chimpanzee adenovirus 63 (ChAd63) vector followed by modified vaccinia Ankara (MVA), both encoding multiple epitope string thrombospondin-related adhesion protein (ME-TRAP) in African adults and pediatric populations. Early cellular responses of prime-boost approaches with ChAd63 MVA ME-TRAP are correlated with elevated levels of both T cells and antibodies, particularly CD8+ effector and effector memory responses to vaccination. While the vaccine efficacy of these heterologous prime-boost regimens has been extensively studied, transcriptomic correlates of immunogenicity and efficacy is yet to be characterized. Transcriptomic analyses to vaccine responses have reliably been used to provide a global picture of the immune mechanisms and type of responses a vaccine induces. With this in mind, this project will utilize samples from previous studies that investigated the immunogenicity of ChAd63 MVA ME-TRAP and correlate it to transcriptomic signatures induced during the immunization to inform vaccine efficacy.

0339

INCREASED PLASMA LEVEL OF INTERLEUKIN-8 IS ASSOCIATED WITH FATAL OUTCOME IN CHILDREN WITH CEREBRAL MALARIA

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Malaria remains a major public health problem despite major scientific advances. WHO reports 241 million cases of malaria in 2020 compared to 227 million cases in 2019, with more than 400,000 deaths attributed to malaria each year, mainly among children in Sub-Saharan Africa. Cerebral malaria (CM) is one of the most severe forms of malaria and remains fatal in 15 to 40% of cases. Despite the administration of effective anti-malarial drugs, it unfortunately leads to very high mortality rates. Although the late management of these cases contributes to the severity of the disease, it seems that the disruption of the cellular immune response also contributes to the fatal outcome due to blood-brain barrier damage. Cytokines, chemokines and lipid mediators are key molecules in the intercellular dialogue. Therefore, our study aimed to study such plasma and urine markers in CM patients and identify markers of death. The study was conducted in Beninese children presenting with CM. Plasma and urine samples were collected at inclusion and following clinical management at Day 3 and Day 30. Using Luminex technology, levels of 17 markers of pro-and anti-inflammatory responses were simultaneously measured in plasma. For urine markers, levels were measured using commercial enzyme immunoassays kits. Socio-demographic, clinical and biological data were analyzed by univariate analysis and logistic regression. A total of 70 CM cases were included, corresponding to 50 children who survived and 20 who died. Multivariate linear regression analysis revealed a strong correlation between increased plasma IL-8 and death. Plasma IL-8 concentration ≥ 57.5 pg/ml increased dramatically the risk of mortality during CM [adjusted OR = 15.3, 95% CI 2.75-85.4, P = 0.002]. By contrast, the other plasma and urine markers measured were not associated to death outcome. Interestingly, plasma TNF-α, IL-6, IL-10, CXCL10 and ICAM-1 decreased gradually from Day 0 to Day 30, whereas CXCL5, CCL17 and CCL22, suggesting deleterious and protective roles, respectively. This study highlighted plasma IL-8 as a marker of death in childhood cerebral malaria.

0340

INVESTIGATION OF MONOCYTE GENE REGULATORY NETWORKS BEFORE, DURING, AND AFTER ACUTE MALARIA USING SINGLE CELL TRANSCRIPTOMICS AND EPIGENOMICS

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Acute malaria is associated with systemic inflammation and altered monocyte functions. In addition, longer-term changes in innate immune homeostasis may follow acute malarial illness. We collected peripheral blood mononuclear cells (PBMC) from a 7-yr-old boy from western Kenya at 3 timepoints: healthy baseline (Pf PCR neg), 7 wks later during an episode of uncomplicated malaria, and 6 wks after treatment and clinical recovery. PBMC nuclei were analyzed simultaneously for transcriptomes and chromatin accessibility at the single cell level (10X Multiome ATAC+Gene Expression). Single cell identities were inferred from the Human Cell Atlas. Among monocytes, there were 701 differentially expressed genes (DEG) in baseline vs. malaria, 197 DEG in malaria vs. recovery, and 75 DEG in recovery vs. baseline (FDR<0.01). Inflammation-related DEG with higher expression at recovery vs. baseline included *IL1B, NLRP3, LYN, NAMPT, NFKB1,* and *CD80*; DEG with lower expression at recovery vs. baseline included *PPARG, TGFB1,* and *CXCR4*. ATAC (Assay for Transposase Accessible Chromatin) data revealed increased peak size in the *IL1B* promoter in recovery vs. baseline monocytes, indicating open chromatin at this locus that is consistent with higher *IL1B* transcription at recovery. Gene set enrichment analysis of recovery vs. baseline monocytes showed enrichment in the "Reactome Immune System" pathway, containing the upregulated genes reported above, as well as in the "Benporath MYC Max Targets" pathway. Transcription factor (TF) activity was compared across timepoints by analyzing ATAC peak data for enrichment in TF motifs. The most statistically significant difference in TF activity between recovery vs. baseline was for *SPI1*. *SPI1* encodes PU.1, a critical regulator of monocyte development. Of the DEG in recovery vs. baseline in the "MYC Max Targets" pathway, 81% are known *SPI1* targets. Collectively, these data suggest longer-term malaria-induced changes in monocyte gene regulatory networks controlled by *SPI1* that may be related to augmented inflammatory signaling. Future experiments will address temporal stability of chromatin changes.

0341

THE ANALYSIS OF CROSS-REACTIVITY OF INHIBITORY ANTIBODY AND MEMORY B CELL RESPONSES TO DUFFY BINDING PROTEIN II VARIANTS AFTER *PLASMODIUM VIVAX* INFECTION

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Duffy binding protein region II (DBPII) of *Plasmodium vivax* is a critical microneme protein involved in parasite invasion, thereby being chosen as a potential vaccine candidate. However, a major challenge for vaccine design remains as the highly polymorphic nature of this protein often misdirects immune response to be strain-specific. Details of cross-reactive humoral immunity to DBPII variants have therefore become an important focus for the development of broadly protective vaccine. Here, we demonstrated the presence of cross-reactive inhibitory antibody against a panel of Thai DBPII variants (DBL-THs) at post-infection phase of *P. vivax*. The cross-reactivity of inhibitory antibodies against DBL-TH variants was determined in immunized mice and in infected individuals (n=15) by *in vitro* erythrocyte binding inhibition assay. Using anti-DBL-TH sera at 50% inhibitory concentration (IC50), anti-DBL-TH2 sera showed cross inhibition while anti-DBL-TH5 exhibited strain-specific inhibition. In *P. vivax* patients at 12-month post-infection, 6 subjects produced and maintained cross-reactive inhibitory antibodies against more than three DBL-TH variants, whereas all subjects showed no inhibition to reference strain Sal I. To explore cross-reactive memory B cell (MBC) responses against DBL-TH variants, *P. vivax*-infected subjects recovered for 1-3 months (n=8) were tested. The plasma samples from 5 subjects showed broadly inhibition. However, MBC-derived IgG of these patients after 11-day MBC cultures revealed the strain-specificity to DBL-TH antigens. Altogether, this study demonstrated the potential capability of DBL-TH variants in eliciting broadly inhibitory antibodies both in animal and human models. Cross-reactive antibodies with varying inhibitory activities could persist for 12 months after parasite clearance. However, MBC responses to DBP-TH variants were stain-specific. These findings will guide the design of long-lasting, broadly protective DBPII-based vaccine against vivax malaria.

0342

DISTINCT TRANSCRIPTIONAL RESPONSES ASSOCIATED WITH VACCINATION STATUS AND PROTECTION OUTCOMES AFTER MALARIA CHALLENGE

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Understanding immune mechanisms that mediate malaria protection is critical for improving vaccine development. Vaccine strategy using radiation-attenuated *Plasmodium falciparum* sporozoite (PfRAS) induces high level of sterilizing immunity against malaria and serves as a valuable tool for the study of protective mechanisms. To identify vaccine-induced and protection-associated responses during malarial infection, we performed transcriptome profiling of whole blood and high dimensional flow cytometry profiling of PBMC from volunteers receiving either suboptimal dose of PfRAS or noninfectious mosquito bites followed by controlled human malaria infection (CHMI) challenge. Whole blood transcriptome analysis revealed that gene sets associated with interferon responses and T and B cell signatures were upregulated and downregulated, respectively, in protected vaccinees one day following CHMI. Dynamic transcriptome changes were observed in non-protected vaccinees that were similarly shared with mock-vaccinated individuals after CHMI and were characterized with downregulation of innate cell signatures and inflammatory responses. Additionally, immunophenotyping data showed that there was a long-term expansion of the vδ2+ subset of γδ T cell in individuals who developed blood-stage parasitemia, even after treatment and resolution of infection. Our data provide key insights in understanding immune mechanistic pathways of PfRAS-induced protection and infective CHMI. We demonstrate that protective immunity by PfRAS is associated with early changes in interferon and adaptive immune responses.

0343

DYSFUNCTIONS OF REGULATORY T AND B CELLS ASSOCIATED TO THE RISK OF NENATAL SEPSIS IN MALARIA ENDEMIC AREA IN BENIN

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Regulatory T and B cells (Tregs & Bregs) play a prominent role in tolerating the haploidentical mother *in utero,* and at birth, an essential role in the tolerance and control of immune responses to pathogens. Malaria in pregnancy (MiP) alters the newborn immune development and is a risk factor predisposing to malaria and also to other infections during the first year of life. Based on the specific interactions between MiP and prematurity, it is essential to understand the dysfunctions of regulatory immunity in relation to the risk of sepsis in a group of newborns affected by MiP and/or prematurity. Tregs and Bregs might be impacted by MiP or prematurity and consequently associated to a risk of sepsis and infections during the first 3 months of life. This study aims to identify biomarkers of regulatory T and B for diagnosis and prognosis of neonatal sepsis in West Africa where sepsis, MiP and prematurity remain a major public health problem. A cohort of 580 newborns was followed with a full clinical from birth to 3 months in Benin. Mononuclear cells from cord blood of neonates with the most discriminating clinical profiles in terms of occurrence of sepsis, prematurity and MiP are selected. We are evaluating the phenotypes and frequencies of different subpopulations of Tregs and Bregs with immunosuppressive function markers. We focused the immunological analysis on the subgroup of neonates according to the occurrence of sepsis or not in order to assess the outcome of sepsis. Our preliminary results show that neonates who developed sepsis within 72 hours were born with significantly decreased FoxP3 expression on Tregs and higher Breg frequencies. Also, the frequencies of *de novo* generation of Recent Thymus Emigrant Tregs was lower and is compensated by a higher production of peripherally induced Tregs whose Th1 stability and suppressive power are often impaired. Our preliminary results suggest that neonates at risk of developing sepsis were born with an altered phenotypic profile compared to non-sepsis neonates. Ongoing analysis of functional markers are performed to evaluate the impact of MIP and preterm neonates on Treg and Breg and the risk of sepsis in early life.

0344

FACTORS ASSOCIATED WITH HUMAN IGG ANTIBODY RESPONSE TO *ANOPHELES ALBIMANUS* SALIVARY GLAND EXTRACT: ARTIBONITE DEPARTMENT, HAITI, 2017

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Malaria prevalence in Haiti is low, often not exceeding 1% rapid diagnostic test (RDT) positivity throughout the country. In malaria low-transmission settings, serological data can provide an accurate estimation of human exposure both to the malaria vector and the parasite. This study utilized data from a 2017 cross-sectional easy access group survey conducted in southern Artibonite department, Haiti. Participant enrollment occurred at places of congregation: schools, health facilities, and churches. Enrolled persons of all ages completed a questionnaire and provided a blood sample for malaria RDT and later serological assays. A multiplex bead-based assay was developed to simultaneously detect IgG to *Anopheles albimanus* salivary gland extract (SGE) and 23 *Plasmodium falciparum* antigens among 4,185 participants enrolled. Logistic regression estimated odds of an above-median ("high") IgG response against SGE by adjusting for individual-level covariates, IgG against *P. falciparum* antigens, and environmental covariates of enrollment sites. When compared to participants >15 years, children under 5 years and 6-15 years old were found to have 3.7- (95% CI: 2.3, 6.0) and 5.4-fold (95% CI: 3.7, 7.9) increase in odds, respectively, of high anti-SGE IgG. Seropositivity to *P. falciparum* CSP, Rh2_2030, and SEA-1 antigens was significantly associated with high IgG response against SGE, with CSP and SEA-1 having a positive association. Enrollment at study sites under 200m was associated with significantly higher anti-SGE IgG levels compared to elevations above 200m. The ability to approximate population exposure to malaria vectors through SGE serology data is strongly dependent on age categories—possibly pointing towards differing immunological responses to salivary antigens with age. SGE antigens can be easily integrated into a multiplex serological assay with other targets for malaria parasites. Characterization of factors associated with IgG response to SGE can advance understanding of how anopheline salivary antigens can be used as a biomarker for malaria risk.

0345

COMPARATIVE IMMUNOGENETICS OF SEVERE MALARIAL ANEMIA IN PRIMATE MODEL

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Rhesus and cynomolgus macaques present contrasting pathogenesis to *Plasmodium coatneyi* malarial infection with the former but not the latter recapitulating the features of severe malarial anemia (SMA) seen in children. The underlying molecular mechanisms of SMA in children or macaques are not fully understood. Published results indicate that SMA in macaques are associated with activated $CD8^+$ and $CD4^+$ T-lymphocytes, and preliminary data from our group suggest that $CD8^+$ T-lymphocyte depletion alleviates SMA in rhesus. In order to elucidate the mechanism of the cellular immune response and the contributions of major histocompatibility (MHC) and killer cell immunoglobulin-like receptors (KIR) genomic regions in SMA, we analyzed transcription profiles in Rhesus and Cynomolgus during *P. coatneyi* infection. Our results indicate that four MHC allelic profiles in class I and II regions were common between the two macaques. Serological specificities for two other MHC alleles are strongly associated with resistance to SMA compared to only one that is associated with susceptibility. Understanding the immunogenetics of severe malarial pathogenesis in macaque model may offer us better insight into the characteristic antimalarial immune responses that contribute to SMA in children.

0346

PLASMODIUM FALCIPARUM INFECTIONS INDUCE TRANSCRIPTIONAL AND SPATIAL CHANGES IN HOFBAUER CELLS ASSOCIATED WITH IMPAIRED FETAL DEVELOPMENT

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Plasmodium falciparum infections during pregnancy cause placental damage. Placentas exposed to *P. falciparum* accumulate and retain parasite-derived hemozoin (Hz). Hofbauer cells (HBCs) are fetal tissue macrophages that play a role in placental development. We hypothesized that HBCs are differentially activated in placentas with *P. falciparum* Hz and contribute to the risk of small-for-gestational-age and low birth weight. Leveraging clinical and demographic data from a trial of iron in pregnancy in Malawi (ACTRN12618001268235) we applied spatial transcriptomics and multiplexed imaging to interrogate *in situ* expression and spatial interactions of HBCs in placentas with or without Hz. We used the GeoMx Digital Spatial Profiler (NanoString) on FFPE sections of placenta

to identify differentially expressed genes (DEGs) in HBCs. In addition, we used multiplexed Opal staining on tissue microarrays to identify, quantify and validate HBC markers and assess population enrichment and proximity/distance to other cell populations and to maternal and fetal circulation. Early results show that women whose placentas have Hz delivered smaller babies (mean difference (MD), [95% Confidence Interval]: -378.0 g, [-61.4 to -694.6]). Human Phenotype Ontology analysis shows genes upregulated in HBCs from placentas with Hz are implicated in pathways leading to abnormal cerebral vasculature morphology and brain immune cell activation. In addition, placentas with Hz tend to show HBCs at higher frequencies (+4.8%, [-4.5 to 14.1]) and closer in contact to maternal vasculature (-2.8 µm, [-9.3 to 3.8]). Hofbauer cells are activated in placentas with *P. falciparum* Hz and remain differentially activated through to delivery. Differentially expressed genes in HBCs may reflect a close transcriptional profile to brain microglia and be markers of brain development. Further spatial analyses between tissues with or without Hz will provide insights into the interaction of HBCs with their environment. Transcriptional and spatial profiles of HBCs associate with detrimental fetal outcomes and may represent an early accessible marker of cognitive development.

0347

GUT MICROBIOTA INFLUENCES SUSCEPTIBILITY TO *PLASMODIUM FALCIPARUM* MALARIA

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The gut microbiota has recently been associated with malaria susceptibility/resistance in animal models and humans, but the impact of the gut microbiota on the risk of malaria attacks remains to be evaluated. The objective was to evaluate the influence of the gut microbiota on malaria attacks and asymptomatic carriage of Plasmodium in children in a malaria endemic area, Mali.Three hundred healthy children were included in a 16 month cohort study in Bandiagara. The community structure of intestinal bacteria and fungi of the children was characterized by 16S, ITS metagenomics from stool collected at inclusion. Clinicians monitored for malaria attacks. Asymptomatic Plasmodium carriage was assessed by qPCR.During the study, 107 vs 82 children had at least one malaria attack and one asymptomatic *Plasmodium* episode, respectively. Higher bacterial richness was associated with susceptibility to episodes of asymptomatic and malaria attacks while fungal diversity and richness were relatively homogeneous in children with and without *P. falciparum* infection. Linear discriminant analysis of the effect size of operational taxonomic units showed that: 17 bacteria including Clostridiaceae, Eubacteriaceae, Senegalimassilia sp and 7 fungi including *Dioszegia fristigensis*, *Ogataea polymorpha* were associated with susceptibility, whereas 8 bacteria including *Bifidobacterium* spp, *Weissela confusa* and 3 fungi including *Malassezia* sp., *Niesslia exosporoides*, were associated with malaria resistance. In addition, 15 bacteria including *Coproccus eutactus*, *Klebsiella pneumoniae* and 13 fungi including *Wallemia mellicola* were associated with susceptibility while 19 bacteria including *Bifidobacterium* spp, *Bacteroides fragilis* and *Lactobacillus ruminis* and 3 fungi including *Cryptococcus neoformans* were associated with resistance to asymptomatic Plasmodium episodes.Further studies are needed to confirm these findings, which provide an avenue for strategies to reduce malaria risk by modulating components of the gut microbiota in vulnerable populations.

0348

ASSESSING SOCIOECOLOGICAL RISK FACTORS FOR MALARIA AND SCHISTOSOMIASIS AMONG CHILDREN IN MISUNGWI, TANZANIA, AN AREA OF CO-ENDEMICITY

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More than 240 million malaria cases are reported annually, with over 600,000 deaths, mostly in Sub-Saharan Africa (SSA). In addition, Neglected Tropical Diseases, which include schistosomiasis, affect over 1.7 billion people worldwide with more than 200 million people in SSA requiring preventive treatment in 2019. Malaria and schistosomiasis transmission and infection are both dependent on environmental determinants that create favorable conditions for vectors and parasites, and on social determinants, i.e. demographic and socioeconomic factors and behaviors related to disease exposure. In the present study, we investigated factors that are independently and jointly associated with malaria, schistosomiasis, and co-infection among school-aged children. A cross-sectional study was conducted in January 2022 in Misungwi, Tanzania, that sampled 4,200 children aged 6 months to 14 years old. Malaria rapid diagnostic tests (RDTs) were administered for all children (n=4200) while novel schistosomiasis IgM/IgG RDTs were administered for a sample of the children 5 years and older (n=1300). The prevalence of malaria, seroprevalence of schistosomiasis, and co-infection were 31% (1301/4240), 93% (1038/1115), and 38% (428/1115), respectively. Mixed effects regression analyses will be used to assess associations between risk of infection or co-infection and hypothesized individual-, household- and community-level risk factors: low socioeconomic status, poor housing and/or sanitation, poor disease-related knowledge, higher ambient temperature, and closer proximity to Lake Victoria. Spatial cluster analyses will be used to identify hotspots of disease exposure. This study will improve our understanding of social and environmental factors that are associated with malaria, schistosomiasis, and co-infection to inform potential entry points for integrated disease prevention and control.

0349

KNOWLEDGE, ATTITUDE, AND PRACTICES (KAP) ON MALARIA PREVENTION AMONG ADOLESCENTS LIVING IN AN AREA OF PERSISTENT TRANSMISSION IN SENEGAL: A CROSS-SECTIONAL STUDY

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Despite decrease of malaria burden due to the scaling up of control measures, transmission is still persistent in the southern part of Senegal with many cases among adolescents. This is challenging for the country in the pre-elimination stage of malaria as these adolescents will contribute significantly to onward transmission. Therefore, this present study assesses the Knowledge, Attitude, and Practices (KAP) of adolescents living in the health district of Saraya, regarding malaria. A community-based cross-sectional survey was conducted. Households were selected using multistage sampling method. Socio-demographic data, household assets, and KAP were assessed using an electronic questionnaire. Factors associated with adolescents' prevention practices were assessed using logistic regression analysis. Overall, 391 adolescents were included in the study. Nearly, one-third of the participants had good knowledge and good practice of prevention while three-quarters had a positive attitude

and good care-seeking behavior regarding malaria. Multivariate analysis revealed that primary (aOR=5.43, p=0.002) or secondary education (aOR=10.41, P=0.000) level is associated with good knowledge while male individuals have lower knowledge compared to female ones (aOR=0.40, P=0.001). The rich (aOR=0.29, P=0.015), the poor (aOR=0.13, P=0.000), and the poorest (aOR=0.18, p=0.001) were less likely to have a positive attitude towards malaria compared to the richest. Those with a positive attitude were two times the odds (aOR=2.32, P=0.011) of reporting good malaria prevention practices compared to a negative attitude. In contrast, the rich (aOR=0.40, P=0.018), the medium (aOR=0.32, P=0.03) and the poor (aOR=0.44, P=0.035) wealth index are less likely to apply good practices of malaria prevention compared to the richest. The odds of good care-seeking behavior was lower among poor adolescents. Adolescents' knowledge level and their practice on malaria prevention were poor. Programs aiming to improve access to health care services and to increase sensitization among adolescents to raise awareness on malaria prevention are urgently needed.

0350

IMPROVED ADHERENCE TO TEST, TREAT, AND TRACK (T3) MALARIA STRATEGY AMONG OVER-THE-COUNTER MEDICINE SELLERS (OTCMS) THROUGH INTERVENTIONS IMPLEMENTED IN SELECTED RURAL COMMUNITIES OF FANTEAKWA NORTH DISTRICT, GHANA

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Prompt diagnosis and treatment of malaria prevents a mild case from developing into severe disease and death. Unfortunately, parasitological testing of febrile children is greater in the public and formal private sector than in the informal private sector where some people with malaria-like symptoms first seek treatment. This study aimed at improving adherence to the test, treat, track (T3) policy among OTCMS through interventions that could be scaled-up easily at the national level was conducted in some rural communities of Ghana. Interventions were evaluated using a two-arm, cluster randomized trial across 8 rural communities (4 clusters per arm), in two adjacent districts (Fanteakwa North and Fanteakwa South districts) of Ghana. A total of 12 OTCMS (7 in the intervention arm and 5 in the control arm) in the selected communities participated in the study. Five (5) interventions were implemented for 12 months in the intervention arm only. The primary outcome was the proportion of children under 10 years with fever or suspected to have malaria visiting OTCMS and subjected to a parasitological test before treatment. Outcomes were measured using mystery client surveys supplemented by a household survey. Data was analyzed using chi-square test or fisher exact test. Following implementation of interventions, mystery client survey showed that OTCMS' adherence to malaria protocol in the intervention arm (66.7%) was significantly higher ($p<0.05$) compared to the control arm (40%). Household surveys in the intervention arm showed that caregivers self-treating their children or visiting drug vendors significantly decreased from 8.6% and 13.8% to 3.9% and 3.2% in favor of visits to OTCMS shops for treatment. From our findings, interventions targeting OTCMS have the potential of improving management of uncomplicated malaria in rural communities with limited access to quality healthcare, thus reducing morbidity and mortality rates.

0351

UNDERSTANDING PSYCHOSOCIAL DETERMINANTS OF MALARIA BEHAVIORS IN LOW TRANSMISSION SETTINGS: A SYSTEMATIC REVIEW

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Human behavior plays an important role in malaria elimination, including acceptance and use of prevention measures and prompt care seeking for fever. These behaviors depend in part on psychosocial factors such as knowledge, attitudes, perceived risk, and perceived community norms. The current state of research on these factors in low malaria transmission settings, including sampling approaches and association with key behaviors, is unknown. To address this gap, Breakthrough ACTION conducted a systematic review of recent peer-reviewed and grey literature in low transmission settings (as defined in the WHO Framework for Malaria Elimination and key terms) using PRISMA guidelines. Records were screened (n=966) and retained publications (n=96) analyzed to assess sampling approaches, data collection instruments, and factor behavior associations. Purposive and cluster random sampling were common study designs. Knowledge, attitudes, and perceived risk were commonly measured variables, but measurement was incongruent across studies. Perceived response efficacy, perceived self efficacy, and perceived community norms were rarely measured, although recent evidence within high-transmission context suggests they influence behavior. Positive associations between malaria knowledge, favorable attitudes, and behavior were consistently found. A subset of studies (n=19) focused on populations at increased risk of transmission such as miners and forest workers, where rates of correct knowledge tended to be lower than others. Currently, there is insufficient evidence to assess the relationship between other psychosocial factors and behavior in low transmission settings, a gap that offers opportunities for innovative social and behavior change programming. Results of this review highlight the need for malaria research to employ more consistent, comprehensive measures of psychosocial constructs that shape behavior, and offer promising existing instruments and sampling approaches. Interventions seeking to address remaining gaps toward malaria elimination should consider the pivotal role of psychosocial factors.

0352

SOCIODEMOGRAPHIC TRENDS IN MALARIA KNOWLEDGE AND IMPLICATIONS FOR BEHAVIOR CHANGE INTERVENTIONS IN ZANZIBAR

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Zanzibar is among the few places within East Africa that have documented a significant reduction of malaria morbidity and mortality. Despite tremendous gains over the past decade, malaria transmission still persists in Zanzibar. This study aimed at understanding levels of malaria knowledge to provide recommendations that can be used to reinforce and scale-up targeted malaria social and behavior change interventions. A descriptive cross-sectional survey was conducted through an administered questionnaire to 431 households selected randomly. The interviewees were the heads of household or representative adults above 18 years. This study investigated the levels of knowledge about the causes, symptoms, and prevention of malaria in areas with high (> 1.9 per 1,000) and low (<1 per 1000) incidence of local malaria cases. The Principal Component Analysis (PCA) was used to compute the composite variable of each

category. Descriptive statistics were calculated to understand variables of interest between low and high transmission areas. Multinomial logistic regression model was used to compare knowledge on malaria based on key variables. Respondent age, education level, and wealth status were significantly associated with variations in the level of malaria knowledge. Old age was found to be significantly associated with low knowledge of malaria (P<0.001). The majority of study participants who had secondary and higher education levels had good knowledge of malaria (P<0.006). Participants characterized as middle-income had good knowledge compared to those characterized as low-income (P<0.001). Low levels of malaria knowledge were documented among the elderly and populations with lower education and income levels. There is a need to extend mobilization, advocacy, and expand channels of communication to reach all community members. The reported gaps in knowledge are important to consider when designing strategies to engage communities in malaria elimination in Zanzibar. Tailored social and behavioral change interventions aiming to increase malaria knowledge could enhance the uptake of malaria prevention services in the community.

0353

WHAT IS THE MALARIA COST BURDEN AND WHO BEARS IT? A COST-OF-ILLNESS STUDY IN UGANDA

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In Uganda, the burden of malaria remains high, and treatment imposes a large economic burden on households and the health system. Cost-of-illness studies can guide development of efficient and equitable control programs and decisions on allocation of scarce resources. However, a gap in this evidence exists for Uganda and elsewhere in Africa. To evaluate the societal and provider cost of malaria illness and to assess the distribution of the economic burden of malaria in Uganda through an equity lens, we conducted a cost-of malaria illness study from November 2021 to May 2022 in 10 randomly selected public health facilities in 10 districts of Uganda. These sites have been established as Malaria Reference Centres for the LLINEUP2 trial, a study to evaluate the impact of long-lasting insecticidal nets (LLINs) distributed through the 2020-2021 national campaign in Uganda. Provider costs for diagnostics, drugs, health worker time and overheads were collected from health facility registers; observations and a time-in-motion study were also conducted. Care-seeking behavior and household expenditure on malaria treatment including out-of-pocket payments, transportation and productivity losses were collected from cross-sectional surveys conducted in 3,200 households across all 64 LLINEUP2 trial communities in 32 districts of Uganda. Average values overall, and by geographic, socio-economic and age subgroups, were estimated for household-level and individual-level access to treatment, quality of treatment and cost burden. Preliminary results indicate that the average household cost of a malaria episode was $15.32 (95% CI: $13.79-16.85), with 84% of costs attributed to productivity losses. Household average cost per episode varied by region (max: Acholi $19.28 ; min: Bunyoro $13.88) and age of patient (under 2 years $5.77 less; p-value: 0.04). We will present final results of this analysis which will inform resource-allocation decisions about malaria control by providing an average cost of malaria treatment, which can be applied in economic evaluations and for policymaking in Uganda and across Africa.

0354

TRANSCRIPTIONAL PROFILING OF PRIMARY SIMIAN HEPATOCYTES INFECTED WITH THE REPLICATING FORM OF THE MALARIA PARASITE *PLASMODIUM CYNOMOLGI*

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The simian parasite *Plasmodium cynomolgi* develops into replicating schizonts and dormant hypnozoites during the infection of hepatocytes and is used as a model organism to study relapsing malaria. Using FACS-purification of cells infected with GFP-expressing parasites, we previously reported the transcriptional profiling of *P. cynomolgi* liver stages and revealed many important biological features of the parasite but left out the host response to malaria infection. Here, we aligned our published RNA sequencing data obtained from primary simian hepatocytes infected with *P. cynomolgi* to the reference rhesus monkey genome rheMac7 and quantified the expression of host genes in comparison to either uninfected samples or uninfected bystander cells. Although the dataset could not be used to study hypnozoite-infected cells because of sample contamination, we found that it provides a snapshot of the transcriptional response of hepatocytes to *P. cynomolgi* schizonts at 9-10 days post-infection. Our results show that schizont-infected cells modulate the expression of genes associated with multiple host processes in comparison to uninfected samples, including the upregulation of pathways involved in the response to DNA damage, cell division and the response to viral infection and cytokines, and the downregulation of metabolic genes. Results also identified host pathways more specifically modulated in schizont-infected cells in comparison to uninfected bystander cells, such as the upregulation of genes associated with the Rho GTPase cycle and membrane trafficking, and the downregulation of genes associated with protein translation. This study constitutes a valuable resource characterizing the hepatocyte response to *P. cynomolgi* infection and provides a framework to build on future research that aims at understanding hepatocyte-parasite interactions during relapsing malaria infection.

0355

AN INSIGHT OF THE PERCEPTION OF FRANCOPHONE AFRICAN IMMIGRANTS ON MALARIA-RELATED KNOWLEDGE OF HEALTHCARE PROFESSIONALS IN WESTERN CANADIAN MINORITY REGIONS

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Despite decades of study, malaria remains one of the world's greatest killers, with populations living in Sub-Saharan African (SSA) regions being at the highest risk. However, the disease is not restricted to SSA. Promoted by population movements, imported malaria (IM) or travel-associated malaria is a growing public health threat in many industrialized non-endemic countries including Canada. Similar to European countries and the United States, Canada's reported IM cases are densely concentrated within regions exhibiting a steady growth of immigrants especially from SSA. Studies have demonstrated that Canadian health practioners malaria

knowledge can be incomplete, affecting traveler's confidence when seeking for medical advice before a trip to malaria endemic settings. Remarkably, the number of immigrants, especially French-Speaking immigrants from SSA (FISSA) has significantly increased in Edmonton, a predominant English-speaking Canadian city. Thus, challenges related to trust in health professional malaria knowledge when trying to access pre-travel medical advice may increase this population's susceptibility to IM infections. We used a structured survey to assess a Healthcare Competency Perception (HCP) index score (negative, neutral and positive scores) and malaria related healthcare statements within a cohort of 382 FISSA (48% female; 52% male) living in Edmonton. We observed that while 264/382 (69%) of FISSA were satisfied with the healthcare they received in Canada, confidence in the healthcare system's ability to treat and deal with malaria effectively appear to be significantly lower, with only 148/382 (39%) receiving a positive score on the HCP index. Moreover, in comparison with other respondents, respondents with a positive HCP index score were significantly more likely to visit a hospital or a doctor if they or their family member were sick after coming back from a trip to an endemic region (OR 2.98, 95% CI 1.23-8.33). This study suggests that low confidence in healthcare workers may be a barrier to health-seeking behaviour post-travel for FISSA.

0356

COMMUNITY EDUCATION, PERCEPTION AND BEHAVIORAL CHANGE ARE THE KEY DETERMINANTS OF MALARIA OUTBREAK AT DOLONIBASTI SUB-CENTRE OF UDALGURI DISTRICT, ASSAM, NORTH-EAST INDIA

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Despite the malaria control efforts like long-lasting insecticidal nets distribution, rounds of indoor residual spray, introduction of bi-valent rapid diagnostic tests and artemisinin combination therapy; malaria remained consistent in Dolonibasti sub-centre (outbreak region) of district Udalguri and followed by an outbreak in 2008. This necessitates us to investigate the factors driving the malaria transmission and outbreak. We collected malaria epidemiological data for the years 2008-2018 of Udalguri district and Orang block primary health centre (BPHC) covering outbreak region, as well as yearly (2011-2018) and monthly (2013-2018) data of outbreak region. An entomological survey, Knowledge, Aptitude and Practices study among malaria cases (n=120) from outbreak region was conducted. Annual (2011-2018) and monthly (January, 2013-December 2018) meteorological data was collected for the point location of outbreak region. Overall, annual parasite incidence (API) was declined in Udalguri by 82% but Orang BPHC and specifically outbreak region remained unaffected with the previous intervention efforts from the Government. Out of 2130 confirmed cases in outbreak region, 55% were adults (n=1176) and rest were children. *Anopheles minimus* was the major vector with 28.6% positivity and high larval density in paddy fields/drainage area. Annual relative humidity was associated with rise in malaria cases, API (r_s=0.69, 90%CI; p=0.06) and slide positivity rate (r_s=0.83, 95%CI; p=0.01). Older people were less educated (r_s=-0.66; p=0.00), had lesser knowledge about malaria cause (r_s=-0.42; χ^2=21.80; p=0.00) and prevention (r_s=-0.18; p=0.04). Malaria control practices were followed by those having knowledge about cause of malaria (r_s=0.36; χ2=13.50; p=0.00) and prevention (r_s=0.40; χ2=17.71; p=0.00). Education, though influenced the adoption of malaria control measures, but its magnitude was relatively weak. This shows that formal education can help in improving the malaria control practices but only to a certain extent, and more concerted efforts are needed to educate the community towards malaria control practices.

0357

IMPROVEMENTS IN THE INTEGRATED DISEASE SURVEILLANCE AND RESPONSE (IDSR) SYSTEM FOR MALARIA SURVEILLANCE IN MAINLAND TANZANIA

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Tanzania has made remarkable progress in reducing malaria burden and aims to transition from malaria control to sub-national elimination. In 2013, electronic weekly and monthly reporting systems using the District Health Information System-2 were introduced. Weekly reporting was implemented through the Integrated Disease Surveillance and Response (eIDSR) system using mobile phones and progressively scaled-up from 67 health facilities (HFs) in 2013 to >7,000 HFs (100%) by 2020. This study aimed to describe the implementation of eIDSR and compare the accuracy of malaria indicators between weekly and monthly data to ascertain its usefulness for malaria outbreak detection and case-based surveillance (CBS) in low transmission areas. The indicators included were number of patients tested for malaria, number of confirmed malaria cases, and number treated presumptively for malaria (clinical cases). The analysis described the trend of reporting, testing, test positivity, and incidence per 1000 population. Comparisons of weekly and monthly reporting rates and incidence were performed for 2020 and 2021 and were stratified by malaria epidemiological strata (parasite prevalence: very low <1%, low 1≤5 %, moderate 5≤30%, and high >30%). Between 2020 and 2021, overall weekly reporting rates increased from 90.2% to 93.9%, while monthly reporting rates were 98.9% in 2020 and 98.7% in 2021. Overall reporting rates and timeliness of weekly reports were highest in very low strata. Confirmed malaria incidence from weekly data was 87.0 per 1000, which was 17.5% lower than monthly data in 2020, and 66.3 per 1000, which was 12.4% lower in 2021. For 2020 and 2021, incidences were the same across weekly and monthly data in the very low strata. Weekly reporting improved steadily over time, while reporting rates and malaria incidence were lower compared to monthly. Nonetheless, the concurrence of weekly and monthly annual reporting rates and incidence in very low strata suggests that eIDSR could be useful for early outbreak detection, and the eIDSR platform could reliably be expanded by adding more indicators and modules for CBS in very low epidemiological strata.

0358

CATALYTIC ROLE OF GOVERNANCE IN IMPROVING UPTAKE OF MALARIA IN PREGNANCY INTERVENTIONS: EXPERIENCES FROM PARTICIPATION OF COUNTY LEADERSHIP IN QUALITY IMPROVEMENT (QI) IN IPTP UPTAKE IN VIHIGA COUNTY, KENYA

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Malaria in pregnancy (MiP) is associated with poor pregnancy outcomes including anaemia, intrauterine growth restriction, low birth weight,

stillbirths, and maternal and neonatal death. To reduce these effects, WHO recommends the use of insecticide-treated nets (ITNs), a minimum of 3 doses of sulfadoxine-pyrimethamine (SP) starting at 13 weeks gestation, and prompt diagnosis and treatment of malaria during pregnancy. The Impact Malaria (IM) project baseline assessment 2019 indicated that in Vihiga County the uptake of the second and third dose of Intermittent Preventive Treatment for Malaria in pregnancy (IPTp2 and IPTp3) was 50% and 35% respectively. To improve this, IM supported a Quality Improvement (QI) learning session for 23 health care providers (Emuhaya Sub-County 10 and Sabatia Sub County 13). The session focused on the use of QI tools to conduct root-cause analysis to identify the bottlenecks to scaling up MiP interventions and generating and monitoring change ideas and improvement. Two follow-up sessions were conducted 3 months apart to review the implementation of the solutions. The leadership provided support for the establishment and revival of QI teams. The key causes of low performance included frequent SP stockouts, non-functional Directly Observed Therapy (DOT) corners, poor community linkages with health facilities (HFs), and inadequate documentation of IPTp doses. County leadership delegated authority to facility in-charges to purchase SP using facility funds when the central level experienced stockouts. Health care providers established 14 QI teams in the facilities to address causes of missed opportunities including the provision of safe water for DOT corners and the revival of facility-community linkages. The Sub-County managers established a WhatsApp group for monitoring weekly IPTp uptake in the 23 HFs. Uptake of IPTp2 and IPTp3 improved from 50% to 92 % and 32 % to 77% respectively from January 2021 to December 2021. Understanding of the causes of bottlenecks at all service delivery levels by county leadership enabled locally developed, pragmatic solutions that led to an increase in intervention coverage.

0359

MALARIA AND ECONOMIC GROWTH IN IVORY COAST

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The objective of our study was to determine the effect of malaria incidence on economic growth in Côte d'Ivoire over the period 1971-2019. To achieve this objective, we used the ARDL model using ordinary least squares (OLS) estimator on data from the WDI (2019). The results of the ARDL model showed that in the short term, malaria incidence, gross fixed capital formation, and trade openness positively influence economic growth while mortality rate negatively influences it. In the long run, while malaria incidence, labor force, and public expenditure contribute positively to growth, mortality and morbidity deteriorate it.

0360

ASSOCIATION OF ANTHELMINTHIC TREATMENT WITH MALARIA PREVALENCE: A SECONDARY DATA ANALYSIS OF THE SUSSUNDENGA MALARIA STUDY

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Malaria remains a serious public health problem in Sub-Saharan Africa. Hence, the need for complementary malaria control strategies. Community mass treatment with Ivermectin, an anthelminthic has emerged in recent times as an effective vector control tool. However, reported effects of other classes of anthelminthic such as the benzimidazoles on the prevalence of malaria in observational settings are conflicting. We explored the relationship between treatment with anthelminthic and the prevalence of malaria in Sussundenga village, Mozambique. We used data from a cross-sectional community-based survey designed to study malaria risk in Sussundenga village. Participants were asked if they had ever received an anthelminthic and were tested for P. falciparum malaria using a rapid diagnostic test (RDT). With logistic regression models, we tested the association between outcome of malaria rapid diagnostic test and patient characteristics to determine independent predictors of malaria prevalence. Similarly, the differences between anthelminthic group and anthelminthic-unexposed group were investigated using simple logistic regression models. 277 participants were included in the analysis. 77% reported ever receiving an anthelminthic. Malaria prevalence by RDT was 30%. Age, ITN use and heads of households of participants with full-time jobs were identified as independent predictors of malaria prevalence. There was no statistically significant association between prior receipt of anthelminthic and malaria prevalence after adjusting for age, ITN use and household heads with full-time jobs (OR = 1.21, p = 0.5573; aOR = 1.37, p= 0.3569). This finding was consistent regardless of the timing of anthelminthic administration ((OR = 0.44, 95% CI, 0.09 - 2.09, p = 0.3032; aOR = 0.35, 95% CI, 0.07 - 1.80, p = 0.2099) We found no statistically significant association between prior receipt of anthelminthic and malaria prevalence by RDT. Age, ITN use and heads of households of participants with full-time jobs predict malaria prevalence.

0361

PLASMODIUM VIVAX AND SARS-COV-2 CO-INFECTION IN VENEZUELA: A CASE SERIES FROM THE MALARIA HOTSPOT IN LATIN AMERICA

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Malaria-endemic areas are not spared from the impact of coronavirus disease 2019 (COVID-19), leading to co-infection scenarios where overlapping symptoms pose serious diagnostic challenges. Current knowledge on *Plasmodium* and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) co-infection remains limited, especially in Latin America, where *P. vivax* infection is more prevalent than in other global regions. We present here a case series of 12 patients with *P. vivax* and SARS-CoV-2 co-infection seen at two main malaria referral centres of the Capital District and Bolivar state, Venezuela between March 13, 2020 and December 31, 2021. Nine out of 12 patients had moderate to severe COVID-19 disease. All patients with severe COVID-19 disease received steroids, supplemental oxygen, and anticoagulants. Three patients had mild COVID-19 disease, two of whom were managed as inpatients because one was a pregnant woman and one was an infant. Patients' mean age was 42 (SD 18) years. Eight of the patients were men, four were hypertense, one suffered from asthma, and one was diabetic. Fever (12/12), chills (11/12), dry cough (9/12), headache (7/12), and diaphoresis (6/12) were the most frequent symptoms reported. Elevated AST/ALT levels, thrombocytopenia, severe anaemia, and thrombocytosis were the most relevant laboratory abnormalities documented. Mean time span between symptom onset and a positive test for SARS-CoV-2 infection based on RT-PCR or a positive microscopy for *Plasmodium* spp. was 6.3 (SD 3.4; range: 3-15) days and 3.3 (SD 3.4; range: 1-13) days, respectively. Nine patients had previous *P. vivax* malaria episodes (range: 1-11), three of whom within the past six months (possible relapse cases). All patients recovered uneventfully. Mean hospital stay was 11.5 (SD 7.2; range: 3-24) days. In malaria-endemic regions, suspected COVID-19 patients should also be monitored for malaria diagnosis without delays due to overlapping symptoms. *P. vivax* and SARS-CoV-2 co-infection could increase the severity of the disease rapidly. Future studies about the pathophysiology and lasting effects of malaria and COVID-19 co-infection are needed.

0362

DETERMINANTS OF MALARIA-RELATED COMMODITIES STOCKOUTS IN THE FOURTH QUARTER OF 2019, AT THE 34 HEALTH ZONES' DISTRIBUTION WAREHOUSES

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In order to identify potential determinants of commodities stock-outs, we conducted a descriptive cross-sectional analysis regarding the 34 health zones' distribution warehouses (HDW). The evaluation focused on 2019 fourth quarter's data and took place from June 15 to 26, 2020. The dependent variable is 'a minimum of a-day stockout' of any given commodity in the fourth quarter of 2019. We also used the following independent variables: quarantine of commodities, availability of commodities at the central procurement office, compliance with delivery dates, availability of financial resources for the purchase of commodities, availability of means of transport of the commodities for the HDW, and lastly the HDW's managers' command of supply chain management processes, which is routinely assessed by using a standardized technical guide to interview the managers. Using a logistic regression model, the dependent variable was weighed against each of the independent variables. The significance threshold was set at the conventional value of 0.05. A proportion of 63.64% of the HDWs had experienced at least a-day commodity stockout in the fourth quarter of 2019. These stockouts were found to be significantly associated with the lack of command of supply chain management processes standards by the HDW managers (P value= 0.017), availability of commodities at the central procurement centers (P value= 0.001), quarantine of commodities (P value = 0.032), non-compliance with delivery dates (P value = 0.011). More efforts are needed to address aspects including HDW managers' capacity building, availability of commodities at the procurement central offices, quality control and routine monitoring processes.

0363

THE USE OF OUTCOME HARVESTING TO EVALUATE THE INTEGRATION OF PRIVATE SECTOR MALARIA CASE MANAGEMENT TO NATIONAL HEALTH SYSTEMS IN VIETNAM

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Since 2016, PSI has implemented the Greater Mekong Sub-Region Elimination of Malaria through Surveillance project which supports National Malaria Programs (NMPs) in Cambodia, Lao PDR, Myanmar, and Vietnam to engage private health care providers in the provision of quality malaria case management and the generation of data that is integrated into national surveillance systems. The project is currently transitioning activity management to NMPs in each country. In Vietnam, the project was evaluated in 2021 using Outcome Harvesting (OH). OH is an evaluation approach to identify, describe, and verify outcomes from development interventions through key informant interviews and desk reviews. OH is appropriate for evaluation in dynamic, uncertain situations, but is rarely used in malaria programs. Between July and September 2021, 26 outcomes were harvested following reviews of project documentation, national malaria policies, guidelines and interviews with program staff. Outcomes were verified through interviews with NMP staff, provincial Center for Disease Control staff and private providers working with the project. Verified outcomes demonstrated that the project succeeded in influencing stakeholders in target areas. The evaluation generated evidence related to an increased quality of malaria service provision within the private sector and increased integration of private sector data into provincial surveillance systems. National policy changes were also attributed by respondents to the project, including the inclusion of private providers in national training, commodity supply and supervision activities. At the community level, OH demonstrated changes in preferences for place of treatment. The results of this evaluation, demonstrate that the GEMS program contributed to changes in the national context, stakeholder behavior and provider practice, leading to the successful transition of private sector to NMP oversight. These results reaffirm the need for comprehensive engagement of national and subnational stakeholders when transitioning public health programs to government oversight.

0364

FACTORS ASSOCIATED WITH IPTP UPTAKE AMONG PREGNANT WOMEN IN MADAGASCAR

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In 2016, the World Health Organization (WHO) recommended that all pregnant women benefit from 8 antenatal care contacts and receiving monthly intermittent preventive treatment (IPTp) with sulfadoxine pyrimethamine (SP) starting the second trimester of the pregnancy, with at least 3 doses of IPTp before delivery. USAID, through IMPACT (Improving Market Partnerships and Access to Commodities Together), with the NMCP (National Malaria Control Program) implemented a household survey to measure IPTp uptake (defined as receiving at least three doses of SP during pregnancy) and to identify predictors associated with IPTp-3 uptake. A cross-sectional household survey was conducted (March 2021) in 10 USAID-supported regions among women who had given birth in the last 12 months. A total of 44 enumeration areas (EA) were randomly selected using probability proportionate to size from the general census (2018). A representative sample of 3,751 households were systematically selected using census conducted in each EA, allowing to find 616 women having given birth in the last 12 months. Data were analyzed using STATA version 13.0. Logistic regression adjusting for age, marital status, number of children, education level, and location was used to identify factors associated with IPTp uptake. IPTp uptake among the target group was 46.8% [95%CI= 37.4-56.4%]. Regression analysis identified three predictors associated with IPTp uptake: i) women who understand how to take IPTp than those who do not (aOR=2.80; 95%CI=1.67-4.71), ii) women receiving at least one IPTp dose under direct observation of the health provider were more likely to receive the three doses than those who did not (aOR=2.73; 95%CI=1.49-5.04), and iii) women in the 4th and 5th quintiles for socio-economic status were more likely to complete the three doses than those who are not (aOR=2.20; 95%CI=1.34-3.85). The results help identify factors that may be addressed in the communication strategy: providing instruction on how to take the SP, targeting poorest women (free service), and ensuring provider training on direct observation.

0365

UNDERSTANDING ANTENATAL SERVICE QUALITY THROUGH SUPPORTIVE SUPERVISION DATA IN TANZANIA

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Malaria in pregnancy (MIP) is a major global public health problem associated with increased maternal anemia, spontaneous abortion, and infant and maternal death. The Tanzania Ministry of Health delivers MIP and other antenatal care (ANC) services to pregnant women through an integrated ANC platform guided by the National Malaria Control Program and the Reproductive and Child Health Department. The U.S. PMI Impact Malaria project, in collaboration with regional and council health management teams, reviewed records of women who had delivered in three project-supported regions using a structured assessment tool during malaria service and data quality improvement (MSDQI) supportive supervision at ANC between October 2020 and December 2021. The ANC register was used to track adherence to guidelines as reflected in the records. The team assessed recording of the following at first ANC: gestation age, hemoglobin, malaria RDT, iron/folic acid and ITN provision; as well as visit number and number of IPTp doses throughout the pregnancy. Records of 5079 women who attended ANC were reviewed and found the interventions delivered and documented as follows: 96% gestation age, 94% RDT results, 94% ITN provided, 86% iron/folic acid, 44% Hemoglobin level and 59% IPTp3+. Many who received IPTp3+ attended first ANC between 13-26 weeks, had gravida 2-4 and made 4-6 ANC visits. Women who attended first ANC very late in their pregnancy had significantly higher odds of only getting IPTp1 compared to women who attended first ANC at ≤12 weeks (Month (M) 7: OR1.8; M8: OR2.4). Women who began ANC ≥13 weeks had significantly higher odds of getting IPTp3 compared to those beginning ≤12 weeks (M4: OR2.0; M5: OR2.1, M6: OR1.5). ANC intervention coverage was high, indicating high-quality integrated services. The data has identified a challenge in adherence to guidelines in provision of IPTp, root cause analysis will be conducted to identify the root cause of the problem and develop plans to address it.

0366

THREE DELAYS OF MALARIA CARE-SEEKING: COMPARING STRUCTURAL AND PSYCHOSOCIAL FACTORS INFLUENCING PROMPT CARE-SEEKING IN MALAWI

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The three-delays (1st- deciding to seek, 2nd- getting to, and 3rd- receiving adequate) care model was used to explore delay-related factors influencing prompt care-seeking for children under five with fever to inform the design of effective social and behavior change (SBC) interventions. We analyzed responses from 913 female caregivers in a nationally representative cross-sectional survey conducted in Malawi in 2021. The outcome variable was prompt care-seeking from a qualified provider. Delay factors included: 1st level- knowledge, attitudes towards malaria, the perception that prompt care-seeking is effective, perceived malaria susceptibility and discussion of malaria with family or friends; 2nd level- proximity to facility, transportation, and urban versus rural location; 3rd level- perceptions of provider knowledge, perceived quality of care, and perceived availability of commodities. Logistic regressions explored the association of delay factors at each level with prompt care-seeking, controlling for contextual variables. Delay factors were summed into three continuous variables to compare their relative associations with prompt care-seeking. Statistically significant factors associated with prompt care-seeking included knowledge of malaria, positive attitudes towards care-seeking, and recent discussion of malaria with family or friends (aOR ranging 1.22-1.42)[1] at the 1st level, and proximity to a health facility (aOR: 1.46; 95% CI: 1.06-2.00) at the 2nd level. Each additional positive factor present in the 1st level increased the odds of prompt care-seeking by 29% (aOR: 1.29; 95% CI: 1.16-1.44), while additional factors at the 2nd and 3rd levels had no effect. Amidst the backdrop of free malaria services in Malawi, key correlates of prompt care-seeking for fever were primarily psychosocial factors occurring at the 1st delay phase that may be addressed with community-based SBC interventions. Interventions may use a mix of SBC approaches to address key correlates of care-seeking, including improved knowledge, attitudes, and household discussions about prompt care-seeking for fever.

0367

PERFORMANCE OF COMMUNITY HEALTH INFLUENCERS, PROMOTERS AND SERVICES (CHIPS) ON CASE MANAGEMENT OF UNCOMPLICATED MALARIA

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Nigeria has the second highest childhood mortality in the world. Most of these deaths are preventable through proven and cost-effective interventions. Substantial inequalities still exist in child health outcomes based on differences in economic status, education, place of residence and sex. Kano State has one of the highest malaria prevalence and under-five mortality in the country. The Nigerian Ministry of Health adopted a new community health workers' model called Community Health Influencers, Promoters, and Services (CHIPS) to improve access to and quality of primary health care in rural communities and also contribute to the attainment of UHC. Support to the National Malaria Programme2 (SuNMaP2) supported the introduction of CHIPS in hard-to-reach communities in Kano through harmonization of integrated community case management (iCCM) and CHIPS modules, training of 1,130 CHIPS agents (99% female) and provision of malaria and non-malaria commodities with proper linkage to health facilities for clinical mentoring, supportive supervision and data collection. A performance assessment of 320 CHIPS agents was conducted in Kano focusing on four thematic areas: service provision; use of CHIPS guideline and job aids; patient's records management; and stock management. The assessment showed that job aids for malaria rapid diagnostic test (RDT) and rectal artesunate were available and in use by 84.3% of CHIPS agents. About 90% of children under five with confirmed malaria were treated with artemisinin-based combination therapy (ACT) by CHIPS agents. Patient's record management was good, with 85.1% of them having updated household record information. 88.7% of the CHIPS agents maintained good stock management practices including use of inventory control card and First-Expiry-First-Out (FEFO) method. Overall, 85% of CHIPS agents were performing according to standards. We recommend that routine supervision that includes observation of case management of malaria should be done more regularly in all CHIPS implementing localities. Linkages between facility based and community-based malaria treatment should also be strengthened.

0368

THE CONTRIBUTION OF THE U.S. PMI IMPACT MALARIA PROJECT IN BUILDING THE CAPACITY OF MATERNITY PROVIDERS ON MALARIA IN PREGNANCY IN MALI

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In Mali in 2018 there were no specific malaria in pregnancy (MIP) training materials, nor did the outreach training and supportive supervision (OTSS) approach include MIP. Maternity providers referred pregnant women who tested positive for malaria to the outpatient clinic for treatment. In 2019, the U.S. President's Malaria Initiative Impact Malaria (IM) project supported the National Malaria Control Program and the Sub-Directorate of Reproductive Health to produce specific training materials on MIP prevention and management and respectful antenatal care (trainer's guide and reference manual), and developed MIP checklists to integrate into OTSS, part of the upgrade to OTSS+. These documents and checklists were validated by the MIP technical working group (TWG) and disseminated through cascade training to maternity providers in five regions: Ségou, Mopti, Kayes, Koulikoro, and Bamako. A total of 1,121 maternity providers were trained in 2019 and in 2021: 34% midwives, 32% obstetric nurses, 31% matrons, and 3% other cadres, from 1,063 health facilities including 958/1,408 Community Health Centers and 42/62 Referral Health Centers which is equivalent to 68% of functional public health facilities in the country. During these combined trainings (classroom theory and clinical practice), participants scored an average of 75% at pre-test and 97% at post-test. After these trainings, OTSS+ visits assessed the competence of a subset of 282 trained providers in the regions of Ségou and Mopti in 2019. Overall, 53% of providers met the competency score of 90% in MIP prevention, and 60% of providers reached a score of 90% in MIP treatment. When IM moved to Kayes, Koulikoro, and Bamako in 2020, a baseline OTSS+ round was conducted before the MIP training in 2021. In 2021, after the training, OTSS+ reached 294 of the trained providers, 58% of whom reached the competency threshold in MIP prevention vs. 22% at baseline, and 47% of them reached the competency threshold in MIP treatment vs. 17% at baseline. The MIP TWG subsequently endorsed a change in practice such that all trained maternity providers now treat MIP in the maternity department.

0369

ENGINEERING A TRANSGENIC ASAIA BOGORENSIS STRAIN TO CONTROL AN EFFECTOR PLASMID WITH A CONDITIONAL ORIGIN OF REPLICATION FOR PARATRANSGENESIS USE

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Malaria is a dangerous vector-borne disease caused by parasitic protists of the genus *Plasmodium* and transmitted through the bite of infected female *Anopheles* mosquitoes. In 2020, over 600,000 deaths from malaria were reported. Due to its severity, many strategies to mitigate and combat the spread of malaria are currently in place. However, the emergence of resistance to insecticides and anti-plasmodial treatments calls for additional methods for reduction of malaria infection. Paratransgenesis is the genetic engineering of symbiotic bacteria that live in the mosquito midgut to secrete anti-plasmodial effector peptides. Paratransgenesis has the potential to kill *Plasmodium* parasites prior to human infection. The pi protein, Pir, is necessary for the replication of oriR6K plasmids. By inserting *pir* into the *Asaia bogorensis* chromosome, an oriR6K effector plasmid will be able to replicate in the engineered bacterial strain only, preventing its horizontal transfer to unintended hosts. To this end, *pir* with three variable ribosome binding sites (RBSs) have been inserted into a neutral phage site within the *Asaia* chromosome. These variable RBSs have been shown to control low, medium, and high oriR6K plasmid copy numbers within the respective transgenic strains. By supplementing Pir in trans, the plasmid will be unable to replicate in unintended hosts, preventing its transfer to other organisms in the mosquito midgut environment. The use of three separate RBSs also allows for replication of the plasmid at optimal levels for survival and competitiveness of the transgenic strains. Thus, this provides the first step towards a plasmid-based paratransgenesis system that will not be transferred to other bacteria within the mosquito midgut.

0370

EFFECT OF FIVE ROUNDS OF SEASONAL MALARIA CHEMOPREVENTION IN CHILDREN AGED BETWEEN 5 AND 14 YEARS IN DANGASSA MALI

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Despite a significant reduction in malaria burden in children under five years of age, the large-scale implementation of seasonal malaria chemoprevention (SMC) remains a considerable challenge in areas with long periods of seasonal malaria transmission, such as Dangassa Mali. Low coverage, shifting malaria risk in children at least five years of age, and rebound effects in malaria incidence after SMC stoppage are primarily reported in areas with long-term malaria transmission. An open randomized study was conducted to assess the effect of an additional round of the current SMC regimen in older children in Dangassa, Mali, where malaria transmission is highly seasonal. Poisson regression models were used to estimate the reduction in malaria incidence in the intervention group compared to a control group. Overall, a downward trend in participation rates was observed from August (94.3%) to November (87.2%) respectively. One month following the fourth SMC round, the risk of malaria incidence was similar in both comparison groups (IRR=0.66, 95%CI [0.35-1.22]). In December, a decrease of 51% in malaria incidence was observed in the intervention group compared to the control group after adjusting for age and long-lasting insecticidal net use (IRR=0.49, 95%CI [0.26-0.94]). A reduction of approximately 17% in malaria incidence was observed after the fifth round in the intervention group as compared with the control group. Implementing a fifth round of SMC in Dangassa has shown a significant reduction in malaria incidence. These results suggest a critical need to extend SMC to children aged at least five years and include five cycles of treatment in areas with extended transmission seasons, such as Dangassa. **Keywords**: Malaria, Incidence, Seasonal malaria chemoprevention, Mali.

0371

FACTORS ASSOCIATED WITH RECEIVING LONG-LASTING INSECTICIDE TREATED NETS AT REPRODUCTIVE AND CHILD HEALTH CLINICS IN MAINLAND TANZANIA

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Mass distribution of Long-Lasting Insecticidal Nets (LLINs) is an effective malaria prevention intervention. Tanzanian policy is for every pregnant woman attending first antenatal clinic (ANC) and every child receiving their first measles-rubella vaccination to be given a free LLIN. However, routine data shows that not all eligible pregnant women and children get an LLIN at these visits. This study aimed to determine factors influencing the uptake of LLINs in these two vulnerable groups. A health facility-based cross-sectional survey was conducted from July and September 2021 in Mainland Tanzania in 60 health facilities randomly selected from ten districts in five regions representing five different transmission strata and rural and urban areas. The study involved 1320 pregnant women attending first ANC and 1320 children attending first measles-rubella vaccination services. Chi-square tests followed by a modified Poisson regression model were used to identify factors associated with LLIN uptake in both groups separately. About three quarters (N= 980) of pregnant women received an LLIN at their first ANC. This was highest in Babati district (94.6%) and lowest in Mbogwe District (56.7%). Increasing age (p= 0.015), number of children per woman (p= 0.033), number of ANC visits (p= 0.010), and the previous experience of sleeping under a mosquito net (p<0.001) were associated with receiving an LLIN at the visit. Seventy one percent (N=938) of caretakers received an LLIN at their child's immunization visit. This was highest in Kaliua (94.1%) and lowest in Ilala (43.7%). Increasing caretakers' age (p<0.001), higher level of education of caregiver (p<0.001), previous experience of sleeping under a mosquito net (p = 0.037), and previous exposure to health education on LLIN (p<0.001) were associated with receiving an LLIN at the visit. The rates of pregnant women and caretakers of young children receiving LLINs at first ANC and measles-rubella immunization visits were unsatisfactory. The study findings may be used to strengthen education and mentorship programs at all health facilities for both women of childbearing age and health care providers.

0372

IMPACT OF PROACTIVE COMMUNITY CASE MANAGEMENT ON MALARIA AND ANEMIA PREVALENCE AMONG PREGNANT WOMEN IN BANKASS, MALI, 2020

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Malaria and anemia in pregnancy remain common in Mali despite the scale-up of control interventions. We conducted a cross-sectional study to assess whether proactive home visits by Community Health Workers (CHWs) are more effective than conventional, passive workflow in reducing the prevalence of malaria and anemia among pregnant women in rural Bankass, Mali. The study was nested in a three-year (2017-2020) cluster-randomized controlled trial assessing the impact of proactive community case management in reducing under-five mortality among 137 village-clusters randomized to proactive home visit intervention (household visit by CHW at least two times per month) or passive control arms (CHW services provided at a fixed site in the community). CHWs in both arms provided illness management, including malaria rapid diagnostic tests (RDT) and antimalarial treatment for those with positive tests, follow-up care, health education, and reproductive, maternal, and newborn care and referral services. At the end line survey, all pregnant women were tested for malaria using RDTs and anemia. Women who reported completing a pregnancy in the last year were asked about receiving three or more doses of intermittent preventive treatment in the pregnancy (IPTp3+). At end line, 1848 pregnant women were interviewed (control N = 859, intervention N = 989). The prevalence of malaria was similar in the intervention and control arms (16.1%, 95% CI 13.8-18.4 and 17.6%, 95% CI 15.0-20.7, respectively). The prevalence of moderate or severe anemia (hemoglobin < 10 g/dL) was also similar in the intervention and control arms (38.0%, 95% CI 34.8-41.3 and 42.1%, 95% CI 37.4-46.8, respectively). Among 207 women who reported completing a pregnancy in the last year and provided information on IPTp3+, 67.0% (95% CI 56.4-77.5) received three or more doses of IPTp3 in the intervention arm compared to 51.0% (95% CI 42.7-59.3) in the control arm (OR 1.95, p = 0.022). Proactive home visits were not associated with a significant reduction of malaria and anemia prevalence among pregnant women, but improved the coverage of at least three doses of IPTp compared with passive workflow.

0373

FACTORS ASSOCIATED WITH EARLY UPTAKE OF INTERMITTENT PREVENTIVE THERAPY IN PREGNANCY IN BUSIA DISTRICT, UGANDA

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In areas with moderate to high malaria transmission, the World Health Organization recommends monthly Intermittent Preventive Therapy in Pregnancy (IPTp) with sulphadoxine-pyrimethamine (SP) beginning in the fourth gestational month. Women who begin IPTp during the fourth month, compared to later during pregnancy, have better birth outcomes; however, the factors affecting early IPTp uptake are largely unknown. 467 pregnant women attending antenatal care at Busia Health Centre IV and Masafu Hospital, both in eastern Uganda, were enrolled using an explanatory sequential mixed methods design. Qualitative data were gathered through in-depth and key informant interviews. We used modified Poisson regression with clustered robust standard errors at hospital level to predict prevalence ratios (PR). Overall, 30% (95% CI= 26.0%-34.3%) of pregnant women initiated IPTp during the fourth month. Participant age 15-24 years (aPR=1.03; 95% CI=1.01-1.06), being a Protestant (aPR= 1.26; 95% CI= 1.05-1.52), being married (aPR= 1.20; 95% CI= 1.03-1.17), using insecticide treated nets (aPR= 1.11; 95% CI= 1.02-1.20) and listening to a radio more than once a week (aPR=1.46; 95%CI=1.21-1.76) were associated with increased prevalence of early IPTp initiation while being a trader (aPR= 0.47; 95% CI= 0.41-0.55), being a Moslem (aPR= 0.26; 95% CI= 0.22-0.30), having been separated/divorced/widowed (aPR= 0.93; 95% CI=0.87-0.99), being in a wealthy category (aPR=0.65; 95% CI= 0.62-0.67) and having knowledge about IPTp (aPR= 0.23; 95% CI= 0.18-0.28) were associated with reduced prevalence of early IPTp initiation. In qualitative assessments, discouragement from the mother-in-law, a lengthy turn-around time, and IPTp knowledge gaps were

all identified as barriers to IPTp uptake. The government and its partners should consider redoubling their social mobilization efforts, such as radio broadcasts, to educate communities about the importance of early initiation of IPTp.

0374

FACTORS ASSOCIATED WITH SEASONAL MALARIA CHEMOPREVENTION (SMC) COVERAGE ACROSS ALL CYCLES AND ADHERENCE TO DAY 2 AND 3 MEDICATION: A MULTI-YEAR REVIEW OF INDEPENDENT HOUSEHOLD MONITORING SURVEYS FROM TWO COUNTRIES

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Seasonal Malaria Chemoprevention (SMC) consists of the intermittent administration of antimalarial medications during the rainy season to prevent clinical malaria. Full treatment courses of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) are given to children aged 3-59 months at 28-day intervals. SP and AQ are given on day 1 as directly observed treatment by community distributors, and caregivers administer another two AQ doses on subsequent days unobserved. To ascertain factors associated with coverage of SP and AQ on day 1 and adherence to day 2 and 3 AQ the NMCPs, supported by the U.S. PMI Impact Malaria, conducted independent household monitoring surveys in Cameroon and Mali. In Cameroon, 96% of nearly 2 million children targeted were reached in all 4 cycles in 2020 (93% of nearly 1 million in Mali) per caregiver declaration and 95% took their second and third dose during each cycle (97% in Mali) per caregiver declaration. In Cameroon, the most cited reason for a child not being treated in cycle 1- home not visited by a distributor - dropped from 50% to 30% in cycle 4 . Children treated in cycle 4 had significantly lower odds of having side effects (except for loss of appetite) than children treated in cycle 1. Even though children under one year old had higher odds of side effects than children over one year old, it did not affect adherence to medication on day 2 and 3. Ineligibility of the child on day 1 of each cycle due to fever (they do not test for malaria as part of their campaign) decreased from 22% of all reasons for not being treated in cycle 1 to 14% in cycle 4 of 2020 in Cameroon, while in Mali it increased from 10% to 26% that year. This may be due to differences in campaign start dates, as Cameroon starts cycle 1 at the beginning of July, and Mali at the end of July. In Mali, which does test as part of the campaign, the proportion of positives out of suspected cases tested increased from cycle to cycle in both under-fives and over fives in both 2019 and 2020. Analyses are ongoing, and the results may be used to tailor the delivery and communications strategies to each country.

0375

KNOWLEDGE AND PRACTICES ON MALARIA AMONG COMMUNITIES INVOLVED IN A SEASONAL MALARIA CHEMOPREVENTION STUDY IN NANYUMBU AND MASASI DISTRICTS, TANZANIA

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Utilization of malaria interventions are influenced by the level of knowledge and perception of the community on the infection and the availability of the interventions. This study assessed knowledge, perception, and utilization of malaria control tools in Masasi and Nanyumbu districts, Tanzania, areas with seasonal malaria transmission. A community-based cross-sectional survey among heads of households of under-five children conducted between August and September 2020. A structured questionnaire was administered to the heads of the households to gather information on knowledge and perception of malaria infection and utilization of the available malaria interventions. Screening of malaria infection was carried out on children aged between 3 and 59 months using a malaria rapid diagnostic test (mRDT). A total of 1556 household heads were interviewed, 1167 (75.0%) were male, and 1067 (68.6%) were couples. Only 47.3% and 13.8% of the household heads had moderate and adequate knowledge on malaria infection and control, respectively. The level of knowledge on malaria infection and control was significantly influenced by gender and level of education of the household head, and the number of under-five children in the household. Likewise, about 95% of the household heads perceived sleeping under the bed net to be beneficial. Majority of the household (95.9% (1492/1556) reported using bed nets as malaria intervention, but only 84.0% (1305/1556) of the households had bed nets. In this area with seasonal transmission about half of household heads had a moderate level/adequate of knowledge on malaria infection and control interventions.

0376

COMPARING CHEMOPREVENTION APPROACHES FOR SCHOOL-BASED MALARIA CONTROL IN MACHINGA DISTRICT, MALAWI

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Prevalence of *Plasmodium falciparum* (*Pf*) infection in school-age children (5-15 years, SAC) is often higher than in younger children and adults. Asymptomatic infection and uncomplicated malaria disease lead to decreased school attendance, impaired cognitive function, and continued parasite transmission. School-based preventative treatment is a promising strategy to reduce the burden of malaria among SAC. However, optimal design of an intervention is not clear. We aim to compare intermittent preventive treatment (IPT), in which all students receive treatment to both clear parasites and provide a period of prophylaxis, and intermittent screening and treatment (IST), in which only students with a positive test are treated. In February 2022, we enrolled 745 primary school students in a 3-arm randomized controlled clinical trial: IPT, IST, and control. All students in the IPT arm and students with positive high-sensitivity rapid diagnostic test (hsRDT) in the IST arm were treated. Girls <10 years old and all boys were treated with dihydroartemisinin-piperaquine (DP). Older girls were treated with chloroquine as DP is contraindicated in the first trimester of pregnancy. The intervention will be performed three times during the peak malaria transmission season (Feb-June). Outcomes including *Pf* infection, clinical malaria, anemia, school attendance and household infection prevalence will be assessed 6-8 weeks after the final intervention. At each visit, students are interviewed about symptoms and treatment history and a fingerprick blood sample is obtained to characterize *Pf* infection. At baseline, mean hemoglobin level was 12.7g/dL (SD:1.3); 8.0% of students were anemic (<11g/dL); 30% reported fever

in the last 48hrs; 49% reported sleeping under a bednet the night prior to the interview. *Pf* infection prevalence by hsRDT in the IST arm was 47.9%. Full baseline, follow-up and outcome results will be presented. Thus far our study confirms the high prevalence of *Pf* infection in SAC. Results of this trial will inform the design of school-based malaria chemoprevention programs.

0377

ACCOUNTING FOR REGIONAL TRANSMISSION VARIABILITY AND THE IMPACT OF MALARIA CONTROL INTERVENTIONS IN GHANA: A POPULATION LEVEL MATHEMATICAL MODELLING APPROACH

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Background: Assessing the effectiveness of malaria control measures in Ghana will require taking transmission dynamics of the disease into account given the influence of climate variability in the region of interest. The impact of preventative interventions on malaria incidence and the prospects of meeting program timelines in Ghana have been investigated using mathematical models based on regionally diverse climatic zones. Methods: An ordinary non-linear differential equation model with its associated rate parameters was developed incorporating the transitions between various disease compartments for three ecological zones in Ghana. Model parameters were estimated using data captured on the District Health Information Management System in Ghana from 2008 to 2017.The impact of insecticide treated bed nets and indoor residual spraying on the incidence of malaria were simulated at various levels of coverage and protective effectiveness in each ecological zone. To fit the model, Approximate Bayesian Computational sampling approach was adopted. Results: Increasing the coverage levels of both long lasting insecticide treated bed nets or indoor residual spraying activities without a corresponding increase in their proper use or patronage does not impact highly on averting predicted incidence of malaria in Ghana. Improving on the protective efficacy of long lasting insecticide treated bed nets through proper usage could lead to substantial reductions in the predicted incidence of malaria. Similar results were obtained with indoor residual spraying across all zones. Conclusions: Projected goals set in the National Strategic plan for malaria control 2014-2020 as well as WHO targets for malaria pre-elimination by 2030 are only likely be achieved if a substantial improvement in treated bed net usage is achieved coupled with targeted deployment of indoor residual spraying with high efficacy.

0378

COMPARATIVE ANALYSIS OF FACILITY AND COMMUNITY DISTRIBUTION OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY: EVIDENCE FROM MATERNITY RECORD BOOKLET IN OHAUKWU, EBONYI STATE NIGERIA

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Nigeria has the highest malaria burden globally, contributing to 31.9% of global malaria deaths, and is one of the two countries with the greatest burden of malaria during pregnancy. According to the 2018 Nigeria Demographic and Health Survey (DHS), even though up to 57% of pregnant women attend ANC four or more times, only 17% received three or more doses of IPTp as recommended by the WHO. Nigeria supported this demonstration project of CHWs in delivering intermittent preventive treatment of malaria in pregnancy (IPTp) at the community-level, complementing IPTp at antenatal care (ANC) in three districts. Data were extracted from 735 maternity record booklets (MRB) at 25 public health facilities in Ohaukwu for women presenting for ANC between April and September of 2019. The MRB allowed for the longitudinal analysis of client-level data that is not available from routine data sources. Sixty percent of women received IPTp doses only in the community, while 28% received IPTp only at ANC and 12% received IPTp in both locations. One-way ANOVA and post-hoc Tukey tests were used to examine the difference in mean number of ANC visits and number of IPTp doses between the three groups. The mean number of ANC visits was significantly higher in the group of women receiving IPTp at both locations compared to those only receiving IPTp in the community (0.89 ± 0.18 visits, $p<0.01$) and those only receiving IPTp during ANC (0.61 ± 0.20 visits, $p<0.01$). There was no statistically significant difference in the mean number of ANC visits between the groups receiving IPTp only in one location (0.29 ± 0.13 visits, $p=0.077$). The difference in number of doses was statistically significant across all groups, whereby women in the facility-only group received the fewest IPTp doses. Receipt of IPTp in both locations was associated with both greater numbers of ANC visits and IPTp doses. Only receiving IPTp in the community was not associated with a decrease in ANC attendance. These data suggest complementing ANC-based IPTp distribution with community-based distribution is beneficial.

0379

LONG-TERM IMPACT OF SEASONAL MALARIA CHEMOPREVENTION (SMC) ON MONTHLY DISTRICT- AND CLINIC-LEVEL MALARIA CASES IN CHILDREN AGED UNDER FIVE USING ROUTINE CLINICAL DATA, 2013-2018

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Since its recommendation by the World Health Organization in 2012, seasonal malaria chemoprevention (SMC) targeting children aged 3-59 months with administration of sulfadoxine-pyrimethamine plus amodiaquine (AQ) in four-cycle annual rounds during the high transmission season has been scaled up across Sahelian countries. As SMC in Burkina Faso has matured, it has been delivered over eight consecutive years in some areas. We investigated whether impact of SMC on monthly district-level counts of suspected and confirmed malaria cases among children aged 0-59 months in Burkina Faso remained consistent between annual rounds. Data were extracted from the national Health Management Information System, covered 64 districts with at least one year of SMC delivery and spanned 2013-2018. We fitted quasi-Poisson generalized additive mixed models with cyclic cubic spline terms for each district to adjust for seasonality in cases, and random intercept terms for years within districts. Models included interactions between periods of SMC delivery and number of annual SMC rounds previously delivered in that district by year to test for differences in effect between years. SMC delivery was significantly associated with lower adjusted monthly district-level counts of cases (rate ratio: 0.23, 95% CI: 0.22-0.24, $p<0.0001$), corresponding to a 77% reduction. Interaction terms indicated reductions of 84%, 93%, 94% and 96% in monthly malaria cases in areas with one, two, three and four previous rounds respectively, and a significant improvement in effect with successive rounds. The results highlight the effectiveness of SMC in Burkina Faso and are consistent with trials showing a 75% reduction in confirmed cases. It may be hypothesized that increasing effectiveness of SMC over time reflects increasing coverage and adherence to AQ administration. Next steps include obtaining additional clinical data from Burkina Faso, Togo and other Sahelian countries; fitting models to clinic-level data using a supercomputer; estimating impact in districts with five annual SMC cycles; and investigating potential SMC "rebound effects" in children aged over five years.

0380

OPTIMIZING THE ROLE OF LEAD MOTHERS IN SEASONAL MALARIA CHEMOPREVENTION (SMC) CAMPAIGNS: INSIGHTS FROM FORMATIVE RESEARCH IN KANO STATE, NORTHERN NIGERIA

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Seasonal malaria chemoprevention (SMC) is effective in preventing malaria. Lead mothers (LMs) are community health volunteers that undertake health promotion activities during SMC campaigns aimed at ensuring caregivers' compliance with administering the complete dosage for SMC. The LMs approach is used in several SMC implementing states across Nigeria, however, there is lack of evidence about structure or impact of this approach. We sought to better understand the current role of LMs and identify areas for improvement by obtaining feedback from stakeholders, to possibly improve SMC outcomes in Nigeria. Formative research, utilizing qualitative methods, was undertaken in Kano State, northern Nigeria. Twenty semi-structured interviews were conducted with stakeholders from National, State, Local government health systems as well as from the community. Transcription and thematic analysis were conducted on the qualitative data. Study findings indicate that recruitment and supervision guidelines for LMs should be reviewed and strengthened within the SMC programme in Nigeria. There is also a clear need to improve the knowledge and skills of LMs through adequate training, so that they better deliver targeted health messages to caregivers during SMC campaigns. Appropriate job aids such as flipbooks, should be developed and provided to LMs. In addition to their current role, LMs should discuss other malaria prevention interventions [beyond SMC] with caregivers, encourage better nutrition and sanitation practices within households as well as promote better health-seeking behaviour among community members. To promote sustainability, respondents also noted policy-makers should work to transition the role of LMs to the Community Health Influencers Promoters Services (CHIPS) agents during SMC campaigns; since CHIPS agents have government policy and funding support, in contrast to the current LMs intervention which is not sustainable and heavily supported by donor organizations. In addition to feedback from some study respondents that CHIPs agents have more training and capacity to contribute to the SMC programme than the current LMs.

0381

SAFETY AND EFFICACY OF DIHYDROARTEMISININ-PIPERAQUINE FOR SEASONAL MALARIA CHEMOPREVENTION IN SCHOOL AGED CHILDREN, MALI

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Implementation of Seasonal malaria chemoprevention (SMC) with Sulfadoxine pyrimethamine and Amodiaquine (SP-AQ) has reduced malaria burden in children under 5 but contrasted with increased cases in school-aged children. Extending SMC to school-aged children will contribute to reduce malaria morbidity and transmission. SP-AQ currently used for SMC are threatened by apparition of resistance. Alternative drug is needed in case of spread of SP-AQ resistance strains. We assessed the safety and efficacy of DHA-PQ for SMC in school-aged children in Bandiagara. A double-blind randomized controlled trial was conducted with 345 participants from 6-15 years old randomized in ratio 1:1:1 in 3 arms to receive either DHA-PQ or SP-AQ or albendazole. Albendazole used in control group was administrated to all participants to reduce treatment bias. Four SMC rounds were conducted from September to December and participants were followed to assess safety and efficacy of the drugs. The adverse events frequently reported were abdominal pain (12.87% vs 45%), headaches (15.44% vs 26.08%), vomiting (9.35% vs 22.42%) and nausea (6.14% vs 14.65%) respectively in DHA-PQ and SP-AQ arms. In SP-AQ arm adverse events increased significantly with age. Biological analysis showed that the median (Q1-Q3) ALT level was higher in DHA-PQ arm (15.55 IU/l, 12.2-21.70) compared to SP-AQ and control arms with 12.00 IU/l (9.0-16.70) and 12.70 IU/l (9.4-16.45) respectively ($p = 0.0006$). The mean of hemoglobin was similar in the 3 treatment arms. Prevalence of clinical malaria was lower in both DHA-PQ and SP-AQ arms (1.5%) compared to the control arm (15.9%). Prevalence of malaria infection was higher in the control arm (40.4%) compared to the DHA-PQ (9.9%) and SP-AQ (6.1%) arms. Kaplan Meier model showed that in subsequent rounds of MSC the presence of parasitemia was more frequent in control arm. Gametocyte density was higher in control arm (mean = 44.4 ± 0.0) and lower in SP-AQ and DHA-PQ arm (0.4 ± 1.8 and 0.3 ± 1.2) respectively. DHA-PQ showed high efficacy and good safety in SMC in school aged children and may be an alternative to SP-AQ for SMC.

0382

FACTORS AFFECTING COVERAGE OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY AND INFANCY UNDER PROGRAMMATIC CONDITIONS: A SYSTEMATIC REVIEW

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Despite the efficacy of Intermittent preventive treatment in infancy (IPTi) with Sulphadoxine-Pyrimethamine and WHO's recommendation, its adoption has been slow across Africa; only Sierra Leone attempted implementing at scale. One of the many bottlenecks to IPTi policy uptake is its limited efficacy and the lack of demonstrable impact in real world settings, which is dependent on the coverage of the intervention. Missed opportunities for IPTi uptake during immunization clinics causing low coverage, have been demonstrated. This review, planned for June 2022, seeks to systematically identify and synthesize evidence on the barriers to achieving high coverage of IPTi and the determinants of coverage drawing from literature on IPTi and lessons from implementation of IPTp, a similar but more widely implemented intervention. Search will include electronic bibliographic databases, grey literature and bibliographies of retrieved articles. Inclusion criteria: quantitative, qualitative, or mixed methods research studies; studies assessing barriers to, facilitators of, or determinants of uptake or coverage of IPTp or IPTi; reports; peer-reviewed or grey literature; and sub-Saharan African region. Search will include concepts like 'Intermittent preventive treatment', 'Factor', 'Barrier', 'Determinant', 'infant', 'routine immunization clinic', 'malaria', 'coverage', 'Policy uptake' etc. The search strategy will be run on databases, lists of titles and abstracts of articles retrieved will be exported to Endnote library and duplicates removed, and eligible full articles meeting inclusion criteria will be retrieved. Quality assessment of the studies will be done using the relevant checklists to deal with the risk of bias. A descriptive analysis of the selected studies will be done with a narrative synthesis to bring the findings together. Data extraction will be aided by a tool and verified by a second reviewer. Pre-existing themes used by the authors will be identified and stratified based on user or provider perspectives. This review will contribute to the development of a logic model for optimal IPTi coverage when implemented at scale.

0383

SULFADOXINE PYRIMETHAMINE/AMODIAQUINE (SPAQ) ADMINISTRATION DURING SEASONAL MALARIA CHEMOPREVENTION (SMC) CAMPAIGNS IN BURKINA FASO: PRACTICES AND CHALLENGES

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Malaria transmission in Burkina Faso is seasonal, with peaks observed during the rainy season. Seasonal malaria chemoprevention (SMC) is positioned as a major prevention intervention to reduce the burden of malaria. The results of a study conducted in 2020 on the implementation of SMC in the context of COVID 19, as well as the various campaign reports, showed that caregivers had difficulties administering SMC drugs (SPAQ) to their children. We conducted an exploratory study to identify &lt role models &gt within the communities, that is, individuals who exhibit uncommon, positive behaviours that aid the successful administration of SPAQ. These behaviours were then shared with other community members through interactive monthly sessions (e.g. roleplay and story-telling). The health district of Saponé, located in the Center South region, served as the framework for this study. Role models were identified through focus group discussions and key informant interviews were conducted to further explore their beneficial behaviours. Many themes as caregiver's perception on malaria, adverse event of SMC and SPAQ administering practice for children aged under five by caregiver, had been identified. In general, caregiver have a good perception of SMC and quote that the number of their visit in the health facility because of malaria, decreases and their expense for health service fees also. However, even if they do not observe adverse effect of SPAQ to their own children, they said that their neighborhood mentioned vomiting, diarrhea and lethargy as adverse effect. Caregivers described many practices related to SPAQ administration; some flatter the child with candy or threaten children with injection. The most commonly reported behaviour was mixing SPAQ with food or drink (e.g. porridge or tea) prior to administration. The role model approach allowed good engagement of community members at throughout the study. However, the efficiency of these practices on malaria incidence needs to be explored by a further study.

0384

RESULTS OF THE ROLE MODEL STUDY TO EXPLORE CAREGIVER ADMINISTRATION OF SULFADOXINE-PYRIMETHAMINE (SP) &LT AMODIAQUINE (AQ) DURING SEASONAL MALARIA CHEMOPREVENTION (SMC) CAMPAIGNS &GT CHAD

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Seasonal malaria chemoprevention (SMC) is an intervention recommended by WHO since 2012 to prevent malaria cases in children under five. It consists of intermittent administration of a full course of sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) [SPAQ] to children aged 3-59 months during peak malaria transmission season. The first dose of SPAQ is administered by caregivers under the direct supervision of Community Distributors (CDs), while dose 2 and 3 of AQ are left for caregivers to administer. Previous studies found that, some caregivers skip doses or sometimes children refuse to take SPAQ, not allowing for complete administration of the full drug course. The Role Model study provided a promising social and behavioral change approach to addressing community challenges and finding existing local solutions. The study was conducted in Tersefe (Chad). The area comprised of 14 villages with a total population of 14,442, including 2838 children under five. Data were collected through focus group discussions (FGDs) with female and male caregivers and CDs and in-depth interviews (IDIs) with potential Role Models identified. The villages were divided into three clusters according to their distance from the health center. An equal number of FGDs and IDIs were conducted in each cluster. The study identified easily replicable Role Model behaviors existing within communities. Among others, these included strategically placing blister packs next to commonly used household products to be reminded of administration, having family members support primary caregivers, providing rewards to children, as well as practicing other malaria prevention strategies. Role Model volunteers identified during the study were trained and held sessions in their respective communities to promote positive behaviors prior to the 2022 SMC campaign. The evaluation FGDs conducted with caregivers at the end of the study showed that the approach is feasible and accepted by communities. Results and related messaging are being integrated into the 2022 SMC campaign to improve the administration of SPAQ.

0385

A PHASE 1, OPEN-LABEL, DOSE ESCALATION AND ROUTE OPTIMIZATION TRIAL WITH CONTROLLED HUMAN MALARIA INFECTION TO EVALUATE PROTECTIVE EFFICACY OF AN ANTI-MALARIA HUMAN MONOCLONAL ANTIBODY IN HEALTHY MALARIA-NAÏVE ADULTS

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Human monoclonal antibodies (mAb) may offer an important new tool to reduce malaria morbidity and mortality. The antimalarial mAb, CIS43, was derived from a protected subject immunized with *Plasmodium falciparum* (Pf) whole-sporozoite (SPZ) vaccine, targets a conserved epitope within the junctional region of Pf circumsporozoite protein, and was modified with an LS mutation found to increase antibody half-life (CIS43LS). The mAb has been found to confer high level protection at doses of 20 or 40 mg/kg intravenously (iv) following controlled human malaria infection (CHMI). To assess whether CIS43LS could mediate protection at lower doses and by a subcutaneous (sc) route of administration, malaria-naïve volunteers aged 18-50 years received mAb at doses of 1 (n = 7), 5 (n = 4), and 10 (n = 3) mg/kg iv and 5 (n = 4) and 10 (n = 4) mg/kg sc. Pharmacokinetic (Pk) assessments and safety analysis were performed. Volunteers underwent CHMI by the bites of five mosquitoes infected with 3D7 strain Pf at approximately 8 weeks following mAb inoculation. Six additional naïve control volunteers underwent CHMI simultaneously. Volunteers were followed daily from Days 7-18 with qualitative PCR used for Pf detection. Volunteers were treated with atovaquone-proguanil or terminally treated at Day 21. The mAb inoculation was safe and well tolerated with mild adverse events reported. No serious adverse events occurred. All 6 controls and 4 of 7 volunteers dosed at 1 mg/kg (57%) developed parasitemia following CHMI. No volunteers developed parasitemia following dosing at 5 mg/kg iv (0/4), 5 mg/kg sc (0/4), 10 mg/kg iv (0/3) and 10 mg/kg sc (0/4). The mean prepatent period for volunteers infused 1 mg/kg mAb was 11.75 (range 11-12) days vs. 7.67 (range 7-9) days in controls (P< 0.0001). Pk analysis to determine antibody levels of CIS43LS at the time of CHMI are underway. We conclude that volunteers dosed at 5 mg/kg or greater by iv or sc were protected following CIS43LS inoculation at 8 weeks. These findings show that mAbs can mediate protection at low doses and by the sc route providing data that this approach may be useful across a number of clinical use cases.

0386

THE ROLE OF CELL-TRAVERSAL PROTEIN FOR OOKINETES AND SPOROZOITES IN STERILE IMMUNITY INDUCED BY RADIATION-ATTENUATED SPOROZOITE VACCINES IN THE NATURAL HOST

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*Pf*SPZ Vaccine, a promising malaria vaccine consisting of radiation-attenuated *Plasmodium falciparum* (*Pf*) sporozoites (RAS), provides sterile and partial protection against controlled human malaria infection (CHMI) and natural infection in humans, respectively. It presents a wide range of antigens, but it is unclear whether Cell-Traversal Protein for Ookinetes and Sporozoites (CelTOS) plays a major role in RAS-induced protection. Studies in mice have shown that anti-CelTOS response elicited by direct or passive immunization can inhibit parasite infection. Here, we investigated the role of CelTOS in RAS-induced protection using *Grammomys surdaster* thicket rats (TR), a natural host *for Plasmodium*, and C57BL/6 mice, a non-natural host. Two transgenic *Plasmodium berghei* ANKA (*Pb*) parasites *Pb*PfCelTOS and *Pb*PvCelTOS (wherein PbCelTOS was replaced with PfCelTOS and PvCelTOS, respectively) were used as both RAS immunogens and sporozoite (SPZ) challenge strains to assess homologous (ho) and heterologous (ht) protection. TR and mice received 3 doses of 50K RAS and 10K RAS, respectively, at least 3 weeks apart followed by ho challenge (same parasite) or ht challenge (transgenic parasite, different CelTOS sequence). *Pb*PfCelTOS RAS immunization conferred the same ho and ht (Pb) protection in mice and TR 100% (10/10) and 42.6% (6/14) respectively. *Pb*PvCelTOS RAS immunization conferred the same ho and ht (Pb and PbPfCelTOS) protection in mice, 100% (10/10); but different in TR, 60% (6/10) ho protection and only 30% (3/10) ht protection. This suggests CelTOS responses are required for full protection in outbred TR but not in inbred mice. We observed lower efficacy of SPZ vaccines in the natural host compared to the non-natural host, consistent with previous studies, and this more potent immunity in mice might mask any contribution of CelTOS responses to protection. More studies are needed to confirm these preliminary results, but the findings suggest that CelTOS contributes to sterile immunity in the natural host, and generally support efforts to identify novel antigens for subunit pre-erythrocytic malaria vaccines.

0387

EXPERIENCE WITH THE CRYOGENIC COLD CHAIN FOR DISTRIBUTION OF PFSPZ VACCINES

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Experience with the Ebola and SARS-CoV-2 RNA vaccines has expanded the repertoire of cold chain options for vaccine distribution to include ultra-low freezer storage and dry ice distribution. The immunogen in PfSPZ platform products (PfSPZ Vaccine, PfSPZ Challenge, PfSPZ-LARC2 Vaccine) is *Plasmodium falciparum* (Pf) sporozoites (SPZ), which, being eukaryotic organisms, must therefore be stabilized by cryopreservation. Distribution occurs through a liquid nitrogen (LN2) vapor phase (LNVP) cold chain that maintains temperature below -150 °C. There are several veterinary vaccines distributed using LN2 or LNVP and the huge livestock breeding, human IVF and expanding CAR-T/cellular therapies industries employ LNVP for distribution. Cryopreserved products are stable essentially indefinitely. It is surprising, therefore, that manufacturers of human vaccines have not also moved to cryogenic distribution yet: the main reason may be that the standard vaccine vial does not work below -80 °C. We have solved this issue by creating a cryovial with a heat-annealed foil-seal-protected septum that maintains CCI in LNVP and functions like a standard vaccine vial once thawed. This cryovial has now been introduced into our manufacturing process. For the Phase 1 and 2 trials, over 550 shipments supplying >38 clinical trials at 14 sites in the USA, Europe and Africa have used our LNVP cold chain to date. Additionally, volunteer samples (sera and cells) are often reverse shipped in LNVP dry shippers as dry ice is frequently difficult and/or expensive to obtain in Africa whereas LN2 is more widely available. The LNVP dry shippers range in static hold time between ~10 days to 50 days and payload capacities range from 259 to 1,554 cryovials, and they require no electricity and are thus highly suited for extending distribution down the last mile to remote locations. Our LNVP distribution experience is being translated into expanded distribution network designs for Phase 3 clinical trials and into post-launch distribution models for malaria elimination campaigns and for travel medicine clinics.

0388

PFSPZ-LARC2 GMP MANUFACTURE AND CLINICAL ASSESSMENT OF A GENETICALLY MODIFIED PFSPZ VACCINE ATTENUATED AT THE LATE-LIVER STAGE

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In 2020 malaria caused 627,000 deaths, the greatest numbers of annual deaths since 2012. There is an urgent unmet medical need for a malaria vaccine that prevents infection and disease in individuals and can be deployed in mass vaccination programs for malaria elimination. Of vaccines under development, only Sanaria's PfSPZ vaccines have the efficacy against Pf infection to be considered for prevention of Pf infection in individuals and for geographically focused Pf malaria elimination campaigns. Sanaria's 1st generation vaccine, Sanaria® PfSPZ Vaccine, is composed of radiation-attenuated *Plasmodium falciparum* (Pf) sporozoites (SPZ), which arrest early in the liver stage. The immunogen of Sanaria's 2nd generation vaccine, Sanaria PfSPZ-CVac (Chemoprophylaxis Vaccine) is infectious PfSPZ, which replicate in the liver, biologically amplifying the immunogen load by up to 50,000-fold, and then are killed in early blood stage by an anti-malarial drug like chloroquine (CQ). PfSPZ-CVac (CQ) provides 100% vaccine efficacy (VE) against heterologous controlled human malaria infection (CHMI) 12 weeks after vaccination using only 22% of the PfSPZ dose used in PfSPZ Vaccine which achieves 80% VE at 9-10 weeks against heterologous CHMI. Thus, PfSPZ-CVac (CQ) is more protective than PfSPZ Vaccine, at ~1/5 the dose (=cost). However, administration of infectious PfSPZ has safety concerns. To retain the enhanced potency of PfSPZ-CVac and eliminate its potential drawbacks, 2 genes, *Pfplasmei2 and Pflinup* were deleted from Pf (NF54 strain) leading to complete parasite arrest at the late liver stage. PfSPZ-LARC2 parasites invade and develop to the late liver stage *in vitro*, and are tested for full arrest and absence of blood stage infection in FRG mice with humanized livers. We have produced a master cell bank (MCB) of PfLARC2, and it is now being manufactured in compliance with GMPs to produce PfSPZ-LARC2 Vaccine, which will be assessed for safety and efficacy in clinical trials in the 2nd half of 2022. We expect PfSPZ-LARC2 Vaccine to mirror PfSPZCVac (CQ) efficacy without safety concerns. Thus, it is our best and essentially ideal PfSPZ vaccine candidate.

0389

PLASMODIUM VIVAX SPOROZOITES FOR CONTROLLED HUMAN MALARIA INFECTION

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One of Sanaria's goals is to develop a vaccine against *Plasmodium vivax* (Pv) malaria, the most wide-spread cause of malaria-associated

morbidity outside of Africa. Using sporozoite (SPZ)-based vaccines, we aim to prevent all blood stage infections with Pv. We also aim to produce quality-controlled stocks of aseptic, purified, cryopreserved PvSPZ (PvSPZ Challenge) to promote well-controlled, reproducible studies in Pv including controlled human malaria infection (CHMI). We have overcome the significant challenge of propagating the life cycle of Pv *in vitro*, by growing Pv blood stages in *Saimiri boliviensis* (Sb) instead and have produced multiple stocks of purified, cryopreserved PvSPZ from mosquitoes fed on Pv-infected Sb blood, vialing as many as 80 million PvSPZ from 2000 mosquitoes in 1 day. In addition, we have 1) Developed assays to test and characterize PvSPZ for infectivity *in vitro* in monolayer and in micro-patterned co-cultured primary human hepatocytes over 3-21 days; 2) Tested the functional activity of drugs on inhibiting liver stage parasite development *in vitro;* 3) Infected NHPs *in vivo*; 4) Demonstrated that vialed, cryopreserved PvSPZ, Chesson strain infect humanized FRG KO huHep mice and produce hypnozoites *in vivo*. In compliance with regulatory standards for human use we have further 5) Standardized methods to propagate Pv in Sb maintained in specific pathogen free (SPF) colonies; 6) Vialed and cryopreserved aseptic, purified, infectious PvSPZ from aseptic mosquitoes fed on Pv-infected SPF blood; 7) Established conformance of the aseptic PvSPZ products of 5 pilot runs to in-process asepticity, *in vitro* potency, and release criteria; 8) Produced a master cell bank; 9) Prepared a pre-IND package ready for submission to the FDA and 10) Anticipate equivalent infectivity of aseptic PvSPZ in FRGKO huHEP mice. This enabling technology is now intended for initial CHMI trials planned in Germany and the US. PvSPZ Challenge also forms the basis of a powerful vaccine approach to preventing Pv malaria when administered with anti-malarial chemoprophylaxis, the PvSPZ **c**hemoprophylaxis **vac**cine (PvSPZ-CVac).

0390

SEMI-AUTOMATED PRODUCTION OF ASEPTIC MOSQUITOES FOR THE MANUFACTURE OF PFSPZ VACCINES

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Sanaria has moved to Phase 3 GMP compliant manufacturing of Sanaria® PfSPZ Vaccine to support licensure applications and commercialization. *Plasmodium falciparum* sporozoites (PfSPZ) are manufactured using aseptic *Anopheles stephensi* mosquitoes. To meet the needs of the extensive world markets, at an affordable price, the scale of manufacturing must be greatly increased and cost of goods (COGs) reduced. Some of the most labor- and space-intensive steps in PfSPZ manufacture are production of aseptic Pf-infected mosquitoes. Mosquito eggs are disinfected in bulk, hatched, and then seeded into flasks containing mosquito growth medium that allows the larvae to grow to pupae under aseptic conditions. The pupae are harvested and transferred to Big Adult Mosquitoes Containers (BAMC), in which adult mosquitoes emerge and maintained through Pf- gametocyte feeding and harvest of PfSPZ. Currently, these steps are all performed manually. Exploiting the biology of newly emerged adult mosquitoes, we developed a container that will allow the movement of aseptic mosquitoes from culture flasks to BAMC aseptically. Using this as proof concept, we have designed a re-usable bioreactor container that will allow for the production of 3x the number of *A. stephensi* pupae than our current culture container. This container will allow for aseptic media changes outside of a biosafety cabinet and will eliminate the need for manual harvesting of pupae and transfer into BAMCs by inclusion of a novel aseptic connection of the bioreactor container to a modified BAMC. Mosquito pupae will eclose within the larval bioreactor container, and newly emerged adults will fly upward into the attached modified BAMC. The modified BAMC can be disconnected aseptically within a biosafety cabinet without mosquito escape with the inclusion of a shutter that can be closed prior to the disconnection of the BAMC from the bioreactor. Progress on the effectiveness of this bioreactor will be reported. This Bioreactor based semi-automated aseptic mosquito production will reduce the cost of mosquito production by at least 50%.

0391

IN VITRO PRODUCED *PLASMODIUM FALCIPARUM* SPOROZOITES: GENE EXPRESSION AND IN *VITRO* INFECTIVITY AND CELLULAR IMMUNOGENICITY OF CRYOPRESERVED PARASITES

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Sanaria has developed methods to mass produce *Plasmodium falciparum* (Pf) sporozoites (SPZ) *in vitro* (iPfSPZ) in bioreactors without mosquitoes to replace mosquito-produced PfSPZ (mPfSPZ) in our PfSPZ-vaccines. Using a mini bioreactor, we produced up to 4.5 x 10^8 iPfSPZ per culture, and in a bioreactor that was 6.25 times larger, we produced up to 1.5 x 10^9 iPfSPZ per culture. As we move toward a final method of production and product, we have been characterizing the iPfSPZ. In RNA-seq, of the 50 genes most highly expressed in mPfSPZ, 32 had higher expression levels in mPfSPZ than in iPfSPZ and 18 had greater expression in iPfSPZ. For PfCSP, PfSSP2/TRAP, PfCelTOS, and PfAMA, all of which had lower expression in iPfSPZ, the results were confirmed by qRT-PCR with iPfSPZ having 64%, 75%, 81% and 76% the level of expression of mPfSPZ respectively. In a 6-day *in vitro* hepatocyte potency assay, cryopreserved iPfSPZ produced 95% the numbers of late liver schizonts expressing PfMSP1 as did fresh iPfSPZ, and cryopreserved mPfSPZ produced 82% the numbers as did fresh mPfSPZ. Both fresh (20% more) and cryopreserved (33% more) iPfSPZ produced more late liver stage schizonts than did mPfSPZ. When mice were immunized with fresh or cryopreserved iPfSPZ or mPfSPZ and assessed for T cell responses to stimulation with Pf-infected erythrocytes, there was no significant differences between responses in iPfSPZ or mPfSPZ immunized mice, although responses were higher overall in mPfSPZ immunized mice. PfCSP and other protein expression in iPfSPZ is lower in mPfSPZ than expected by gene expression studies. We speculate that absence of mosquito extracellular proteins and lipids in our cultures impairs optimal formation of the oocyst capsule leading to sub-optimal uptake of nutrients by the *in vitro* oocysts, and this is a reason for the reduced protein expression levels. We are focusing on optimization of iPfSPZ production in bioreactors by addition of extracellular proteins and other nutrients. The goal is inexpensive, large-scale manufacture of the iPfSPZ needed for mass vaccination programs to eliminate Pf malaria.

0392

PROTECTIVE TARGETS OF SPOROZOITE-BASED WHOLE ORGANISM MALARIA VACCINES IDENTIFIED FROM GENOME-WIDE SIEVE ANALYSIS OF *PLASMODIUM FALCIPARUM* ISOLATES FROM FIELD EFFICACY TRIALS

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Identification of protective targets of *Plasmodium falciparum* (Pf) sporozoite (SPZ)-based immunization will elucidate the genomic architecture of whole organism vaccine-induced protection and may lead to novel vaccine formulations with broader efficacy. PfSPZ-based malaria vaccines have shown significant, but partial vaccine efficacy (VE) against endemic malaria in field studies. Furthermore, clinical trials in which VE was assessed against controlled human malaria infection using either homologous or heterologous strains revealed that these vaccines are susceptible to allele-specific efficacy, the process by which vaccine protection is strongest against pathogen strains immunologically similar to the vaccine strain at protective loci. Here, we take advantage of allele-specific efficacy in field trials of PfSPZ-based vaccines to identify candidate targets of vaccine-induced protection. These target loci will be those in which allele frequencies differ significantly between infections in vaccinees and controls, with the vaccine allele depleted in the vaccine arm, due to the vaccine sieve effect. One study, in Burkina Faso, used Sanaria® PfSPZ Vaccine, composed of radiation attenuated SPZs of the PfNF54 strain, while the second study used Sanaria® PfSPZ CVac, consisting of fully infectious PfNF54 SPZs administered under the cover of the chemoprophylactic chloroquine. Both studies were randomized, double-blind, placebo-controlled trials in malaria-experienced adults. Sieve analyses in the Malian trial revealed 179 non-synonymous (NSYN) sites significantly differentiated between vaccinees and controls, in 145 protein-coding loci. In Burkina Faso, 358 significantly differentiated NSYN sites in 295 loci were identified. Products of these loci are enriched for functions such as host cell binding, including proteins intrinsic to or anchored in the cellular membrane. The intersection of both sets of loci resulted in 36 protein-coding genes, including those encoding a well-characterized sporozoite antigen, an exported protein, and several membrane-associated conserved proteins and variant surface antigens.

0393

SEASONAL VACCINATION WITH THE RTS,S/AS01E MALARIA VACCINE GIVEN WITH OR WITHOUT SEASONAL MALARIA CHEMOPREVENTION: EXTENSION OF A RANDOMIZED, DOUBLE-BLIND PHASE 3 TRIAL UNTIL CHILDREN REACH THE AGE OF FIVE YEARS

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An individually-randomized, controlled trial involving 5920, 5-17 month old children undertaken in Mali and Burkina Faso showed that seasonal malaria vaccination (SMV) with the RTS,S/AS01$_E$ vaccine was not inferior to seasonal malaria chemoprevention (SMC) and that the combination of SMV and SMC was superior to either intervention given alone, reducing the incidence of uncomplicated malaria, severe malaria and deaths attributable to malaria over a period of three years by about 70%. Because SMC is recommended until the age of five years, the trial has been extended for a further two years to determine whether administration of SMV with RTS,S/AS01$_E$ until children reach the age of five years is non-inferior to SMC alone in preventing clinical malaria, and whether administration of the combination of these two interventions is superior to either intervention alone in preventing clinical malaria and other severe outcomes (Clinicaltrials.gov NCT04319380). 5033 children enrolled in the initial phase of the study received study interventions in 2020. In 2021, 2289 children who were ≤5 years received the interventions and 2106 children who had reached the age of 5 did not receive interventions but remained under surveillance. The primary endpoint of the both the extension study and overall trial is a clinical episode of malaria with a parasite density of ≥5000 parasites per µl, detected at study health facilities. The prevalence of malaria parasitaemia has been measured among all children in the trial at the end of each transmission season. Sera have been collected for determination of anti-CSP antibody concentrations before and after vaccination in a randomly selected subset of approximately 400 children each year. Data collection was completed on 31 March 2022. Analysis of data will be completed by September 2022 and the results will be presented at the conference.

0394

MALARIA SYMPTOMS IN RELATION TO DETECTION OF PARASITEMIA BY QUANTITATIVE REAL-TIME PCR AND MICROSCOPY IN CONTROLLED HUMAN MALARIA INFECTION TRIALS AT WALTER REED ARMY INSTITUTE OF RESEARCH

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Plasmodium 18S rRNA/DNA quantitative real-time PCR (qRT-PCR) is a promising diagnostic alternative to microscopy for controlled human malaria infection (CHMI) studies that has recently received biomarker qualification through the U.S. Food and Drug Administration for use in this context at non-endemic sites. Compared to microscopy, qRT-PCR has demonstrated earlier detection of parasitemia allowing for treatment before symptoms develop, which can reduce the duration and resources needed for post-exposure monitoring in CHMI studies. qRT-PCR also mitigates the inter-observer variability inherent to malaria microscopy which can result in errors in clinical trials and affect outcomes. Walter Reed Army Institute of Research (WRAIR) has assessed qRT-PCR in recent CHMI studies alongside microscopy. We report time-to-positivity for qRT-PCR and microscopy in comparison with time-to-onset, duration, and subject reported severity for malaria symptoms in a total of 23 control subjects infected with *Plasmodium falciparum* from two CHMI studies conducted at WRAIR. Our results were largely consistent with those of previous similar studies, with qRT-PCR detecting parasitemia a mean 4.37 days before microscopy and a mean 3.76 days prior to symptom onset. We also detected a statistically significant positive correlation between fever duration and severity, and negative correlation between headache duration and severity. While our study is limited by the small number of subjects and the short duration of symptoms, it does reinforce the growing evidence for the use of qRT-PCR in CHMI and provides further insight into malaria symptomology.

0395

IMPLEMENTATION POTENTIAL AND PUBLIC HEALTH IMPACT OF FIRST-GENERATION MALARIA VACCINES

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Following decades of vaccine development, in 2021 WHO gave a recommendation of the first malaria vaccine, RTS,S, for paediatric use and seasonal vaccination against *P. falciparum* for children in moderate to high transmission areas. As global malaria burden reduction has stalled, there are renewed efforts to optimize current strategies and develop new interventions to accelerate progress towards elimination, including for RTS,S and other malaria vaccines. To support better understanding of the role of vaccines, we used an individual-based model of malaria transmission combined with statistical approaches to identify factors driving public heath impact in seasonal and perennial settings. We assessed the potential impact of a first-generation vaccine by exploring trade-offs between key vaccine characteristics such as efficacy and duration, alongside population-level characteristics of vaccination coverage and deployment strategies. We modelled RTS,S deployed as part of the Expanded Programme on Immunization in children 6-9 months, with annual boosters until age five co-administered with a blood-stage antimalarial. We found vaccine anti-infective initial efficacy and duration similarly drive impact in the first year. At least a 50% burden reduction is predicted if new vaccines achieve initial efficacy of >90% and half-life >12 months, but impact is limited if coverage is inadequate. We found there is potential for multi-seasonal protection if half-life duration can be extended beyond 10-12 months, however, there's little understanding of mechanisms with which long-term protection is conferred. Our modelling implies that extending antibody half-life by 3-5 months longer than RTS,S may result in sustained impact in the year following seasonal vaccination. Such a vaccine, combined with antimalarials or other interventions may reduce severe disease, mortality, and interrupt transmission. To maximize public health impact of next-generation vaccines, priority use-cases and target settings should be ranked through stakeholder engagement, considering the impact that can be achieved with improved first-generation vaccines.

0396

DIFFERENTIAL SEX-SPECIFIC IMMUNE RESPONSES FOLLOWING PRIME-AND-TRAP VACCINATION ALTERS PROTECTION AGAINST MALARIA IN MICE

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Generating liver resident-memory CD8$^+$ T (T_{RM}) cells is critical for effective liver-stage malaria vaccines. The role of biological sex in liver-stage vaccine protection is understudied. Here we report sex-specific immune responses and protection outcomes for the two-step heterologous 'Prime-and-Trap' liver-stage malaria vaccine designed to induce liver T_{RM} cells. The Prime-and-Trap strategy combines peripheral sporozoite antigen DNA priming with a single intravenous dose of liver-homing radiation-attenuated sporozoites (RAS) to direct and "trap" activated and expanding T cells in the liver. This strategy induces robust liver CD8$^+$ T_{RM} cell responses and confers sterile protection in the *Plasmodium yoelii* (Py) rodent malaria model in female BALB/cj mice. However, when tested in male BALB/cj mice, this vaccine induces fewer liver CD8$^+$ T_{RM} cells that yield lower rates of protection from sporozoite challenge. We examined sex-divergent immune responses in the spleen and liver following each step of the Prime-and-Trap regimen. The frequency of antigen-specific CD8+ IFN-γ T cells were lower in male mice following gene gun prime and RAS trap compared to female mice. Sexually dimorphic activation of certain immune pathways appears to drive attenuated downstream retention of T_{RM} cells in the liver, leading male mice to generate sub-optimal immune responses that yields less effective protection from challenge. Our findings emphasize the importance of incorporating biological sex as a variable when designing and evaluating liver-stage malaria vaccines.

0397

PLASMODIUM VIVAX MULTISTAGE VACCINE BASED ON THE HETEROLOGOUS VIRAL-VECTORED PLATFORM ACHIEVES STERILE PROTECTION AND TRANSMISSION BLOCKING

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Plasmodium vivax (Pv) vaccine development research is lagging far behind *P. falciparum* (Pf). In 2020, there were 241 million malaria cases worldwide, of which Pv-infection accounted for 3%. Very recently, we have developed a multistage Pf vaccine based on LC16m8Δ (m8Δ)/ adeno-associated virus (AAV) effective both for pre-erythrocytic (100% protection) and sexual stages (>99% transmission blocking; TB). The present study aims to applicate this vaccine platform for the development of a Pv multi-stage vaccine with high protection levels and TB efficacy. We developed a Pv vaccine [m8Δ/AAV-Pv(s25-CSP)] harboring the fusion gene encoding the pre-erythrocytic stage antigen PvCSP and the sexual stage antigen of Pvs25. Its protective and TB efficacies were assessed by PvCSP transgenic (TG) sporozoite challenge and direct membrane feeding assay (DMFA) using blood from Pv-infected patients in Brazil, respectively. The vaccine elicited robust PvCSP- and Pvs25-specific antibodies with titer of more than 10^5 and achieved high sterile protection up to 90% protection against PvCSP-TG sporozoites challenge. The vaccine also provided a high level of TB efficacy (>90%). In this study, we have successfully applied the new vaccine platform consisting of m8Δ/AAV for developing a Pv multistage vaccine. We are planning to evaluate its safety and immunogenicity in a non-human primate model.

0398

RECOMBINANT FULL-LENGTH *PLASMODIUM FALCIPARUM* CIRCUMSPOROZOITE PROTEIN-BASED VACCINE EXPRESSED IN *PSEUDOMONAS FLUORESCENS AND* ADJUVANTED WITH GLA-LSQ: RESULTS OF PHASE 1 TESTING WITH MALARIA CHALLENGE

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The *Plasmodium falciparum* circumsporozoite protein (CSP) is an effective antigen for malaria vaccination. Antibodies targeting the junction between the CSP N-terminus and central repeat region can provide sterilizing protection. Full length recombinant CSP (rCSP) vaccines may offer an advantage over CSP-based vaccines that do not include the junctional region, including RTS,S and R21. We present clinical trial results of immunogenicity and efficacy against controlled human malaria infection (CHMI) for a full-length rCSP vaccine given with adjuvant, Glucopyranosyl

Lipid A-liposome *Quillaja saponaria* 21 formulation (GLA-LSQ). Twenty healthy, malaria-naïve Baltimore participants aged 18-45 years old were enrolled into two dosing arms: 60 µg rCSP + 5 µg GLA-LSQ (high dose, n = 10) and 10 µg rCSP + 5 µg GLA-LSQ (low dose, n = 10) given on days 1, 29, and 85. Vaccinated participants and six unvaccinated infectivity controls underwent CHMI 28 days after third vaccinations. Study endpoints included anti-CSP IgG antibody and time to *P. falciparum* asexual parasitemia following CHMI. The high dose group had higher geometric mean anti-rCSP IgG fold rise (day of CHMI/baseline, 236.2-fold, 95% CI: 32.4, 1721.1) than the low dose group (55.4-fold, 95% CI: 8.3, 370.0). All vaccinated participants developed *P. falciparum* asexual parasitemia following CHMI (vaccine efficacy: 0%). No difference in median time to parasitemia existed: parasitemia was detected eight days after CHMI in all groups. Median peak parasite density (cycle threshold) was 34.45 (IQR: 32.25, 35.45) in the high dose group, 33.40 (IQR: 33.00, 33.80) in the low dose group, and 32.20 (IQR: 31.70, 33.30) in infectivity controls. While the vaccine was highly immunogenic, the lack of vaccine efficacy suggests that the vaccine construct and schedule given did not induce functional antibodies that reduce parasitemia or provide sterile protection. Further dissection of the immune responses to this vaccine may help define protective responses for future CSP-based vaccines.

0399

EVALUATION OF THE IMMUNOGENICITY AND PROTECTIVE EFFICACY OF A CHEMICALLY ATTENUATED WHOLE PARASITE *PLASMODIUM FALCIPARUM* BLOOD-STAGE MALARIA VACCINE IN MALARIA-NAÏVE VOLUNTEERS.

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Malaria is a leading cause of morbidity and mortality. There is an urgent need for additional tools, e.g. a highly effective malaria vaccine, if we are to continue towards the ambitious goal of malaria parasite eradication. The possibility of a malaria vaccine was first realized in the 1940s, however a vaccine capable of inducing long-lasting protective immunity remains elusive. We have shown that a chemically attenuated whole parasite blood-stage vaccine, consisting of blood-stage malaria parasites attenuated with the seco-cyclopropyl pyrrolo indole analogue, Tafuramycin-A (TF-A), offers strong protection against homologous and heterologous challenge in rodent models of malaria. Additionally, a single dose of TF-A attenuated ring-stage *Plasmodium falciparum* 7G8 parasites was shown to be safe and immunogenic in malaria-naïve human volunteers, inducing a broad parasite-specific cellular immune response. The protective efficacy of this vaccine candidate has now been evaluated in malaria-naïve volunteers. Three doses of chemically attenuated *P. falciparum* 7G8 trophozoite-stage malaria parasites were administered one month apart to the vaccine group (n=5). The control group (n=2) were unvaccinated. One month after the final vaccine dose, vaccinated and control study participants were challenged with 1,800 *P. falciparum* 7G8 parasitised red blood cells. Two out of five participants in the vaccinated group did not develop blood-stage parasitemia, as detected by qPCR. The blood of these two participants supported the growth of the parasite *in vitro*. The remaining participants (both vaccinated and control) developed blood-stage parasitemias that required intervention with Riamet to resolve the infection. Parasite-specific antibody and cellular responses were measured and will be presented. This is the first time, to our knowledge, that a blood-stage malaria vaccine has completely prevented the development of blood-stage parasitemia in humans. This data provides proof-of-principle for the whole parasite blood-stage malaria vaccine approach in humans.

0400

PRE-ERYTHROCYTIC AND TRANSMISSION-BLOCKING MULTI-STAGE MALARIA VACCINE STRATEGY SHOWS A STRONG SYNERGIC EFFECT TO CONTROL MALARIA DISEASE

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The Malaria Vaccine Technology Roadmap 2013 aims to develop safe and effective anti-malarial vaccines by 2030. It targets a minimum of 75% protective efficacy. Recently, we have developed a highly effective multi-stages vaccine against both the pre-erythrocytic and sexual stages of *Plasmodium falciparum.* This multi-stage vaccine encodes a pre-erythrocytic stage antigen circumsporozoite protein (PfCSP) and one sexual stage antigens s25 (Pfs25). The combination between the pre-erythrocytic vaccine (PEV; i.e. anti-PfCSP) effect and transmission-blocking vaccine (TBV; i.e. anti-Pfs25) effect brings the synergy to enhance the vaccine more potent in malaria prevention than a single antigen target strategy. In this study, we evaluated the effects of immunization against the PEV and TBV stages singly, and the effects of combining vaccine moieties as part of a multi-stage vaccine. The single vaccine moieties indicated 100% protection as PEV against PfCSP-transgenic *P. berghei* sporozoites and more than 90% oocyst reduction in mosquito midgut as TBV against Pfs25-transgenic *P. berghei*. Next, we evaluated the synergy of TBV+PEV on a double transgenic *P. berghei* expressing both PfCSP and Pfs25. We performed the assay in conditions that weaken our vaccine effect to measure the benefit of synergy. As a result, while the individual efficacy decreased to about 50% in TBV and about 60% in PEV respectively, the synergy of TBV+PEV remained over 90%. These findings propose the potential of our vaccine as a" next-generation malaria vaccine" to achieve the landmark goals of the malaria vaccine technology roadmap.

0401

MOSQUITOCIDAL EFFECT AND PHARMACOKINETICS OF DIFFERENT IVERMECTIN DOSE REGIMENS IN PREPARATION FOR BOHEMIA CLUSTER RANDOMIZED CONTROLLED TRIAL

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Ivermectin (IVM) is an endectocide currently being considered for malaria vector control through mass drug administration (MDA) campaigns. Its mode of action is independent of vector behavior or insecticide resistance therefore having the potential to directly address residual malaria transmission. Several trials using different IVM dose regimens are underway. Evidence from IVERMAL study indicates that 300mcgIVM/Kg given once a day for three days results in a significant reduction in mosquito survival up to 28 days. However, MDA strategies may operationally struggle to deliver high coverage and adherence rates using a 3-day long regimen. For this reason, we designed an open-lab randomized controlled trial (RCT) to compare the pharmacokinetics (PK) and mosquitocidal effect of single high-dose of IVM 400mcg/Kg to the 3-day regimen of 300mcg/Kg of IVM. Furthermore, we investigated the mosquitocidal activity of albendazole as a potential comparator for future trials. Healthy participants were randomized to receive either 1) Single-dose oral IVM 400 mcg/Kg; 2) Oral IVM 300 mcg/Kg given once a day for

three consecutive days; 3) single-dose oral 400mg albendazole; or 4) no treatment. Participants were followed-up for 28-days post-treatment with blood samples drawn at regular intervals and fed through a membrane to *Anopheles gambiae* s.l. which were observed for mortality for 28-days. Plasma concentrations of IVM at each timepoint were determined using HPLC. We present here the mosquito and PK results. Data will be presented in form of Kaplan-Meier curves. Survival rates between groups will be compared using log rank tests. PK parameters will be derived using observed data (Cmax, Tmax) and non-compartmental analysis of the concentration-time profiles. The results will inform the design of IVM MDA interventional trials and implementation strategies. The PK results could form estimates of the expected impact of ivermectin on mosquito populations and malaria transmission using mathematical models.

0402

THE UGANDA HOUSING MODIFICATION STUDY - PILOTING FOUR DIFFERENT HOUSING MODIFICATION DESIGNS FOR MALARIA CONTROL IN PREPARATION FOR A CLUSTER RANDOMIZED TRIAL

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Once a key pillar of malaria control, housing modification remains underutilized in most endemic areas. In advance of a cluster-randomised trial to evaluate the impact of housing modification on malaria incidence in Uganda, we conducted a pilot study to assess the acceptability, feasibility, durability, cost, and entomological impact of four types of housing modifications. Between January-July 2021, 200 houses were randomized to 1) full screening: screening eaves or ceilings, windows, and ventilation openings, and patching holes in the walls; 2) partial screening: screening eaves or ceilings; 3) eave tubes; 4) eave ribbons; or 5) control arm. Evaluations included baseline and endline household surveys, monthly entomological surveys, installation process and cost analysis, and qualitative evaluation. All four interventions were acceptable, feasible, and had a significant entomologic impact. Full screening was most accepted, used locally available materials, and gave the highest reductions in vector density compared to the control arm (for *Anopheles gambiae*, density ratio: full screening 0.25 [95% CI 0.12; 0.53]; partial screening 0.36 [95% CI 0.17; 0.76]; eave tubes 0.45 [95% CI 0.21; 0.99]; eave ribbons 0.39 [95% CI 0.17; 0.90]; similar results for *An. funestus*). Eave tubes were most feasible, quickest to install (on average, per house: eave tubes 3.9hr; full screening 7.65hrs; partial screening 7.73hrs; eave ribbons 13.2hr), were durable, and had the second-lowest cost (average societal, economic cost per house projected to trial conditions: partial screening $42.41; eave tubes $45.25; full screening $87.70; eave ribbons $102.27). Partial screening was well-received initially but showed poor durability and was redundant for houses with closed eaves. Eave ribbons were moderately accepted and durable but time-consuming, labour-intensive to install, and expensive. Full screening and eave tubes were selected for further evaluation in an ongoing large-scale trial. Beyond informing the trial intervention selection, the pilot has contributed to the wider knowledge base for a range of housing modifications for malaria prevention.

0403

EXPLORING THE IMPACT OF CONTROL INTERVENTIONS ON INSECTICIDE-RESISTANT MOSQUITOES THROUGH IMPROVED BIOLOGICAL REALISM IN MALARIA MODELS

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Mathematical models of malaria often assume age-independent mortality rates of mosquitoes despite evidence that senescence can occur. In this study, we investigate whether the age-independent assumption yields quantitatively different results in assessing the impact of interventions to control malaria and subsequent policy recommendations arising from modelling. Firstly, we use survival data on insecticide-resistant *Anopheles gambiae s.l.* to fit age-independent and age-dependent mortality functions to mosquitoes exposed and not exposed to insecticide-treated nets (ITNs). By incorporating age dependency, we obtain biologically realistic survival functions and explore the effects of insecticide exposure on mosquito mortality rates. We calculate the expected number of infectious bites a mosquito takes in its lifetime, and, by extension, the vectorial capacity. We observe a significant decrease in the predicted vectorial capacity when mosquitoes are exposed to ITNs and a further reduction when age-dependent mortality rates are included. Next, we extend a Ross-Macdonald-type host-vector model to include the more biologically realistic mortality functions by formulating an age-structured system, with the age-structure present in the mosquito compartments. Using our previously parameterised survival functions, we compare the dynamics with the age-independent system (with constant mortality), which is most commonly utilised. In addition, to further increase biological realism in the model, we use an Erlang distribution for the extrinsic incubation period (EIP), and, again, compare results against the more frequently used distributions (such as fixed EIP). We explore the predicted impact of ITNs in the model from a pre-control baseline and increased mortality as observed in the experimental mosquito data. We outline the circumstances in which the standard non-age-structured model gives alternative results or recommendations for malaria control measures and highlight the importance of collecting detailed age-structured vector data for parameterising malaria models for different vector species and climates.

0404

ASSESSING NATIONAL VECTOR CONTROL MICRO-PLANNING IN ZAMBIA USING THE 2021 MALARIA INDICATOR SURVEY

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In 2020 the Zambia National Malaria Elimination Centre (NMEC) targeted the distribution of long-lasting insecticidal nets (LLINs) and indoor-residual spraying (IRS) campaigns based on sub-district micro-planning. Detailed population and structure count maps were developed and reviewed with district health office staff to assign areas to receive either LLIN or IRS at health facility catchment level, using a 'mosaic' approach. The objective of this analysis is to assess how well the micro-planning was followed in distributing LLINs and IRS. The analysis compared coverage of the interventions among household clusters in the 2021 National Malaria Indicator Survey (MIS), against the micro-plan area under which the households fell. The 2021 MIS was implemented in April-May, and the sample included 202 standard enumeration areas that served as 'clusters' selected at first stage with probability of selection proportional to cluster population size. A total of 4,155 households across all clusters were sampled via simple random sampling at second stage. Household

LLIN and IRS coverage was ascertained with a standardized questionnaire. The proportion of households with ≥1 LLIN, and those which received IRS within the past 12 months were estimated for each cluster and overlayed onto microplanning maps. Preliminary results from the analysis suggest that overall LLIN and IRS coverage may have declined compared to previous years. The proportion of households that received their assigned intervention under the micro-plan was 70.5% (95%CI: 67.9, 73.1) for LLIN-assigned households and only 47.7% (95% CI: 45.7, 49.7) for IRS-assigned households. Overall coverage across the sampled population, regardless of the micro-plan, was 53.3% (95% CI: 49.6, 56.9) for LLINs compared to 39.0% (95%CI: 35.7, 42.1) for IRS, while 70.6% (95% CI: 67.5, 73.6) of households received either intervention compared to 29.4% (95% CI: 26.4, 32.5) who received neither. We will also present the factors contributing to adherence or non-adherence to the micro-plan, with the aim of informing future micro-planning exercises by the Zambia NMEC, as well as other national programs.

0405

DEVELOPING FIELD-DEPLOYABLE RT-PCR TOOL FOR MOSQUITO INSECTICIDE RESISTANCE SURVEILLANCE

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We are developing a field-deployable molecular diagnostic system to survey insecticide-resistance at field conditions. Insecticide resistance surveillance is a key component of malaria vector control and can be performed through lengthy phenotypic assays and PCR-based molecular assays. However, even the molecular assays require transporting of collected mosquitoes to centralized laboratories for testing, thereby representing a major rate-limiting step that can even lead to months-long delays in obtaining crucial information. We are developing a qPCR-based diagnostic assays for *Anopheles gambiae* target site and metabolic resistance-type insecticide resistance markers using the field-deployable portable bCUBE qPCR system. We specifically focused on the *An. gambiae* knockdown resistance genes (L1014F, L1014S, N1575Y), Ace-1 (G119S), RDL (A296S), GST (I114T-GSTe2), and P450 (CYP4J5 -L43F, Coeae1d). The qPCR genotyping assay combines a modified allele-specific primer with a common wild-type primer to distinguish resistant from wild-type SNPs. We designed multiple primer pairs for the different SNPs and selected combinations that can discriminate the markers. Discrimination of SNPs is determined by the melting curves, enabling the determination of homozygous, or heterozygous insecticide resistance alleles in the field-caught *An. gambiae* from Cameroon. We also explore the identification of resistance SNPs in pooled samples to enable a greater throughput. The insecticide surveillance system is designed for autonomous operation and will also generate data that will enhance our understanding of insecticide resistance dynamics in mosquito populations.

0406

SEASONAL DYNAMICS OF AN EMERGING AFRICAN MALARIA VECTOR, *ANOPHELES STEPHENSI*: IMPLICATIONS FOR MALARIA CONTROL

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Increasing urbanisation has contributed to reductions in malaria burden across sub-Saharan Africa with urban areas typically experiencing lower levels of transmission. Recent invasion and proliferation of the urban malaria vector *Anopheles stephensi* across the Horn of Africa threatens this progress. Understanding the vector's seasonal dynamics in these settings represents a crucial input to its control, given that the effectiveness of many malaria control interventions depends on timing delivery relative to seasonal peaks in transmission. Here we collate longitudinal catch-data for the species from across South Asia and the Middle East to better understand these dynamics and explore their implications for malaria transmission in urban settings across the Horn of Africa where the disease is currently largely absent. Our analyses reveal pronounced variation in the extent and timing of seasonality across *Anopheles stephensi* populations, ranging from single seasonal peaks to bimodality and near-perennial patterns of abundance. This diversity is underpinned by patterns of land use, as well as variation in seasonal patterns of rainfall and temperature across locations. Dynamics frequently differ between rural and urban settings, suggesting structural differences in how these environments shape patterns of vector abundance. Integrating these seasonal profiles with a model of malaria transmission, we show that the impact of IRS is highest in settings with the highest seasonality, but that crucially, achieving this impact requires an understanding of when *Anopheles stephensi* populations are likely to peak. Our results highlight a critical lack of studies from the Horn of Africa able to directly inform this understanding, underscoring the need for longitudinal entomological monitoring of the vector across the region.

0407

EVALUATING THE ASSOCIATION BETWEEN NEXT GENERATION LONG-LASTING INSECTICIDE TREATED NETS WITH PIPERONYL BUTOXIDE AND MALARIA PARASITE PREVALENCE AMONG CHILDREN UNDER FIVE IN ZAMBIA

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Zambia recently began introducing new long-lasting insecticide treated nets (LLINs) containing piperonyl butoxide (PBO) to improve community protections against pyrethroid resistant vectors and to reduce malaria infections. PBO inhibits a mosquito's ability to break down insecticides and acts as a synergist to improve the efficacy of insecticides. The National Malaria Elimination Centre began mass distributing these PBO nets in 2020 to seven out of the ten provinces in Zambia. We used the 2021 Zambia Malaria Indicator Survey to investigate associations between LLINs and malaria parasite prevalence identified through rapid diagnostic tests among children under five. We assessed RDT positivity among LLIN households and PBO households using a logistic regression, controlling for indoor residual spraying and community LLIN density. Other covariates included in the model are urbanicity, household socioeconomic status, parental education, gender, and age of the children. Our preliminary results show a significant inverse relationship between having LLINs and malaria parasite prevalence. Among those with LLINs, PBO nets further decreased the likelihood of an RDT positive test (OR: 0.60, 95% CI: 0.43 to 0.82). Plasmodium falciparum parasite rates estimated by the Malaria Atlas Project at the cluster level will be later added to the analysis to control for variation in malaria endemicity. This analysis is one of the first opportunities to evaluate these next generation PBO LLINs after actual malaria program implementation and scale-up. Initial results from this evaluation are encouraging and highlight possible effects PBO nets may have on the reduction of malaria parasite prevalence in Zambia.

0408

THE SYMBIOTIC TC1 BACTERIUM IS A NOVEL MOSQUITO-BASED MALARIA INTERVENTION TOOL

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The intolerable burden of malaria demands the urgent development of novel approaches to fight this deadly disease. We describe the properties of a non-modified symbiotic bacterium – TC1 - originally isolated from mosquitoes that had lost the ability to sustain the development of *Plasmodium falciparum* parasites. TC1 is a potent inhibitor of *Plasmodium* development in mosquitoes via secretion of an inhibition factor that blocks early stages of *Plasmodium* development. We have identified the inhibitor as a small hydrophobic compound that can penetrate the cuticle and inhibit *Plasmodium* development on mosquito contact. TC1 does not impose a fitness cost to the mosquito, as it does not affect mosquito survival, blood feeding behavior, fertility, or fecundity. TC1, and its secreted molecule constitute a novel tool for malaria intervention.

0409

EFFECT OF DELTAMETHRIN-PIPERONYL BUTOXIDE (PBO) INSECTICIDE-TREATED NETS ON MALARIA CASE INCIDENCE AND ENTOMOLOGICAL INDICATORS IN EBONYI, NIGERIA

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Pyrethroid resistance has been widely documented throughout Nigeria, threatening the effectiveness of insecticide-treated nets (ITNs), the primary malaria vector control intervention in the country. New types of ITNs, such as pyrethroid nets treated with piperonyl butoxide (PBO), have been developed to address this resistance. Based on entomological evidence collected under the U.S. President's Malaria Initiative VectorLink project, the National Malaria Elimination Program in Nigeria deployed 1.7 million PBO ITNs in Ebonyi State in November 2019. A study using an interrupted time series approach was designed to evaluate the epidemiological and entomological impact of the PBO ITN campaign using routine data from December 2017 to November 2021. Monthly data on confirmed malaria cases were obtained from the national HMIS and incidence rates were calculated at the ward level. Entomological impact was determined by collecting data on indoor and outdoor human biting rates and indoor resting density of *Anopheles* mosquitoes in Ezza North Local Government Area. Annual malaria case incidence increased from 14.5 cases per 1,000 population to 18.7 between the first and second years of the pre-distribution period (rates calculated from December to November each year), before falling to 16.6 in the first year post-distribution and then to 7.3 the following year. The indoor biting rate decreased from 0.6 bites/person/night pre-distribution (June-October 2019) to 0.2 in the first year post-distribution and then to 0.0 the following year. The outdoor biting rate decreased from 2.9 bites/person/night during the pre-distribution period to 1.4 in the first year post-distribution and then to 1.3 the following year. Average indoor resting density decreased from 9.8 mosquitoes/room/night during the pre-distribution period to 3.6 during the first year post-distribution before increasing slightly to 5.0 in the second year. While these initial results show a promising impact of PBO ITNs, final analyses are ongoing. Results from the final model will be presented to provide a clearer understanding of the impact of PBO ITNs in pyrethroid-resistant areas.

0410

EXPLORING THE EFFECT OF WOLBACHIA-INDUCED IMMUNITY GENES ON *PLASMODIUM FALCIPARUM* SUPPRESSION IN *ANOPHELES STEPHENSI*

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Malaria causes an estimated 240 million cases every year with about half million deaths annually. Due to the heavy disease burden and the lack of effective vaccines, resistance of the parasite to drugs and resistance of the mosquitoes to insecticides, the development of novel malaria control strategies is becoming increasingly important. *Wolbachia*, an intracellular bacterium is known to infect about 66% arthropod species. While it successfully naturally infects mosquito species such as *Aedes albopictus*, infection in *Anopheles* spp. is not widely known. Previous studies have shown that *An. stephensi* transinfected with *Wolbachia* are more resistant to *Plasmodium* infection. The interaction between *Plasmodium*, *Anopheles* and the *Wolbachia* is complex, and the mechanism by which *Wolbachia* renders the mosquito more resistant to parasite infection largely remains unknown. To explore this, we compared transcriptome of midguts and carcasses between *Wolbachia* infected and uninfected *An. stephensi*. Our data have shown that many immunity genes, like thioester-containing proteins (TEPs) and other components of the complement-like system, are upregulated upon *Wolbachia* infection in both midguts and carcasses. The effect of these candidate *An. stephensi* immunity genes on *P. falciparum* infection is investigated using dsRNA-mediated gene silencing. Results obtained from this study will further elucidate the *Anopheles-Wolbachia-Plasmodium* tripartite interactions and inform the development of *Wolbachia*-based malaria control.

0411

IMPLEMENTATION OF COMMUNITY-BASED LARVAL SOURCE MANAGEMENT FOR ENHANCING MALARIA CONTROL IN MAINLAND TANZANIA. A PROCESS NARRATION

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In mainland Tanzania, implementation of insecticide treated nets and indoor residual spraying has helped in reducing malaria prevalence from 18.1% (2008) to 7.5% (2017). In enhancing malaria control, the country is planning to deploy Larval Source Management (LSM). LSM is the management of water bodies that are potentially mosquito breeding sites. WHO recommends LSM as a supplemental vector control intervention, suitable mostly in urban settings and where breeding habitats are few, fixed and findable. Little evidence is available on LSM implementation in rural settings. Tanzania is piloting routine LSM implementation in three councils: Handeni DC, Lushoto DC and Tanga CC, selected to represent both rural and urban settings, as well as different malaria risk strata: low (1-≤5 *Pf*$PR_{5\text{-}10yrs}$), moderate (5-≤30 *Pf*$PR_{5\text{-}10yrs}$) and high (>30% *Pf*$PR_{5\text{-}10yrs}$). Implementation follows a community-based approach set up following

extensive consultations between Ministry of Health, implementing partners and research institutions. Two community owned resource persons implement LSM at the ground level, supervised by officers at village, ward and council levels using existing local government structures. The country uses two biolarvicide products that are produced locally by Tanzania Biotech Products Limited; *Bacillus thuringiensis var. israelensis* (Bti) and *Bacillus sphaericus* (*Bs*). LSM is conducted in all selected areas following a temporal approach based on rainfall patterns. Implementation is guided by standard operating procedures through the following phases: advocacy, training, logistical set-up, mapping, baseline data collection, application, monitoring and evaluation. All councils have conducted baseline data collection and biolarviciding is expected to start in May 2022. This implementation experience using exclusively governmental mechanisms as well as locally produced biolarvicides is expected to contribute important real-world experience on the potential of this form of vector control across a range of ecologies and transmission situations. We will be reporting on this experience after six months of implementation.

0412

ONE-HALF OF BYSTANDER EXPOSURES OF ENTERIC PATHOGENS TO ANTIBIOTICS WERE DUE TO RESPIRATORY ILLNESSES, ONE-QUARTER DUE TO DIARRHEAL ILLNESSES

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During the course of treating a diarrheal or respiratory illness, pathogens carried subclinically at the time of treatment can be exposed to antibiotics, resulting in bystander selection pressure for antimicrobial resistance. We quantified and attributed exposures to antibiotics for subclinical enteric pathogens by type of illness. We included 15697 antibiotic courses amongst 1715 children in the MAL-ED birth cohort. We calculated the proportion and incidence per 100 child-years that bystander exposures to antibiotics for enteric pathogens were due to the treatment of acute lower respiratory infection (ALRI), dysentery, diarrhea, upper respiratory tract infection (URTI), and other causes for all courses of antibiotics and specifically for fluoroquinolone and macrolide courses. We identified subclinical infections by linking the most recent stool within 30 days to the start of an antibiotic course. Any pathogen exposed to an antibiotic course and was not the cause of the diarrheal illness was considered a bystander pathogen. For all bystander pathogens, more than one-third of antibiotic courses given were attributed to the treatment of URTIs; this proportion increased to one-half when ALRIs were included. Diarrheal and dysentery illnesses accounted for nearly one-quarter of antibiotic exposures, however, dysentery illnesses accounted for only a small proportion (<3%) for each bystander pathogen. When antibiotic courses were subset to fluoroquinolone or macrolide use, respiratory infections (ALRI and URTI) continued to account for nearly 50% of courses, however, the proportion of antibiotic courses attributed to diarrheal and dysentery illnesses increased to over one-third for all bystander pathogens. Half of subclinical enteric pathogen exposures to antibiotics occurred during the treatment of respiratory infections. Interventions focused on the reduction of antibiotics during respiratory illnesses would not only reduce exposure of respiratory pathogens to antibiotics, but could have a profound effect on bystander exposure to antibiotics for enteric pathogens and thus, the development of antimicrobial resistance.

0413

OPTIMIZING ISOLATION OF *VIBRIO CHOLERAE* FROM STORED VOMIT AND STOOL SAMPLES

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The gold standard for isolation of *Vibrio cholerae* (Vc), the causative agent of cholera, is culture of fresh stool in alkaline peptone broth for enrichment of *Vibrio* species and sub-culture on a selective media, such as thiosulphate citrate bile salts (APW>TCBS). However, for isolation of Vc from stored clinical samples, this method is often low yield. We compared isolation methods using clinical samples from 20 cholera patients who had Vc positive stool cultures, collected in Dhaka, Bangladesh at the International Centre for Diarrhoeal Disease Research, Bangladesh. One aliquot of both vomit and stool was frozen unprocessed and another was stored with ~30% glycerol added. Samples were stored at -80C for one year. We then attempted to isolate Vc from the vomit and rice-water stool samples by 1) direct plating on Luria-Bertani (LB) agar, 2) TCBS agar, and 3) tryptic soy agar (TSA) +5% blood, and 4) inoculation into APW enrichment and 5) inoculation into LB broth with subsequent plating for methods 4 and 5 onto both LB agar and TCBS agar. Successful isolation was defined as recovery of 10 or more Vc colonies from a vomit or rice water stool sample. Vc was isolated successfully from 4/20 (20%) unprocessed vomit samples and 7/13 (54%) glycerol vomit samples. Among stool, 6/20 (30%) unprocessed and 5/10 (50%) glycerol samples resulted in Vc isolation. Use of glycerol to store vomit did not increase the yield of APW>TCBS but did increase stool Vc isolation using this method. Sample pH and the colony forming unit count from the time of sample collection did not predict success in Vc recovery. We found that direct plating of stored clinical samples onto TSA+ 5% blood plates was as successful and less labor and resource intensive as the gold standard method of APW>TCBS. APW>TCBS and TSA+5% blood direct plating resulted in catching >80% of successful isolations. Multiple media types may be needed to recover the most possible Vc from stored samples, and isolation using TSA+5% blood plating may save time and resources.

0414

EFFECT OF A HOMESTEAD FOOD PRODUCTION PROGRAM ON THE PREVALENCE OF DIARRHEA AND ACUTE RESPIRATORY INFECTION IN CHILDREN IN SYLHET, BANGLADESH: A CLUSTER-RANDOMIZED CONTROLLED TRIAL

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Nutrition-sensitive agricultural interventions may reduce child illness by improving child nutrition and increasing caregivers' knowledge of optimal health and hygiene practices. The impact of such interventions on child illness has not yet been rigorously evaluated. We assessed the impact of a multi-year Homestead Food Production intervention on diarrhea and respiratory infections in children. The Food and Agricultural Approaches to Reducing Malnutrition (FAARM) cluster-randomized controlled trial enrolled over 2,700 married women and their children under three years of age in 96 clusters in Sylhet Division, Bangladesh. The intervention promoted home gardening and small-scale poultry rearing alongside child nutrition and health counseling over three years (2015-2018). From

mid-2017, an additional food hygiene training was delivered over eight months to reduce food contamination. Caregiver-reported diarrhea and symptoms of acute respiratory infection (ARI) were recorded every two months from 2015 up to one year post-intervention. We assessed the effect of the intervention on 7-day period prevalence of diarrhea and ARI using mixed-effects logistic regression with settlement-level random effects. Overall, we analyzed 32,465 observations of 3,262 children 0-36 months old. The 7-day period prevalence of diarrhea across all survey rounds was 4.0% in the control group and 3.8% in the intervention group. There was no relevant overall effect of the intervention on diarrhea prevalence (Odds Ratio [OR]: 0.92, 95% CI: 0.71 to 1.19) nor any effect by year of intervention. There was also no difference in the 7-day period prevalence of ARI between the control (25.5%) and intervention (26.0%) groups (OR: 1.00, 95% CI: 0.72 to 1.39). Our results show that a three-year Homestead Food Production intervention with food hygiene training in Bangladesh had no effect on child diarrhea or ARI. Nutrition-sensitive agricultural interventions may need to incorporate more comprehensive public health measures to achieve immediate improvements in child health outcomes.

0415

INTERACTIONS OF A COMMENSAL GUT MICROBIOME MEMBER WITH *VIBRIO CHOLERAE*

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Cholera is a diarrheal disease caused by the intestinal bacterium *Vibrio cholerae* (Vc). Cholera affects millions of patients each year and is transmitted in contaminated food or water. Vc infected patients can be asymptomatic or develop severe acute diarrheal symptoms. We previously used metagenomic sequencing to characterize the gut microbiota of persons exposed to Vc in Dhaka, Bangaldesh, and in a machine learning analysis we found that *Rothia mucilaginosa* (Rm) was more likely to be present in Vc infected persons (22.7%, 5/22) compared to uninfected persons (11.1%, 4/36, P=0.01, Mann Whitney U-test). We have previously found that other commensal gut microbes associated with cholera impact Vc biofilm formation through bacterial cell-to-cell interaction. In this study, we investigated how a Rm strain isolated from this study population might impact Vc virulence. We co-cultured Rm with Vc at 37C for six hours and quantified biofilm biomass using a microtiter dish assay with crystal violet staining. We found that Rm spent-cell supernatant (SCS), but not heat-killed Rm or Vc:Rm co-culture, increased Vc biofilm formation compared to Vc in fresh media (P=0.002, unpaired t test). Rm SCS had no impact on Vc growth by colony forming unit count. To further characterize the Rm metabolites in SCS that are impacting Vc biofilm production, we will evaluate the effects of Rm SCS fractions on Vc biofilm production, including using Vc biofilm mutants. In conclusion, we found that metabolites from Rm, a native member of the gut microbiota, can increase formation of biofilm for this enteric pathogen. Because biofilm is a known virulence factor in Vc infection, this interaction has the potential to affect patient clinical outcomes.

0416

ESTIMATING THE PROPORTION OF SUSPECTED CHOLERA CASES THAT REPRESENT TRUE *VIBRIO CHOLERAE* INFECTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Current estimates of cholera burden rely on clinical diagnosis of cases that present with acute watery diarrhea (i.e., suspected cholera cases), with rare laboratory confirmation. Typical suspected cholera case definitions have high sensitivity but low specificity, and definitions can vary by location across seasons. In this study we use existing data from multiple locations to estimate the relationship between suspected and confirmed cholera cases and identify factors that may explain variation in positivity rates. Specifically, we conduct a systematic review of published research and surveillance studies conducted during 2000-2022 that tested at least 10 suspected cholera cases for the presence of *Vibrio cholerae* O1 or O139 using culture, PCR and/or a rapid diagnostic test (RDT). In total, we include 102 studies from 28 countries. Using a random-effects meta-analysis, we estimate that the proportion of suspected cholera that represents true *V. cholerae* infection is 39% (95% Confidence Interval 34%-44%) by culture, 44% (26%-64%) by PCR, and 55% (44%-65%) by RDT. We also find substantial variation in positivity rates between studies (I^2 values: 99% for culture, 97% for PCR, and 98% for RDT). In addition, we investigate how positivity rates are influenced by season, cholera endemicity, outbreak vs. routine surveillance, suspected case incidence rate, geographic region, walking time to health facilities in catchment area, study methodology, and sensitivity/specificity of the laboratory test. Finally, we discuss how our findings will help to refine global estimates of cholera burden while informing new strategies for laboratory testing of suspected cholera cases.

0417

INVESTIGATING THE IMPACT OF SOCIAL AND ENVIRONMENTAL EXTREMES ON CHOLERA TIME VARYING REPRODUCTIVE NUMBER IN NIGERIA

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Cholera is one of the most reported enteropathogens and was re-introduced to Africa in the 1970s during the seventh and ongoing cholera pandemic. Since its re-introduction it has caused significant mortality and morbidity, especially in the most vulnerable people such as children under five. Nigeria currently reports the second highest number of cholera cases in Africa, with numerous socioeconomic (poverty, water, sanitation) and environmental (climate, waterbodies) risk factors. Less investigated is the role of extreme social (i.e., conflict) and extreme environmental (i.e., floods, droughts) events, despite recent work showing their potential importance and the frequency of these events in Nigeria. To address this gap, we analysed cholera data provided by the Nigeria Centre for Disease Control, with covariate data from a range of sources. We estimated time varying reproductive number (R) from confirmed cholera incidence in Nigeria for 2018 and 2019 and used a machine learning approach (Random Forest) to evaluate its association with extreme events (conflict, flood, drought) and pre-existing vulnerabilities such as poverty, sanitation and healthcare. The best fit model in terms of predictive power included monthly conflict events, the Palmers Drought Severity Index, access to sanitation and Multidimensional Poverty Index. We used historical exposure periods, split by month and state and R threshold (R = >1 or <1) to evaluate the relationships between the covariates and R. We used the historical median values and error to inform hypothetical exposure periods and to create a traffic-light system for cholera outbreak risk, highlighting

environmental and social thresholds for outbreaks to occur. By varying the exposure periods, we showed that reduced poverty and greater access to sanitation lessened vulnerability to increased cholera risk caused by extreme events (conflicts, floods and drought). The work presented here shows the need for sustainable development to increase community resilience to disasters; beyond this, increasing adaptation capabilities improves overall health and quality of life.

0418

MODELING ACQUISITION AND CLEARANCE DYNAMICS OF CAMPYLOBACTER IN CHILDREN IN LOW- AND MIDDLE-INCOME COUNTRIES

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Undertaken in eight settings in low- and middle-income countries (LMIC) with high child diarrhea and malnutrition burdens, MAL-ED was a study unveiling associations between the cumulative burden of enteric infections and malnutrition in children under two. Colonization by zoonotic enteric pathogens from livestock feces, especially *Campylobacter* spp., has been identified as an important risk factor of malnutrition in children in LMIC. Here, we developed a two-stage time-inhomogeneous Markov model for the dynamics of *Campylobacter* acquisition and clearance among children. This model was validated using simulation studies and applied to the longitudinal data from MAL-ED. Acquisition of *Campylobacter* was slower than clearance in India, Nepal, South Africa, Brazil, and Peru over the whole 24-month study period, while the two rates were comparable and crossed over during the study period in Bangladesh, Pakistan, and Tanzania. We further estimated the average acquisition interval and duration of colonization for each month and obtained the median of these monthly averages for each country. For the whole study period, Bangladesh and Brazil had the shortest and longest median acquisition intervals (22 days and 254 days), while South Africa and Tanzania had the shortest and longest median durations of colonization (10 days and 49 days). The force of infection is inversely proportional to the acquisition interval. Using site-specific model-estimated parameters, we simulated the underlying acquisition and clearance dynamics and their realized longitudinal trends of *Campylobacter* prevalence, which were consistent with the observed prevalence trend at each site, suggesting adequate goodness of fit. Our work suggests further research to incorporate host-specific characteristics and site-specific environmental features into the model to identify risk drivers for the acquisition/clearance dynamics of *Campylobacter*, which may explain the heterogeneity across sites found in this study and inform intervention strategies.

0419

ASSESSMENT OF GUT MICROBIOME IN ANGOLAN SICKLE CELL DISEASE CHILDREN. EFFECT OF HYDROXYUREA TREATMENT

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In Sub-Saharan Africa Sickle cell disease (SCD) can contribute up to 80% of under-5 mortality. Clinical manifestations are very heterogeneous and the intestinal microbiome has recently been reported to be crucial in the modulation of inflammation, cell adhesion and induction of aged neutrophils, key interveners of recurrent vaso-occlusive crises. Since gut bacteria can regulate aged neutrophils, defects in either the integrity of the intestinal walls or a chronic disequilibrium of the microbiota are very likely to emerge in SCD patients. Moreover, it has been suggested that Hydroxyurea (HU) shows a multimodal action and may reduce microbiome dysbiosis and aged neutrophils. In this context, we aimed to understand how SCD and HU treatment modulates the microbiome and if these changes could be related with disease severity.

A SCD pediatric population, was studied before and after 6 months of continuous HU treatment. A total of 66 stool samples were collected, DNA was extracted, quantified and the bacterial 16SRNA gene for the V3-V4 regions was sequenced by NGS. Microbiome taxonomic profiling analysis was performed with the EzBioCloud pipeline and differences between the two groups were assessed with the Statistical Analysis of Metagenomic Profiles (STAMP) software, using Welch's t-test. Significant associations were observed in alpha-diversity between the two groups, with higher values for the children naïve for HU, namely in OTU species count ($p<0.001$), phylogenetic diversity ($p=0.004$) and microbial richness ($p<0.001$), which was calculated by the ACE, Chao1 and Jackknife indices. We also noticed that children after HU treatment had higher proportions of some bacteria associated with health, including Blautia luti, Roseburia inulinivorans, Lactobacillus rogosae and Faecalibacterium, when compared to the beginning of the study. Additionally, the proportion of Firmicutes phylum was significantly lower before HU.

This was the first study to report gut microbiome changes before and after HU treatment in SCD children. Overall, our findings provide a rationale for further research about gut microbiota dysbiosis in this population.

0420

EVALUATE SNP BASED NOVEL DIAGNOSTIC ASSAY FOR ENTERIC FEVER DETECTION IN LIMITED RESOURCE SETTINGS

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Enteric fever, caused by *Salmonella enterica* serovars Typhi, Paratyphi A, remains a major cause of morbidity and mortality in low and middle-income countries (LMIC). The diagnosis of enteric fever has become difficult due to nonspecific clinical syndrome of typhoid and paratyphoid infection from other febrile illnesses. Moreover, the lack of robust, reliable, accurate currently available diagnostic methods and the emergence of fluoroquinolone-resistant, multi-drug resistant, extensively drug-resistant *S. Typhi* highlights the urgent need for highly sensitive molecular techniques. The wide advent of whole genome sequencing (WGS) approach has introduced a robust SNP based genotyping scheme 'GenoTyphi' that can identify specific SNP for H58 and other emerging lineages. Here we implemented WGS data to evaluate the performance of a rapid, reliable, and cost-effective genome-based diagnostic approach for *S.* Typhi including globally dominant H58 lineage and *S.* Paratyphi A detection that can be used as part of routine diagnostics in limited-resource settings including Bangladesh. An in-house built conventional PCR was carried out on a collection of blood culture positive Bangladeshi *S.* Typhi, *S.* Paratyphi A strains by utilizing *in silico* designed primer sets that target unique genes for *S.* Typhi, H58 Typhi, and *S.* Paratyphi A detection and comparison on the specificity was made with standard blood culture method. Our PCR results showed that SSPA2308, STY2513, STY0307 target genes demonstrated 100% specificity for blood culture positive *S.* Paratyphi A (22/22, 100%), *S.* Typhi (20/20,100%), H58 *S.* Typhi (20/20, 100%) DNA respectively. Moreover, WGS data of 202 Bangladeshi *S.* Typhi strains revealed that the majority of the *S.* Typhi (83/202, 41.1%) belonged to the H58 lineage in which 89.2% of H58 Typhi acquired MDR genes. Besides, *S.* Typhi and *S.* Paratyphi A detection, this genome-based diagnostic approach has added a new dimension to designing unique markers for MDR-associated H58 lineage detection and has the potential to inform local treatment algorithms based on regional antibiotic susceptibilities.

0421

DIGESTIVE TOLERABILITY AND ACCEPTABILITY OF FIBERSOL-2 IN HEALTHY AND DIARRHEAL CHILDREN 1-3 YEARS OLD AT A RURAL FACILITY, BANGLADESH: RESULTS FROM A FOUR ARM EXPLORATORY STUDY

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Fibersol-2 is a fermentable, non-viscous dextrin which has some beneficial effects on human health. We aimed to evaluate its digestive tolerability and acceptability in terms of reducing abdominal symptoms, like pain, distension, rumbling, and bloating in healthy and diarrheal children, as well as improvement in stool consistencies in diarrheal children 1-3 years old. Sixty children of either sex, 1-3 years old, thirty each at hospital and home, were included into this exploratory study having four groups (healthy/low, healthy/high, diarrheal/low and diarrheal/high) during the period of 1st August to 23rd October 2017 to find out the digestive tolerability of Fibersol-2 by administering its low (2.5g) and high (5g) doses twice daily with 50 ml drinking water during the intervention period of seven days. Age was significantly associated in the model in relation to the factors, dose and status of all the four groups (p=0.026). There was no change in stool consistency among healthy children throughout the study period and among diarrheal children, the median duration of resolution of diarrhea was [3.9 (2.9, 5.1) days vs. 3.5 (2.0, 8.0) days; p=0.885] in low dose and high dose groups, respectively. Significant difference was observed in terms of abdominal pain (27% vs. 7%, p=0.038) and distension (40% vs. 0%, p<0.001) in diarrheal children, compared to healthy children during the pre-intervention period. We also observed significant difference in respect of abdominal distension (23% vs. 0%, p=0.011), rumbling (27% vs. 0%, p=0.005) and bloating (43% vs. 3%, p=0.001) in diarrheal children, compared to healthy children during the intervention period. However, no significant difference was observed in connection with abdominal pain (p=0.347) and distension (p=0.165) during the pre-intervention period, compared to the intervention period in diarrheal children. Moreover, no significant difference was observed during the post intervention period for the diarrheal and healthy children. Fibersol-2 was found to be well tolerated in healthy and diarrheal children of 1-3 years old.

0422

GUT MICROBIOTA-DERIVED LIPIDS CORRELATE WITH ORAL CHOLERA VACCINE RESPONSES AND THESE LIPIDS IMPACT INNATE IMMUNE RESPONSES IN *VITRO*

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Oral cholera vaccines (OCV) are critical for cholera control yet immune responses to vaccination vary, and host factors and demographic variances do not fully explain these differences. Gut microbes are known regulators of mucosal immune function, and we have observed correlations between gut microbes and responses to OCV. Our prior microbiome study of stool from OCV recipients demonstrated that specific gut microbes predict O-specific polysaccharide memory B cell responses (OSP MBC) after vaccination and a common factor among these microbes is the ability to produce unique sphingolipids.To investigate this correlation, we conducted lipid profiling on fecal extracts from OCV recipients in Dhaka, Bangladesh, and found increased ceramides (a precursor to sphingolipids that can be made by bacteria) among individuals with OSP MBC responses compared to vaccine recipients without OSP MBC responses (P=0.03, Mann-Whitney test). We next isolated gut microbes known to produce sphingolipids from the stool of persons living in Dhaka, Bangladesh, and tested them for the presence of serine palmitoyltransferase (SPT), the gene that enables ceramide and sphingolipid production in bacteria. One of the microbes that we found to be *spt+* is *Bacteroides xylanisolvens.* We extracted lipids from *B. xylanisolvens* culture using the Bligh-Dyer method and measured immune responses to these lipids in our macrophage model derived from the human monocytic cells. When SPT activity in the bacterial culture was inhibited, the proinflammatory response from our model was increased. For example, interleukin-6 was significantly increased in response to stimulation with the non-sphingolipid-containing lipid layers of *B. xylanisolvens* compared to those with sphingolipids (P<0.0001, t test).We have identified sphingolipid-producing microbes that correlated with OSP MBC responses in OCV recipients and found that the presence of these sphingolipids may impact innate immune responses. Our studies may contribute to the development of microbe-derived molecules that enhance immune responses to OCV.

0423

LONGEVITY OF ANTI-VI IGG AND IGA RESPONSES IN 15-MONTH-OLD CHILDREN VACCINATED WITH A TYPHOID CONJUGATE VACCINE IN BURKINA FASO

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Typhoid conjugate vaccines (TCV) have demonstrated efficacy against typhoid fever. A recent study showed TCV-induced IgA and IgG responses to *Salmonella Typhi* Vi polysaccharide correlate with protection in a controlled human infection model. The aim of this study was to measure anti-Vi IgG and IgA responses at 28 days and 30-35 months post-vaccination in children 15–23 months of age. We randomized children 2:1 to receive single-dose TCV or inactivated polio vaccine (IPV). We compared anti-Vi IgG and IgA responses at 28 days and 30-35 months after vaccination using Vi-coated plates and reagents (Binding Site, San Diego, CA) based on a protocol adapted from the commercial VaccZyme assay. Seroconversion was defined as ≥ 4-fold increase in titer.150 children were recruited and enrolled. At day 28 post-vaccination, anti-Vi IgG seroconversion was 94·9% (95%CI 88·4-98·3%) in TCV recipients compared to 3·9% (95%CI 0·5-13·5%) in the IPV group. Anti-Vi IgG GMT at day 28 in the TCV group was 3210·1 EU/ml (95%CI 2311·7-4457·6) versus 5·3 EU/ml (95%CI 4·1-6·9) in the IPV group. At 30-35 months, the same trend for %IgG seroconversion was observed, with 88·7% (95%CI 79·0-95·1) in the TCV group compared to 6·8% (95%CI 1·4-18·7) in IPV recipients; however, GMT decreased to 79·3 EU/ml (95%CI 63·1-99·6) in the TCV group versus 5·7 EU/ml (95%CI 4·4-7·3) in the IPV group. Participants who received TCV achieved higher anti-Vi IgA GMT (41·1 EU/ml, 95%CI 33·8-49·9) at day 28 than IPV recipients (1·7 EU/ml, 95%CI 1·5-1·8). Analyses of anti-Vi IgA immunogenicity at 30-35 months post-vaccination are ongoing. TCV conferred similarly strong anti-Vi IgA and IgG responses at 28 days post-vaccination in children vaccinated at 15-23 months of age. However, the anti-Vi IgG responses decreased at 30-35 months. Results confirm TCV is highly immunogenic in this population. The durability of the immune response is also demonstrated, but a correlate of TCV protection is unknown. Future studies should continue to investigate vaccine-induced protective responses and consider the need for, and timing of, routine booster vaccination in target populations.

0424

ASSOCIATION BETWEEN ANTE-NATAL SYPHILIS TEST RESULTS AND BIRTH OUTCOMES IN WESTERN KENYA

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Maternal syphilis remains a major contributor to poor pregnancy outcomes. Syphilis point-of-care tests are now employed for pregnancy screening, but the effect of screening on outcomes is unclear. We enrolled women presenting to routine antenatal care clinic in a matched case-control study at a single site in western Kenya. Syphilis point of care test-positive women were matched 1:2 with test-negative women on gravidity, gestational age, and HIV status, and followed through delivery. A confirmatory treponema pallidum hemagglutination assay (TPHA) testing was done for all participants at enrollment while syphilis serum testing was performed serially during subsequent antenatal clinic visits. Pregnancy outcomes were assessed up to 1 month after delivery and compared using prevalence ratios. We enrolled 51 syphilis test-positive (cases) and 100 test-negative (controls) women at a mean of 22 weeks gestation; 24% were HIV-positive and 40% were paucigravid. A positive TPHA was more common among cases than controls ($p < 0.001$). Only 2 women met the definition for incident syphilis. Pregnancy outcomes were available for 147 women. The prevalence of low birthweight was higher among cases (15.2%) than controls (5.4%; $p = 0.052$). Among the 109 women with concordant point of care and TPHA results at antenatal clinic enrollment, the prevalence of low birth weight was significantly higher among test-positive (25%) than test-negative (4.9%) women (adjusted PR 5.84; 95% CI 1.08, 31.5). Despite treatment with penicillin, latent syphilis at antenatal care enrollment was associated with a more than 5-fold increased risk of low birth weight. Alternate implementation strategies for point of care testing may be necessary to realize the potential of antenatal syphilis screening to improve pregnancy outcomes.

0425

THE EXCESS BURDEN OF INPATIENT BLOODSTREAM INFECTIONS CAUSED BY ANTIBIOTIC RESISTANT BACTERIA IN LMICS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Bloodstream infections (BSIs) produced by antibiotic-resistant bacteria (ABR) cause a substantial burden of disease worldwide. However, the magnitude is unclear in low-and-middle income countries as most appraisals come from high-income settings where reduced exposure to antibiotic reservoirs exists. The aim of this meta-analysis was to quantify the excess mortality, length of stay (LOS), ICU admission, and economic costs attributable to BSIs produced by ABR among adult inpatients. A systematic literature review was conducted following the PRISMA guidelines (PROSPERO registration: CRD42021264056). Three reviewers searched three medical databases (PubMed, SCIELO and Scopus; initial search n=11327) without date or language restrictions to determine differences in outcomes for BSIs caused by resistant versus susceptible bacteria. Costs estimates for outcomes were sourced either from WHO-CHOICE, or failing that, from the literature and inflated to 2020 USDs. The final included studies (n=95) showed significantly increased mortality (OR=1.51, 95%CI=1.3-1.7), LOS (SMD=0.47, 95%CI=0.1-0.7), and ICU admission (OR=1.93, 95%CI=1.5-2.5) for resistant versus susceptible BSIs. *Enterobacteriaceae*, *A. baumanii* and *S. aureus* in upper middle-income countries from the African and Western Pacific regions accounted for the highest overall burden. Excess hospital-related costs were estimated at $7378 (95% CI: $4085-$10672) for resistant BSIs. We provide a comprehensive evaluation of the excess burden of BSIs produced by AMR in low-resourced settings. We observed wide heterogeneity between WHO region, income group, and pathogen-drug combinations. Our results are critical for the design of country-specific policies, specifically related to infection prevention and surveillance and the production of new targeted antibiotics and vaccines. Nonetheless, there are still data gaps in AMR literature and surveillance capacity; improved technological development for data collection and culture within healthcare systems are crucial to tackle AMR BSIs.

0426

INAPPROPRIATE USE OF ANTIBIOTICS AMONG CHILDREN IN THE COMMUNITY OF THREE LOW- AND MIDDLE-INCOME COUNTRIES

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Antibiotics resistance is a global public health issue, particularly in low- and middlle-income countries (LMICs) where children bear the highest burden of bacterial infection. Inappropriate use of antibiotics is a major contributor to antibiotic resistance. However, such data are lacking at the community level in low- and middlle-income countries, where the majority of the population is treated outside the hospital. We aimed to characterize the pattern of inappropriate antibiotics use among outpatient children and to identify associated determinants in Madagascar, Senegal and Cambodia. We used data from a child cohort (BIRDY cohort, 2012-2018) conducted both in urban and rural areas of these 3 countries. Children were followed-up from birth up to the age of 24 months to document all their infectious episodes. All symptoms, diagnosis and antibiotics received were documented. We defined inappropriate use as unnecessary use of antibiotics based on the diagnosis of probable bacterial infection. We performed mixed logistic models to identify determinants associated with inappropriate use of antibiotic. Among the 3710 children included, there was 29% (3,448/11,762) consultations with antibiotic prescription. Amoxicillin accounted for 36% of all prescriptions. We found that 57.0%, 15.5% and 57.2% of prescriptions were inappropriate in Cambodia, Madagascar and Senegal, respectively. Bronchiolitis was the most common indication followed by gastroenteritis and rhinopharyngitis with 43.9%, 35.5% and 20% of inappropriate prescription, respectively. Being older than 3 months (aOR ranging from 1.93 [1.65-2.25] to 4.1 [3.1-5.5]) and a diagnosis with a higher severity score (2.1[1.7-2.4] to 3.6 [2.7-4.7]) were associated with an increased risk of inappropriate prescription in the 3 countries. Also, children from urban site were less at risk of receiving an inappropriate prescription (0.2 [0.1-0.3] to 0.5[0.4-0.6]). Our findings show a significant proportion of inappropriate use of antibiotics and underscore the importance of implementing local programs to optimize antibiotic prescriptions at the community level.

0427

NEAR-TERM PREGNANT WOMEN IN THE DOMINICAN REPUBLIC EXPERIENCE HIGH RATES OF GROUP B *STREPTOCOCCUS* RECTOVAGINAL COLONIZATION

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Group B *Streptococcus* (GBS) colonizes an estimated 18% of pregnant women worldwide and is an important cause of stillbirth and serious infection and death in neonates. Populations in low- and middle-income countries (LMICs) experience higher disease burdens and larger gaps in care. Region-specific data on GBS colonization rates and serotype distribution among pregnant women in LMICs are critically needed to inform effective prevention measures like intrapartum antibiotic prophylaxis (IAP) and vaccine development. The Caribbean region has the highest colonization rates identified worldwide. In the Dominican Republic (DR), the only prior study of maternal GBS colonization included women presenting in labor at all gestational ages and identified GBS colonization in 44%, the highest rate ever reported. We sought to determine the rate of GBS colonization among near-term pregnant women in the DR. Spanish-speaking pregnant women at 35 weeks or greater gestation who presented to an urban tertiary referral hospital in Santo Domingo for routine antenatal care between September 2021 and March 2022 were enrolled for rectovaginal sampling. One flocked swab in Liquid Amies medium (COPAN ESwab) was used for anterior vaginal and rectal sampling. Medium was then incubated in chromogenic Strep B Carrot Broth (Hardy Diagnostics) per manufacturer instructions, and color change indicated a positive result. Of 720 near-term pregnant women approached during the study period, 350 women were enrolled. Rectovaginal sampling using carrot broth identified GBS colonization in 26%. In the first 240 enrolled, GBS colonization was not significantly associated with past GBS history, antibiotic use in pregnancy, or vaginal douching practices. Analysis of additional demographic factors and GBS serotype distribution is ongoing. The GBS colonization rate in this cohort of near-term Dominican pregnant women exceeds the global average, highlighting the potential impact of a safe, effective GBS vaccine and the need for further work on the feasibility of routine GBS screening and IAP to reduce neonatal morbidity and mortality in the DR and other resource-limited areas.

0428

DETECTION OF *ORIENTIA TSUTSUGAMUSHI* INFECTION FROM STILLBIRTH CASES: FINDING FROM CHAMPS STUDY IN BANGLADESH

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Orientia tsutsugamushi (OT) is a mite-born obligate intracellular gram-negative bacterium known to cause scrub typhus, a febrile illness endemic in the Asia-Pacific region. Surveillance from Bangladesh from 2009-08 identified that 9% of all patients hospitalized for febrile infections had scrub typhus. Signs and symptoms of illness are non-specific can lead to multiple organ failure and death in up to 30% of cases. OT infection during pregnancy can cause stillbirth, preterm labor, small size for gestational age, or low birth weight. Diagnosis is difficult and research about infections during pregnancy is limited. Here we report three stillbirths from rural Bangladesh where OT was identified using molecular testing. The Child Health and Mortality Prevention Surveillance (CHAMPS) program investigates causes of stillbirths and under-5 deaths in Bangladesh and other countries. Post-mortem blood, cerebrospinal fluid (CSF), nasopharyngeal swabs, and rectal swabs are collected and tested using multiple diagnostic platforms such as microbial culture and TaqMan Array Card Real-Time PCR. Tissues are collected using minimally invasive tissue sampling and reviewed using histopathology. From August 2017 to Aug 2021 specimens from 115 stillbirths were collected; OT was identified by real-time PCR in CSF from 3 cases (2%); one also had the organism detected in blood. Ct for all specimens ranged between 31-34. All three stillbirths were preterm, macerated, low birth weight and detected before delivery (antepartum). Gross observation indicated hepatomegaly and nose bleeding for two cases. For two cases the mother reported febrile illness with shivering 3-4 days before the period of delivery and both received antimicrobial therapy. The expert panel in Bangladesh did not consider the organism as a contributor to the demise of these fetuses, despite the real time PCR results, due to relatively higher Ct value and because stillbirths associated with OT have not been previously described in Bangladesh. The real burden and impact of OT infection among pregnant women in Bangladesh deserves further investigation.

0429

RECOGNISING SEPSIS AS A HEALTH PRIORITY IN SUB-SAHARAN AFRICAN COUNTRY: LEARNING LESSONS FROM ENGAGEMENT WITH GABON'S HEALTH POLICY STAKEHOLDERS

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Sepsis is a life-threatening condition due to organ dysfunction, resulting in a dysregulated host response to infection. It has been recognized as a global health priority by the United Nations World Health Assembly, which adopted a resolution in 2017 to improve sepsis prevention, diagnosis, and management globally. Low- and middle-income countries such as Gabon govern limited resources both human and material, and the health system is challenged by many infectious diseases. This study investigated how sepsis is prioritized in Gabon. From May to November 2021, we conducted a qualitative study on health care stakeholders at the local, regional, and national levels. Stakeholders included the Ministry of Health (MOH), ethics/regulatory bodies, research institutions, training institutions, referral hospitals, international funders, and media. Twenty-three multisectoral stakeholders were interviewed. Respondents indicated that sepsis is not yet prioritized in Gabon due to the lack of evidence of its burden. They also suggest that the researchers should focus on linkages between sepsis and the countries' existing health sector priorities to accelerate sepsis prioritization in health policy. Stakeholder awareness and engagement might be accelerated by involving the media in the generation of communication strategies around sepsis awareness and prioritization. There is a need for local and national evidence to be generated by researchers and taken up by policymakers, focusing on linkages between sepsis and a country's existing health sector priorities. MOH should set sepsis reporting structures and develop appropriate sepsis guidelines for identification, management, and prevention.

0430

BIOMARKERS OF AETIOLOGY IN HOSPITALISED CHILDREN WITH SEVERE ACUTE INFECTIONS

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Despite the improvement in global health over the last three decades, sepsis are still a major cause of morbidity and mortality globally and especially in children under 5 years. Sepsis is a heterogeneous syndrome caused by a dysregulated host response to infection. Different pathogens cause infections that manifest with sepsis-like symptoms thus limiting symptomatic clinical diagnosis. Determining the aetiology of sepsis remains a global challenge. This complicates care decisions, leading to increased antimicrobial resistance and mortality. Preventing death and long-term morbidity due to infectious diseases requires better diagnostics. Understanding the molecular processes that underlie different aetiologies would enable initiation of appropriate and timely treatment. We aimed to characterise the host response in plasma of children under 5 years admitted at the Kilifi County Hospital with severe acute infections. Admission levels of plasma proteins were determined using untargeted liquid chromatography tandem mass spectrometry (LC-MS/MS). Protein profiles of children with bacterial infections (N = 63) were compared with those of children who had viral infections (N=75). Healthy children (N=20) were used as controls. Using linear models, we assessed the relationship between baseline plasma proteins and infection. Bioinformatic analysis of differentially expressed proteins showed elevation acute phase proteins such as C-reactive protein in children with bacterial infections. In addition, angiotensinogen, lipopolysaccharide binding protein and Serpin Family A Member 1 were associated with bacterial infections while Apolipoprotein A-2, and paraoxonase-1 were associated with viral infections. Acute phase responses and neutrophil degranulation were enriched in bacterial infections while platelet degranulation was negatively associated with bacterial infections. These results show the changes plasma protein levels and biological processes during bacterial and viral sepsis that can be leveraged to design biomarkers and future interventions of sepsis.

0431

IMMUNOGENICITY OF A PSORALEN-INACTIVATED WHOLE-CELL *NEISSERIA GONORROHOEA* VACCINE IN MICE

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Gonorrhea is a major global health threat compounded by increasing multidrug resistance. There is currently no vaccine. We examined a method of inactivating *N. gonorrhoeae* (GC) with 4-aminomethyl-4,5', 8-trimethylpsoralen (AMT), a psoralen derivative, and UVA light (PUVA) to introduce DNA crosslinks, disabling DNA replication without altering the proteins on the cell surface. This inactivation technique protects protein epitopes and produces "killed but metabolically active" bacteria which could allow for the development of a more robust vaccine than other inactivation methods. GC strain FA1090 was inactivated using either 2 cycles of AMT at a dose of 40 ug/ml and 1 Joule/cm^2 of UVA or formalin (10% for 2 hours at room temperature). Four groups of 7-8 mice received a 0.1 ml injection containing 5 x 10^6 CFU equivalents of PUVA or formalin inactivated bacteria with or without 0.25 µg dmLT, a mucosal adjuvant, on days 0 and 21. Sera was analyzed for antibody response (IgM+G+A) by whole cell ELISA using GC as the coating antigen. Histopathologic exam of colorectal tissue collected on day 35 was performed. Significantly higher titers were demonstrated for PUVA-GC than formalin-GC ($p = 0.0009$), PUVA-GC vs PUVA-GC+dmLT ($p<0.0001$), formalin-GC vs formalin-GC+dmLT ($p=0.009$) and PUVA-GC+dmLT vs formalin-GC+dmLT ($p<0.0001$). Notably the nonadjuvanted PUVA-GC vaccine induced significantly higher titer antibodies than the adjuvanted formalin-GC vaccine ($p = 0.0005$). Histologically, both vaccines induced increased cellularity composed predominantly of tightly packed lymphocytes within the colonic lymphoid aggregates, but the lymphoid aggregates were more cellular and organized in the PUVA-GC+dmLT compared to the formalin-GC+dmLT group. This study demonstrates a proof of concept for an PUVA inactivated gonorrhea vaccine. The vaccine elicited a robust humoral response and promising mucosal changes in the mouse model. Future studies are planned to further characterize the immune response and evaluate protection.

0432

DEEP NECK INFECTIONS IN DIABETIC PATIENTS: A COMPARATIVE STUDY WITH NON-DIABETIC PATIENTS

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The global burden of diabetes, as well as diabetic-related comorbidities, is steadily rising. Infections are more common in people with diabetes. Deep neck infections, especially in immunocompromised hosts such as diabetic patients, can be fatal if life-threatening complications arise. Due to a growing concern regarding antibiotic resistance, we aim to investigate if there has been a change in the microbiology and antibiotic sensitivity of deep neck infection February 2019- January 2020 infections in diabetic and non diabetic patients group over the period of one year. Study was conducted 150 consecutive patients with deep neck infection treated in the Otolaryngology / Head & Neck Surgery Department of IMS & SUM Hospital, Bhubaneswar, Odisha. Out of which 47 patients were diabetic and 103 were non diabetic group. Demographics, clinical features and microbiological data, etiology, duration of hospital stay and other complications were analyzed. Among the 150 patients (47 diabetic and103 non-diabetics) with deep neck infection, Clinical samples were obtained from 150 patients, and were identified by conventional method and Vitek 2 sytem. Antibiotic profiling also done by Vitek 2 system. *Streptococcus pyogenes* is the common bacteria found in non-diabetic cases and *Pseudomonas aeruginosa, Klebsiella pneumonniae* were predominant in diabetic patients with infection. Diabetic patients are more likely to develop abcesses than non-diabetic patients. In the diabetes group, surgical drainage was performed more frequently than in the nondiabetic group. The diabetic group had a longer hospital stay, more problems, and more tracheostomy or intubation than the nondiabetic group. In both groups, odontogenic and upper airway infection were the most frequent infections. Diabetes mellitus patients are more likely to have infection. When dealing with deep neck infections in patients with diabetes mellitus, we should pay special care because these patients are more likely to have longer stay in the hospital. Empirical antibiotics should cover *K. pneumoniae* and *P. aeruginosa* in patients with deep neck infection who have diabetes mellitus.

0433

DEVELOPMENT OF DEEP GENOME MINING BASED DIAGNOSTICS FOR CURABLE SEXUALLY TRANSMITTED INFECTIONS

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Gonorrhea, caused by *Neisseria gonorrhoeae* (NG) accounted for approximately 87 million cases globally in 2016. Although the disease is a major global burden causing adverse outcomes including ectopic pregnancies, pelvic inflammatory disease and infertility the most preferred laboratory method for diagnosis is bacterial culture. However, basic sample handling can make culture unreliable. Several other methods

available for NG diagnosis include molecular methods, which are less labor intensive and are accurate. However, are not widely field deployable especially in low resource settings. In this study, we leveraged genome-mining approaches to select identical multi repeat sequences (IMRS) distributed throughout the NG genome to design primer pair that target numerous regions. Genomic DNA was extracted from bio-banked NG positive urethral swabs, and 10-fold serially diluted (100pg/µl to 1×10^{-3} pg/µl) and used as DNA template for PCR reactions using the IMRS primers. As a control, conventional PCR with 16s RNA primers was also run, and both assay products resolved on agarose gel. We observed that the IMRS PCR assay was more sensitive with a lower limit of detection of 0.006 pg/µl, representing >1052 times better sensitivity. The IMRS assay was comparable ($P \geq 0.1573$) to the conventional 16s RNA PCR in detecting cultured NG from infected patients. We further showed that Loop-mediated isothermal amplification (LAMP) using IMRS PCR primers is both reliable and sensitive for detecting cultured and field NG isolates. Put together, algorithm-based de novo genome mining of IMRSs as amplification primers can serve as a novel platform technology for developing ultrasensitive diagnostics for NG genome and potentially a wide range of infectious pathogens. In addition, there is a potential to implement this concept in miniaturized, point-of-care, isothermal, microfluidic platforms and laboratory-on-a-chip diagnostic devices.

0434

A MENINGOCOCCAL MENINGITIS RAPID DIAGNOSTIC TEST IN CEROBROSPINAL FLUID (CSF)

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Meningitis is a devastating infectious disease and remains a major public health challenge. *Neisseria meningitis* (Nm), causing meningococcal meningitis, is the pathogen with the potential to produce large epidemics within countries in the meningitis belt of sub-Saharan Africa. Meningococcal meningitis being a deadly disease, is associated with high mortality (up to 50% when untreated) and survivors are often left with crippling neuro developmental sequelae. Early diagnosis and prompt application of specific antimicrobial therapy are the most important measures to save lives and reduce complications. The use of laboratory methods has become necessary as it can inform decision-makers of the Nm serogroup involved. However, countries most affected face real limitations in laboratory diagnostics. A Point of Care (POC) device that would be rapid, cheap and simple enough to be performed in local health structures is needed. To meet this demand, a rapid diagnostic test (RDT) to enable identification of six serogroups of Nm from the cerebrospinal fluid (CSF) is being developed. This test is composed of two strips in the same cassette. The serogroups A, C and W135 will be detected on one strip whilst B, Y and X will be detected using another one. Currently in phase 2 of development (optimization phase), the prototypes are being tested with different concentration of polysaccharides with promising results (a detection limit of 0.5ng/ml per serogroup except for Y 0.75 ng/ml and A 1ng/ml with an optimization that is ongoing). On the other hand, samples from hospitals are being collected and characterized (gold standard methods) for the next step of validation. This RDT could be useful both as a first-line diagnostic tool for epidemiological surveillance of outbreaks and at the patient's bedside for improved case management.

0435

COMMUNITY SURVEY OF LEPROSY, SCHISTOSOMIASIS, STRONGYLOIDIASIS, SARS-COV-2, AND ASSOCIATIONS WITH WASH AND SES IN EASTERN MINAS GERAIS, BRAZIL

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Neglected tropical diseases (NTDs), including Hansen's disease (HD), or leprosy, and soil-transmitted helminths, remain public health concerns in Brazil. This cross-sectional serosurvey aims to assess the burden of and risk factors for HD and parasitic infections in municipalities in Minas Gerais, while also measuring SARS-CoV-2 seroprevalence. Participants aged 3 years and older were randomly sampled from neighborhoods in Governador Valadares, Inhapim, and Turmalina. A survey assessing demographics, water, sanitation, and hygiene (WASH), and environmental conditions was administered. Blood spots were collected and tested for antibody reactivity to *Mycobacterium leprae* (LID-1), *Schistosoma mansoni* (SEA), *Strongyloides* spp. (NIE), and SARS-CoV-2 using a multiplex beaded assay (MBA). Descriptive and bivariate analyses were conducted. Initial results include survey data on 594 individuals, of which serological data was available for 220 participants. The mean age was 51.5 years and 66.3% were female with 23.4% black, 21.4% white, and 54.1% mixed race. Most participants (74.8%) had an elementary school education or less and 37.3% made below minimum wage (approximately 8 USD per day). Two-thirds (65.4%) of survey participants self-reported ever having been diagnosed with a parasitic infection and 20 (3.4%) self-reported past history of HD. Four (1.8%) were positive for anti-LID-1, 28 (12.7%) were positive for anti-SEA, and 12 (5.5%) were positive for anti-NIE. One hundred eighty-two (82.7%) were positive for SARS-CoV-2 antibodies via either infection or vaccination. Occupational or recreational contact with bodies of water was found to be associated with self-reported history of a parasitic infection (OR=1.72; 95% CI: 1.11, 2.69). Using a public faucet as a source for cooking water was found to be associated with self-reported HD diagnosis (OR=10.27; 95% CI: 2.27, 46.39). These initial findings begin to characterize the burden of NTDs with further analyses of the associations of WASH, socioeconomic status, and seroreactivity of the full sample expected.

0436

EXPLORING THE BIOACTIVITY OF *KHAYA SENEGALENSIS* (DESR.) A. JUSS. FOR COMBATING MULTIPLE DRUG-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTIONS

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Since antiquity, antibacterial agents have been a blessing in the fight against diversified bacterial infections saving millions of lives. However, despite efforts to combat infections caused by multiple drug-resistant

Staphylococcus aureus (MDRSA), infections due to MDRSA is still on the rise and remain a significant public health burden globally. Currently, effective antibiotics to address this urgent need are limited, warranting the search for new compounds using the medicinal approach to discover antimicrobial therapies. Here, we investigated the bactericidal effect of cold macerated 70% ethanolic stem bark extract of *Khaya senegalensis* (KS) on twenty MDRSA isolates, using the agar well-diffusion and micro-broth dilution techniques. The test organisms were challenged with two-fold dilution concentrations of extract, 100 to 6.25 mg/mL and 50 to 0.02 mg/mL for the agar well-diffusion and micro-broth dilution assays, respectively. Our work showed that the ethanolic extract from KS inhibited all the tested organisms with appreciable inhibition zones ranging from 18.3 ± 0.6 to 8.3 ± 0.6 mm in a dose-dependent manner compared to Ciprofloxacin (15 µg/mL) 15.3 ± 0.6 to 19.0 ± 0.0 mm. Also, the extract showed promising activity against the MDRSA strains with very low minimum bactericidal concentrations of 0.39 to 1.56 mg/mL. Further studies on phytochemical screening and bioassay-guided fractionation of extract from KS to isolate the bioactive compounds are ongoing.

0437

COMMON ENVIRONMENTAL EXPOSURES IN INDIVIDUALS WITH HANSEN'S DISEASE IN THE SOUTHERN UNITED STATES

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Hansen's disease (HD), or leprosy, is a disease caused by *Mycobacterium leprae* and less commonly, *Mycobacterium lepromatosis*. There are approximately 250,000 new cases of HD each year globally, and an estimated 150 new cases annually in the United States. A recent increase in case reports from Florida and other southern states suggest a rise in locally acquired infection. The 9-banded armadillo (*Dasypus novemcintus*) is the only known natural reservoir in North America and a likely source of zoonotic transmission in Gulf states. *Mycobacterium leprae* has also been shown to survive in free-living amoebae in soil. The objective of this study is to describe common exposures among patients with suspected locally acquired HD infections. We designed and conducted a phone survey for past and current non-immigrant patients of the Emory HD Program. Survey questions included states of residence, foreign residence, occupation, outdoor activities, and exposure to armadillos. A descriptive analysis was performed to identify commonalities among the participants. Preliminary results include 5 individuals who were diagnosed with HD. The median age of patients was 70 years old. 2 patients resided in Florida at the time of the survey and 3 resided in Georgia. However, 2 of the patients residing in Georgia had previously lived in Florida and continue to visit the state. 3 of the patients lived internationally, although none in a country with endemic HD. 2 of the patients had physical contact with armadillos and the other 3 reported seeing armadillos around their home. All participants reported spending at least 3-5 hours per week outdoors and taking part in activities such as gardening, hiking, golf, and kayaking. 4 of the 5 participants had associations with central and northern Florida and contact with armadillos or soil that could potentially be contaminated with armadillo bodily fluids. The information from this study starts to explore common exposures among non-immigrant US patients with HD. Further research and a larger patient sample is needed to better understand the association between these risk factors and HD.

0438

EFFECT OF EFFLUX PUMP INHIBITORS ON CLINICAL STRAINS OF MULTIRESISTANT *KLEBSIELLA PNEUMONIAE*

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The study was undertaken to evaluate the effect of the inhibitors phenylalanine-arginine β-naphthylamide (PAβN) and carbonyl cyanide 3-chlorophenylhydrazone (CCCP) in isolated multiresistant clinical strains of *K. pneumoniae* from hospitalized patients in Lima, Peru. Cross-sectional study that included 16 clinical samples collected from hospitalized patients in Lima, Peru. *Klebsiella pneumoniae* was identified by the MicroScan WalkAway system. Samples were cultured on BHI agar, analyzed by Universal 16S PCR, and confirmed by genetic sequencing. The minimum inhibitory concentration (MIC) for the studied antibiotics was determined by the broth microdilution method. A range of concentrations from 0.25 µg/ml to 256 µg/ml was used in a 96-well microplate with 100 µl Muller-Hinton broth.The activity of the efflux pumps was evaluated by adding the inhibitors phenylalanine-arginine β-naphthylamide (PAβN) and carbonyl cyanide 3-chlorophenylhydrazone (CCCP). The change from 4 to more dilutions in the MIC was considered as a criterion of significance. The non-susceptibility rates obtained by MIC were the following: amikacin (1, 6.25%), ciprofloxacin (10, 62.50%), piperacillin/tazobactam (0, 0%), tigecycline (11, 68.75%), cefepime (6, 37.50%) and colistin (4, 25%). In the presence of PAβN, a significant increase in amikacin susceptibility was obtained in 1 strain (6.25%), ciprofloxacin in 3 (18.75%), piperacillin/tazobactam in 1 (6.25%), tigecycline in 4 (25%), cefepime in 2 (12.50%) and colistin in 4 (25%). The addition of CCCP led to a significant increase in the susceptibility of ciprofloxacin, tigecycline and cefepime in 3 (18.75%) strains, piperacillin/tazobactam in 2 (12.50%) and colistin in 1 (6.25%). No significant inhibitory effects on the MIC of amikacin were seen in the presence of CCCP. In conclusion, the use of PAβN and CCCP can enhance the antibiotic effect of ciprofloxacin, piperacillin/tazobactam, tigecycline, cefepime, and colistin in clinical strains of *K. pneumoniae*. Efflux pump inhibitors may be useful in treating multidrug-resistant *K. pneumoniae*.

0439

RELATIONSHIP BETWEEN ACUTE FEBRILE ILLNESS AND EMERGING AND RE-EMERGING BACTERIAL PATHOGENS IDENTIFIED IN PATIENTS AT A HEALTH FACILITY IN THE PERUVIAN JUNGLE

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The study was undertaken to determine the relationship between acute febrile illness and emerging and re-emerging bacterial pathogens identified in patients treated in the Leoncio Prado health network. Observational, descriptive, comparative, cross-sectional studies were conducted. A

secondary database obtained from an initial study carried out in the health establishment of the Leoncio Prado Health Network is analyzed. All samples were analyzed by polymerase chain reaction (PCR) to determine the presence of infectious bacterial agents. A surveillance strategy for febrile syndromes based on the patient's symptoms was established. Of the 279 samples analyzed, 23 (8.2%) were positive for infection by *Rickettsia spp*. As for the positive samples for *Leptospira spp.*, there were a total of 15 (5.4%). Women had a higher frequency of infection by *Rickettsia spp.*, 13 (53.3%) while men had a higher frequency of infection by *Leptospira spp.* 10 (66.7%). Fever was present in all patients, the most common general symptom reported was headache with a frequency of 100.0% (n = 23) and 86.7% (n = 13) followed by myalgia with 91.3% (n = 21).) and 66.7%(n=10) for *Rickettsia* + and *Leptospira* + respectively. The finding shows an epidemiological precedent for these pathogens in the region. The frequencies of infection by *Rickettsia spp*. and *Leptospira spp.* indicate that these emerging and re-emerging bacterial pathogens do not play a predominant role in the etiology of acute febrile syndrome in the region studied.

0440

SPATIOTEMPORAL DISTRIBUTION AND DETERMINANTS OF SCRUB TYPHUS IN THAILAND

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Scrub typhus is an important vector-borne infectious disease with more than one billion people at risk and approximately one million annual cases. In Thailand, scrub typhus incidence has increased significantly over the past two decades. Despite recent efforts towards understanding transmission dynamics, comprehensive provincial level analyses to identify risk areas and identify the mechanisms driving transmission are lacking. Here, we incorporate high resolution case data from Thailand to understand the spatiotemporal dynamics and associated meteorological determinants of scrub typhus. To explore the relationship between meteorological factors, such as cloud cover, specific humidity, relative humidity, temperature, and precipitation with scrub typhus, data were fitted with linear regression models for hypothesis testing and analyzed using Pearson correlation. Cross-correlation was used to identify lagged relationships, and nonlinear relationships discovered were fitted with LOESS. The mountainous provinces in the northern and northeastern regions of Thailand had the highest incidence of scrub typhus, with peaks in cases occurring between July and October. High-risk provinces included Chiang Rai, Chiang Mai, Mae Hong Son, Nan, and Tak, which experience similar meteorological conditions. We found that relative and specific humidity, which are both influenced by temperature, explained much of the observed incidence. Additionally, we discovered a 4-5 month lag between when the temperature first increased above the minimum optimum temperature for vector larval activity and egg-hatching rate and peak incidence. Increases in humidity, which chigger mites rely on for water source, and average temperatures around 23°-25°C, which are optimum for egg-hatching rate and larval activity, can be used as thresholds for when scrub typhus transmission is likely increasing. This work can inform public health officials when and where prevention and control efforts need to be focused.

0441

ETIOLOGICAL AGENTS OF DIARRHEAL DISEASES DETECTED AMONG UNDER-5 DEATHS IN MANHIÇA AND QUELIMANE DISTRICTS, MOZAMBIQUE IN THE CHAMPS NETWORK, 2017-2021

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Diarrhea is the 3rd leading cause of mortality in children under-5 globally, being responsible for 525,000 deaths worldwide each year; however, there is a scarcity of studies that evaluate the role of specific pathogens in death among children under 5. In this analysis, we aim to study etiological agents causing diarrhea detected in deceased children in Manhiça and Quelimane districts, Mozambique from January 2017 - April 2021. Real-time polymerase chain reaction for detection of enteric pathogens in post-mortem rectal swabs was performed using TaqMan Array Cards and expert panels determined the cause of death. At least one enteric pathogen was detected in 281 deaths (152 Neonates, 51 Infants and 78 Children). Among neonates, Enterococcus faecalis (E. feacalis) was more frequent (43%), followed by enteroaggregative Escherichia coli (EAEC) (36%) and Aeromonas spp. (30%). In infants, EAEC was most detected in 76% cases, followed by E. faecalis (61%) and Aeromonas spp. (35%). E. faecalis (54%) followed by EAEC-aatA (53%) and EAEC-aaiC (37%) were mostly detected in children. From the 281 deaths, 81% (228) had a cause of death attributed. Diarrhea was the immediate cause of death in 1% (2/228, 1 infant and 1 child) and underlying cause in 9% (21/228, 1 neonate, 10 infants and 10 children) of deaths. In deaths where diarrhea was the underlying cause, EAEC and Rotavirus (14%, 3/21), Vibrio cholerae and Norovirus GII (5%, 1/21) were in the causal chain of death, however, major causes of deaths were due to unspecified pathogens (62%, 13/21). Although diarrhea was immediate cause of death in few deaths, it was important as underlying cause of death. Even though a high proportion of deaths where diarrhea was the underlying cause of death were due to unspecified pathogens, EAEC and Rotavirus, two well-known pathogens with high burden in diarrhea in children from Low and Middle-income Countries, had a very important role in infants and child deaths. Further investigation such as genotyping of Rotavirus and antimicrobial resistance profile of the EAEC isolates is required for better evaluation of diarrhea burden and the role of specific pathogens in the cause of deaths.

0442

THE UTILIZATION OF PARTOGRAM AMONG NURSES AND MIDWIVES, IN THE LABOUR WARD AT EDWARD FRANCIS SMALL TEACHING HOSPITAL

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Partograph is a graphic record of progress of labor, maternal and fetal condition plotted against time for intrapartum monitoring. Its aim is to provide a pictorial overview of labor, to alert obstetric care providers about deviations in maternal, fetal condition and progress of labour, as reported previously. The study aimed to describe the utilization of partogram among nurses and midwives, in the labour ward at Edward Francis Small Teaching Hospital (EFSTH). A descriptive quantitative research design to gather information on utilization of the partogram among nurses and midwives in the labour ward of Edward Francis Small Teaching Hospital was employed using a convenient sampling procedure. All the nurses and midwives in the labour ward were selected who were willing to participate in the study and consent was sought from both EFSTH and the participants. Questionnaires were used to collect data and analysis was done using spss version 21. The results indicate that 80% of all of respondents knew what a partogram

was. The knowledge on the function of the action line and alert line was poor amongst nurses and midwives who participated in the current study. Only 40% (N=4) of the respondents could explain the function of action line on the partogram. There was poor utilization in labour monitoring. Only 40% (N=4) were found to properly use the partogram while 60% (N=6) were found to not properly use the partogram. The findings confirm the problem of shortage of nurses and midwives with only (N=10) covering the labour ward of EFSTH for all shifts. The recommendation includes deployment of nurses and midwives to EFSTH, training of nurses and midwives on the utilization of the partogram.

0443

SHORTENING BURULI ULCER TREATMENT: WHO RECOMMENDED *VS.* A NOVEL BETALACTAM CONTAINING THERAPY - PHASE II AND PHASE III STUDIES IN WEST AFRICA (THE BLMS4BU CLINICAL TRIAL)

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Buruli ulcer (BU) is a skin neglected tropical disease, caused by *Mycobacterium ulcerans (Mul),* that affects mainly children under the age of 15 years. Current WHO-recommended treatment requires 8-weeks of daily rifampicin and clarithromycin, wound care and, sometimes, tissue grafting and surgery. Healing can take up to one year and may pose an unbearable financial burden to the household. Recent repurposing studies demonstrated that beta-lactams combined with rifampicin and clarithromycin are synergistic *in vitro* against *Mul* (PMID: 30689630) leading to the hypothesis that the inclusion of amoxicillin-clavulanate may improve and shorten BU therapy. The aim of the BLMs4BU clinical trial is to evaluate whether co-administration of amoxicillin/clavulanate with rifampicin-clarithromycin can shorten BU treatment from 8 to 4 weeks. A randomized, controlled open label non-inferiority Phase II, multi-centre trial started in Benin in December 2021 (*ClinicalTrials.gov Identifier: NCT05169554*). A Phase III multi-centre trial in Ghana, Togo and Côte d'Ivoire is planned to start in December 2022. Patients are stratified according to BU category lesions and randomized in two regimens: (i) standard [RC8]: rifampicin-clarithromycin (RC) for 8 weeks; and (ii) investigational [RCA4]: standard RC plus amoxicillin-clavulanate for 4 weeks. Patients will be followed-up for 12 months and managed according to standard clinical procedures. Decision for excision surgery will be made at week 14 after treatment initiation. The primary efficacy outcome is cure (i.e., lesion healing without recurrence) without excision surgery 12 months after start of treatment. If successful, this study will create a new paradigm for BU treatment, which could lead to a change in WHO policy and practice for this disease. A shorter, highly effective, all-oral treatment will improve the care of BU patients, adherence to treatment and will lead to a decrease in direct and indirect costs. This trial may also provide information on treatment shortening strategies for other mycobacterial infections, such as tuberculosis or leprosy, where rifampicin is the cornerstone drug.

0444

FIRST-IN-HUMAN EVALUATION OF CUTANEOUS INNATE AND ADAPTIVE IMMUNOMODULATION BY MOSQUITO BITES

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Mosquito-borne viruses are a growing global threat. Initial viral inoculation occurs in the skin via the mosquito 'bite', eliciting immune responses that shape the establishment of infection and pathogenesis. To understand these phenomena, we assessed the cutaneous innate and adaptive immune responses via controlled *Aedes aegypti* feedings in human volunteers living in an *Aedes*-endemic country. Gene expression profiling and immunophenotyping revealed induction of neutrophil degranulation and recruitment of skin-resident dendritic cells and M2-macrophages. As the immune reaction progressed over time, T-cell priming, and regulatory pathways were upregulated along with a shift to a Th2-driven response and CD8+ T cell activation. In accordance, participants' bitten skin cells produced less pro-inflammatory cytokines when stimulated by *Aedes aegypti* salivary gland extract. These results identify key immune genes, cell types, and pathways in the human response to mosquito bites that can be leveraged to develop novel therapeutics and vector-targeted vaccine candidates to arboviral diseases.

0445

DEVELOPMENT AND ADVANCEMENT OF THE DIRECT SKIN FEEDING ASSAY AS AN IMPORTANT TOOL FOR EVALUATING THE EFFICACY OF MALARIA TRANSMISSION BLOCKING VACCINE IN FIELD TRIALS

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Direct skin feeding assays (DSF) have been performed for many decades to evaluate transmissibility of different Plasmodium species from humans to a range of mosquito vectors. More recently, DSF assays have begun to be utilized as an endpoint assay to evaluate the efficacy of transmission blocking vaccines (TBV) in field trials. Our teams have led the way in optimizing and expanding a DSF platform now suitable to generate endpoints for TBV efficacy trials. Over a ten-year period in Mali, we have expanded from DSF performed on several volunteers (~100-200 female mosquitoes) weekly in 2013 to our current capacity of up to 400 DSF (~24,000 female mosquitoes) per week. Community acceptance of the assay and an excellent safety profile have been established in both adults and children (5-18 years). From a capacity standpoint, success requires attention to numerous aspects of mosquito production, maintenance, and dissection as well as the logistics of setting up this assay at a field site distant from the contained insectary where mosquitoes are produced. Optimization of DSF has examined several parameters for conduct of the feed (anatomical location of feed, number of mosquitoes per feed, time of day) as well as the target population (age, parasite/gametocyte status) to ensure maximal numbers of positive DSF that provide suitable power to measure vaccine efficacy. Finally, we will review how this assay compares

to other established feeding assays such as direct membrane feeding and the standard membrane feeding assay and thus how DSF can be a significant tool for evaluating TBV efficacy in the field.

0446

REGIONAL VARIATION OF CAESAREAN SECTIONS IN THE DOMINICAN REPUBLIC

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The Dominican Republic has one of the highest Caesarean section (CS) rates worldwide, with substantial regional variation. Understanding this regional variability may further advance understanding of factors contributing to the high CS rate and inform initiatives aimed at reducing excessive CS. This study aimed to determine whether the regional variation of CS in the Dominican Republic can be explained by variation in key socioeconomic, demographic, and healthcare variables across regions. Nationally representative household survey data from the Multiple Indicator Cluster Survey from 2019 was used. The sample was composed of 3,224 women who had singleton births in the two-year period prior to the survey. Across the ten regions of the Dominican Republic, the CS prevalence rate varied from a low of 45.0% in El Valle to 76.9% in Cibao Nordeste. Despite adjusting for covariates, women in Cibao Nordeste had higher odds, and those in Valdesia and El Valle had lower odds, of having a CS compared to the reference region of Ozama, which houses the nation's capital. Of the covariates, delivering in a private compared to public healthcare facility had the highest odds for having a CS in the final logistic regression model at 7.32 (95% confidence interval: 5.09-10.53). This variable explained at least some of the association between certain regions and the CS rate. A total of 90.8% of deliveries in private healthcare facilities were CS compared to 47.1% in public healthcare facilities. Additional investigations are required to further examine the persistence of at least some associations between regions and CS despite adjustment for multiple possible confounders. However, there is also a need for focused investigation into factors contributing to the exceptionally high rate of CS in private healthcare facilities in the Dominican Republic.

0447

SLOW BUT STEADY: WORKING TO INCREASE CHAGAS DISEASE TESTING THROUGH AN EDUCATIONAL INTERVENTION AT A SAFETY NET HOSPITAL

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Chagas disease remains a poorly recognized cause of cardiac disease among migrants from endemic regions to the United States due to low clinician awareness and a lack of systematic screening programs. To address low screening rates and diagnosis, we implemented a multi-disciplinary educational program about Chagas disease within our institution, a safety net hospital that serves a large migrant population. The intervention consists of a case-based presentation accompanied by a pre- and post-lecture quiz at grand rounds, noon conferences, and other venues; over twenty presentations have been given to date. *Trypanosoma cruzi* serological test orders throughout the institution were analyzed during the 29 months pre-intervention (11/2016 - 4/2019) and 29 months following the start of the lecture program (4/2019 - 9/2021). There were 548 patients tested, including 170 (31.0%) in the pre-intervention phase and 378 (69.0%) in the post-intervention phase. General Internal Medicine providers ordered the most tests (overall, 162/548, 29.6%). Obstetrics/Gynecology had the greatest increase in test ordering from pre- to post-intervention phase (6 patients tested in the pre-intervention phase vs. 118 in the post-intervention phase); this coincided with a concurrent initiative to add *T. cruzi* testing to a routine prenatal test panel in the electronic medical record. Attending providers tested the most patients overall (247, 45.1%), followed by resident/fellow trainees (187, 34.1%); trainee test ordering more than doubled from the pre- to post-intervention phase (from 56 to 131). Of 49 patients who had at least one positive commercial screening test, 38 had confirmatory testing performed at the CDC; of those, 24 (63.2%) had positive confirmatory testing. We found an increase in *T. cruzi* test ordering over time, coinciding with the educational intervention to raise awareness of this disease. Our analysis highlights opportunities for increasing Chagas disease screening, particularly through outreach to trainees and obstetrics providers, as well as incorporation of information technology tools such as order panels.

0448

KNOWLEDGE AND PERCEPTIONS OF ANTIBIOTICS AMONG VILLAGE HEALTH WORKERS IN SOUTHWESTERN UGANDA

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In rural Uganda, ill children under the age of five years often present first to village health workers (VHW) for healthcare. VHW are lay volunteers trained in the evaluation and management of uncomplicated diarrhea, malaria, and pneumonia; the latter of which includes the prescription of antibiotics. Yet little is known about their knowledge and perceptions of antibiotics. Therefore, we conducted a knowledge, attitudes, and practices survey based on previously published tools of 67 VHW from 15 villages participating in a prospective study of pediatric acute respiratory illness. All VHW completed the survey prior to study protocol training to ensure it did not influence responses. The median age of participants was 40 (IQR: 35-47) and 60% (40 of 67) were female. The majority were subsistence farmers (84%, 56 of 67) and had completed secondary school (84%, 56 of 67). They had a median of 9.5 (IQR: 4-14) years of experience as a VHW and saw a median of 10 children per month (IQR: 7-15). Knowledge of antibiotics was high with 96% (64 of 67) of VHW aware that amoxicillin is an antibiotic and 84% (56 of 67) correctly identifying that it treats bacteria. Nearly all VHW (91%, 61 of 67) knew that antibiotics should be stopped only once the full course is completed, and all but one thought it was not acceptable to obtain antibiotics without seeing a VHW or clinician. Perceptions of antibiotic use were more variable. While all but two VHW felt "very confident" or "confident" in their ability to accurately prescribe antibiotics, 77% (50 of 65) responded that they "strongly agreed" or "agreed" that antibiotics are over-prescribed by VHW in Uganda. Most VHW (82%, 55 of 65) agreed that prescribing antibiotics if not needed can cause harm, but nearly half (48%, 31 of 65) also thought that when in doubt, it is better to prescribe them just in case. All but one VHW welcomed more training or reference materials about antibiotics. In sum, understanding VHW knowledge and perceptions of antibiotics is integral to the design of interventions to improve antibiotic stewardship in rural Uganda. As trusted community members, VHW could be important advocates for this cause.

0449

CONTINUOUS NON-INVASIVE HAEMODYNAMIC MONITORING FOR VIETNAMESE CHILDREN WITH DENGUE SHOCK SYNDROME

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Dengue shock syndrome (DSS) is a severe and potentially life-threatening complication of dengue, caused by vascular leakage and particularly affects children. Meticulous fluid balance and giving just the right amount of fluid replacement is the cornerstone of treatment. Accurate and dynamic assessment of intravascular volume during fluid resuscitation is challenging, particularly in resource poor settings and using non-invasive technology. We investigated the utility of a new continuous non-invasive haemodynamic monitoring technique using bioimpedance (NICaS - Non-invasive Cardiac System) in patients admitted with DSS. We conducted a prospective observational study in a Paediatric Intensive Care Unit (PICU) in Vietnam between 2018-2020. Patients were monitored continuously using NICaS from admission with shock until PICU discharge. In addition to continuous haemodynamic monitoring, we performed serial point-of-care echocardiograms at shock onset and multiple time points during the 48hrs of fluid resuscitation. Haemodynamic data derived from NICaS was recorded every 20 seconds then integrated with clinical data and echo data. We used 5-minute-moving average SVI for graphical descriptions and association analyses. 92 patients were enrolled into the study. The median age is 12 years (IQR 10, 13). The second episode of shock (recurrent shock) occurred in 16/92 patients. No patients required respiratory support. Stroke volume index (SVI) was seen to have a negative correlation with heart rate (r = -0.57 [95% CI -0.67, -0.45], p <0.001) but not with systolic blood pressure (r= -0.07 [95% CI -0.25, 0.11], p = 0.45) or diastolic blood pressure (r = -0.07 [95%CI -0.23, 0.09], p = 0.40). SVI decreased considerably after 6 hours from shock onset and remained low before recurrent shock. NICaS derived SVI, had a positive correlation with echo-SVI up to 18 hours from shock onset. In conclusion, continuous haemodynamic monitoring during fluid resuscitation using NICaS is a useful non-invasive tool to monitor patients with DSS and can guide fluid management as well as identify patients at risk of recurrent shock.

0450

HOW EXTERNAL QUALITY ASSESSMENTS (EQAS) HELP IDENTIFY ISSUES IN CLINICAL DIAGNOSIS OF PARASITES

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The need for robust, reproducible and reliable diagnostic Parasitology remains pertinent for public health in both endemic and non-endemic settings. UKNEQAS Parasitology has been successfully running External Quality Assessment (EQA) schemes for microscopy-based detection of faecal parasites since 1986. The schemes are designed to improve the diagnosis of parasitic infections in participating laboratories by identifying gaps and encouraging learnings. Here, we present a review of performance of participating labs in our morphology based EQA scheme for faecal parasites over the last seven years to identify trends, if any. 537 labs participate in the scheme which is comprised of eight distributions in each calendar year. The participants received appropriate clinical details for each sample. The specimen type included faecal sample for concentration and direct microscopy, stained faecal smear, urine and hydatid fluid. In total 113 samples were analysed for this presentation. Common problems encountered by participants were as follows: missed identification of one or more parasites within a mixed infection sample, poor recovery of parasites due to incorrect techniques in the processing of samples, confusing vegetable matter with cysts and ova, failure to identify or specify the stage of the parasites, failure to identify and differentiate ova and small cysts. Faecal parasites remain important public health burdens globally. This is in part because microscopy remains the gold standard for clinical diagnosis, yet microscopy requires skills attainable only through years of experience, proper training plus refresher courses. Through this study, UK NEQAS Parasitology has identified, and flagged issues commonly encountered in microscopy-based diagnosis of parasites.

0451

THE CHOICE OF REFERENCE CHART AFFECTS THE STRENGTH OF THE ASSOCIATION BETWEEN MALARIA IN PREGNANCY AND SMALL FOR GESTATIONAL AGE. AN INDIVIDUAL PARTICIPANT DATA META ANALYSIS COMPARING THE INTERGROWTH 21 WITH A TANZANIAN BIRTHWEIGHT CHART

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The prevalence of small for gestational age (SGA) may vary depending on the chosen weight-for-gestational-age reference. We conducted an individual participant data meta-analysis assessing the implications of using a local reference (STOPPAM) instead of a universal reference (Intergrowth-21) on the association between malaria in pregnancy (MIP) and SGA. We pooled data from 6,236 newborns from seven conveniently identified studies conducted in Tanzania and Malawi from 2003-2018 with data on MIP, birthweight, and ultrasound estimated gestational age. We used mixed-effects regression models to compare the association between MIP and SGA. The odds ratios were adjusted for gestational age at enrolment and delivery, gravidity, maternal age, hemoglobin level, and body mass index at enrolment, utilization of insecticide treated bednet, the number of antenatal visits, and syphilis or HIV-positivity. The 10th percentile for birthweights-for gestational age was lower for STOPPAM than for Intergrowth-21, leading to a prevalence of $SGA_{STOPPAM}$ of 14.2% and SGA_{IG21} of 18.0%, p<0.001. The association between MIP and SGA was stronger for STOPPAM (adjusted odds ratio (AOR) 1.30 [1.09-1.56], p<0.01) than for Intergrowth-21 (AOR 1.19 [1.00-1.40], p=0.04), particularly among paucigravidae ($SGA_{STOPPAM}$ AOR 1.36 (1.09-1.71), p<0.01 vs SGA_{IG21} AOR 1.21(0.97-1.50), p=0.08). The prevalence of SGA may be overestimated, and the impact of MIP on SGA underestimated when using Intergrowth-21. Comparing local reference charts to global references when assessing and interpreting the impact of MIP may be appropriate.

0452

MOBILIZING HEALTH CARE FOR NEWLY ARRIVED HUMANITARIAN PAROLEES IN MINNESOTA: A MULTIDISCIPLINARY, MULTI-AGENCY COLLABORATION

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In September 2021, the withdrawal of American troops from Afghanistan resulted in Afghan evacuees arriving at eleven military bases around the country. These humanitarian parolees were then urgently resettled to their final state of residence. The purpose of this effort in Minnesota was to welcome the new arrivals, address immediate, emergent medical needs, increase access to primary care, avoid urgent care and emergency room visits while they are in temporary housing pending integration into the community. Through a multi-agency partnership, a team of volunteer medical, behavioral health specialists, health advocates experienced in providing trauma informed care and state health departments prepared to address the acute mental and physical health concerns within 24-48 hours of their arrival to the state. Minnesota received 1260 Afghan newcomers and 1,233 were screened. The mobilized team provided over 1300 hours of in person, Telehealth and on-call care to the new arrivals in the temporary housing. A standardized health intake form was developed to identify acute health concerns on arrival to the temporary housing site, and 53% of arrival screenings resulted in at least one specialty referral. The team followed a post-intake referral plan with options to establish primary care at a local Federally Qualified Health Center or to refer to specialty, vision, dental, mental health or other health services. An onsite mental health team, conducted patient intakes at the temporary housing site and arranged continued outpatient follow up. Care plans were developed for patients with complex mental health and medical needs to provide expedited outpatient follow-up.

0453

AFGHAN EVACUEE WOMEN'S CLINIC - A MODEL FOR CULTURALLY INCLUSIVE CARE

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Operation Allies Welcome has supported more than 76,000 Afghan nationals in resettlement to the United States. In Minnesota, the Department of Health and the University of Minnesota Mobile Health Initiative coordinated a robust interdisciplinary response to support the medical needs of 1260 newcomers as a bridge to the formal healthcare system. A one room clinic was created at the temporary housing site to conduct initial medical screenings. For time and space efficiency, an entire family was screened simultaneously. This model, though efficient for large scale screening, was suboptimal to elicit private health concerns from individuals. Previous studies have revealed, especially amongst women from Afghanistan, there is a high burden of exposure to war-related events and trauma, including gender-based violence. Thus, a model of a Women's Clinic staffed by female medical providers and interpreters gained traction with a goal of "women serving women '' in a psychologically safe and private environment. It provided the foundation for focused programming to address health concerns such as somatic manifestations of acute stress and trauma. In this one-on-one environment, women were more likely to report physical concerns like genitourinary symptoms, reveal mental health challenges, and discuss reproductive and family planning preferences. A total of fourteen weekly 3-hour clinics were held as part of the Women's Clinic initiative. Of the 206 total women over the age of 18 who were eligible for participation, 103 (50%) attended the clinic, which offered a visit with a medical provider and the opportunity for domestic violence screening. Local resources were gathered for referrals including Domestic Abuse Project and Asian Women United, acknowledging the tenuous immigration status of this group and potential harm of pursuing typical referral routes such as police departments. Several opportunities for improvement occurred through feedback from staff and patients. Future directions include qualitative analysis of the experience for providers and patients with consideration of incorporating the model into formal healthcare systems.

0454

CAUSES OF FEBRILE DISEASE IN HOSPITALIZED PATIENTS IN A TROPICAL COUNTRY : A RETROSPECTIVE TERTIARY CARE HOSPITAL COHORT STUDY

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Infectious diseases are the main causes of morbidity and mortality in tropical areas like Madagascar. Fever is the most frequent symptom of infectious diseases, often prompting patients to consult. The causes are often serious: the delay in diagnosis and treatment increases the morbidity/mortality of patients. It is therefore essential to know the main diagnoses of febrile illnesses and the main causes of death in order to improve their management to reduce mortality linked to these tropical diseases. The objectives of our study were to determine the causes of febrile illnesses and to determine the outcome of patients hospitalized in a tropical country. This is a descriptive retrospective study, during 12 months from January to December 2018. It was included all patients hospitalized for fever of infectious origin in an Infectious Diseases department of a teritiary care hospital in Madagascar. Four hundred and seventy-two patients were included. The main reasons for consultation were: rash (23.7%), infectious syndrome (20.3%), cough/dyspnoea (16.3%) and altered consciousness (15.9%). The causes of hospitalisation were : Measles (26.7%), tuberculosis (21.4%), malaria (15.5%), HIV infection (13.4%), bacterial pneumonia (7.2%), central nervous system infection (5.1%), typhoid fever or febrile diarrhoea (4.4%), urinary tract infection (2.3%). The association of tuberculosis and HIV infection was found in 47.6% (n=224) of subjects. The most frequent location of tuberculosis was the lung (38.1%), followed by the meninges (35.9%), pleura (19.8%), miliary (10.7%) and lymph nodes (7.6%). The overall mortality rate was 15%. Tuberculosis was the main cause of death (46.5%), followed by HIV infection (18.3%), bacterial pneumonia (11.3%), malaria (11.3%) and bacterial meningitis (9.9%). In conclusion, measles, tuberculosis, malaria and HIV infection were the main causes of hospitalization. Tuberculosis and HIV infection were the main causes of death. Screening and research for strategies to improve the management and to reduce the mortality associated with these main diseases should be a priority in a tropical country like Madagascar.

0455

COMPARISON OF COMMERCIALLY-AVAILABLE, RAPID, POINT-OF-CARE C-REACTIVE PROTEIN ASSAYS AMONG CHILDREN WITH FEBRILE ILLNESS IN SOUTHWESTERN UGANDA

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In Uganda, children with febrile acute respiratory illness (ARI) are often treated with antibiotics even though bacterial pneumonia is relatively uncommon. C-reactive protein (CRP) can help identify those who are more likely to have a bacterial infection and therefore need antibiotic treatment. Implementation of a CRP rapid diagnostic test (RDT) at the point-of-care in resource-constrained settings with minimal laboratory infrastructure could reduce unnecessary antibiotic use. We evaluated the performance of two CRP RDTs (Actim, BTNX) against a laboratory-based CRP assay requiring an analyzer (Afinion). Actim and BTNX tests are semi-quantitative (<10, 10-40, 40-80, >80 mg/L), whereas the Afinion test is quantitative (range = 5-200 mg/L); Afinion test results were categorized to align with the semi-quantitative tests. From October to December 2020, we enrolled 150 children who presented with febrile ARI to the outpatient department of Bugoye Health Centre III in Kasese District, Uganda. The median age of study participants was 24 months (IQR: 13 to 36), and 43% were female. The most frequent symptoms were fever (96%), cough (69%), runny nose (33%), and diarrhea (25%). 29% (43/150) of participants were positive for malaria by an antigen-based RDT. All individuals underwent CRP testing; results for all three CRP tests were available for 89% (134/150) of participants. The Actim test had slightly better agreement (weighted Kappa = 0.70 (95% CI 0.62 to 0.78) than the BTNX test (weighted Kappa = 0.62 (95% CI 0.54 to 0.70)) with the Afinion test. Using McNemar's test and CRP of 40 mg/L as the cut-off for a positive test, the likelihood of obtaining a positive or negative result did not differ between the Afinion and Actim tests ($p = 0.80$), whereas it did differ with the Afinion and BTNX tests ($p < 0.0001$). Our results demonstrate the potential of CRP RDTs with the Actim CRP performing slightly better as compared to a laboratory-based test than the BTNX RDT. A stepped-wedge cluster-randomized trial is underway to evaluate the use of the Actim CRP RDT within a clinical algorithm for guiding antibiotic treatment decisions among children with febrile ARI.

0456

DEVELOPMENT OF A CLINICAL PREDICTION RULE IDENTIFYING PROTOZOAL ETIOLOGY OF DIARRHEAL ILLNESS

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Protozoal gastrointestinal pathogens including *Cryptosporidium* species, *Cyclospora cayetanensis*, and *Giardia* species are causes of both acute and persistent diarrheal illness. Protozoal infections may be associated with international travel, but can be found in non-travelers including immunocompromised patients who are at particular risk for morbidity and mortality. Diagnosis of protozoal diarrhea allows for targeted antimicrobial therapy; however, testing of all cases of diarrheal illness for protozoal infection is not financially feasible, and availability may be limited in some settings. To date, there are limited studies investigating clinical predictors of protozoal diarrhea. Given the significant difference in treatment between parasitic and other diarrheal infections, we aim to create a predictive model differentiating protozoal from non-protozoal etiologies of diarrheal illness using machine-learning algorithms. Using the electronic data warehouse of a multihospital healthcare system, we identified 14,238 adult patients who received multiplex molecular GI pathogen panel testing. Of these, we compared the clinical, laboratory, and demographic data from 267 patients who tested positive for protozoal pathogens, against 13,971 patients without protozoa detected. In the setting of unbalanced data, we used weighted random forest regression to identify variables representing the strongest predictors of protozoal disease. Currently, our top predictors of protozoal disease include county of residence in a county with a population less than 250,000 and evaluation in an outpatient rather than inpatient setting. However, we are awaiting additional data on social vulnerability, immunocompromising conditions, vital signs, and laboratory testing. Next steps in analysis include consideration of all data sources, and cross-validation using logistic regression and random forest algorithms to identify the model with the highest discriminatory performance using the fewest variables. Additional results on specific clinical predictors of protozoal diarrhea will be available by the time of presentation.

0457

AN ALTERNATIVE NANOPORE SEQUENCING-BASED DIAGNOSTIC APPROACH FOR ARBOVIRUS SCREENING

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Diseases caused by arboviruses such as dengue (DENV), chikungunya (CHIKV) and zika (ZIKV) present a very similar acute febrile clinical picture that has made clinical diagnosis difficult and favoured underreporting events resulting from false-negative results, including co-infection cases. As serological methods have presented limitations due to cross-reactions between correlated viruses, there is a need for new sensitive, specific, rapid methods capable of discriminating antigenically related viruses in areas where co-circulation of multiple arboviruses occurs. Thus, in this work, we optimized a method of Multiplex PCR Targeted Amplicon sequencing (MTA-seq) for arbovirus genotyping from viral RNA. For that, we combined the high sensitivity and specificity of multiplex PCR with the practicality and rapidity of data generation from nanopore sequencing by MinION. We used primer pairs from published genome sequencing schemes to amplify specific fragments of 400 to 900 base pairs. We selected primer pairs for CHIKV, DENV (serotypes 1 to 4), ZIKV, yellow fever virus (YFV), and West Nile virus (WNV) that were combined into a pool and used for the one-step amplification reaction performed on 27 clinical serum samples from previous outbreaks of DENV, CHIKV and ZIKV in Brazil. Sequencing data were analysed using the open and easy-to-use Genome Detective web software, whose initial results after 2 hours of sequencing showed that MTA-seq was able to detect the target virus present in 88.8% (24/27) of the samples (median of 40,254 mapped reads), of which 79% showed a classification for the genotype which indicated 66.6% (6/9) of the DENV-1 positive samples belonged to the genotype V, 100% (n=8) of the DENV-2 samples belonged to the genotype III, and 44.4% (4/9) of the CHIKV samples belonged to the ECSA lineage. MTA-seq was able to retrieve and genotype 4,728 reads of the Asian lineage of Zika virus from a 2016 old sample. These results suggest a high sensitivity and specificity of the MTA-seq and indicate this method might assist not only in the diagnosis but also in the elucidation of the molecular epidemiology of arboviruses in endemic regions.

0458

FOOD INSECURITY AS A BARRIER TO ANTI-RETROVIRAL THERAPY IN POPOKABAKA HEALTH ZONE, A CASE STUDY

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Food insecurity is a considerable challenge in sub-Saharan Africa, disproportionately affecting persons living with HIV/AIDS. HIV epidemic largely overlaps with populations already experiencing low diet quality & quantity. Considering the generally high prevalence of food insecurity in rural areas of the DRC (~54%), it was interesting to know the real situation of PLHIV adherence in Popokabaka. Indeed, it is not clear how PLHIVs manage to cope with issues that relate to food insecurity, how they meet their treatment. This study aimed to understand how food insecurity constitutes a barrier to Antiretroviral therapy (ART) in Popokabaka. This qualitative study collected data via in-depth interviews with 15 HIV-positive who had been on ART for at least six months. By using a thematic analysis approach deductive, five themes were identified: Knowledge of HIV, Perception of family & friend's support, Perception of health care service, belief of ART's effectiveness, Nonadherence pathway. Food insecurity was a common & important barrier to ART adherence among patients in Popokabaka. Two pathways were identified to explain how food insecurity & ART non-adherence may be linked, including the anger that came from lack of food which pushes to postpone medication-taking & the belief that ART is not effective when there is no food. Notwithstanding the overwhelming number of inhibiting factors, most patients in this study were highly motivated to achieve adherence. Freedom from hunger is a basic human right & warrants immediate attention in its own right. The link between food insecurity & poor ART outcomes further heightens the importance of addressing food insecurity in the context of sociocultural related factors, as part of comprehensive patient adherence to ART & ultimately long term success of HIV treatment among HIV-infected individuals in the region.

0459

EVALUATION OF SEXUAL DYSFUNCTION AND IDENTIFICATION OF RISK FACTORS OF WOMEN INFECTED BY HUMAN IMMUNODEFICIENCY VIRUS DURING THE COVID19 PANDEMIC IN 2020 IN CONAKRY

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Female sexual dysfunction is a highly prevalent sexual health problem but under-investigated in Guinea. This study determined the prevalence and risk factors associated with sexual dysfunction among women infected with human immunodeficiency virus (HIV) in Conakry. Guinea notified its first case of Covid19 on March 12, 2020 and on 02/28/2022, thirty-six thousand three hundred and ninety-seven (36397) confirmed cases, thirty-two thousand nine hundred and thirty- nine cured (32,939) and four hundred and forty (440) hospital deaths. The Female Sexual Function Index (FSFI) was used in a cross-sectional study design involving 401 women aged 18 years or more in large HIV cohort sites in Conakry, Guinea. A score of less than 26.55 indicated sexual dysfunction. Clinical and sociodemographic characteristics were collected. Multivariate logistic regression analysis was performed to identify factors associated with sexual dysfunction. The prevalence of sexual dysfunction was 22.2% (95% CI: 18.2–25.9). The types of sexual dysfunctional detected included desire disorder (32.2%), sexual arousal (25.4%), lubrication (23.9%), orgasm (30.7%), sexual satisfaction (32.7%) and pain (28.2%). Multivariate analysis showed that unmarried (adjusted OR 4.6, 95% CI 1.6 to 14.0), age above 35 years old (adjusted OR 7.2, 95% CI 2.1 to 24.0), voluntary HIV screening (OR 4.69: 95% CI: 1.07, 21.93), and current use of antiretroviral drugs (OR 2.68: 95% CI: 1.28, 5.61) were factors associated with sexual dysfunction. Sexual dysfunction is prevalent in women infected with HIV in Conakry, Guinea. Sociodemographic and clinical factors were associated with the risk of sexual dysfunction. Health care workers should be trained on the screening and management of sexual dysfunction in HIV care services.

0460

IMPLEMENTING WHO PACKAGE OF CARE FOR PERSONS WITH ADVANCED HIV DISEASE IN ETHIOPIA

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AIDS is still common in sub-Saharan Africa, despite improving access to ART. Cryptococcosis and tuberculosis are the most common causes of death in HIV patients with CD4 count <200 cells/μL. From our 2015 data published in Clinical Infectious Disease Journal, we face 68% mortality from cryptococcal meningitis in Adama. Despite recommendations for rapidly initiating HIV treatment, many persons in sub-Saharan Africa present to care with advanced HIV disease. In 2017, the World Health Organization (WHO) recommended a package of care for persons with advanced HIV disease. The package consists of cotrimoxazole prophylaxis to prevent PCP pneumonia, Tuberculosis (TB) screening, and prophylaxis, Cryptococcal (CrAg) screening and treatment, rapid initiation of antiretroviral therapy (ART) (for naïve persons) and enhanced patient adherence counseling. These packages of care are based on expert recommendations and need to be validated in real-world health care settings. It is yet to be proven if the package of care will improve survival. We enrolled 275 participants with CD4 count below 200 cells/mcL from January 2020-July 2021. The participant had a point of care OI screening and Same day ART initiation as part of the 2017 Recommended WHO package of care which includes, Screening for tuberculosis (TB) and cryptococcal infection, Treatment and prophylaxis for major opportunistic infections, Rapid initiation of ART, and Intensified treatment adherence support and 6 months follow up.

0461

SARS-COV-2 SPECIFIC NEUTRALIZING ANTIBODIES IN VACCINATED AND UNVACCINATED HIV-POSITIVE INDIVIDUALS IN THE DOMINICAN REPUBLIC

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Occurrence of COVID infection in high burden HIV countries has been observed and associated to chronic infections and variants emergence. In the Dominican Republic it is estimated 1% of the population living with HIV. The aim of this study was to evaluate specific SARS-CoV-2 neutralizing antibodies in PLWHIV in a HIV Clinic, and to determine the clinical characteristics of reported COVID-19. Blood samples were collected after informed consent was signed for SARS-CoV-2 neutralizing antibodies detection. Data was collected from March 2020-October 2021. All participants completed a questionnaire. Samples were analyzed using IchromaTM II using a cut-off index (COI) for fluorescent interpretation. A total of 213 participants fulfil the study inclusion criteria. Mean age was 31 years old (SD 14). SARS-CoV-2 neutralizing antibodies were detected in 75% of participants. None experienced severe COVID-19. Vaccination status with at least one dose was reported in 71% of participants. The

most common symptoms reported were anosmia 69% (n=65), dysgeusia 65% (n=61) and cough 60% (n=56). The most frequent comorbidity was arterial hypertension 61% (n=43), and diabetes mellitus 10% (n=7). A weak negative correlation were found between antibody detection and immune status (CD4 counts/HIV viral loads), rho=-0.218, $p < 0.05$. Knowing the most frequent clinical manifestations of people with SARS-CoV-2 and living with HIV helps us to offer a timely diagnosis and avoid future complications. Detection of specific neutralizing antibodies in immunosuppressed and/or not virally suppressed will facilitate immunological comprehension of vaccine campaigns (including boosters) and other preventive interventions.

0462

HIV PRE-EXPOSURE PROPHYLAXIS (PREP) MODELS OF DELIVERY IN LOW TO MIDDLE INCOME COUNTRIES: A PROPOSED MODEL FOR AN INTEGRATED CARE MODEL

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As the global pandemic of HIV continues, many low- and middle income countries also have an increasing burden of non communicable diseases (NCDs). When used consistently pre exposure prophylaxis (PrEP) can reduce the risk of HIV acquisition by over 90%. In 2015 the World Health Organization (WHO) expanded their previous recommendation from offering PrEP to MSM to all populations at significant risk of acquiring HIV. The aim of this study was to identify which models for PrEP service delivery have been successful in low-to-middle income countries, their key components, and how better to include NCD screening and treatment cross sectionally with HIV screening, testing, and treatment programs. A revision of current scientific literature and specialized reports was conducted from November through December of 2021 on PubMed and examined articles published between 2019-2021. 326 articles were reviewed from 7 primary searches. Additional articles were found from references cited by reviewed articles and smaller searches related to individual article findings. 97 articles were read in full, 68 of which were selected for informing this review because they directly addressed the research questions. Our findings reveal that PrEP service provision should be guided through:a) Community engagementb) On-site PrEP servicesc) Partner referralsd) Integrated services along with PrEP. PrEP has been delivered through various models depending on target populations, country policies, and established health infrastructure. Predictive models and implementing project have indicated that PrEP delivery is feasible and cost-effective when delivered in different ways. There are numerous barriers to PrEP uptake that should be considered when implementing PrEP delivery, many of which involve deep-seeded cultural beliefs or reflect community relationships rather than simply presenting logistical challenges and awareness gaps. In addition to PrEP integration, research has shown that using HIV healthcare infrastructure is feasible for delivery of NCD screening and care.

0463

PERINATAL HIV EXPOSURE IN SIX-TO TEN-YEAR OLD UGANDAN CHILDREN AND ITS ASSOCIATION WITH CAREGIVER DEPRESSION SYMPTOMS

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Survival is possible for children perinatally exposed to or infected by HIV in the post-combined antiretroviral therapy era, and the identification of factors affecting children's ability to thrive has great public health significance. Caregiver mental health is important given its impact on child development. Previous studies on the topic have not included a full complement of HIV exposure or infection groups or considered how caregiver's mental health may depend on child serostatus, and rarely taken place in HIV endemic areas. To address these issues, we compared depressive symptoms among caregivers of 3 groups of 6-10 year old children in Uganda with known HIV exposure status: children HIV-infected perinatally (CPHIV, n=102), children born to HIV-infected mothers, but HIV negative (CPHEU, n=101), and HIV-unexposed, uninfected community controls (CHUU, n=103). Self-reported caregiver depression symptoms were assessed using the Hopkins Symptom Checklist. We used general linear models to estimate mean differences among the three HIV exposure groups. Adjusted models included caregiver age, education, social support, lifetime trauma, and wealth as covariates. We also evaluated effect modification of the child HIV exposure status by caregiver social support. Depression symptoms were higher among CPHEU compared to CPHIV caregivers (model coefficient *[B]*=-3.5, 95% confidence interval [CI] -5.3, -1.8). This finding remained significant in the adjusted model (*B*=-2.2, 95% CI -4.1, -0.4). No other group differences were observed, and findings were unchanged after limiting the analysis to biological caregivers. At lower levels of caregiver support, CPHEU reported higher levels of depression symptoms than CPHIV (*B*=-0.2, 95% CI -0.3, -0.1), but at high levels of social support, depression symptoms did not differ according to perinatal HIV status. Our findings point to an unmet mental health need among HIV-positive caregivers who care for CPHEU. Elucidating the factors that underlie this finding may inform future intervention targets to improve caregiver well-being.

0464

VASCULAR FACIAL SKIN LESIONS IN A FEBRILE IMMUNOCOMPROMISED PATIENT IN RURAL KWAZULU-NATAL, SOUTH AFRICA

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A 47-year-old female with HIV/AIDS (CD4 5, VL 33,524) presented with facial skin lesions to Church of Scotland Hospital, in rural Tugela Ferry, KwaZulu-Natal Province, South Africa. Exam revealed three dark purple, raised, non-tender facial skin lesions (right eyebrow [2.5 x 1 cm], right cheek [1 x 1 cm], nasal tip [2.5 x 2.5 cm]). We performed a skin biopsy of the cheek lesion, with histopathology revealing nodular tumor comprising fascicles of spindled cells (showing nuclear pleomorphism with mitoses, lymphocytes, plasma cells, hyaline globules) with positive human herpesvirus-8 (HHV-8) immunostain, confirming Kaposi's Sarcoma (KS). Classic KS-associated histopathology shows spindle cells, neovascular proliferation, inflammation. Given the local cutaneous nature of the KS, the treatment was to optimize her antiretroviral regimen to restore immunocompetency. A histopathological confirmatory diagnosis of KS can guide management, particularly in the clinical scenario of disseminated or systemic involvement. While hospitalized, she had recurrent fevers, attributed to poorly controlled HIV/AIDS with KS and/or other opportunistic co-infection(s). KS—a vascular tumor caused by HHV-8—is an AIDS-defining illness which can be sub-categorized into cutaneous and visceral disease. We highlight this clinical case, as it is important to recognize Kaposi's Sarcoma as a potential diagnosis consistent with the clinical syndrome of vascular-appearing cutaneous lesions in a febrile, immunocompromised host. This syndrome may be underrecognized due to a broad differential diagnosis, including bacillary angiomatosis, hemangiomas, angiomas, purpura. Though a presumptive KS diagnosis can be made clinically, it may be challenging to reach a definitive KS diagnosis in a rural clinical setting due to limited resources to provide confirmation.

0465

LEVERAGING ECONOMICS TO OPTIMIZE RETENTION IN CARE FOR HIV: A SYSTEMATIC REVIEW

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According to the UNAIDS Fast-Track Targets, by 2030 95% of people living with HIV should know their status; among them, 95% should receive antiretroviral treatment (ARV), and, among the latter, 95% should achieve viral suppression. Retention in care for HIV (RICH) is a cornerstone of the Fast-Track Targets, which leads with certainty to viral suppression. However, globally, coverage of ARV and retention in HIV care are below our desired targets. We must improve these indicators by implementing innovative strategies. Traditional and behavioral economic prinicples have been successfully used to improve a myriad health outcomes. Here, we present the results of a systematic literature review conducted to synthesize the state-of-the-art knowledge regarding the use of financial incentives and traditional economic strategies to improve RICH. We searched Pubmed, CINHAL, Psychinfo and Embase using the following search terms: HIV-related terms, monetary incentive terms, and retention in care terms. We included qualitative, quantitative or mixed-methods studies that reported outcomes related to retention in care of interventions involving financial incentives for people living with HIV. Initial search resulted in 269 peer reviewed papers. Two people from the research team undertook independent title and abstract reviews, and full text reviews. Studies found used several different strategies including financial incentives, food incentives, cash transfer programs, etc. Overall, studies show that strategies that leverage traditional economic principles (i.e., financial incentives or similar) are successful in either engaging, re-engaging, or retaining people in HIV care. Our preliminary results suggest that traditional economic principles can be successfully leveraged in the fight against HIV towards achieving the 95-95-95 Fast-Track Targets. Further research should evaluate and synthesize the evidence regarding the use of behavioral economics to optimize RICH as well as other HIV-related outcomes.

0466

DISSEMINATED CRYPTOCOCCOSIS IN HIV/AIDS - A SUCCESS OF ALTERNATIVE REGIMEN OF AMPHOTERICIN-B

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Disseminated cryptococcosis can be the first manifestation of acquired immunodeficiency syndrome (AIDS). Management of such patients is difficult in resource poor settings. A 39-years-old man with a history of significant high-risk behavior in the form of multiple sexual partners presented to a tertiary care center with non-productive cough for one week and altered mental status for three days, associated with severe malaise, fatigue, and significant weight loss. On initial examination, the patient was cachexic, disoriented, and pale with the presence of a small umbilicated centrally necrosed papule over the upper lip on the left side. Initial workup revealed the presence of HIV positive status, and CSF India ink was positive for Cryptococcus. Chest imaging shows the presence of a lobar consolidation in the right upper lobe with internal breakdown necrosis and cavitation suggestive of fungal etiology and punch biopsy of skin lesion had features suggestive of cryptococcosis. After the initial workup, induction therapy was started in lines of disseminated cryptococcosis with liposomal Amphotericin-B (3 mg/kg/day) and fluconazole (800mg/day, flucytosine is not available). The induction therapy was modified and extended because of the persistence of CNS cryptococcosis after two weeks (liposomal amphotericin 10mg/kg every third day for five doses with fluconazole 800mg/day). There was clinical improvement in symptoms, and CSF was negative for Cryptococcus after five doses of high dose liposomal Amphotericin-B. Patient was discharged with fluconazole 800mg/day as a part of consolidation therapy. The above case shows how disseminated cryptococcosis can be a primary manifestation in a patient with HIV infection and the challenges in managing the same. The modification of induction therapy in case of persistence has shown a dramatic response in the clearance of the organism due to better CNS penetration.

0467

DIAGNOSIS AND PREVALENCE OF *CRYPTOSPORIDIUM AND GIARDIA* INFECTIONS IN CHILDREN UNDER FIVE YEARS WITH MODERATE TO SEVERE DIARRHOEA ATTENDING TWO HEALTH FACILITIES IN BLANTYRE, MALAWI

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Diarrhoeal diseases are major causes of morbidity and mortality among children in low and middle income countries (LIMCs). *Cryptosporidium* and *Giardia* are considered to be the main parasitic causes of moderate and severe diarrhoea (MSD) in LMICs. The diagnosis of these parasitic protozoa is usually by microscopic detection of the parasite oocysts in stool samples, but might be cumbersome, time-consuming and prone to errors. Rapid Diagnostic Tests (RDTs) provide an attractive alternative by combining sufficient diagnostic accuracy with speed and ease to operate. The present study aimed to determine the prevalence of *Giardia* and/or *Cryptosporidium* infections by RDT among children, 0-60 months, with MSD attending two primary health facilities in Blantyre (Malawi); Limbe health centre with a catchment population of 105,347 and Ndirande with a catchment area that has 145,187 people accessing outpatient health services. In total, 972 children were included and their stools examined by RDT for the presence of *Giardia* and/or *Cryptosporidium*. It was found that 166 children (17.1%) had a *Giardia* infection, 73 (7.5%) were infected with *Cryptosporidium* and only 15 (1.5%) had a mixed infection. Girls and boys were equally infected by the parasites and there was no clear correlation between weight/height and infection. However, children aged 10-44 months had the highest prevalence of infections. The vast majority of *Cryptosporidium* infections were caused by *C. hominis* (as determined by genetic typing) suggesting antroponotic transmission. Of 718 children (73.9%) the cause of diarrhoea remains to be established, and testing for Rota and Noro viruses with RDTs is warranted to improve diagnosis and clinical management.

0468

EFFECT OF CLINICIAN INFORMATION SESSIONS ON DIAGNOSTIC TESTING FOR CHAGAS DISEASE

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Chagas disease is a potentially life-threatening neglected disease of poverty that is endemic in continental Latin America. Caused by *Trypanosoma cruzi* (*T. cruzi*), it is one of six parasitic diseases in the United States (US) targeted by the Center for Disease Control as a public health problem in need of action. An estimated 300,000 people are infected with Chagas disease in the US. Awareness of Chagas disease is lacking among many healthcare providers in the US. The purpose of this analysis is to determine if the number of diagnostic tests performed at a community health center serving an at-risk population for Chagas disease increased after information sessions. A secondary aim was to determine if there was a difference by provider type. A retrospective data analysis of the number of Chagas serology tests performed at the East Boston Neighborhood

Health Center (EBNHC) before and after information sessions for clinicians was performed. A time series analysis was conducted focusing on the Adult and Family Medicine Departments at EBNHC. Across both departments, there were a total of 4,580 *T. cruzi* serology tests performed in the twenty-two-month study period; 1,957 (43%) prior to information sessions and 2,623 (57%) following the sessions. Interrupted time series analysis across departments indicated that testing volume was stable over time prior to the sessions (pre-period slope=+4.1 per month; p=0.12), followed by an immediate shift after the session (+51.6; p=0.03), while testing volume remained stable over time after the session (post-period slope=-6.0 per month; p=0.11). Prior to the sessions, the majority of tests (53%) were ordered by nurse practitioners while 43% were ordered by physicians. After the sessions, nurse practitioners and physicians ordered an equal proportion of tests (both 48%). In this study, Chagas testing increased after information sessions. Clinicians who began testing their patients for Chagas disease after learning of the importance of this intervention added an extra task to their already busy workdays without external incentives or recognition.

0469

EVALUATION OF SCID MOUSE MODEL FOR EXPEDITING CHAGAS DRUG DISCOVERY

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Chagas disease, common in Mexico, Central and South America with approximately 6-8 million people infected, is caused by the parasite *Trypanasoma cruzi*. The disease causes symptoms in 2 stages, a milder acute stage, and a chronic stage occurring years after original infection. Treatment options are limited, new therapies are needed and current rodent models can be time intensive, hindering rapid drug discovery process. Here we investigate the use of a SCID mice model of acute Chagas disease to provide a robust, short duration model to aid drug discovery. Eight week old SCID mice were infected with $1x10^3$ bioluminescent tissue-cultured derived trypomastigotes via intraperitoneal injection. Bioluminescent parasites infected various tissues reaching high parasite load by day 10. On day 10 post infection, mice were treated daily for 5 days via oral gavage with varying doses of benznidazole (BENZ, 0-100mg/kg) or vehicle alone (0.5% Methylcellulose + 0.5% Tween80) or Dulbecco's phosphate buffer saline (background control). Mice were imaged before and after treatment and total flux was used to investigate efficacy of treated groups compared to vehicle control. For imaging, mice were injected with 150mg/kg D-Luciferin and imaged under isoflurane anesthesia in an IVIS Lumina X5. Untreated animals showed an approximate 2-$\log_{10}$ increase in total flux values from levels at the start of dosing and a dose dependent reduction in parasitemia was observed following treatment with BENZ. Maximum effect was observed with BENZ dosed at 100mg/kg which reduced total flux 1.5-$\log_{10}$ below levels at start of dosing. Chagas infection established in SCID mice could be monitored using bioluminescence. Parasitemia increased over the course of the study and was treatable, although complete parasite clearance was not observed with the compound doses and schedule used. This model could now be used to screen ability of novel compounds to reduce parasitemia, prioritization of scaffolds and further support drug development efforts for this neglected tropical disease.

0470

ASSESSMENT OF SYNTHETIZED BRIDGED-LACTAM ORGANIC COMPOUNDS FOR IN VITRO ACTIVITY AGAINST *LEISHMANIA MAJOR,* AN AGENT OF HUMAN LEISHMANIASIS

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Leishmania are protozoan parasites and causative agents of leishmaniasis. This vector-borne disease is transmitted to the vertebrate hosts including humans, by blood-sucking female phlebotomine sand flies. The clinical forms range from cutaneous leishmaniasis with facial and body disfigurations to visceral leishmaniasis in which the parasite spreads into the reticuloendothelial system with fatal outcome in the absence of treatment. The leishmaniases are prevalent in over 88 countries with more than 15 million infected globally. It is estimated that worldwide, there are about 3 million new cases of leishmaniases each year leading to as many as 50,000 fatalities annually. The World Health Organization lists the leishmaniases among the leading causes of deaths by infectious agents. Today, there is no approved vaccines for the prevention of leishmaniasis. The major control tools include measures against the vector such as bed nets and therapeutics against the parasite. For almost a century, treatment of the disease has relied on pentavalent antimonials. However, antimonials are very toxic chemotherapeutics with frequent and sometimes life-threatening side effects such as cardiac arrythmia and acute pancreatitis. The pentavalent antimonials were replaced in some endemic countries by formulations of amphotericin B. However, this latter option is again limited with severe toxicity, long hospitalization, and overall high cost of treatment. Based on the above, it is evident that the chemotherapeutics available do not match the high burden of the leishmaniases. Consequently, there is an urgent need of antileishmanial therapeutics that are effective, not/less toxic, and affordable to population in impoverished endemic areas. In order to address this shortage, we have embarked on the development of new organic compounds and their evaluation for leishmanicidal activity. We will present data showing that synthetized bridged-lactam organic compounds have potentials as antileishmanial therapeutics. Interestingly, our study shows that activity is directly linked to chemical structures of the compounds evaluated.

0471

DRAMATIC INCREASE IN THE NUMBER OF MICROTUBULE ASSOCIATED PROTEIN GENES IN *TRYPANOSOMA CRUZI* COMPARED WITH *TRYPANOSOMA BRUCEI*

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MARP1 is a *T*rypanosoma *brucei* microtubule associated protein (MAP) that is localized on the microtubules of the parasite's cell body. It is comprised of 50 repeats of a 38 amino acid motif. Search of the putative MARP1 amino acid sequence by BLASTp at NCBI in the nih.gov website disclosed five homologous genes in the *T. brucei* genome that showed an exact sequence identity. MARP1 also showed a 54% amino acid sequence identity to the *T. cruzi* MAP protein encoded by Genbank M21331. We have previously shown that M21331 has partial gene sequence identity to human immune genes such as TRIM21. A BLASTp search of Genbank M21331 showed that there are 30 other genes which are 100% identical to it in the *T. cruzi* genome. These genes encode for proteins ranging in size from 38 to 2011 amino acids in length and contain up to 50 repeats of the 38 amino acid sequence motif. The MAP genes in *T. cruzi* appear to have expanded five-fold in number compared to similar MAP genes in *T. brucei*. The sequences, functions, and roles of these numerous *T. cruzi* proteins are a fascinating area for further scientific study.

0472

EVALUATION OF TWO FDA-APPROVED ANTISEPTICS USED IN WOUND CARE AND ORAL HYGIENE FOR EFFICACY IN THE TREATMENT OF LEISHMANIASIS

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Leishmaniasis affects poor communities worldwide, with about 1 million new cases annually and more than 20 species of the parasite affecting humans. In infected hosts, the parasites exist in 2 forms-promastigotes in blood and amastigotes in tissue macrophages. The disease manifests in 3 clinical forms: Cutaneous (most common), Mucocutaneous and Visceral

(most serious). Available therapies are very toxic, expensive, selective for specific species of the parasites, and often complex to administer. Hence, effective treatment requires specific identification of parasite specie (difficult in resource-limited areas), long-term administration by adequately skilled personnel and severe side effects, often leading to patient non-compliance. New drugs are desperately needed, and drug repurposing could offer quick intervention.We identified two compounds that are commonly used in wound care and oral hygiene that have impressive anti-leishmanial activity in vitro. Results of promastigote assays show that the two compounds have better anti-leishmanial activity than most currently available drugs which are often toxic and expensive, with an IC_{50} of 2.5-4uM. These compounds have shown efficacy against 6 different species of Leishmania tested so far. Experiments are underway to test the compounds against amastigotes and in mouse models of Leishmaniasis, and to elucidate their mechanism(s) of action. The compounds will also be assayed for synergistic effects with other antimicrobials for enhanced efficacy and drug delivery.This study will deliver two prospective drug-repurposing candidates that are cheap, safe, easy to administer and have broad-spectrum anti-leishmanial activity for the effective treatment of various forms of Leishmaniasis, thereby reducing the disease burden.

0473

TRYPANOSOMA CRUZI-SPECIFIC B CELL RESPONSES IN SERODISCORDANT SUBJECTS FOR CHAGAS DISEASE

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A proportion of subjects screened for *Trypanosoma cruzi* infection have what is termed "discordant serology," i.e., a positive result in only one out of three conventional serological tests performed. Serodiscordant subjects (SD) have more functional *T. cruzi*-specific T-cell responses compared with seropositive subjects, suggesting that some subjects exposed to *T. cruzi* might eventually resolved the infection and developed T cell memory. Here, we have evaluated the presence of antibody secreting cells and memory B cells specific for *T. cruzi* and Leishmania antigens using B cell ELISPOT, and the phenotype of total B cells in SD, seropositive and seronegative subjects for *T. cruzi* infection.Based on a cut-off value defined by the mean values of antibody secreting cells plus 2SD in uninfected subjects, none of the 17 SD subjects evaluated showed circulating antibody secreting cells specific for *T. cruzi* or *Leishmania* antigens whereas 24/29 subjects seropositive for *T. cruzi* infection had antibody secreting cells specific for *T. cruzi* antigens. In contrast, SD subjects had higher levels of *T. cruzi* -specific memory B cells compared with seropositive and uninfected subjects. SD and uninfected subjects also showed higher levels of memory B cells specific for tetanus toxoid compared with seropositive subjects. No differences in *Leishmania*-specific memory B cells were found among groups. The phenotype of total B cells in SD was not different from that found in uninfected subjects. The monitoring of conventional serology of SD showed that a proportion of them had been seropositive for T. cruzi infection and became serodiscordant or seronegative over time. Sera from SD (n = 58) had low reactivity to *T. cruzi* antigens using a commercial ELISA technique and a proportion of them also had low reactivity to Leishmania antigens using an in-house ELISA. These findings support that *T. cruzi* -specific antibodies in SD did not appear to derive from an active infection but more likely reflect prior exposure to *T. cruzi* and the establishment of immunological memory suggestive of a resolved infection.

0474

DIAGNOSIS OF *BALAMUTHIA MANDRILLARIS* ENCEPHALITIS BY TA CLONING TARGETING UNIVERSAL EUKARYOTIC GENE

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A 50-year-old man without a history of neurological disease was referred to our department for the evaluation of an intracranial lesion observed on brain MRI scans, and the pathology results suggested protozoal infection. We identified the species responsible for encephalitis using thymine-adenine (TA) cloning. We extracted DNA from a paraffin-embedded brain biopsy sample and performed TA cloning using two universal eukaryotic primers targeting the V4-5 and V9 regions of the 18S rRNA gene. The recombinant plasmids were extracted, and the inserted amplicons were identified by Sanger sequencing and a homology search of sequences in the NCBI BLAST. The protozoa was identified as the free-living amoeba *Balamuthia mandrillaris*. Two of 41 colonies recombinant with 18S V4-5 primers and 35 of 63 colonies recombinant with the 18S V9 primer contained *B. mandrillaris* genes; all other colonies contained human genes. Pathogen-specific PCR ruled out *Entamoeba histolytica*, *Naegleria fowleri*, *Acanthamoeba* spp., and *Toxoplasma gondii* infections. This is the first report of *B. mandrillaris*-induced encephalitis in Korea based on molecular identification. TA cloning with the 18S rRNA gene is a feasible and affordable diagnostic tool for the detection of infectious agents of unknown etiology.

0475

DNA DIAGNOSIS OF CUTANEOUS LEISHMANIASES (CL) USING MULTIPLEX PCR ASSAY COUPLED TO LATERAL FLOW (LF) DNA CHROMATOGRAPHY

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In Tunisia and countries in MENA region, CL are a group of diseases representing a complex epidemiological situation with the proven implication of at least 3 *Leishmania (L.)* species (*L.infantum:L.i, L.major:L.m, L.tropica:L.t*) and diverse clinical presentations. There is an urgent need for a rapid diagnosis tool that could facilitate etiological diagnosis and patient management. The aim of this study was to develop an innovative, sensitive and specific molecular tool for simultaneous *L.*species detection and identification using PCR multiplex-LF DNA chromatography that could be used as a point of care (POC) diagnosis test. Comparative genomic analyses of *L.m* & *L.i* genomes were performed to select species-specific targets. Twenty-four primer pairs were designed and assessed for criteria of taxa-specific DNA amplification of the 3 principal *L.* species in MENA. Species/group of species-specific primers aiming at 3 different targets were selected and showed consistent species-specific reactivities when tested on 32 *L.* DNAs. The analytical sensitivity on agarose gel was 0.2-0.02ng. The assay included a 4thtarget corresponding to a human-DNA control. For the detection on a LF test using a proprietary DNA-DNA hybridization technology, the different forward-primers were tagged on their 5'end with different tags while reverse-primers were biotinylated on their 5'end. On the LF strip, within 3mn, the targeted DNA amplicons appear as blue test lines on the strip through a streptavidin-Biotin interaction. The test was shown to consistently identify the studied *L.*species and to have an analytical sensitivity of detection of 0.01ng. The performance of the test was evaluated on 80 cutaneous samples made during routine diagnosis at the Parasitology department of the Farhat Hached UH in comparison to Direct-examination (DE) & PCR-RFLP-ITS1. The multiplex PCR-LF test showed 100%sensitivity and 100%specificity in congruence to DE & PCR-RFLP-ITS1. The study delivers a simple, specific

and sensitive tool for accurate simultaneous detection and identification of *L.* parasites in clinical samples that could be used as a POC-CL diagnosis test.

0476

POST-KALA-AZAR DERMAL LEISHMANIASIS DRUG EFFICACY STUDY LANDSCAPE: A SYSTEMATIC REVIEW OF CLINICAL AND OBSERVATIONAL STUDIES TO ASSESS THE FEASIBILITY OF ESTABLISHING AN INDIVIDUAL PARTICIPANT-LEVEL DATA PLATFORM

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Post-kala-azar dermal leishmaniasis (PKDL) is a dermatosis which can occur after a conventional treatment for visceral leishmaniasis (VL). There are numerous limitations in our knowledge of PKDL pathology, immunology and risk factors. Recommended treatments are either expensive, raising safety concerns, or are of long durations. We conducted a systematic review to assess the characteristics of PKDL studies and to explore the feasibility and value of developing a PKDL individual patient data (IPD) platform. We searched ten databases to include prospective studies in humans with PKDL diagnosis, treatment and follow-up measurements. We extracted variables on patient characteristics, treatment regimens, diagnostic methods, geographical locations, efficacy endpoints, adverse events and statistical methodology. The literature searches identified 3,217 citations. A total of 54 studies were included in this analysis, 16 clinical trials and 38 prospective observational studies published between 1983 and 2021. The studies were conducted in India (63%), Bangladesh (11%), Nepal (4%) and Sudan (22%) and enrolled a total of 2,462 patients. Of the 16 clinical trials, 12 were conducted in India, 3 in Sudan and 1 in Bangladesh with a total of 21 arms testing 8 different drugs or combinations involving 891 patients. A wide range of heterogeneity in dosage and duration was observed in the different treatment regimens. Antimony formulations and miltefosine each being tested in 33% (7/21) of treatment arms, followed by amphotericin B formulations in 14% (3/21) of arms. Paramomycin alone and in combination with miltefosine was tested in 4.8% (1/21) of arms each. This review provides a landscape of previously and currently tested treatments for PKDL. Only a third of the published studies were from clinical trials while the others were observational with a large variability in treatment regimens tested. Assembling IPD from identified studies would provide granular details on efficacy and safety outcomes and would be a unique resource to answer questions that cannot be addressed using standalone trials and aggregated published results.

0477

IMMUNODIAGNOSTIC POTENTIAL OF CD1A MARKER TO DETECT CUTANEOUS LEISHMANIASIS CAUSED BY *LEISHMANIA DONOVANI*

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Immunoexpression of CD1a by *Leishmania* amastigotes has been recently demonstrated in several strains including *Leishmania major*, *L. tropica* & *L. infantum*. We studied CD1a status of amastigotes of *L. donovani* for the first time and evaluated its diagnostic potential. Hundred and sixteen cases of cutaneous leishmaniasis skin biopsy sections were stained with both CD1a clone 010 & CD1a clone MTB1. Results of positive staining for parasites were compared with previously obtained cytological and histological confirmations for the presence of the parasite. The proposed diagnostic tool was evaluated for its accuracy, specificity, and sensitivity against the gold standards for cutaneous leishmaniasis diagnosis obtained through slit skin smear results (SSS). 75 cases had shown positive parasite staining for CD1a clone MTB1. CD1a clone O10 had failed to detect any parasites of the *L. donovani* strain. Staining was accentuated on one side of the parasite corresponding to the kinetoplast of the organism. Staining was seen mostly in the upper dermis. The number of parasites showing positive staining for clone MTB1 gradually decreased through the depth of the dermis. When the number of parasites in the section was too high, the probability of getting them stained with clone MTB1 was low therefore leading to a considerable amount of cases being false negative. The test accuracy, sensitivity, and specificity were 72.4%, 70.9% and 84.6% respectively. In an effort to see if this diagnostic method is more appropriate for patients with low/no LD bodies, test statistics were repeated on the same cohort by removing the 25 patients who had parasite loads of more than 100 LD bodies, then the sensitivity of the test increased to 74.4%. CD1a clone MTB1 successfully stains *Leishmania* amastigotes of *L. donovani* strain and can be used as a reliable diagnostic tool in patients whose parasite counts are extremely low & whose diagnostic confirmation got failed using other conventional methods. This tool may come in handy for hospital settings where SSS sampling is fairly poor due to the lack of expertized personnel.

0478

A NOVEL ASSAY BASED ON RECOMBINASE AMPLIFICATION AND LATERAL FLOW CHROMATOGRAPHY FOR THE DIAGNOSIS OF *LEISHMANIA INFANTUM* CUTANEOUS LEISHMANIASIS

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Cutaneous leishmaniasis (CL) due to *Leishmania infantum* (*L.i*) is known to occur sporadically in North Africa and Middle East regions. However, recent changes in eco-epidemiology of the disease led to geographic expansion and emergence of *L.i* CL infections. *Leishmania* (*L.*) species identification is central for disease monitoring and control but also for effective patient management and treatment. In this context, we aim at developing a novel molecular diagnosis test to detect and identify *L i* in CL lesions. The study involved four endemic areas in MENA regions including North and Center of Tunisia, Morocco, and Lebanon. Our test is based on an isothermal Recombinase based Amplification (RPA/RAA) coupled to a lateral flow detection (LF). For the set up of these assays, we identified 7 targets by a computational analysis complemented by a literature search. For each target, a sequencing survey was performed on a selection of *L.* strains belonging to different species assessing for inter and intra species polymorphisms to design primers and probes. Ten sets of designed primer pairs/probes were tested for their specificity to *L.i* and their sensitivity using RPA-RAA/LF tests. One set was retained; its specificity to *L. i* strains' DNA was assessed on a panel of *L.* DNAs belonging to different species, and its analytical detection sensitivity was 0.2pg. With this assay, the time to results delivery after DNA extraction was less than one hour, with

40mn for the amplification, done at 39°C, and 2mn for the read out of the FAM-Biotin labeled amplicons on the LF cassette.The evaluation of this amplification/detection assay was done on a selection of CL samples (N=34) collected from the different study site sand has shown a sensitivity and a specificity of 90% and 100% respectively as compared to direct microscope examination; identification results were congruent to PCR RFLP ITS1 species assignment. No cross reactivity with *L. major* or *L. tropica* was observed. These results showed that this novel DNA assay has a good potential to be used as a point of care diagnosis tool for the detection and the identification of *L.i* infections.

0479

PEER-NAS-USAID 518 PROJECT: RECOMBINASE POLYMERASE AMPLIFICATION (RPA) AND LATERAL FLOW (LF) ASSAYS FOR POC DNA DIAGNOSIS OF CUTANEOUS LEISHMANIASES IN MENA AND DEVELOPMENT IMPACT

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Cutaneous leishmaniases (CL) constitute major public health issues. Caused by multiple *Leishmania* species, they have diverse transmission cycles. More than 80 % of the cases occur in countries of the MENA region, where *L. major(L.m)* or *L. tropica(L.t)* are the predominant CL causing species, while *L. infantum(L.i)* or *L. donovani(L.d)* are involved to less extent. *Leishmania* species identification is central to control strategies, early alert on emergence, and timely and effective patient management. Notably, treatment algorithms are highly dependent on *Leishmania* species. Emergence and changing trends in CL eco-epidemiology called for development of POC DNA assays for accurate disease diagnosis, patient management, control, and surveillance. We aimed at developing species-specific isothermal RPA coupled to LF on dipstick targeting L.m, L.t, L.i/L.d that would be implemented in a second step for multiplexed concomitant detection and identification of these species. We worked on a range of 70 targets identified through bibliography and databases scans; 14 were selected and submitted to a sequencing survey for species- specific primers and probes designs and refinement through multiple sequence alignments. Thirty-five sets were screened for species specific amplification and 15 were selected for further characterization of analytical specificity and sensitivity of detection. Proof of principle validation for detection and identification of the species in cutaneous samples was assessed on consented patients' samples collected in different sites of the collaborative consortium in MENA. Results were compared to smear examination and ITS1 PCR-RFLP. This way we already validated two assays specific to L.m and L.i, respectively. A third one, L.t specific is under evaluation. Multiplexing reaction set up is ongoing. Training workshops were held, and development impact plans were developed. Our approach spares precious samples, is rapid (<1h), is appropriate for limited settings to support POC diagnosis, and addresses current gaps and priorities defined by the WHO NTD roadmap.

0480

CIDALSDB: A NOVEL RESOURCE FOR ANTI-*LEISHMANIA* DRUG DISCOVERY USING MACHINE LEARNING AND LIGAND-BASED APPROACHES

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Computer-aided drug discovery (CADD) is nurtured by late advances in big data analytics and machine learning (ML) towards enhanced drug discovery (DD) outcomes. In this context, reliable datasets are of utmost importance. We herein present CidalsDB a novel ready-to-use resource for the development of ML-assisted DD against Leishmaniases. In a first step, we performed an extensive search of the literature and retrieved data on molecules with validated anti-leishmanial effects. We defined a data dictionary of published information related to the anti-pathogenic effect of chemical compounds and used it to build the database CidalsDB. A web interface was implemented to facilitate the database browsing and use. In a second step, we generated a curated set of molecules from CidalsDB and the PubChem assay AID1258 to constitute an equilibrated dataset of active and inactive molecules against Leishmania promastigotes. We used RDkit to generate the topology torsion fingerprints and implemented four ML algorithms that we trained and tested for their ability to classify molecules into active and inactive.We collected data on 1145 molecules from 753 scientific publications. Molecules revealed validated effects on Leishmania species at different stages (in vitro, in cellulo, in vivo). 79% had validated effects on the promastigote form of the parasite, while only 12% reached the in vivo validation stage. For the second part, we selected the set of 904 molecules with anti-promastigote activity within CidalsDB to which we added 146 active and 963 inactive molecules from the PubChem assay to constitute a dataset for ML models building. Out of 4 ML algorithms, Support Vector Machine presented the highest accuracy of 90% through a 5-fold cross-validation. We further optimized the model and used it to predict potential anti-Leishmania effectors out of the FDA approved drugs. Top10 drugs with a probability >90% of being active included 4 validated anti-Leishmania drugs which confirms the robustness of our approach.CidalsDB will be made publicly available through the web interface along with the ML module for a democratized and no-code CADD.

0481

STANDARDIZATION OF HIGH-CONTENT (HC) PHENOTYPE IMAGING AND VALIDATIONS FOR NOVEL DRUG DISCOVERY AGAINST INTRACELLULAR *TRYPANOSOMA CRUZI*

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Trypanosoma cruzi is the causative agent of Chagas disease, endemic to mainly Latin American countries. Current global annual *T. cruzi* infection rate stands at 7 million people with nearly 10,000 reported deaths per year. Infection of *T. cruzi* has two phases, an acute phase and a chronic phase that can last decades, often resulting in myocarditis, megacolon or megaesophagus due to the untreated replication of the *T. cruzi* amastigote. With only two clinically accepted drug treatments, nifurtimox and benznidazole, which have well reported toxic side effects, and the ongoing spread of the disease to non-endemic areas, there is an urgency to identify new treatments against the clinically relevant form of *T. cruzi* -the intracellular amastigote. Being a NTD, chagas research lacks coordinated, multifaceted efforts for a drug discovery i.e. to ensure a high-throughput (HT), cost effective method to rapidly identify novel compounds as potential therapeutics from large libraries. Herein, we describe a robust *in-silico* and *in-vitro* integrated drug discovery workflow implementing a HC phenotypic imaging screening using STD compounds and repurposable, FDA approved drug compounds against the amastigote stages of *T. cruzi* CL strain expressing transgenic EYFP utilizing VERO/A549

cells. Additionally, initial HT- virtual screening against a selected target, i.e. glycosomal Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was performed followed by MD simulations to select hits from FDA approved library. Positive hits were tested *in vitro* using newly established HC method on amastigote form of *T. cruzi* CL. Using Image-Express PICO, we can determine the true efficacy of test compounds following this HC phenotype screening protocol. As part of the validation of HC method, we have identified an FDA approved Epigallocatechin gallate (EGCG) as a lead natural compound specific to parasite GAPDH, with binding energy of -10.6 kcal/mol and an IC_{50} of 46.5μM against epimastigotes, and cytotoxicity levels below Amphotericin B. Additional experiments are underway to expand validations using *T. cruzi* brazil strain expressing luciferase reporter gene.

0482

DIAGNOSING AMERICAN TEGUMENTARY LEISHMANIASES USING ELISA WITH LB6H RECOMBINANT ANTIGEN

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American tegumentary leishmaniases (ATL) are mainly caused by *Leishmania (L.) braziliensis*, *L. (L.) guyanensis,* or *L. (L.) amazonensis*. The ATL diagnosis is based on Epidemiology-Clinical-Laboratory data. Since the varied clinical presentations are not pathognomonic, laboratory exam data are required to confirm the diagnosis. Furthermore, the discontinuity of the Leishmanin skin test antigen production brought problems for the diagnosis. Currently, no single gold standard diagnostic test is available; thus, laboratory assays that suggest *Leishmania* infection are needed. This study aimed to validate the Lb6H recombinant antigen (rLb6H), derived from *Leishmania (Viannia) braziliensis* gene sequence in an ELISA platform for application in ATL diagnosis. We analyzed 1.091 samples from leishmaniasis and other diseases patients and healthy controls living in various Brazilian endemic and non-endemic localities. The rLb6H-ELISA showed 98.6% sensitivity and 100.0% specificity with the reference panel (70 ATL patients and 70 healthy controls). Analyzing 393 ATL patients' samples from five research and health care centers in endemic and non-endemic areas, rLb6H-ELISA showed 84.0% sensitivity; no significant statistical difference was observed among the five centers (chi-square test, p=0.13). With 392 healthy controls from four areas with different endemicity, a specificity of 92.4% was obtained; lower specificity was obtained in a visceral leishmaniasis endemic locality (chi-square test, p<0.001). Cross-reactivity was assessed in 166 samples from patients with other diseases with positivity of 13.9%. Of note, a considerable number of rLb6H-ELISA positive samples were previously considered negative in different diagnostic tests: 25% in the parasitological exam, 40% in culture, 20% in immunohistochemistry, 10% in PCR, 60% in *L. major*-like indirect immunofluorescence assay and 20% in *L. major*-like-ELISA. Based on the good diagnostic performance and the reproducibility and stability of the antigen, we suggest using ELISA-rLb6H for ATL diagnosis.

0483

DEVELOPMENT OF CDC-LIKE ASSAYS FOR HIGH THROUGHPUT SCREENING OF NOVEL CLK1 INHIBITORS

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Chagas disease is caused by a kinetoplastid parasite *Trypanosoma cruzi*, affecting 6-7 million people worldwide. Current drugs used to treat Chagas disease suffer from poor safety and suboptimal efficacy. There is a need to find novel inhibitors that are safe and efficacious. Protein kinases are promising targets for the therapeutic intervention. We had shown that CDC-like kinase (CLK1) inhibition by amido-benzimidazoles efficiently killed all kinetoplastid parasites, thereby chemically validating the target. The current study focuses on characterizing a unique CLK1 enzyme from *T. cruzi* and development of biochemical assay amenable for high throughput screening to identify novel CLK1 inhibitors. Kinetoplastid CLK1 is a part of kinetochore complex essential for chromosome segregation as well as cell division whilst, the human CLK1 plays a vital role in phosphorylating serine arginine-rich proteins and proteins involved in pre-mRNA processing. We successfully expressed *T. cruzi* CLK1 and characterized the Km concentrations for ATP, substrate and buffer conditions, thereby developing a robust, reproducible biochemical assay. We also expressed human CLK1 enzyme and characterized the enzyme, in order to use as a counter screen. Standard kinase inhibitor staurosporine and AB1, known CLK1 inhibitors were used as positive control, thereby helping in developing robust 1536 well assay with signal to noise window of >10. Both enzymes tolerate DMSO upto 5%. The final screening TcCLK1 assay used 0.2 nM of TcCLK1 enzyme, 0.3 μM RS peptide substrate, and 4 μM of ATP; and the hCLK1 assay uses 2 nM of hCLK1 enzyme, 0.3 μM RS peptide substrate, and 10 μM of ATP. These assays are ready to be used for screening for novel TcCLK1 selective inhibitors.

0484

TRICHOMONAS VAGINALIS ISOLATES FROM SYMPTOMATIC WOMEN IN EGYPT: GENOTYPIC ANALYSIS AND METRONIDAZOLE SUSCEPTIBILITY

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Trichomonas vaginalis (*T.V*) is the most common curable non-viral sexually transmitted pathogen in Egypt & worldwide.Vaginal swabs were collected from 150 symptomatic Egyptian women attending Obstetrics & Gynaecology outpatient clinics of Kasr Al-Ainy hospitals for 8 months duration. Vaginal swabs were cultured & nPCR- RFLP was done for molecular genotypic analysis. Positive-PCR samples were further in-vitro treated by metronidazole & their phenotypic changes were observed using Transmission Electron Microscopy (TEM) to assess the susceptibility of isolated *T.V*. *T.V* was detected in 18% by Culture method which is the gold standard. Trichomoniasis was highest in sexually active women (>28 years old) & those using contraceptive methods, especially IUD. Genotype (H) was the only genotype detected using nPCR- RFLP & the phenotypic changes indicated that this genotype (H) is sensitive to metronidazole drug.

0485

PLASMODIUM FALCIPARUM PARASITE PREVALENCE DIFFERS BY TYPE OF DOMESTICATED ANIMAL OWNED BY HOUSEHOLDS IN DEMOCRATIC REPUBLIC OF CONGO

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Household domesticated animal ownership is an understudied aspect of the human environment that influences mosquito biting behavior and malaria transmission. The few existing studies have widely varying results, likely due to context-specific mosquito preferences, animal husbandry, and other factors. To evaluate the effect of domesticated animal ownership on malaria prevalence in a high burden setting, we used data and samples from a large, nationally representative Demographic and Health Survey (DHS) conducted in 2013-14 in Democratic Republic of Congo (DRC), where the anthrophilic *Anopheles gambiae* vector predominates and 12% of the world's malaria cases occur. Quantitative PCR (qPCR) targeting the *Plasmodium falciparum* lactate dehydrogenase gene (*pfldh*) was previously performed using DNA extracted from dried blood spot samples. We used generalized estimating equations to account for clustered data structure, adjusted for age, sex, modern housing, treated bed net use, wealth, and rurality, and applied sampling weights to calculate population-level estimates. Among 16,787 participants with *pfldh* qPCR results and domesticated animal ownership data, weighted *P. falciparum* PCR prevalence was 31% (95% CI 29-33%). Chickens were the most common animal owned (42% of participants, 95% CI: 39-44%), followed by goats (20%, 95% CI: 18-22%) and cattle (2.0%, 95% CI: 1.4-3.0%). We observed stark differences in malaria prevalence across types of animals owned by households in both crude and adjusted models. Household chicken ownership was associated with 3.7 (0.5, 6.9) more *P. falciparum* infections per 100 people in the adjusted model, while cattle ownership was associated with 9.6 (-15.8, -3.5) fewer infections per 100 and goat ownership did not result in a difference in infections, when compared to individuals from households without each animal. These findings demonstrate animal-specific malaria risk that may be amenable to intervention in DRC and other high burden countries, and require studies of animal husbandry practices and associated mosquito behaviors to inform future One Health malaria interventions.

0486

SPATIAL DISTRIBUTION AND RISK FACTORS ASSOCIATED TO CASES OF HUMAN LEPTOSPIROSIS IN CORDOBA DEPARTMENT, COLOMBIA

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Leptospirosis, caused by a spirochaete from the genus *Leptospira* is a neglected zoonosis with high incidence in tropical and subtropical regions. Patients with clinical suspicion of leptospirosis attending Healthcare institutions from the department of Cordoba during from January 2016 to March 2021 were included. Cases were confirmed by PCR and Microagglutination (MAT). Univariate and multivariate information analysis were used to establish the association between leptospira cases and risk factors. Bernoulli model and Kulldorff technique were used for the detection of spatial conglomerates with SaTScan™ v9.4. A total of 339 patients (220 men and 119 women) suspected of human leptospirosis were part of the study; 19.2% of suspicious cases were confirmed as leptospirosis. Serological reactivity to serogroups utilized in MAT showed a spatial distribution not geographically concentrated, with the following showing the highest reactivity: Australis 38.5%, Grippotyphosa 37%, Sejroe 29%, Autumnalis 23% y Pyrogenes 21.5%. pig or equine cattle and floods 30 days before symptom onset represented a 2-fold higher risk of contributing to illness presentation ($p<0.05$, IC:95%). Patients referring to having bathed in lakes/lagoons increases 4-fold the risk of acquiring leptospirosis when compared to a those who did not practice this activity ($p<0.05$, IC: 95%). Median temperature (28°C) was statistically significant for the risk of acquiring leptospirosis. Four high illness rate clusters were identified, one of them was statistically significant ($p=0.023$), having a centroid in the coordinate 8.389397 N, -75.434916 W corresponding to Center, Medio Sinu, savannah, San Jorge and Alto Sinu subregions. Leptospirosis in the department of Cordoba is endemic and dispersed in urban and rural areas. The environment in which population develops has characteristics that act as coadjuvants in the presentation of leptospirosis.

0487

PREVALENCE OF ANTIBODIES TO *TOXOPLASMA GONDII* IN FELINES IN FAMILY LIFE THE CITY OF MONTERIA. DEPARTMENT OF CÓRDOBA-COLOMBIA

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120 serological tests were performed on felines living with families in 15 neighborhoods of the city of Montería, Córdoba-Colombia with the objective of determining the presence of reactors for *Toxoplasma gondii* through the Indirect Hemagglutination technique (IHA). The animals were chosen at random in the different neighborhoods and their owners provided information regarding age, sex and origin; they were bled adequately, obtaining the sample that was processed in the Clinical Laboratory of the Hospital San Jerónimo de Montería. The serological study revealed 87.5% seropositivity with titers ranging between 1:160 and 1:10240. Of the 105 samples positive to the serological reaction, 2 (1.9%) presented low titers, 11 (10.5%) intermediate titers, and 92 (87.6%) high titers. The relationship between serology and the sex variable determined similar prevalences of 49.5% and 50.5% for females and males, respectively, with a predominance of titers equal to or greater than 1:1280 in both sexes. According to age groups, serology showed values equivalent to: Animals <3 years old 75 (84.4%), 3-6 years old 17 (94.11%), 6-9 years old 5 (100%) and > 9 years old 8 (100%). Statistical analysis using the Chi Square test indicated significant differences between the serological dilutions, with the presence of intermediate and high titers being observed in a greater proportion. The serology found did not show significance with respect to age, but highlights high titers at all ages and especially the tendency of overreaction in older animals. The observed overreaction demonstrates the dynamics of toxoplasmosis as a zoonotic disease given by coexistence with this animal species.

0488

PRELIMINARY STUDY OF VISCERAL LEISHMANIASIS IN CANINES IN FAMILY COEXISTENCE IN THE MUNICIPALITY OF SHEEP-SUCRE, COLOMBIA

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Serological tests and direct tests were carried out on canines in family life in the village of "La Europa" in the municipality of Ovejas, department of Sucre-Colombia, with the objective of determining the presence of fluorescent antibodies for canine Visceral Leishmaniasis, by means of the Indirect Immunofluorescence technique. and presence of the parasite by taking a biopsy through hepatic and lymph node puncture. Blood samples were taken from the study animals for serological study and liver and lymph node puncture samples to determine the presence of the parasite. The 52 animals examined constituted the total population of existing canines in the dwellings of the study area. The owners of the animals

reported the data of their animals related to age, sex and time spent in the home, clinical signs, relationships with people and with other animals. The Indirect Immunofluorescence study revealed 3.84% the presence of fluorescent antibodies for canine Visceral Leishmaniasis, with titers ranging between 1:20 and 1:40. The study of the samples obtained by liver and lymph node puncture for direct diagnosis indicated that all the animals were negative. The investigation evidences the predisposing factors that favor the presentation of leishmaniasis in the studied area. The coexistence of families with canines and felines inside and outside the house and the existence of animals with advanced ages that could behave as reservoirs for the transmission of the parasite were observed. Although no significant differences were found when relating the study area with the serology found, it is necessary to carry out educational dynamics that make known the problem of Leishmaniasis and how to keep animals to avoid the transmission of parasites and consequently suffer from the disease.

0489

A ONE HEALTH PERSPECTIVE ON THE RESURGENCE OF FLEA-BORNE TYPHUS IN TEXAS IN THE NEW MILLENNIUM

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Flea-borne typhus (FBT) is an infection caused by *Rickettsia typhi* and *R. felis* The infection is transmitted to humans by a flea bite or by the inoculation of a bite site, a skin abrasion, or mucous membranes with feces from an infected flea. In this paper, county-level epidemiological data from Texas for two decades, 1990-1999 and 2010-2019, were compared. From 1990-1999, there was an average of 30.7 cases/yr from 26 TX counties, whereas during 2010-2019 there was an average of 375 cases/yr from 91 counties; 90.5% of the recent cases occurred in urban counties. The six highest counties during 2010 to 2019 were Hidalgo (major city McAllen) > Nueces (Corpus Christi) > Cameron (Brownsville) > Bexar (San Antonio) > Harris (Houston) > Travis (Austin); these 6 counties had 2824 cases (75% of the total). Compared to 1990-1999, cases increased in Hidalgo, Nueces, Cameron, Harris, and Bexar Counties in 2010-2019 by 8.5-, 5.0-, 17.5-, 252-, and 211-fold, respectively. (Travis County had zero cases in 1990-1999). Texas is divided into 10 climate divisions. In 2010-2019, the four cooler northern set of climate divisions had only 6.1% of the total cases. FBT cases are focused in the warmer Post-Oak Savannah and Lower Rio Grande Valley divisions (39.1 and 36.4% of the cases, respectively). A One Health model is presented to explain the increase of cases of FBT in TX in the last decade. Population growth in TX has resulted in an increase in pet dogs and cats and strays. The urban/suburban environment has also promoted opossum population growth, due to greater food availability. Increasing temperatures in TX may affect various aspects of the cat flea lifecycle, including: flea infestation rates of cats, dogs, and opossums; feeding and mating frequency; and reducing the time to complete the lifecycle. Rickettsial replication within the cat flea is also increased by higher temperatures, increasing the concentration of infectious rickettsiae in the flea feces. Increased numbers of flea-infested opossums and stray cats and dogs in the urban/suburban landscape increases the risk of flea transfer to pets and to humans.

0490

MOLECULAR DIAGNOSIS OF INTESTINAL PROTOZOA IN YOUNG ADULTS AND DOMESTIC ANIMALS FROM CALI, COLOMBIA

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Intestinal parasitic infections have been considered a relevant public health problem due to an increase of the incidence worldwide. In developing countries, diarrhea and gastrointestinal symptoms cause impaired work capacity in adults and delayed rate growth in children. Enteric infections of unknown etiology can often lead to misdiagnosis, increased transmission, and morbidity. The aim of this study was to determine the prevalence of intestinal parasites in a young adult population and their pets. Stool samples from 139 university students and 44 companion animals were subjected to microscopy diagnosis using wet mounts, concentration by zinc sulphate flotation and permanent stains (Ziehl -Neelsen and trichromic smears). Molecular diagnosis of protozoa was also performed by conventional PCR. The mean age was 24 yo, 54% individuals were female, 46% were men, and 66% had at least one pet. The overall prevalence for at least one parasite was 72.7% and 27.3 % showed polyparasitism. Sixty-three patients (45.3%) were positive for microscopy and parasite rates were: *Blastocystis* sp 33%, *Endolimax nana* 15.1%, *Entamoeba histolytica/dispar/moshkovskii* complex 5% and *Giardia intestinalis* 1,4%. *Cryptosporidium* and *Dientamoeba fragilis* were not detected. Eighty-one (58.3%) patients were positive for PCR: *Blastocystis* sp, 43.1% and *Cryptosporidium* sp. 24,5%. Samples from 27 dogs, 15 cats, one rabbit and one hen were examined, and parasites were detected in 7(16%) as follows: *Giardia intestinalis* (4), hookworm (3), *Endolimax nana*(2) and *Toxoplasma* (1). Preliminary molecular analysis showed that 9 out of 10 pets from *Cryptosporidium* positive owners were also positive for PCR. Overall, university students showed high prevalence of parasitism and polyparasitism suggesting exposure to contaminated environments. *Cryptosporidium* was the predominant pathogen which was only detected by PCR in humans and domestic animals, pointing out the need for sensitive diagnosis tests in surveillance. Control strategies to prevent the effects of parasitic infections in young population should consider pets as reservoirs and transmission source.

0491

SNAKEBITE IN TANZANIA - NOW WHAT?

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The risk of getting bitten by a venomous snake is an everyday reality for many communities in sub-Saharan Africa. Nevertheless, the problem remains a neglected tropical disease, despite causing death or permanent disability to an estimated 500 000 people annually, worldwide. Pastoralists and agro-pastoralists in northern Tanzania are at a particularly high risk from snakebite, but information on risk factors and challenges of receiving and providing treatment still remains very limited. To find out about risk factors, health seeking behavior and challenges, we visited the local "Maasai" and "Maarusha" groups in two affected districts in Tanzania, and interviewed 101 snakebite victims or their guardians. We also looked at 12 years of case records of 1386 patients admitted to the local Meserani Snakebite Clinic to learn more about bite and patient characteristics and spoke to health professionals from 3 health centers in the most affected districts. Among the main findings were significant demographic characteristics exposing individuals to a higher risk of snake bite. Adults and males for example were bitten more often and working outside significantly increased the risk. The majority of victims received traditional treatment (52.7%), partly due to difficulties to reach formal healthcare services and over-reliance on traditional treatments. Victims and their families reported challenges of accessing any kind of medical care in a timely manner and long lasting effects such as pain and difficulties moving as consequence of a bite. Only one of the 3 health centers in the 26 347km2 area, the Meserani Snake Park Clinic, had antivenom available and, apart from 1 nurse at the district hospital, had training in snakebite treatment. At the district hospital and dispensary, patients were therefore usually referred to the Meserani Snake Park clinic. Our results present crucial information on the present situation. To reduce and eliminate deaths and disability from snakebite, research in Tanzania has to be expanded to enable researchers, the government, clinicians and the public to work together and join the global snakebite initiative.

0492

EXPOSURE TO INDUSTRIAL HOG AND POULTRY PRODUCTION AND URINARY TRACT INFECTIONS IN NORTH CAROLINA, USA

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An increasing share of urinary tract infections (UTIs) are caused by extraintestinal pathogenic *Escherichia coli* (ExPEC) lineages that have also been identified in poultry and hogs with high genetic similarity to human clinical isolates. We investigated industrial food animal production as a potential source of community uropathogen transmission by examining relationships of hog and poultry density with emergency department (ED) visits for UTIs in North Carolina (NC). ED visits for UTI in 2016-2019 were identified by ICD-10 code from NC›s ZIP code-level syndromic surveillance system and livestock counts were obtained from permit data and aerial imagery. We calculated separate hog and poultry spatial densities (animals/km^2) by census block with a 5km buffer on the block perimeter and weighted by block population to estimate mean ZIP code densities. Associations between livestock density and UTI incidence were estimated using a reparametrized Besag-York-Mollié (BYM2) model with Poisson likelihood and ZIP code population offset to account for spatial autocorrelation. We excluded metropolitan and offshore ZIP codes and assessed effect measure modification by calendar year, ZIP code rurality, and patient sex, age, race/ethnicity, and health insurance status. In single-animal models, hog exposure was associated with increased UTI incidence (rate ratio [RR]: 1.21, 95% CI: 1.07-1.37 in the highest hog-density tertile) but poultry exposure was associated with reduced UTI rates (RR: 0.86, 95% CI: 0.81-0.91). Increases in UTI incidence were most strongly associated with exposure to hogs alone (in the absence of poultry), while poultry-only exposure was largely unassociated with UTIs. Low-density poultry exposures attenuated relationships between hogs and UTIs, but UTI rates remained elevated in ZIP codes with large numbers of both hogs and poultry (RR: 1.28, 95% CI: 1.10, 1.48). While relationships with low-density poultry are ambiguous and warrant further analysis using individual-level exposure and outcome data, high-intensity industrial livestock production may contribute to increased UTI incidence in neighboring communities.

0493

LONG-TERM STABILITY OF ORTHOBUNYAVIRUSES IN SERA AND WHOLE BLOOD

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Orthobunyaviruses represent an understudied group of viruses with potential to cause human and animal health, as well as economic issues. In 2018, we identified Bunyamwera (BUNV) in samples from cattle in Rwanda suspected of having Rift Valley Fever virus (RVFV) and found evidence suggestive of Batai (BATV) infection in another animal. This provided evidence of alternative etiologies for disease assumed to be RVFV in cattle in Rwanda, and suggests more basic research into these viruses is warranted. Previously we showed BUNV and BATV are stable and infectious at 37°C in cell culture media for up to 30 days. In this follow-up, we established a daily Rwandan temperature profile representative of peak transmission season (May-July) from public data (min: 16.2°C, median: 19.98°C, max:24.9°C). Using this temperature profile, we investigated the stability and infectiousness of BUNV and BATV in bovine whole blood and serum up to 28 days (sampled weekly). In both substrates, stability was observed as a lack of change in RNA copies from 7 dpi to 28 dpi. When infectiousness was assessed *in vitro,* both viruses retained infectivity at 28 dpi in whole blood (5/5 BUNV samples, 4/5 samples). In serum, only BATV retained infectivity at 28 days, but only in 1/5 samples, likely an indication of a low number of viable virus particles. At 14 and 21 dpi, 5/5 and 3/5 samples were infectious, respectively. For BUNV, no samples were infectious at 21 or 28 dpi while at 14 dpi all samples (5/5) were infectious. These results do provide evidence that these viruses retain infectiousness for relatively long periods of time, and that there is an interaction between types of fluids and Orthobunyavirus with respect to retention of infectiousness over time. This has implications for biosafety and laboratory practices, and potential field-relevance to encourage increased use in PPE when handling animals and animal fluids in laboratory or food-animal processing contexts.

0494

CHARACTERISTICS OF SNAKEBITE IN TANZANIA AND TREATMENT CHALLENGES

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Continuous occurrence of snakebite incidences and vulnerability of some communities remain a critical problem in sub-Saharan Africa. Despite causing death and permanent disability to almost half a million people annually, information on snakebites and treatment challenges is still very limited, particularly in Northern Tanzania. We accessed case reports from 1386 patients visiting the Meserani Snake Park clinic in Northern Tanzania between 2007 and 2019 and studied the characteristics of snakebite. Additionally, we talked to health professionals from 3 health centers serving the local communities, to learn more about treatment challenges for snakebite. From the case studies and interviews we learnt that snakebite is common in the area. Victims reported several challenges to receiving treatment such as cost, distance to the clinic, availability of expertise and most of all, availability of antivenom. Records show an increase in the number of victims over the years, with adults significantly more affected than children. The majority of snakebites (41%) occurred on the lower limbs; whereby hands accounted for 23% of the all injuries reported. The snake responsible for the bite could not always be identified, but red spitting cobra, black spitting cobra and puff adder were recorded most often. The main treatment challenge was the fact that antivenom in the region was only available at the privately run Meserani Snake Park Clinic, but even with available antivenom, allergic reactions to the antivenom and delayed arrival at the clinic were serious challenges affecting the overall outcome. Of the 13 health professionals interviewed, only 4 had received any training in the treatment of snakebite. Notably, in the local Monduli hospital, while overall more medical expertise is present, knowledge on snakebite treatment is low while at the Meserani Snakebite Clinic, 2 out of the 3 health care workers also trained the community on snakebite prevention and treatment. The results of this study present crucial information on snake bite characteristics in Northern Tanzania and what is needed to improve the accessibility to appropriate treatment.

0495

PRESENCE OF ZOONOTIC PARASITES IN CANINE FECAL MATERIAL COLLECTED FROM THE ENVIRONMENT IN INGHAM COUNTY, MICHIGAN, USA

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Ingham County, Michigan has numerouspublic parks and dog parks that allow pet owners to spend time with their canine companions, increasing physical activity levels and therefore benefiting the overall health. However, canine fecal material left behind in these environments may pose a serious hazard to human health due to the possibility of the presence of zoonotic gastrointestinal parasites and other pathogens. This study aimed to assess environmental contamination with parasitic agents of public health importance due to canine fecal material left behind at multiple public parks and dog parks within Ingham County in the State of Michigan, USA. A total of 111 canine fecal samples were collected from seven randomly selected park locations. Zoonotic gastrointestinal parasites were detected in 42.34% of the samples using qualitative zinc sulfate fecal flotation. These parasites included: *Giardia* spp. (25.23), *Ancylostoma caninum* (17.12%), *Isospora* spp. (9.91%), *Trichuris vulpis* (1.8%), and *Toxascaris leonina* (0.9%).

0496

MICROBIAL SOURCE TRACKING OF HUMAN AND ANIMAL FECAL CONTAMINATION IN HOUSEHOLD SETTINGS IN NORTHERN ECUADOR TO INFORM EXPOSURE ASSESSMENT

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Human exposures to animals and their feces pose health risks, particularly for children in settings where domestic animals are common, hygiene is poor, and enteropathogen transmission is high. To improve understanding of potential sources of fecal contamination in households (HHs), we validated qPCR assays for and measured microbial source tracking (MST) markers in samples collected from 59 HHs along an urban-rural gradient in northern Ecuador. We used the GenBac marker to test for general fecal contamination, and the markers HF183, Rum2Bac, Pig2Bac, DG, and GFD to test for human, ruminant, swine, dog, and avian-associated fecal contamination, respectively. We collected ~10 samples per HH, including rinses of child (*n*=31) and adult (*n*=59) hands, swabs of objects and surfaces (*n*=282), soil (*n*=54), domestic (*n*=48) and drinking (*n*=55) water, and food (*n*=58). Data from hand rinses, domestic and drinking water, and floor swabs have been processed to date. GenBac was detected in 88% and HF183 in 27% of currently processed samples, with mean $\log_{10}$ gene copies (GC) per sample of 5.6 for GenBac and 3.1 for HF183. Hand rinses had the highest mean concentrations of both GenBac and HF183, followed by floor swabs and domestic water. GenBac was the only marker frequently detected in drinking water, with 2.8 mean $\log_{10}$ GC per 100 mL. Rum2Bac Pig2Bac, DG37, and GFD were detected in 0.80%, 3.2%, 7.1%, and 8.3 % of samples analyzed to date and had $\log_{10}$ concentrations of 2.5, 3.1, 2.4, and 2.6 GC per sample, respectively. Pig2Bac was detected in a single drinking water sample at low concentration. These preliminary results indicate that general (GenBac) and human (HF183) fecal contamination is common in study HHs. Detection of animal-associated MST markers was less frequent, but animal markers were present at relatively high concentrations when detected. This work demonstrates that MST can be used to characterize sources of HH fecal contamination, and will inform a larger analysis of child exposure to animal-sourced HH fecal contamination that incorporates both microbiological and qualitative data to offer insights into animal-associated enteric disease risk.

0497

EVALUATION OF A RECOMBINANT ANTIGEN ELISA FOR DETECTION OF *TRYPANOSOMA CRUZI* IN DOGS

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Chagas disease, or American trypanosomiasis, is an infectious tropical disease caused by the protozoan parasite, *Trypanosoma cruzi* (*T. cruzi*). It is endemic to 21 countries across Latin America and the southern United States. The diagnosis of chronic infection in humans relies solely on serological tests based on laboratory assays, such as two immunochromatographic strips (SP and IB), indirect fluorescent antibody (IFA), and enzyme-linked immunosorbent assay (ELISA) tests. However, existing serological tests for Chagas disease are prone to inconclusive or false-positive results and poor concordance among different assay formats. For this reason, current recommendations include using at least two different serological techniques, one being ELISA, for diagnosing chronic Chagas disease in humans. These challenges exist in both human and canine testing. Dogs are a known *T. cruzi* reservoir and host for the triatomine vector. Our study examined over 70 dog serums from multi-dog kennel environments in Texas, selected based on prior test results, to compare three available Chagas tests to our Tc-24 recombinant antigen ELISA. The immunochromatographic tests were subjectively graded by visualization. The IFA and Tc-24 ELISA produce a quantitative result. Comparing individual tests to Tc-24 ELISA resulted in SP strips having an association to Tc-24 ($p < 0.001$) and Spearman correlation = 1.0 ($p = 0.0167$). The IB strips compared to Tc-24 also showed an association to Tc-24 ($p = 0.0001$) and Spearman correlation = 0.9 ($p = 0.0833$). There was an association of IFA to Tc-24 ($p < 0.0001$) and Spearman correlation = 0.6273 ($p = 0.044$). Comparing any two positive tests to the Tc-24 ELISA showed an association of determining positive versus negative results ($p < 0.0001$) with an 82.5% sensitivity and 89.7% specificity. Comparing high IFA titers to positive Tc-24 resulted in a 100% sensitivity and 94.1% specificity. Similarly, comparing high immunochromatographic values to positive Tc-24 revealed a 100% sensitivity and 95.8% specificity. These results provide a potential new serological assay to diagnose *T. cruzi* infection in dogs with one test.

0498

ZOONOTIC AGENTS AT THE ANIMAL-HUMAN CONTEXTS GENERATED BY THE PRIMATE TRAFFICKING IN PERU

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Wildlife trafficking creates favorable scenarios for intra- and inter-specific interactions that can lead to pathogen spread and disease emergence. Among the diverse species affected by this illegal activity, monkeys gain attention for their potential to acquire and share zoonoses. Though it is known that most primate pathogens can affect multiple hosts and many of them are zoonotic, comparative studies of primate infections across different contexts for animal-human interactions are scarce. We conducted a multi-pathogen screening targeting the detection of zoonotic infections in wild-caught primates in nine Peruvian cities across three contexts: Trafficked or recently confiscated, n=132; pets, n=69; zoos and rescue centers, n=187. We detected 32 infectious agents including helminths, protozoa, bacteria, mycobacteria, and simian foamyvirus. Pathogen communities showed overall low variation between contexts. However, trafficked and confiscated monkeys had the highest prevalence of hemoparasites (including *Plasmodium malariae/brasilianum, Trypanosoma cruzi,* and microfilaria), and enteric parasites were less common in pet monkeys. Pathogen species richness (PSR) was best explained by host genus and the city where the animal was sampled. Squirrel (genus Saimiri) and wooly (genus Lagothrix) monkeys had the highest PSR, which was ~2.2 times the PSR found in tufted capuchins (genus Sapajus) and tamarins (genus Saguinus/Leontocebus) in a multivariable model adjusted for context, sex, and age. Our findings illustrate that the threats of primate trafficking to One Health encompass multiple zoonotic infections well-known to cause disease in human, monkeys, and other species. We demonstrate these threats continue beyond the markets where these animals are initially sold; primates trafficked for the pet market remain a reservoir for and translocator of zoonotic pathogens in households and other captive facilities where contact with humans is frequent. Our results inform practical applications for the healthcare of rescued monkeys and call for urgent action against wildlife trafficking and ownership of monkeys as pets.

0499

IMPACT OF THE INTRODUCTION OF PCV7/13 ON ANTIMICROBIAL RESISTANCE IN INVASIVE PNEUMOCOCCAL DISEASE IN SENEGAL

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We describe antimicrobial resistance in invasive pneumococcal due to all serotypes and non-vaccine type (NVT) pre andpost pneumococcal conjugate vaccine (PVT) implementation in Senegal in all age groups. We identify, serotype, andperformed antimicrobial susceptibility testing using disc diffusion methods on pneumococcal isolates obtained frominvasive samples collected from standardized population-based pneumococcal disease surveillance in the Casamance &demographic surveillance system. The study commenced May 2012. Pcv7 was introduced in august 2013 and pvc13 in May2016. Antibiotic susceptible were interpreted using clinical laboratory standard institute guidelines. 500 pneumococcalisolates were screened against five antimicrobial agents. There was a moderate decline in antibiotic resistance in all agegroups in invasive pneumococcal disease during vaccine implementation. In the 2 months to 2-year age group, annualcounts of oxacillin. Chloramphenicol, and tetracycline resistant cases fell from 10-15 in 2013 & 2014 to 6-7in 2017 & 2018. In the 24-59-month age group, there was a large fell in tetracycline resistance cases.in those >5 years, oxacillin,chloramphenicol, and tetracycline resistance fell to zero cases in 2015 & 2016. Resistance due to reductions in vaccine serotypes1, 5,14 & 23f. The proportion of resistant NVT cases increase over time, particularly in the 2-23-month age group,with tetracycline resistance mainly in serotypes 10A, 12F, 11B, 7C and 25A & tetracycline resistance in serotype12F in 2016.Isolates were generally sensitive to erythromycin but 95-98 were generally sensitive to cotrimoxazole throughout the study.Although there is an overall reduction in case of antimicrobial resistance IPD, resistance is emerging in NVT. We hypothesisthat increased transmission of NVT after the introduction of PCV and exposure to antimicrobials facilitates the emergence ofresistance in NVT. Ongoing surveillance is important to determine future trends in resistance as it has both clinical andpublic health importance in PCV era.

0500

PERCOLATION ACROSS HOUSEHOLDS IN MECHANISTIC MODELS OF NON-PHARMACEUTICAL INTERVENTIONS IN SARS-COV-2 DISEASE DYNAMICS

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Since the emergence of the novel coronavirus disease, mathematical modelling has become an important tool for planning strategies to control the pandemic by supporting decision-making, as well as allowing an assessment of the effect of different intervention scenarios. A proliferation of compartmental models was observed in the mathematical modelling community, aiming to understand and make predictions regarding the spread of COVID-19. Such an approach has its own advantages and challenges: while compartmental models are suitable to simulate large populations, the underlying well-mixed population assumption might be problematic when considering non-pharmaceutical interventions (NPIs) which strongly affect the connectivity between individuals in the population. Here we propose a correction to an extended age-structured SEIR framework with dynamic transmission modelled using contact matrices for different settings in Brazil. By assuming that the mitigation strategies for COVID-19 affect the connections between different households, network percolation theory predicts that the connectivity across all households decreases drastically above a certain threshold of removed connections. We incorporated this emergent effect at population level by modulating the home contact matrices through a percolation correction function, with the few remaining parameters fitted to hospitalisation and mortality data from the city of Sao Paulo. We have shown how different model implementations can affect the system's basic reproduction number and found significant support for the model with implemented percolation effects using the Akaike Information Criteria (AIC). Besides better agreement to data, this improvement also allows for a more reliable assessment of the impact of NPIs on the epidemiological dynamics and can be applied to model any infectious disease dynamics undergoing a similar contact network fragmentation process.

0501

ESTABLISHING SARS COV-2 VIRAL SEQUENCING CAPACITY IN A RESOURCE-LIMITED, HIGH-RISK AREA IN THE PERUVIAN AMAZON REGION. PRELIMINARY RESULTS

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Peru has recorded some of the highest rates of morbidity and mortality from COVID-19 in the world. The city of Iquitos in the Peruvian Amazon region has been particularly vulnerable due to its isolation, with accessibility by air and river only; its limited clinical facilities; its severe oxygen shortages; and its river commerce with other Amazonian hot spots in Brazil, leading to attack rates and mortality figures well above the Peruvian national average. Robust surveillance to detect new COVID-19 variants is critical to identify epidemiological shifts and direct public health resources, but strain sequencing capacity has only been available at a few sites in the capital city of Lima, with limited capacity for analyzing strains from any one region and delays in providing results. With funding from the NIH Fogarty Global Infectious Diseases training program and the CDC Conducting Public Health Research in South America program, and in collaboration with the public health reference laboratory of the regional Ministry of Health (DIRESA de Loreto), the Laboratorio Iquitos has established COVID-19 sequencing capacity in Iquitos and trained a core group of biologists in genetic sequencing. Viral sequencing was performed using Illumina COVIDSeq kit with an Illumina iSEQ 100, and sequence data was uploaded to databases housed by the National Center for Biotechnology Innovation (NCBI) and GISAID. We have sequenced viral isolates from 120 patients (69 women [58%]) presenting in January 2022 who were residents of Iquitos (96%) or rural areas (4%). Average age of patients providing isolates was 39 years (range 5-74). All 120 isolates typed as Omicron variant (98% BA.1 sublineage, 2% BA.1.1 sublineage). By comparison, analysis of 24 viral isolates from March to June 2021 all typed as Gamma variant that had first been detected in Brazil several months earlier (46% sublineage P.1, 12% P.1.1, and 42% P.1.4). Further data collection is ongoing, including analysis of sublineages associated with cases among vaccinated individuals and repeat COVID-19 infections.

0502

THE ROLE OF VACCINATION ROUTE WITH AN ADENOVIRUS-VECTORED VACCINE IN PROTECTION, VIRAL CONTROL, AND TRANSMISSION IN THE SARS-COV-2/K18-HACE2 MOUSE INFECTION MODEL

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While vaccination is the most effective mechanism to prevent severe COVID-19, transmission of SARS-CoV-2 among vaccinated persons remains a significant problem. Furthermore, all currently marketed SARS-CoV-2 vaccines are delivered by intramuscular (IM) injection, even though intranasal (IN) delivery may be more effective in limiting transmission

between persons. Utilizing a replication-deficient adenovirus serotype 5-vectored vaccine expressing the SARS-CoV-2 RBD (AdCOVID) in the K18-human ACE2 mouse model, we investigated the impact of route of administration on vaccine immunogenicity, survival, and transmission. K18-hACE2 mice were vaccinated with AdCOVID via the IM or IN route and subsequently challenged with SARS-CoV-2. Following challenge, a cohort of vaccinated mice were co-housed with naïve K18-hACE2 mice and the viral load in both vaccinated and naïve recipients was quantified. The results of the study show that IN vaccinated animals had improved mucosal antibody responses, viremic control, and protection from lethal infection as compared to IM vaccinated animals. IN vaccination also resulted in reduced viral transmission to naive co-housed individuals compared to IM vaccination. Overall, our data provides further evidence for the utility of IN vaccination in protecting against SARS-CoV-2 infection and transmission. Additional studies exploring the mechanism surrounding enhanced protection afforded by IN vaccination are needed.

0503

ROADBLOCKS AND RESILIENCE: A QUALITATIVE STUDY OF THE IMPACT OF PEDIATRIC TUBERCULOSIS ON TANZANIAN HOUSEHOLDS

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This study explored the lived experiences of youth and their caregivers in starting and sustaining treatment for tuberculosis (TB). We sought to identify the impact of childhood TB on household members' daily lives and relationships; strengths and barriers important to children's treatment course; and opportunities for improvement in their care. We recruited children ages 4 to 17 years diagnosed with TB and their caregivers from rural and semi-urban municipalities in northern Tanzania. A semi-structured qualitative interview guide was developed, informed by the team's exploratory research questions. Twenty-four interviews were conducted in Kiswahili and audio-recorded. Interviews were transcribed and translated by bilingual interviewers. English transcripts were analyzed qualitatively by coding for emerging themes relevant to the research questions. Themes included the socioemotional impact of TB on households, including adverse effects on work productivity, and facilitators and obstacles to TB care, including general financial hardship and transportation challenges. To end TB, we must improve access to care for populations disproportionately affected by the disease, including rural and semi-urban communities in Tanzania. Healthcare systems must acknowledge the transportation burden shouldered by low wealth families seeking pediatric TB care, provide consultations and medications locally, and increase access to TB-specific communal funds.

0504

CHILDHOOD ACUTE RESPIRATORY INFECTION AND IRON DEFICIENCY ANAEMIA IN RURAL GAMBIA

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Acute respiratory infection (ARI) is a leading cause of morbidity and mortality among young children in the African region. In The Gambia, more than 3 in 5 young children are anaemic, 65% due to iron deficiency anaemia (IDA). In this study, we examined whether lower haemoglobin (Hb) and ferritin levels were associated with ARI. We used data from a double-blind, randomised, placebo-controlled, phase II clinical trial with iron replacement therapy in Gambian children 6-35 months of age. Each arm included active follow-up period of 12 weeks intervention and 4 weeks post intervention and provided round-the-clock appropriate healthcare. We grouped baseline Hb and ferritin levels into low (≤ median values) and high (>median values) based on their respective medians and used logistic regression to examine their association with ARI adjusting for age and gender. During the study period, 1494 children were screened from 45 villages and 642 children 6-35 months with mild to moderate anaemia were randomised and enrolled of which 584 children completed follow up. Among them 47.6% (278/584) had low haemoglobin (≤9.6 g/dL), 50.9% (237/466) had low ferritin (≤9.5). A total of 249 children reported ARI during follow-up among 584 (42.6%) children. Low haemoglobin was associated with increased odds of ARI; the crude and adjusted ORs (95%CIs) were 1.42 (1.02-1.97), Pvalue=0.037 and 1.41 (1.01-1.96), Pvalue=0.045 respectively. Lower odds ratios were observed for the association of adjusted ferritin; the crude and adjusted ORs (95%CIs) were 1.25 (0.87-1.81), Pvalue=0.228 and 1.26 (0.87-1.83), Pvalue=0.226 respectively. Low haemoglobin and ferritin levels, which are indicators IDA, may be risk factors for childhood ARI in rural Gambia. Early and accurate diagnosis, prompt treatment and prevention strategies are needed to prevent IDA in young children.

0505

SARS-COV-2 SEROPREVALENCE AMONG ANTENATAL CARE ATTENDEES IN KENYA, NIGERIA, MALAWI, MOZAMBIQUE, UGANDA, AND ZAMBIA, 2021-2022

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The novel coronavirus SARS-CoV-2, the virus that causes of COVID-19, continues to spread globally. Due to inadequate test availability and the high proportion of asymptomatic infections, case counts using test positivity alone likely under-estimate the true burden of disease. Serological surveys can provide insight into the proportion of the population that has been exposed to SARS-CoV-2. As attendance at antenatal care (ANC) is largely unrelated to illness, pregnant women can be a valuable sentinel population. Women were enrolled during their first ANC visit from health facilities in six countries (Kenya, Malawi, Mozambique, Nigeria, Uganda, and Zambia) during March 2021 through February 2022. The study is ongoing. Consented participants responded to a questionnaire consisting of demographics, COVID-19 risk factors and protective behaviors, and self-reported uptake and perceptions of vaccination. A dried blood spot sample was collected for serologic testing using the FlexImmArray™ 7-Plex SARS-CoV-2 Human IgG Antibody Test (Tetracore). Analysis was conducted in R-software version 3.6.1. A total of 23,040 women were enrolled: 2,550 in Kenya, 3,849 in Malawi, 3,635 in Mozambique, 8,184 in Nigeria, 3,832 in Uganda, and 990 in Zambia. Median age is 25 (IQR: 21 - 30). The proportion of self-reported as vaccinated with at least 1 dose of a COVID-19 vaccine was 10.7% in Kenya, 3.7% in Malawi, 28.6% in Mozambique, 2.5% in Nigeria, 27.6% in Uganda, 12.9% in Zambia. Seropositivity was 33.6% in Malawi, 60.5% in Uganda, and 41.0% in Mozambique (serology data from remaining countries is in progress). Cumulative case data estimates less than 2% of any study countries' population was infected, highlighting that case counts underestimate true rates of infection. Although vaccination rates remain low, a large proportion of the study population has some level of immunity.

0506

SARS-COV-2 INFECTION WAVES IN ASEMBO AND KIBERA, KENYA: FINDINGS FROM POPULATION-BASED INFECTIOUS DISEASE SURVEILLANCE (PBIDS), MAY 2020-FEBRUARY 2022

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Data on SARS-CoV-2 circulation and clinical characteristics of the COVID-19 cases in Kenya are limited. Using Population-Based Infectious Disease Surveillance (PBIDS) in rural (Asembo, Siaya County) and urban (Kibera informal settlement, Nairobi County) settings, we report COVID-19 surveillance data between May 1, 2020 to February 3, 2022. Patients of any age presenting to a clinic in each PBIDS area who met the case definition for acute respiratory illness (ARI: acute onset of cough, difficulty breathing, sore throat or coryza), severe acute respiratory illness (SARI: acute onset of cough, difficulty breathing or chest pain and either fever ≥38.0 °C, oxygen saturation <90% or admission to hospital), acute febrile illness (AFI: axillary temperature ≥38.0 °C) or were contacts of a SARS-CoV-2 positive individual within 14 days of presentation were consented and enrolled. Nasopharyngeal and oropharyngeal swabs were collected and tested for SARS-CoV-2 using real-time PCR. Demographic and clinical data were collected in real time and entered into an electronic patient care system. Infection waves were demarcated by the minimum inflection points on the SARS-CoV-2 epidemic curve. Among 15,261 participants, 1,402 (9.2%) were PCR positive for SARS-CoV-2 (7.0% in Asembo and 12.8% in Kibera). In Asembo, three infection waves were observed with 660 COVID-19 cases while in Kibera there were 742 cases in five infection waves. The timing of the start and peak of the infection waves varied by site. ARI was the most common reason for enrollment in most waves (91.4% of all cases in Asembo and 83.6% of all cases in Kibera), followed by presentation with AFI in Asembo (10.3%) and COVID-19 contacts in Kibera (14.0%). Of the COVID-19 vaccine-eligible patients, 127 (29.1%) reported vaccination in Asembo and 122 (27.1%) in Kibera. Across both sites, there were 45 (3.4%) cases hospitalized and 8 (0.6%) deaths overall. SARS-CoV-2 infection waves were not synchronized between Asembo and Kibera. Most patients had mild respiratory illness. Although vaccination coverage was low, most cases were not severe enough for hospitalization and there was a low case fatality rate.

0507

NONADHERENCE TO ANTI-TUBERCULOSIS TREATMENT AMONGST PATIENTS IN MONTSERRADO COUNTY, LIBERIA

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Non- adherence to tuberculosis treatment is an important barrier influencing TB treatment failure. However, Liberia national prevalence of TB and non-adherence rate is unknown. Therefore, this study aimed to assess factors related with non-adherence to anti-TB treatment amongst patients in Montserrado County, Liberia. A facility based cross sectional study was conducted in four (4) health facilities in Montserrado County, 2019. We collected data using semi-structured questionnaire. The Morisky Medical Adherence 8 item scale (MMAS-8) was used to assessed patients' non-adherence level. We defined non-adherence as an individual scoring < 6 points in the MMAS-8. Variables were assessed using the chi- square test and Fisher's exact tests. Multiple logistic regression analysis was conducted on all factors used to declare the independently associated predictors that were statistically significant at a confidence interval of 95% and P value < 0.05. A total of 317 TB patients participated in the study. Majority of participants were males and age group 30 to 39years accounted for 90 (28.4%). The overall non-adherence to anti-tuberculosis treatment was 25.9% (95%CI = 21.3 - 31.0%). Almost Half 49 (59.8%) of the non-adherents indicated they had ever missed their appointment. Nonadherence was found to be significantly associated with pill burden (cOR 4.00, 95%CI: 2.10 - 7.65), Changes in family/friends relationship (aOR 8.30, 95%CI: 2.40 - 28.73), longest period of time one failed to take TB medication (cOR 2.48, 95%CI: 1.02 - 6.07), and patient ease of strictly following medication (aOR 0.051, 95%CI:0.01 - 0.27). Our findings proposed that non-adherence was high among TB male patients found within the age group 30-39 years. Patients who consumed at least 3-4 pills daily under the direct observation of treatment supporters were less likely to adhere to treatment plan. Family members' poor relationship with patients, and unavailability of drugs contributed to patients' non-adherence. Therefore, we recommended strengthening awareness and decentralization of TB services to ensure regular supply of drugs.

0508

MOLECULAR VIABILITY TESTING ACCELERATES DETECTION OF *MYCOBACTERIUM BOVIS* BCG-ASSAY DEVELOPMENT FOR HUMAN CHALLENGE TRIALS

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Clinical trials of anti-tuberculosis drugs involve human challenge by intradermal inoculation of *M. bovis* bacille Calmette-Guerin (BCG). It is challenging to evaluate live BCG in the skin of inoculated volunteers and to assess the effectiveness of drugs in a timely manner. Molecular viability testing (MVT) uses reverse transcription PCR (RT-PCR) to detect pre-ribosomal RNA (pre-rRNA) present only in viable BCG. This study validated BCG MVT for use in future human clinical trials and included a mouse model study of isoniazid (INH). BCG was cultured in nutrient-limited human serum with or without 0.5 µg/mL INH for 4 days after which diluted samples were cultured in 7H9 liquid media. Aliquots were extracted for nucleic acids followed by RT-PCR and PCR. Pre-rRNA expression normalized by CT values to rDNA. Dormant/dead BCG were expected to generate pre-rRNA:rDNA ratios of ~1. BCG cultured in nutrient-limited human serum generated pre-rRNA:rDNA ratios up to 75 after 3 days, indicating early replication; such growth was confirmed by increasing OD_{600} measurements after 4 days. BCG cultured in INH yielded pre-rRNA:rDNA values ~1 with no change in OD_{600} over 3 weeks of culture. For the mouse study, $2x10^6$ CFU of BCG were intradermally injected into mouse ears (n=10). After 4 days, 5 of 10 mice were treated with a sub-therapeutic dose of INH (1 mg /L water) for 4 days. Inoculated skin was excised, homogenized, diluted, and cultured in 7H9 media with aliquots harvested daily for the next 5 days for MVT. MVT of skin homogenates showed detectable BCG by RT-PCR and PCR but no increase in pre-rRNA. After homogenates were cultured in 7H9 media for ≥1 day, pre-rRNA:rDNA ratios rose 20-69 fold in untreated mice and 20-34 fold in INH-treated mice. One INH-treated mouse showed undetectable BCG pre-rRNA and DNA. This study demonstrated BCG MTV can detect replication of live BCG in liquid culture much earlier than when turbidity-based measures or colonial growth are used. A pilot study in mice showed recoverable, viable BCG in biopsies, showed some drug-related effects, and refined the tissue collection and processing procedures for future human challenge clinical trials.

0509

IMPROVING TUBERCULOSIS MANAGEMENT THROUGH STRONGER HEALTH WORKER CAPACITY ON THE USE OF AN ELECTRONIC REPORTING SYSTEM IN BANGLADESH

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Bangladesh is one of 30 high tuberculosis (TB) burden countries with a mortality rate of 24 per 100,000 population. Monitoring and managing of TB patients is a critical element in controlling TB. The USAID Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program supported the National Tuberculosis Control Programme (NTP) of the Ministry of Health and Family Welfare (MOHFW) of Bangladesh and WHO to adopt e-TB Manager, a web based electronic recording and reporting system for managing TB patient care. The USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program has continued the collaboration with the MOHFW to support the NTP to complete the nationwide scale up through the capacity building of health care workers (HCWs) at TB reporting centers to efficiently use the e-TB Manager system. MTaPS developed training materials and user guidelines and provided hands-on training to HCWs. The training includes how to capture individual TB patients' data on medicines, laboratory testing, diagnosis, treatment, and outcomes in the electronic system. As a result of these capacity building efforts under SIAPS and MTaPS, around 2500 HCWs across the 868 TB reporting centers in the country were trained on the system between 2013 to 2021. The number of e-TB Manager active users increased 92% between 2013 and 2022 and 100% of TB reporting centers are now routinely using the system to manage individual TB patient records. HCWs' strengthened capacity to use eTB manager has improved data quality, reduced the data validation and report preparation time (relative to paper-based reporting), and increased the real-time reporting of TB patients, which allows for informed decision and action by the relevant authorities. HCWs are now better able to contribute to achieving the goal of limiting TB infection and ensuring better health outcomes for TB patients in Bangladesh.

0510

LONG TERM IMPACT ON LUNG FUNCTION OF PATIENTS WITH MODERATE AND SEVERE COVID-19: A PROSPECTIVE COHORT STUDY

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There is a wide knowledge gap about lung function capacity among the COVID-19 survivors. In this study, we aim to determine the long-term impact on lung function capacity in patients recovered from moderate or severe COVID-19 disease. A prospective cohort study was conducted at Aga Khan University Hospital, Karachi Pakistan. Patients of age ≥15 years who recovered from moderate or severe COVID-19 disease were included. Pulmonary function was assessed by performing spirometry and diffusion lung capacity for carbon monoxide (DLCO) along with chest x-ray at the three- and the six-month interval following time since discharge. Univariate logistic regression was done to measure the association between abnormal lung function and independent variables. A total of 67 patients completed three-months follow up. Of them, 7 were lost-to-follow-up at six months. Majority of the participants were males 54 (81.0%) and median (IQR) age of participants was 55 (11) years. Abnormalities on chest x-ray were detected in all patients at the time of discharge, in 5 patients (7.5%), at three months and 8/60 (13.3%) patients, at the six-month interval. DLCO was impaired in 23 (34.3%) patients, at three months and in 26/60 (43.3%), at six months. In 2 patients there was mild basal septal hypertrophy on ECHO at three months follow-up. Age (years), severity of disease, comorbidities, Intensive Care Unit stay, length of hospital stay in (days) and C- reactive protein (mg/L) were significantly associated with impaired lung function at three months' follow-up on univariate analysis. In addition to factors significant at three-month interval, duration of steroids in days, neutrophil lymphocyte ratio and lactate dehydrogenase level were significantly associated with impaired lung function at 6 months interval. None of the variables was statistically significant on multivariable analysis. We conclude that patients who survived from moderate -severe COVID-19 had poor lung function capacity over 6 months follow up period. Robust, larger scale follow-up studies can be planned to better understand the impact of COVID-19 on lung function capacity of survivors.

0511

HIGH COVID-19 VACCINATION COVERAGE IN URBAN SLUM POPULATIONS IN BRAZIL

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Inequities in COVID-19 vaccine coverage have contributed to disparate outcomes among socially deprived communities globally. We sought to estimate the prevalence of COVID-19 vaccination and identify factors associated with vaccination in a socioeconomically vulnerable population of an urban informal settlement. We conducted two serial surveys in an urban slum community in Salvador, Brazil, before and after the rollout of COVID-19 vaccines in February 2021. In an initial survey (November 2020 to February 2021), we assessed participants' willingness to get vaccinated. In a follow-up survey (July 2021 to February 2022), we assessed completion of vaccination. We limited our analysis to 801 adults who participated in both surveys since vaccination was not offered to minors until December 2021. Most participants were women (62.2% vs 37.8% men), identified as Black (54.1%) or Brown (40.1%), and were unemployed (52.7%). In the first survey, 68.2% of participants expressed willingness to get vaccinated. Of these, 499/546 (81.9% [95% CI 72.6-88.6%]) received a vaccine. Of the 255 participants who were initially unsure or uninterested in a COVID-19 vaccine, 60.9% [95% CI 50.6-70.4%] nevertheless were vaccinated. Overall, 75.8% [95% CI 72.6-78.7%] of participants had initiated or completed a primary vaccination series. The most common formulations received were BNT162b2 (36.7%), ChAdOx1 nCov-19, (34.5%), and CoronaVac (24.5%). Women were more likely to be vaccinated than men (78.5% [95% CI 68.9-85.8%] vs 71.3% [95% CI 61.2-79.7%], p=0.03). However, we did not observe significant differences in vaccine coverage by employment (p=0.22), or eligibility for social welfare programs (p=0.48). Our results indicate high acceptance of COVID-19 vaccines in this vulnerable population, even among individuals who had previously expressed reluctance. These findings suggest that hesitancy is a modifiable barrier to COVID-19 vaccination in populations that inhabit urban informal settlements, highlighting the importance of ensuring equitable access to vaccines and the opportunity to reduce inequities experienced by these marginalized communities.

0512

THIRTY DAYS MORTALITY PREDICTORS IN SEVERE ACUTE MALNOURISHED CHILDREN WITH SEVERE PNEUMONIA

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To determine the predictors of mortality within 30 days of hospital admission in a diarrheal disease hospital in Bangladesh. A cohort study of hospitalized children aged 0-59 months with severe acute malnutrition (SAM) and severe pneumonia was conducted in the Dhaka Hospital, icddr,b Bangladesh from April 2015-March 2017. Those discharged were followed up and survival status at 30 days from admission was

determined. Children who died were compared with the survivors in terms of clinical and laboratory biomarkers. Multivariable logistic regression analysis was used for calculating the adjusted odds ratio for death within 30 days of hospital admission. We enrolled 191 children. Mortality within 30 days of admission was 6% (14/191). After adjusting for potential confounders (hypoxia, C-reactive protein and hematocrit) in logistic regression analysis, independent factors associated with death were female sex (aOR=5.80, 95% CI:1.34-25.19), LAZ<-4 (aOR=6.51, 95% CI:1.49-28.44) and Polymorphonuclear Leukocytes (PMNL) (>6.0x10^9/L) (aOR=1.06, 95% CI:1.0-1.11). Using sex, Z-score for length for age (LAZ), and PMNL percentage, we used random forest and linear regression models to achieve a cross-validated AUC of 0.83 (95% CI:0.82, 0.84) for the prediction of 30-day mortality. The results of our data suggest that female sex, severe malnutrition (<-4LAZ) and higher PMNL percentage were prone to be associated with 30 days mortality in children with severe pneumonia. Association of these factors may be used in clinical decision support for prompt identification and appropriate management for the prevention of mortality in this population.

0513

KNOWLEDGE, ATTITUDES, AND PRACTICES ON COVID-19 AMONG BUKAVU'S POPULATION

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The World Health Organization has declared the COVID-19 as a pandemic in March 2020. Through our work, we have assessed the knowledge, attitudes and practices of the population of the city of Bukavu facing this scourge. Using a survey questionnaire made by Sphinx, we conducted a descriptive cross-sectional study on 1063 people in the three residential commune of the city of Bukavu from June to august 2020. Our results, grouped into 13 tables and 14 figures, show in general that 97.9% of our population were informed about the COVID-19 pandemic, especially through the radio at 73.7%. The attitudes of the population are more or less resistant to compliance with so-called barrier measures because only 31.0% of respondents adhere to these measures and only 27.5% actually apply them. We also noticed that the more intrusive the measures are, the more hypothetical their compliance becomes. The respondent's blame the authorities for poor communication around the disease at 10.7% and 22.5% thought that the response would be politicized. Faced with the disease, 21.0% believe that COVID-19 is a real and dangerous disease, but the authorities should improve communication at all costs according to 18.3% of respondents and 17% believe that we should learn to live with the disease. As for the practices, they are relatively conventional because 68.10% of the population would go to the nearest Health Center for treatment, and 57.80% would call the toll-free number. However, for fear of being infected, 19.6% of respondents would not go to a health facility, 20.0% expressed fear of being sequestered and 12.0% assumed exorbitant health care costs. The proportion of those who would do the nebulization (14.4%) in the event of illness is not really to be overlooked. The authorities should therefore think about improving communication around the disease, while depoliticizing the response and offering the traditional media more means to popularize barrier measures even more. In addition, other researchers will be able to do the analysis that we have not been able to carry out to further improve the knowledge, attitudes and practices of the population of Bukavu in the face of COVID-19.

0514

VIRAL PATHOGENS, RISK FACTORS AND OUTCOMES AMONG PNEUMONIA PATIENTS IN WESTERN KENYA

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In the past few years rural communities in Kenya have suffered the dual burden of an epidemic caused by a novel emerging respiratory virus added to high background rates of morbidity and mortality from pneumonia. Active surveillance aimed at identification of specific viral etiologies may provide early warning signs, enabling timely interventions. As part of a wider viral pathogen discovery network, we enrolled 174 patients (target 200) of all ages diagnosed with pneumonia presenting to a district hospital in western Kenya and characterized the viral pathogens, risk factors and outcomes for pneumonia. After completing a questionnaire, nasopharyngeal swabs were collected and interrogated by real time polymerase chain reaction (PCR) for a panel of 12 known viral pathogens. Between February 2021 and February 2022, we enrolled 94 children and 80 adults. To date the most common viral pathogens identified were SARS-CoV-2 (18.4%), Respiratory Syncytial Virus (RSV)-A (16%), Influenza A (2.4%) and enterovirus (4.4%). Influenza B and Parainfluenza type 4 (PIV4) were detected in a small number of cases, but RSV-B has not been identified. Non-pandemic coronaviruses were detected in 39.6% of pneumonia patients, but a large proportion of these were co-infections with other viruses. The majority of patients received supplemental oxygen (57.5%) which is the highest level of supportive care available in this context. 71.8% of cases had no known comorbidities, 14.9% reported hypertension and 7.5% had diabetes. Only 16.1% of cases recalled being in close proximity with other symptomatic individuals and nearly the same proportion had recently travelled (22.4%). Out of 156 with known discharge status, there were 7 deaths, two with SARS-CoV-2 detected and one with human coronavirus HKU-1. On average, patients with SARS-CoV-2 infection stayed in the hospital for 1.5 more days than other patients. Respiratory viruses are a common cause of hospitalization with pneumonia in Kenya where viral diagnostics are not frequently available. Access to rapid viral diagnostics in rural hospital settings could reduce the inappropriate use of antibiotics for viral pneumonia.

0515

CARDIORESPIRATORY ARREST OF COVID-19 PATIENTS ADMITTED IN THE ICU AT THE REFERRAL HOSPITAL OF NYANTENDE AND BIOPHARM CLINIC IN BUKAVU, DEMOCRATIC REPUBLIC OF CONGO

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Since the end of 2019, the world is facing the covid-19 pandemic. The first case was described in China at the seafood market of Wuhan, a severe acute respiratory syndrome due to the Sars-cov-2 virus. Clinical features

are mostly respiratory. A cardiorespiratory arrest is among clinical fatality of covid-19 and was described in many cases in developed countries. In the Democratic Republic of Congo, limited studies focused on the impact of cardiac arrest on covid-19. We have conducted a retrospective, descriptive and analytical multicentric study in Bukavu at the Referral Hospital of Nyantende and Clinical Biopharm. The aim of our study was to improve the health care management of cardiorespiratory arrest in a covid-19 patient admitted to ICU in the two health structures. We screen the databases of covid-19 patients to whom a cardiorespiratory resuscitation was performed. During the study period, 68 covid-19 patients have undergone cardiorespiratory resuscitation. Among them, 38 were admitted to ICU at Biopharm Clinic and 30 at the Referral Hospital of Nyantende. The majority were elderly people (+ 65years). Apnoe and asystolic were the most etiology described. The CPR consists of airway free, external cardiac massage, usage of adrenaline, and Intratracheal intubation. The time of resuscitation was at mean 30minutes. The majority of those patients dead. The age category has significantly impacted the clinical outcome with the *p*-value 0.0017 for patients within 19-30years and 0.0052 for cardiorespiratory resuscitation type. The causes, clinical complications, and resuscitation technic have an impact on the outcome but are statistically nonsignificant. Cardiorespiratory arrest remains a serious problem on which we may focus in covid-19 healthcare patients especially in developing countries with a limited equipment for this purpose.

0516

PERCEPTIONS OF COVID-19 AND COVID-19 VACCINES IN RURAL ZAMBIA

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COVID-19 vaccines are highly effective public health tools to prevent COVID-19-related morbidity and mortality. However, coverage is low throughout much of sub-Saharan Africa, part due to vaccine hesitancy. In Zambia, the national vaccine campaign was launched in April 2021 and renewed in October 2021. To date, coverage is only 12.1%. Within the context of ongoing respiratory surveillance at Macha Hospital in rural Zambia, participants with influenza-like-illness (n=376) were asked about their perceptions of COVID-19 and COVID-19 vaccines between May 2021 and February 2022. The goal of this analysis was to describe how perceptions changed over time. COVID-19 waves were defined based on national case counts as 'post wave 2' (May 2021, n=44), 'wave 3' (Jun 1 to Aug 14 2021, n=61), 'post wave 3' (Aug 15 to Dec 14 2021, n=178), and 'wave 4' (Dec 15, 2021 to Feb 28, 2022, n=94). The proportion of participants reporting being worried that they or their family would get COVID-19 increased from 67.4% in 'post wave 2' to 89.4% in 'wave 4'. The proportion who did not believe COVID-19 was a serious illness decreased from 88.4% to 63.8%. The proportion of participants reporting that they would get themselves or their child vaccinated was 40-55% in 'post wave 2', 'wave 3' and 'post wave 3', and then increased to 78.7% in 'wave 4'. Similar proportions and trends were reported for beliefs that vaccines were safe and would protect them from COVID-19. Participants not wanting to be vaccinated were asked to provide reasons (n=149). The top five reasons were concerns about vaccine safety (64.4%), getting COVID-19 from the vaccine (13.4%), side effects (12.8%), the vaccine being developed too quickly with insufficient human testing (6.7%), and the vaccine altering DNA (4.0%). Overall, only 7.9% of adult participants reported being vaccinated. In summary, vaccine acceptability increased in rural Zambia at the end of 2021 as the national vaccine campaign was renewed, case counts increased, and perceptions about COVID-19 severity increased. These findings can inform strategies to improve vaccine uptake in Zambia.

0517

FASCIOLIASIS COMPLICATING WITH ACUTE NECROTIZING PANCREATITIS IN AN ETHIOPIAN CHILD - A CASE REPORT ON A RARE COMPLICATION OF A RARELY REPORTED EMERGING DISEASE

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Fascioliasis is a zoonotic infection cause by the liver fluke *Fasciola*. Though infrequently diagnosed, it is emerging as a helminth infection of public health importance in many parts of the world. Few reports exist on human fascioliasis from Africa. Acute pancreatitis as a complication of fascioliasis is an even rarely reported syndrome globally. We report a case of a twelve year old Ethiopian boy presenting with a left sided abdominal pain and a dietary history of frequent consumption of leafy vegetables. His work-up showed leukocytosis with marked eosinophilia, increased serum amylase and lipase with imaging confirming multiple sub-capsular hepatic masses complicating with an acute necrotizing pancreatitis. Upon serologic testing for helminths, he tested positive for *Fasciola hepatica* enzyme immunoassay. He was managed with intravenous fluids, proton pump inhibitors, antibiotics and oral Triclabendazole. Fascioliasis should be considered as a possible diagnosis people with predisposing culinary practice and presenting with eosinophilia and liver masses. Chronic Fascioliasis can complicate with pancreatitis.

0518

CERVICOVAGINAL LAVAGE HEMOGLOBIN IS NOT ASSOCIATED WITH GENITAL SCHISTOSOMIASIS IN ZAMBIAN WOMEN

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Female genital schistosomiasis (FGS), caused when *Schistosoma haematobium* eggs are deposited in genital tissue, is prevalent in sub-Saharan Africa. The cervical mucosa in FGS is associated with an increase in abnormal blood vessels and has been associated with contact bleeding. If FGS is associated with the presence of hemoglobin (Hb) in cervicovaginal lavage (CVL) fluid, the use of urinary dipsticks (Hemasticks®) on CVL to detect Hb could supplement FGS diagnosis, but the association of *Schistosoma* with CVL Hb has not previously been described. Women aged 18-31, participating in the HPTN 071 (PopART) Population Cohort, who were sexually active, not currently menstruating and not pregnant were invited to participate in the Bilharzia and HIV (BILHIV) study. Eligible women were enrolled in two communities in Zambia from January - August 2018. Genital self-swabs and a urine specimen were collected and a questionnaire was administered at home visits. A midwife obtained CVL at the cervical cancer clinic and used a hand-held colposcope to evaluate for FGS-associated cervicovaginal lesions. Visual-FGS was defined as the presence of sandy patches, rubbery papules, or abnormal blood vessels. *Schistosoma* real-time PCR was performed on genital specimens (cervical swab, vaginal swab, and CVL). Circulating Anodic antigen (CAA) and microscopy were performed on urine. PCR-FGS was defined

as *Schistosoma* DNA detected by PCR on CVL or genital swab. Of 209 women with CVL Hb results and genital swabs with companion CVL specimens, 66% (138/209) had detectable CVL Hb, 13.4% (28/209) had PCR-defined FGS, 17.2% (36/209) had visual-FGS. Active *Schistosoma* infection, diagnosed by CAA or urine microscopy, was present in 21.0% (44/209) participants. Neither active *Schistosoma* infection (p=0.4), PCR-FGS (p=0.7) nor visual-FGS (p=0.3) were associated with CVL Hb presence. Results did not differ in sub-groups with high infection burden. In conclusion, we found that neither established FGS nor active *Schistosoma* infection was associated with the presence of Hb in CVL. Further research is needed to fully evaluate the etiology and clinical significance of CVL Hb in Zambian women.

0519

IDENTIFICATION OF NOVEL THERAPEUTICS AGAINST HUMAN SCHISTOSOMIASIS

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Human schistosomiasis is a neglected tropical disease caused by parasitic worms. It affects over 250 million people globally. Most human infections are caused by *Schistosoma mansoni, S. haematobium,* and *S. japonicum.* Currently there is only one method of treatment for human schistosomiasis, the drug praziquantel. Constant selection pressure has caused a serious concern because of rise in resistance to praziquantel leading to the urgent need for additional pharmaceuticals, with a distinctly different mechanism of action, to be used in combination therapy with praziquantel. Previous treatment of *S. mansoni* included the use of oxamniquine (OXA), a prodrug that is enzymatically activated by a sulfotransferase, an enzyme produced by *S. mansoni*. Although sulfotransferases are produced by *S. haematobium* and *S. japonicum,* OXA is not effective against these two species. Also, Praziquantel is not effective against juvenile stages of the parasite. Structural data have allowed for directed drug development in reengineering oxamniquine to be effective against *S. haematobium* and *S. japonicum*. Guided by data from Xray crystallographic studies and *Schistosoma* worm killing assays more than 350 OXA derivatives were designed synthesized and tested *in vitro* against the adult parasites. To date, our study has identified powerful reengineered derivatives that are more effective than oxamniquine in killing all three species, juvenile stages, and praziquantel resistance strain *in vitro*. *In vivo* studies revealed that three of these derivatives caused a significant reduction in the number of harvested worms from *S. mansoni, S. haematobium,* and *S. japonicum* infected animals. In addition, treating infected mice with these derivatives during juvenile stages led to significate reduction in the number of immature worms. The later result is an advance over Praziquantel that does not kill immature *schistosomes.*

0520

HEMATOLOGICAL CHANGES IN *SCHISTOSOMA HAEMATOBIUM* INFECTED RETURNED TRAVELERS

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Earlier studies found characteristic hematological changes in African schoolchildren with an active *Schistosoma haematobium* infection. At large, these differences included a trend of decreasing hemoglobin, and an increase of leukocyte count and thrombocyte count. Full blood count (FBC) alterations might not be unique to African children and might be observable in general across geographical areas and age groups and could thus be observable in travelers returning with schistosomiasis from endemic countries. If consistently present, FBC may possibly be used as a surrogate diagnostic parameter for acute *S. haematobium* infection. A retrospective patient record review was performed by six European travel clinics on returned travelers infected with active (egg producing) *S. haematobium*. The means of the FBC parameters were calculated and compared to normal population reference values by a one sample *t*-test. A total of 231 subjects with a mean age of 22.7 years (SD = 9.0) were included into the data analysis. We found lower means of hemoglobin (β = -0.4 g/dL, $p < 0.001$ [males]; β = -0.6 g/dL, $p < 0.001$ [females]) and MCV (β = -4.2, $p < 0.001$), similar hematocrit (β = -0.0%, $p = 0.992$ [males]; β = +0.7%, $p = 0.471$ [females]) and higher erythrocyte counts (β = +0.3 10^6/dL, $p < 0.001$ [males]; β = +0.3 10^6/dL, $p = 0.137$ [females]). Thrombocyte and leukocyte counts were lower (β = -42 10^3/dL, $p < 0.001$ and β = -0.06 10^3/dL, $p < 0.001$, respectively). As to be expected, eosinophils were increased (β = +0.42, $p < 0.001$), whilst the other differential leukocyte counts, including basophils, neutrophils, lymphocytes and monocytes, were all decreased (β = -0.05, -1.93, -0.43, and -0.09, respectively, p for all < 0.001). An active infection with *Schistosoma haematobium* is associated with hematological alterations in travelers. Notably, these changes do not completely match those found in African schoolchildren, as we found lower leukocyte and thrombocyte counts, which calls for further exploration. Furthermore, FBC alterations might also be observable across other *Schistosoma* species infections whilst eggs are produced, which is yet to be investigated.

0521

BIOMARKER DISCOVERY AND ASSAY DEVELOPMENT TO DETECT ANTIBODIES TO *SCHISTOSOMA HAEMATOBIUM*

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The new World Health Organization (WHO) neglected tropical diseases road map for 2021-2030 highlights the need for better diagnostic tests to support the control and elimination of schistosomiasis. Antibody detection could be useful for diagnostic needs to determine when transmission has been interrupted and subsequent surveillance to detect recrudescence of infection. The WHO target product profile for this use case employs a two-step strategy to achieve the necessary specificity. The first screening test should provide high sensitivity with allowances for lower specificity, while the confirmation test requires higher specificity with acceptable lower sensitivity. While several recombinant *Schistosoma mansoni* antigens have been developed and tested for species-specific antibody detection, only a few antigens have been described for *S. haematobium.* We attempted to identify sero-reactive epitopes from *S. haematobium* using serum epitope repertoire analysis (SERA). We screened sera from individuals with *S. haematobium* infection (n = 60) and controls (n = 60). We identified ten candidate epitopes mapped to seven *S. haematobium* proteins. We used *in silico* analysis to discover potential B-cell epitopes for these proteins and identified 34 peptide sequences of interest. We also conducted *in silico* analysis to identify epitopes on *S. haematobium* secretome and membrane-bound, GPI-anchored proteins. We selected 323 antigens and converted them into 1,376 different 15 amino acid linear peptides. Overall screening results identified 50 potential target peptides that were synthesized and re-screened using peptide ELISA. One peptide detected total IgG and IgG1 antibodies with signal-to-noise ratio for IgG3 ~ 29, while the other peptide only detected total IgG with a signal-to-noise-ratio > 15. These peptides will be used to develop into assays using their recombinant proteins or a multi-epitope proteins.

0522

ASSAY DEVELOPMENT TO DETECT ANTIBODY TO *SCHISTOSOMA MANSONI* INFECTIONS BASED ON RGST-SM29.

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The CDC Parasitic Diseases Reference Laboratory diagnoses *Schistosoma mansoni* infection among U.S. travelers, Peace Corps volunteers, and immigrants using two serologic assays. Sera are screened by FAST-ELISA using purified *S. mansoni* adult microsomal antigen (MAMA), followed by confirmation using immunoblots with two diagnostic bands, Sm29 and Sm25. We have sought to develop recombinant versions of these antigens to improve assay reproducibility and overcome the costs and challenges of sourcing enough *S. mansoni* adult worms associated with purifying native MAMA. While rSm25 has been successfully expressed, used, and validated in several assay platforms, efforts over almost 40 years using bacterial and insect cell-culture expression systems have failed to produce functional rSm29. We attempted to express Sm29 using a mammalian cell expression system to overcome these challenges. The recombinant plasmid encoding a glutathione S tranferase-Sm29 fusion protein was transiently transfected into the human embryonic kidney (HEK) 293-6E cells. The target protein was captured from the culture supernatant using glutathione Sepharose 4 columns, followed by buffer exchange. The purified protein was analyzed by Western blot. We compared the performances of rGST-Sm29, rGST-Sm25, and MAMA immunoblot strips against 35 negative and 23 confirmed positive *S. mansoni* sera. The specificity of all immunoblots was 100%; the sensitivity of the rGST-Sm29 and MAMA immunoblot strips was 96% (22/23), and the rGST-Sm25 immunoblot strips had a sensitivity of 91% (21/23). We tested species specificity with 14 *S. haematobium* and 14 *S. japonicum* confirmed positive sera. These sera recognized none of the rGST-Sm29 strips, while rGST-Sm25 and MAMA strips showed cross-reactivities. We then developed an ELISA using the new rGST-Sm29 and tested 16 *S. mansoni* positive and 16 negative sera. ELISA sensitivity and specificity were 94% (15/16) and 100%, respectively. The recombinant antigens will be used to develop a multiplex bead assay and evaluated for diagnostic utility in reference laboratories, verification of transmission interruption, and surveillance.

0523

IMPROVING FEMALE GENITAL SCHISTOSOMIASIS SCREENING WITHIN GOVERNMENT HEALTH FACILITIES IN ZAMBIA

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The World Health Organization (WHO) estimates that up to 56 million women and girls are living with female genital schistosomiasis (FGS) in sub-Saharan Africa. FGS causes reproductive disorders including infertility, pregnancy complications, lost productivity, and stigma. Identification of FGS is difficult due to confusion with symptoms of other genital abnormalities and gold standard diagnosis with colposcopy is not feasible or affordable in most health facilities. Our study aims to develop and pilot test a comprehensive screening algorithm that is feasible to implement in Zambian government clinics. We recruited 497 women from a longitudinal cohort of HIV-negative female sex workers or single mothers ≥ 18 years in Lusaka and Ndola, Zambia. We used demographic, risk factor, and symptom data collected from standardized surveys, gynecological exams, and laboratory tests to develop a risk score for FGS. The area under the receiving operating curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the risk algorithm were calculated using score cut-offs defined as the median score. The prevalence of FGS on colposcopy was 23.5%. The risk score had reasonable discrimination in the full cohort (AUC = 0.69, 95% CI: 0.63-0.74, p-value < 0.001). Using a score cut off of 2, the risk algorithm in the derivation cohort had 70% sensitivity, 56% specificity, 33% positive predictive value (PPV), and 86% negative predictive value (NPV). Additional analyses will consider both the development and performance of the algorithm when data are divided into a 70:30 training- and test-set. We will also examine which factors discriminate between those who are accurately captured by the algorithm (true positives) and those who are missed (false negatives). This work is imperative to understanding the risk factors associated with FGS among a cohort of young adult women in Zambia and the opportunities, as well as challenges, for identifying an algorithm that is feasible to implement in Zambian government clinics.

0524

DETECTION OF DUAL SCHISTOSOME PARASITES IN URINE COLLECTED FROM PREGNANT WOMEN IN GHANA VIA LOOP-MEDIATED ISOTHERMAL AMPLIFICATION (LAMP)

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40 million pregnant women are infected with soil-transmitted helminths (STHs) and Schistosome parasites in sub-Saharan Africa. When parasitic diseases share the same habitat and overlap in distribution then high rates of co-infection occur. Such is the case in Ghana; however, published data on the effect of helminth infections on pregnant women in Ghana are not extensive. The co-infection can lead to consequences for the child, such as intrauterine growth retardation, low birth weight, pre-term delivery, and neonatal mortality. The objective of the study was to determine the prevalence of Schistosomiasis co-infection (*Schistosoma mansoni* and *S. haematobium*) among pregnant women from Battor and Adidome districts of Ghana using loop-mediated isothermal amplification (LAMP) amplification of cell-free species-specific repeat DNA from collected filtered urine samples. We have determined the nature and extent of Schistosome coinfection (single or dual infection) from 100 filtered urine samples collected from Battor (50 samples) and Adidome (50 samples) districts of Ghana in collaboration with Noguchi Memorial Institute for Medical Research, University of Ghana. The overall distribution and frequency of such coinfection in pregnant women (age range 14 - 45yrs) were also assessed. The positive infection rate for the two species and dual infection was highest for women in 20 - 30yrs of the age range. In Adidome district (out of 50 samples), *S. mansoni* had the highest infection prevalence (32 positives) compared to *S. haematobium* (28 positives) and dual infection was 44%. Whereas in Battor district, the infection prevalence for *S. mansoni* (25 positives) was higher than *S. haematobium* with a dual infection rate of 22%. Mixed infection was high in both Adidome (22 out of 50) and Battor (11 out of 50) districts. LAMP detected both Schistosome species with high sensitivity and specificity. LAMP also proved to be a more efficient, sensitive, and specific diagnostic test for co-infection detection among the vulnerable group of the population.

0525

SHIFTING TO COMMUNITY-BASED TREATMENT AND THE IMPLICATIONS OF THE NEW WHO RECOMMENDATIONS FOR SCHISTOSOMIASIS CONTROL?

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In 2022, the World Health Organization (WHO) launched new recommendations on prevalence thresholds and target age groups receiving preventive chemotherapy (PC) against schistosomiasis. "Recommendation 1" is for communities with schistosomiasis prevalence ≥10% to receive annual PC in all age groups above two years.

"Recommendation 2" for communities with prevalence <10% is one of two approaches: PC at the same/reduced frequency or test-and-treat approach if no treatment program in place. To better understand the ramifications of (1) refining PC at the community level (rather than district treatment) and (2) adult treatment (rather than traditional school-based strategies), a schistosomiasis tracker and dashboard were developed by USAID's Act to End NTDs program to calculate sub-district/community treatment needs. We estimated praziquantel (PZQ) calculations using (1) the 2011 WHO program managers guidelines and (2) the new 2022 recommendations across eight countries in Act West. Overall, PZQ quantities did not differ significantly when calculations were based on district or sub-district prevalence. The drug calculations by guideline were significant, however, when adult treatment was included. There was a threefold increase in PZQ needed if PC was expanded to adults in moderate-to-high risk areas using the 2011 guidelines but a fourfold increase using the 2022 recommendations. The adjusted 10% prevalence threshold under the new WHO recommendations combined with the shift to community-wide treatment significantly expands eligibility for PC, beyond the global supply of PZQ via the donation program currently estimated at 300 million annually. This presentation addresses six key points: (1) PZQ calculations by guideline and coordination of donors/WHO/pharmaceutical/implementers to prioritize supplies, (2) country ownership on changing treatment strategies and donor/partner capacity to accommodate large scale shifts; (3) tools that estimate calculate community prevalence; (4) guidelines to support control programs in shifting to a more refined sub-district treatment strategy; and (5) community-wide treatment.

0526

COST-BENEFIT OF CONDUCTING SCHISTOSOMIASIS IMPACT ASSESSMENTS TO CHANGE A TREATMENT STRATEGY: EVEN SURVEYS THAT FAIL CAN SAVE CONTROL PROGRAMS MONEY

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Schistosomiasis control programs typically use annual preventive chemotherapy at the district level based on prevalence surveys conducted at baseline. After five to six rounds of mass drug administration (MDA) the recommendation by the World Health Organization is to conduct an impact assessment to evaluate whether prevalence has reduced, thereby changing the treatment strategy. Implementing intensive impact assessments are costly and logistically demanding. Given the focal nature of schistosomiasis, there is a move towards more granular surveys in smaller evaluation units such as sub-districts or "communities". We present the cost effectiveness of conducting impact assessments for different evaluation unit sizes (district versus sub-district) and the financial implication of undertaking MDA with and without conducting impact assessments. The Tool for Integrated Planning and Costing (TIPAC) helps estimate the cost of such surveys and cost per treatment at the district versus sub-district level, and whether the impact assessment yields a positive return on investment given the change in treatment costs. Togo has advanced considerably on the road to schistosomiasis control. The country conducted baseline mapping in 2009, an impact assessment in 2015, followed by a second re-assessment of sub-district prevalence in 2021. Data presented here examines the cost of conducting the schistosomiasis impact survey in 2021 and the costs of continuing MDA without doing an impact survey versus modifying the MDA where indicated by the survey results. Population size is taken into consideration to examine the threshold at which continuing MDA without impact surveys becomes advantageous in financial cost terms. Although schistosomiasis impact assessments have a non-trivial cost, they can save money overall, depending on the size of evaluation unit and assuming the data generated is reliable.

0527

RISK FACTORS AND COOCCURRENCE OF SOIL TRANSMITTED HELMINTHIASIS AND SCHISTOSOMIASIS IN COMMUNITIES WHERE PREVENTIVE CHEMOTHERAPY IS THE MAIN INTERVENTION IN THE FEDERAL CAPITAL TERRITORY, NIGERIA

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Schistosomiasis (SCH) and Soil-transmitted helminthiasis (STH) are Neglected Tropical Diseases (NTD) of public health importance in Nigeria - one of the countries with the highest burden globally. The Federal Capital Territory (FCT), is a growing urban area with peri-urban communities traversed by rivers and streams that supports the transmission of SCH and settings for STH. The dynamics of both diseases with Preventive Chemotherapy as major strategy, the influence of the environment and behavioural practices in the dynamics of transmission may require additional interventions. A cross-sectional study was conducted among children and adults in five communities, in three Area Councils of FCT. Semi-structured questionnaires were used to obtain Socio-demographic data from 442 participants from whom stool and urine samples were collected and examined for eggs of *Schistosoma mansoni*/STH and *Schistosoma haematobium* respectively. Results were analysed using Pearson's Chi-Square (χ^2) test and logistic regression. Overall, the prevalence of STH and SCH was 42.8%; with 3.8% having concurrent STH-SCH infections. Of those infected, 10% had STH and Hookworm was the most predominant (9.3%). For SCH, 37% were infected, of which 31.4% and 13.6% were *S. mansoni* and *S. haematobium respectively*. Contact with parasite infested water was associated with an increased risk of Urinary-SCH caused by *S. haematobium* (OR = 0.54; 95% CI: 0.31 - 0.94; $P<0.05$). Open defecation was associated with increased risk of both STH (OR = 1.79; 95% CI: 0.89 - 3.60; $P = 0.102$) and Intestinal-SCH (OR = 0.50; 95% CI: 0.33 - 0.77; $P = 0.002$). Participants ≥18 years old had higher rate of concurrent infection than those, <18 years old (4.5% vs 3.5%; OR = 0.76; 95% CI: 0.29 - 2.05, $P = 0.591$) while males were more infected than females (5.0% vs 3.0%). The use of unsafe sources of water for household chores was significantly associated with increased risk of concurrent STH-SCH Infections (OR = 2.82; 95% CI: 1.02 - 7.79; $P = 0.045$). Scale-up of Water, Sanitation, Hygiene and Environment and other interventions will accelerate attainment of control and elimination targets in the FCT.

0528

MALARIA AND SCHISTOSOMIASIS COOCCURRENCE THREE AREA COUNCILS IN THE FEDERAL CAPITAL TERRITORY, NIGERIA

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Malaria and schistosomiasis are endemic in many regions of sub-Saharan Africa with greatest prevalence in Nigeria despite the efforts being made to control these diseases. The geographical overlap of these diseases often results in concurrent infections and with the elimination agenda for both diseases, the need for integration of interventions and strategies become critically important for cost-effectiveness rather than the separate handling by different programmes in the same community when the efforts could be harnessed for impact. There are variations in the distribution and prevalence of malaria-schistosomiasis in different settings of the country. This study determined the prevalence of malaria, schistosomiasis and their co-occurrence in selected communities in Gwagwalada, Abuja Municipal and Bwari Area Council Areas of the Federal Capital Territory (FCT), Nigeria. A cross-sectional study was used in assessing 416 research participants from five communities in three Area Councils in FCT. Urine, stool and blood samples examined using standard procedures for schistosomiasis (*Schistosoma mansoni* and *S. haematobium)* and malaria. Questionnaires were used to collect demographic and work-related data. Of the 416 participants, 42(10.1%) were positive for malaria, Gwagwalada had prevalence of 11.4%, AMAC 9.3% and Bwari had 4.4%. Overall Schistosomiasis prevalence was 151(36.3%). Highest prevalence was seen in Gwagwalada Area Council (50.2%). AMAC and Bwari Area Council showed prevalence rates of 16.7% and 2.2% respectively: The prevalence of *S. haematobium* and *S. mansoni* was 52(12.5%) and 128(30.8%) respectively. Overall Malaria-schistosomiasis co-occurrence was 4.1% with 6.1%, 0.9% and 0.0% in Gwagwalada, AMAC and Bwari respectively. No significant association was seen between malaria and schistosomiasis (p>0.05).The opportunities for integration of diseases control and elimination will accelerate control efforts and data on cooccurrence are relevant to this approach.

0529

VARIATIONS IN THE EFFICACY OF PRAZIQUANTEL IN THE CONTROL OF SCHISTOSOMIASIS IN THE FEDERAL CAPITAL TERRITORY, NIGERIA

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Schistosomiasis is a disease of public health importance and Nigeria is one of the most endemic countries in the world. Caused by majorly *Schistosoma haematobium* (urinary schistososmiasis) and *S. mansoni* (intestinal schistosomiasis), it results in poor cognitive development, urinogenital and gastrointestinal presentations (including Female genital schistosomiasis), bladder carcinoma etc. As a focal disease, schistosomiasis is linked with poor environmental infrastructures, behaviour, poor sanitation, hygiene and poverty. Preventive chemotherapy in mass administration of medicines is effective in reducing morbidity and transmission while snail control is yet to be implemented at scale in Nigeria. Reports of resistance of *Schistosomes sp* to praziquatel (PZQ) has been also been documented elsewhere. We conducted a therapeutic efficacy assessment of praziquantel in a cohort of 65 children above five years and adult participants drawn from 584 participants that were assessed for schistosomiasis morbidity in the Federal Capital Territory (FCT), Abuja in August 2021. Standard dose of PZQ was administered to each participant after collection of pre and two weeks post treatment. Urine and stool specimens were collected from the participants and parasitological tests, including urinalysis was performed using standard protocol. Kato-katze was done for stool samples. All measurements were calibrated as egg count/10 ml of urine and egg per gram for stool samples. Our findings showed that there was variability in the efficacy of PZQ among the participants assessed as cure rates (egg clearance) for the Schistosomes spp. Cure rates was 49% and 29% for *S Haematobium* and *S mansoni* respectively. The egg intensity also varied by age-groups for the Schistosome species while morbidity indicator in the urine was significantly reduced. The study is still ongoing to determine the pharmacokinetics and drug metabolism of PZQ in the study population. Poor outcomes to PZQ could be a great threat to the elimination agenda for schistosomiaiss and periodic drug efficacy monitoring is recommended.

0530

HIGH PREVALENCE OF *SCHISTOSOMA MANSONI* INFECTION AMONG ADULTS WITH CHRONIC NON-COMMUNICABLE DISEASES IN MALAWI - A CROSS-SECTIONAL STUDY AT MANGOCHI DISTRICT HOSPITAL

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Schistosomiasis is a parasitic infectious disease caused by flatworms of the *Schistosoma* genus. The global burden of schistosomiasis is high. In Malawi, schistosomiasis is among the top 20 causes of outpatient department visits in health facilities. Schistosomiasis is among the most important but neglected causes of non-communicable diseases (NCD) peculiar to tropical endemic settings. While much is known about the contribution of *S. haematobium* to the NCD burden in Malawi, the role of *S. mansoni* remains largely unknown. We conducted a cross-sectional study at Mangochi District Hospital. Adults over 18 years diagnosed with NCDs (n = 414), admitted or attending weekly outpatient clinics were recruited between August 2021 and February 2022. Data were collected on sociodemographic characteristics, medical history, body weight, blood pressure, and fasting blood glucose. Stool and midstream urine were collected for Kato Katz (KK) microscopy and urine circulating cathodic antigen (CCA) tests respectively. We computed prevalence of *S. mansoni* as number of positive KK and CCA tests, each divided by total submitted samples. Univariate and multivariable logistic regression were done to evaluate risk factors of NCDs and association between *S. mansoni* infection and NCDs. We recruited 414 participants, mean age 57 years (SD 16), 67% of whom were female. Prevalence of *S.mansoni* based on urine CCA was 15% (95% CI 11 – 19) and 0% on KK microscopy. Hypertension was the most common condition with a prevalence of 85% (95% CI 81 – 89), followed by diabetes mellitus with a prevalence of 42% (95% CI 37 – 46) and heart disease with a prevalence of 3% (95% CI 2 – 5). Age (OR 1.1 (95% CI 1.05 – 1.12)), unemployment (OR 4.7 (95% CI 1.2 – 18)), and body weight (OR 1.04 (95% CI1.01 – 1.07)) were significantly associated with hypertension. *S. mansoni* infection was not significantly associated with hypertension (OR 1.2 (95% CI 0.5 – 3.1)), diabetes (OR 0.6 (95% CI 0.3 – 1.1)) or heart disease (OR 2.0 (95% CI 0.4 – 10)).We observed high prevalence of *S. mansoni* infection among adults in the study. This is within the range observed in children in Mangochi from 10 – 56.7%.

0531

BURDEN OF FEMALE GENITAL SCHISTOSOMIASIS AMONG WOMEN ATTENDING THE SAINT-LOUIS HOSPITAL IN THE NORTH OF SENEGAL

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Female genital schistosomiasis (FGS) is a public health problem in women and girls living in schistosome-endemic areas. Indeed, the presence of schistosome eggs in genital tissue is classically associated with a burning sensation in the genitals, malodorous discharge, and pain as well as infertility, ectopic pregnancies, and miscarriage. The

WHO recommends routine and repeated antischistosomal treatment for those targets to reduce the risk of developing FGS. In Senegal, there is a lack of epidemiological data on the burden of this neglected disease in population at risk. This study was done to describe the profile of FGS cases in patients attending hospitals in the north of Senegal. A descriptive study was carried out to collect epidemiological data on women attending the hospital of Saint-Louis in the north of Senegal from 2019 to 2020. All study participants were examined under colposcopy. The signs and symptoms of FGS were identified using the pocket atlas for clinical health-care professionals developed by the WHO. Each image obtained after colposcopy was examined by two gynecologist and one mid-wife. Socio-demographics and clinical data were described for each participant. A total of 173 women examined under colposcopy have been included in the study. Signs of FGS have been identified in 45 patients (26 %). Among the patients positive for FGS, 46.7% of the patients have shown grainy sandy patch while 24.4% of them have presented rubbery papules. Lesions of homogenous sandy patch and abnormal blood vessels were respectively observed in 17.7% and 11.2% of the women. The Visual inspection with acetic acid has yielded 7 positive results (15%) among the FGS cases. This study has shown the important number of FGS among women attending health facilities in the north of Senegal. Further studies are needed at community level to propose the best strategies for the management of cases.

0532

SCHISTOSOMIASIS SEROPREVALENCE AMONG CHILDREN 0-15 YEARS OF AGE IN NIGERIA, 2018

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Blood samples and risk factor data were collected during the population-based 2018 Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS). Participants consented to storage and future testing of specimens, enabling use of NAIIS data to determine national seroprevalence estimates for other diseases of public health importance. Schistosomiasis seroprevalence was assessed by reactivity to schistosome soluble egg antigen (SEA) in a multiplex bead assay and analyzed in conjunction with NAIIS data to assess risk factors for seropositivity. Frequencies and proportions were compared using univariate logistic regression utilizing Taylor series linearization to account for cluster sampling to generate crude odds ratios (cOR); analyses were repeated adjusting for urban/rural area (aOR). SEA antibody data were available for 31,459 of 32,494 (96.8%) children aged 0-15 years included in the study. Overall seroprevalence was 17.2% (95% confidence interval (CI) 16.3-18.1%). Seroprevalence varied by state. Factors associated with increased odds of seropositivity included: male sex (cOR=1.34, 95% CI 1.24 - 1.45), living in a rural area (cOR=2.2, 95% CI 1.9 - 2.5), and animal ownership (cOR=1.67, 95% CI 1.52-1.85). Access to improved sanitation and drinking water sources were associated with lower odds of seropositivity (cOR=0.52, 95% CI 0.47-0.58 and cOR=0.53, 95% CI 0.47-0.60, respectively), regardless of whether the child lived in a rural (sanitation: aOR=0.7, 95% CI 0.6 - 0.8; drinking water: aOR=0.7, 95% CI 0.6 - 0.8) or urban (sanitation: aOR=0.6, 95% CI 0.5 - 0.7; drinking water: aOR=0.5, 95% CI 0.4 - 0.6) area. Seroprevalence increased with increasing age ($p<0.0001$) and seropositive children were identified in every age group, including <5 years. This is Nigeria's first population-based estimate of schistosomiasis seroprevalence. Population-based survey methodologies, although not designed to identify focal areas of high or persistent schistosomiasis transmission, can identify additional populations at risk (children age <5 years), new risk factors (animal ownership), and monitor changes over time in response to control efforts.

0533

KNOWLEDGE AND AWARENESS OF SCHISTOSOMIASIS AND FEMALE GENITAL SCHISTOSOMIASIS AMONG TEACHERS IN GHANA

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Schistosomiasis and its consequence of repeated infections i.e., Female Genital Schistosomiasis (FGS) continue to pose major health challenges to endemic populations, especially young girls and women in Sub-Saharan Africa (SSA). A major approach adopted in the prevention of schistosomiasis and FGS in Ghana is Mass Drug Administration (MDA) of praziquantel to school children using teachers as distributors. Knowledge and awareness of schistosomiasis and FGS among teachers are therefore very important in ensuring the success of MDA campaigns. This study therefore examined the knowledge and awareness of schistosomiasis and FGS among teachers in Ghana. Data for this paper was collected as part of the FGS Accelerated Scale Together (FAST) package study. The World Health Organization modified Expanded Programme on Immunisation sampling frame was used to sample 313 teachers in the Weija-Gbawe Municipality (Weija) and North Tongu District in Ghana. Data was analysed using frequencies, percentages and the binary logistic regression. The results showed that, while 92.97% of the teachers had heard of schistosomiasis, only 21.5% of them had heard of FGS. Similarly, while 67.7% of the teachers knew that schistosomiasis can be prevented by not performing activities in rivers, very few of them (13.8%) knew that schistosomiasis can be prevented with praziquantel. We also found that, only 40.2% of the teachers knew that pain when urinating is a sign and symptom of schistosomiasis. Results of the logistic regression further showed that, teachers aged 18-30 years, those who teach at the junior high school level as well as teachers with less than two years of teaching experience in the chosen communities, had lesser odds of having knowledge and awareness of schistosomiasis and/FGS. Thus, to ensure the effectiveness of schistosomiasis and FGS MDA campaigns, knowledge and awareness of teachers about schistosomiasis and FGS need to be enhanced. In doing so, young teachers (18-30 years), teachers who teach at the junior high school level as well as those with less than two years of teaching experience in the communities where they teach should be given more attention.

0534

ASSESSMENT OF *SCHISTOSOMA JAPONICUM* INFECTION IN ENDEMIC AREAS IN CENTRAL SULAWESI, INDONESIA, AFTER MASS DRUG ADMINISTRATION PROGRAM

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Schistosoma japonicum infection is resilient in the three valleys of Lindu, Napu, and Bada in Central Sulawesi, Indonesia. To accelerate elimination, two rounds of annual mass praziquantel administration to humans and animals were conducted in 2018 and 2019, followed by targeted treatment, ecological interventions, educational campaigns, and stool surveys. These combined efforts resulted in a decrease in human

infection prevalence from 0.65-3% in 2017 to 0.3% in 2019. We aimed to determine the Kato Katz (KK) positive rate for *S. japonicum* infections in a low-endemic setting after mass drug administration (MDA). After MDA and the 2019 stool survey, a longitudinal cohort was followed from September 2019 to April 2020. Participants were residents of the 9 villages in Napu Valley and ≥2 years old. Participants' selection was guided by data on known KK-positive households identified in the 2019 stool survey. All consenting participants were asked to provide stool samples across three consecutive days (1 pot/day) at enrolment. Stool KK was examined in the field laboratory, and those with positive results were treated with praziquantel and re-evaluated 8 weeks later. Individual and household risk factors were collected using standardized questionnaires. The cohort comprised 185 participants (61 children and 124 adults aged ≥18 years) from 46 households. At enrolment, 29 (15.7%) were KK positive (9/61 (14.8%) children and 20/124 (16.1%) adults). 28/29 (96.5%) with eggs per gram (EPG) <100 and 1 adult with EPG 432. 26 (89.7%) positives KK were treated with praziquantel, and at 8 weeks post-treatment, 24/26 was negative (92.3% cure rate and 96.5% egg reduction ratio). Persistent positives were seen in 2 children with EPGs 24 and 48. *Trichuris trichiura* was found in 2 (1.1%) participants, and *Necator americanus* in 4 (2.2%). Even after two rounds of MDA, schistosomiasis infections were still prevalent. Directly observed treatment should be emphasized and close contact monitoring should be intensified. Additionally, potential reservoirs of transmission should be targeted in conjunction with human infection reduction campaigns.

0535

FOCAL UROGENITAL SCHISTOSOMA INFECTION, MALARIA AND ANEMIA AMONG SCHOOL-AGE CHILDREN IN THE KASSENA NANKANA EAST DISTRICT, GHANA

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In sub-Saharan Africa, co-morbidity with malaria, schistosomiasis, and soil transmitted helminths (STH) is common among young children. The current study investigated malaria, urinary schistosomiasis and their co-infection and anemia among school-age children in an endemic community, Nakolo in the Kassena-Nankana East District of northern Ghana. A cross-sectional survey of 336 school-age children, 5 to 16 years was undertaken. Urine samples were examined for *Schistosoma haematobium* ova using microscopy. Finger prick blood samples were examined for *Plasmodium* parasites using microscopy and haemoglobin concentration measured with HemoCue Hb301 photometer. The mean age was 10.52 (Standard deviation: ±2.27; range: 5 - 16 years), of which 50.6% (170/336) were males. The overall prevalence of urinary schistosomiasis and *Plasmodium (P.) falciparum* was 12.8% (43/336) and 37.8% (127/336), respectively with 6.0% (20/336) coinfection. Participants with only *P. falciparum* infection had 17.8% (19/107) of moderate anemia whilst 21.7% (5/23) of children infected with only *S. haematobium* had moderate anemia and 4.3% (1/23) had severe anemia. 5.0 % (1/20) of moderate anemia was observed in concurrent infections of *P. falciparum* and *S. haematobium*. Use of open water bodies was associated with increased risk of *S. haematobium* infection (OR = 1.21; 95% CI = [1.06-1.39]; p = 0.001), with females being at reduced risk (OR = 0.93; 95%CI = [0.87-0.99]; p = 0.005). Absence of self-reported haematuria had 0.81 times reduced odds of *S. haematobium* infection (OR = 0.81; 95%CI = [0.74-0.87]; p< 0.001). This study has revealed that urinary schistosomiasis remains prevalent in Kassena-Nankana East District and suggests that urinary schistosomiasis may contribute to moderate anemia among school-age children as compared to asymptomatic malaria infection. These findings call for an evaluation of the annual mass drug administration of Praziquantel among in-school children to ascertain its impact on urinary schistosomiasis prevalence across the district.

0536

ENVIRONMENTAL CONTAMINATION WITH *SCHISTOSOMA JAPONICUM* EGGS FROM AGRICULTURAL PRACTICES AND SANITATION INFRASTRUCTURE IN SICHUAN, CHINA

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Environmental contamination of eggs excreted in the fecal waste of infected humans and bovines can perpetuate the transmission of *Schistosoma japonicum*. In China, interventions target both humans and bovines and include improving sanitation infrastructure and penning and replacing bovines with agricultural machinery. *S. japonicum* transmission has been interrupted in many previously endemic areas but continues in others. In Sichuan Province, where *S. japonicum* reemerged in 2007 and transmission persists in limited foci, bovines are used for agricultural labor and night soil harvested from household stool pits is used on all major crops. We aimed to describe the risk of environmental contamination with *S. japonicum* from household sanitation and agricultural practices in seven villages in Sichuan Province from 2007 to 2016. We developed a metric to describe the emissions of potentially contaminated waste (PCW) from households, accounting for uncontained bovine and human waste and night soil harvested from sanitation infrastructure with variable rates of egg removal and inactivation. With this metric, we determined how much PCW was discharged into the environment and evaluated how the risk of environmental contamination with *S. japonicum* has changed over time. While the number of surveyed households increased slightly between 2007 and 2016, total PCW emissions declined by nearly 50% from over 1.1 million kilograms in 2007 to less than 600,000 kilograms in 2016. Reductions in PCW were primarily due to reductions in bovine ownership and, to a lesser extent, improvements in sanitation and reductions in night soil use. Additional analyses will evaluate the association between PCW emissions and *S. japonicum* infection in humans and bovines. In a period in which agricultural and sanitation interventions were implemented, PCW emissions declined but risk remains for environmental contamination with *S. japonicum* eggs, especially from bovine waste. Further efforts to contain bovine waste and inactivate *S. japonicum* eggs through improved sanitation will further reduce environmental contamination and curtail *S. japonicum* transmission.

0537

THE DEVELOPMENT OF MOBILE ENABLED DIAGNOSTICS FOR SCHISTOSOMIASIS CONTROL ANALYTICS (MEDSCAN)

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Schistosomiasis control and elimination efforts have relied heavily on mass drug administration (MDA) campaigns during the last several decades. While this strategy has been undeniably effective in lowering the overall burden of disease, countries that are moving towards elimination continue to struggle with persistent transmission hot spots despite widespread MDA. It is becoming clear that MDA alone is not sufficient to achieve complete elimination, and more targeted interventions are required to avoid a plateau in progress. Before its conclusion, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) released definitive guidance outlining the pressing need for higher-resolution surveillance capabilities in the schistosomiasis sphere. This guidance suggested that the incorporation of these higher-resolution surveillance programs would likely help to unlock underlying geospatial analysis and lead to more data-driven, targeted interventions. In this work, we present

the development process for a mHealth-based geospatial surveillance platform: MEDSCAN (mobile enabled diagnostics for schistosomiasis control analytics). MEDSCAN is a platform designed to incorporate image-processing with existing diagnostics like the point-of-care circulating cathodic antigen (POC-CCA) test for schistosomiasis to provide an instant, automated, semi-quantitative diagnosis. By transforming the already successful POC-CCA test into a "connected" diagnostic, MEDSCAN serves as the gateway to near real-time surveillance with the spatial resolution necessary to shift efforts from control to elimination.

0538

BOTTLED WATER AS A MAIN DRINKING WATER SOURCE IN COUNTRIES WITHIN THE LATIN AMERICA AND CARIBBEAN GROUP

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Whereas part of the worldwide expansion of bottled water use is composed of its role as an occasional convenient supplement, in some countries, it is becoming one of the main sources of drinking water. This study examined the extent of bottled water use as the main drinking water source identified within recent national household surveys in Latin America and the Caribbean (LAC). Inclusion criteria required a LAC country to have available household survey data from 2018 or later which used the same standardized drinking water questions. Of the eight countries meeting these inclusion criteria, the Dominican Republic had the highest prevalence of bottled water identified as the main drinking water source at 78.7% of households. This was followed by Turks and Caicos Islands (TCI) (48.9%) and Honduras (45.6%). Cuba and Costa Rica were at the bottom of the list of eight with minimal use (0.3%). Using a broader classification of "container water" to also include use of water stations to fill up bottles, water delivery trucks, and sachets of water, the Dominican Republic value rose to 90.3%, and was surpassed by TCI at 90.8%. In four countries, the majority of households identified pipe/tap water to their house as their main source of drinking water, ranging from 59.9% (Suriname) to 96.4% (Costa Rica). Lack of access to pipe/tap water did not appear to be a major contributing variable to bottled water use in countries with high bottled water use. For example, amongst bottled water users in the Dominican Republic, 60.7% indicated use of pipe/tap water to their house as their main water source for other purposes (e.g., washing), as did 77.9% in TCI households. Further study is needed to examine what factors are driving the divergent use of reliance on bottled water across LAC countries and the impediments to the development of universal accessible and acceptable pipe/tap drinking water. In addition, further examination is needed on the implications of extensive reliance on bottled water.

0539

CHANGE IN MAIN DRINKING WATER SOURCES OVER TIME IN THE CARIBBEAN ISLAND NATIONS OF CUBA, DOMINICAN REPUBLIC, AND HAITI

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Attaining Target 6.1 of the Sustainable Development Goal (SDG) for universal and equitable access to safe and affordable drinking water for all by 2030 may be especially challenging for some island nations given rising sea levels, salination of fresh water, and constrained options beyond their borders. Understanding changes in the main drinking water sources of island nations over time may inform strategies to achieve Target 6.1. This study focuses on three island nations in the Caribbean, Cuba, Dominican Republic, and Haiti, each of which have publicly available national data on household water use spanning more than a decade. According to a 2021 WHO/UNICEF report, 97% of the populations in Cuba and the Dominican Republic attained "at least a basic level" of drinking water receipt by 2020, but only 65% in Haiti did. From 2006-2019 the most prevalent main source of drinking water in Cuba was piped water to the house, increasing from 58.7 to 62.5% over this 13-year period. Well water, the second most common water source in Cuba, increased from 13.8 to 21.0% over this same time period, with an increasing fraction derived from protected versus unprotected wells. From 2007 to 2019, bottled water has been the main source of drinking water in the Dominican Republic, increasing from 57.0 to 78.7% over this 12-year period. Truck delivered water has variably been the next most common source in the Dominican Republic. In Haiti, from 2005/6 to 20016/7 what had been the most common source, piped water outside the home (neighbour yard or public tap), decreased from 34.2 to 24.9% over this 11-year period. During the same period, reliance on water stations increased from 5.4 to 31.2% in Haiti. Examination of factors influencing variation across site and time in main sources of drinking water may guide initiatives to achieve the "safely managed level" (the indicator for SDG Target 6.1) for these and other island nations.

0540

HOUSEHOLD BIRD OWNERSHIP IS ASSOCIATED WITH RESPIRATORY ILLNESS AMONG YOUNG CHILDREN IN URBAN BANGLADESH (CHOBI7 PROGRAM)

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There is limited evidence on the association between animal ownership and respiratory illness among young children in low- and middle-income countries. In this study, we examined the association between animal ownership and respiratory illness among children younger than 5 years of age enrolled in a prospective cohort study in urban Bangladesh. This prospective cohort study enrolled 884 participants younger than 5 years of age in Dhaka, Bangladesh. At baseline, trained research assistants administered caregivers of children younger than 5 years of age a questionnaire on household animal ownership. Animal ownership was defined as owning chickens, birds other than chickens, cats, and dogs. Respiratory surveillance was conducted monthly for children based on caregiver-reported coughing, rapid breathing, and difficulty breathing in the past 2 weeks during the 12-month study period. At baseline, 48% of children (424 of 884) had reports of coughing, 5% (40 of 884) had difficulty breathing, 3% (25 of 884) had rapid breathing, and 49% (431 of 884) had reports of any of these three respiratory symptoms. Seventeen percent of children (151 of 884) resided in a household that owned an animal. Children residing in households reporting bird ownership had a significantly greater odds of coughing (odds ratio, 1.14; 95% CI, 1.02-1.28) and any of the three respiratory symptoms in the past 2 weeks (odds ratio, 1.14; 95% CI, 1.02-1.28). Household bird ownership was associated with respiratory illness in young children. These findings suggest that interventions aiming to reduce young children's exposure to domestic animals should extend to include birds other than chickens.

0541

FOOD HYGIENE PRACTICES AND FECAL CONTAMINATION ON THE HOUSEHOLD COMPOUND ARE ASSOCIATED WITH PEDIATRIC DIARRHEA IN URBAN BANGLADESH (CHOBI7 PROGRAM)

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Diarrheal disease is a leading cause of death in children globally. In this prospective cohort study, we explored individual and household-level risk factors associated with diarrheal diseases among 251 children under 5 years of age in slum areas of urban Dhaka, Bangladesh. Caregiver reports were collected on sociodemographic factors and hygiene behaviors at baseline. During the 3-month study period, diarrhea surveillance was collected monthly, with diarrhea defined as caregiver-reported diarrhea in the previous 2 weeks (>3 loose stools over a 24-hour period). Unannounced spot checks of the household compound were performed at 7 days, 1 month, and 3 months after enrollment to assess the presence of feces (animal or human) on the household compound and in cooking and food storage areas, and to assess if cooked food was covered and/or refrigerated. Children living in households with feces within 10 steps of cooking and food storage areas during spot checks (Odds Ratio (OR): 8.43; 95% Confidence Interval (CI): 1.01, 70.18), those with feces found on the household compound (OR: 4.05.71; 95% (CI): 1.24, 13.22), and those in households found to keep cooked food uncovered and without refrigeration (OR: 6.16; 95% (CI): 1.11, 34.25) had significantly higher diarrhea at subsequent household follow-up. These study findings demonstrate that the presence of feces on the household compound and within 10 steps of cooking and food storage areas, and poor food hygiene practices were significant risk factors for diarrheal disease in young children in Dhaka, Bangladesh. Health communication programs are needed to target these exposure routes to fecal pathogens.

0542

METHODS TO EVALUATE COVID-19 CONTROL HYGIENE PROGRAMS: OBSERVED MASK WEARING, HANDWASHING, AND PHYSICAL DISTANCING BEHAVIORS IN PUBLIC INDOOR SPACES IN DEMOCRATIC REPUBLIC OF THE CONGO

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The objective of our study was to develop and test observational methods to evaluate COVID-19 preventative hygiene behaviors, and evaluate the effectiveness of a government mandate on indoor fully covered mask wearing. An observational study was conducted of 4736 individuals using 5-hour and rapid (10 minute) structured observations and spots to evaluate mask wearing, handwashing, and physical distancing behaviors, and functionality of handwashing stations in 161 indoor public spaces across Bukavu, Democratic Republic of the Congo (DRC). Indoor public location types included: shops, banks, offices, health facility wards and main entrances, beauty salons, supermarkets, schools, restaurants, large retail centers, universities, religious establishments, saunas, physical therapy offices, and gyms. Sixteen percent of individuals entering indoor public spaces were wearing a mask that fully covered their nose and mouth (fully covered mask wearing). Fully covered mask wearing was lowest inside schools at 1%, in universities at 2%, in religious establishments at 22%, and in health facility wards at 28%. Overall physical distancing > 1-meter inside indoor public spaces was 22%, and was lowest inside schools and religious establishments at 7%. Thirty-nine percent of handwashing stations had water and a cleansing agent present. Ten percent of individuals washed their hands with a cleansing agent before entering an indoor space. Overall, fully covered mask wearing was similar for 5-hour and rapid structured observations (16% vs. 15%). The odds of fully covered mask wearing significantly increased with increased government enforcement through fines in public spaces (Odds Ratio: 2.72 (95% Confidence Interval: 1.02-7.30)). This study presents rigorous methods using structured observations to assess government mandates and programs on COVID-19 preventative hygiene behaviors in indoor public spaces in settings globally.

0543

WATER, SANITATION, AND HYGIENE AND NUTRITIONAL RISK FACTORS FOR ACUTE RESPIRATORY ILLNESS IN THE DEMOCRATIC REPUBLIC OF THE CONGO: REDUCE PROSPECTIVE COHORT STUDY

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The objective of this cohort study was to examine the prevalence of acute respiratory illness among children under 5 years of age and to identify water, sanitation, and hygiene (WASH) and nutritional risk factors. This prospective cohort study was conducted in Walungu Territory, South Kivu, Democratic Republic of the Congo (DRC), and enrolled 512 participants. Spot checks of the household environment were conducted at baseline. Baseline minimum dietary diversity (MDD) was defined by consumption of five or more of the following food groups: 1) breast milk; 2) grains, roots, and tubers; 3) legumes and nuts; 4) dairy products; 5) flesh foods; 6) eggs; 7) vitamin A rich fruits and vegetables; and 8) other fruits and vegetables. Acute respiratory illness was defined as caregiver-reported rapid breathing, difficulty breathing, lower chest wall in-drawing, or coughing in the previous 2 weeks obtained at a 6-month follow-up. A total of 58% of children had acute respiratory illness, 19% had soap present in the household cooking area, 4% in the defecation area, and 21% of children met MDD. A decreased odds of acute respiratory illness was associated with soap being present in the cooking area (odds ratio [OR]: 0.49, 95% confidence interval [CI]: 0.38-0.88) and children with MDD (OR: 0.62, 95% CI: 0.38-1.00). These findings highlight the need for interventions targeting hygiene and improved dietary diversity among rural DRC households to reduce the rate of respiratory illnesses in children under 5 years.

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SANITATION AND HYGIENE IN AN URBAN-WORKING CLASS NEIGHBORHOOD OF SÃO PAULO, BRAZIL

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Accessible and equitable water, sanitation, and hygiene (WASH) fundamentals are needed to slow the spread of WASH-related viruses, bacteria, and protozoa. Rapid urbanization poses challenges to the

provision of adequate WASH services due to increased risk for contact with and exposure to diseases and infected individuals. This is especially noticeable in the highly urbanized Brazilian state of São Paulo, with 96.56% of the state's total population of over 44 million living in urban areas. WASH-related diseases have been a persistent problem in Brazil, which have included malaria, dengue, Zika, cholera, tuberculosis, and other diarrheal diseases. Brazil's water and sanitation industries utilize quality indicators in assessing overall performance to achieve universal access to water and sanitation. While these measures are often embraced by policymakers as an evidence-based tool for policy decision-making, they do not always reflect needs on the ground, such as enhanced equitable access to safe water and specialized health programs addressing WASH issues for vulnerable populations. The goal of this study was to use qualitative research methods, namely thematic analysis of community ethnography field notes, to illustrate the reality of daily-life for those living in an urban-working class neighborhood of São Paulo city. Further, by analyzing historical and contemporary WASH policies in Brazil, this research provides better understandings of inconsistencies between public policy and the reality of daily life in the context of WASH. The study has two primary questions 1) "How has the prioritization of sanitation by policymakers, both historical and contemporary, shaped the health of the urban working-class in Brazil?" 2) "How do living and working conditions among the urban working class relate to the creation and/or implementation of water, sanitation, and hygiene (WASH) services?" Findings from this study suggest that local authorities should employ a bottom-up, equity-centered lens emphasizing distributive justice when creating and implementing WASH-related public policies to ensure inequities are not overlooked.

0545

HANDWASHING AND COVID-19 PREVENTION IN AFRICA: A MULTI-COUNTRY STUDY

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There were over 489 million COVID-19 cases and six million deaths in Africa. Handwashing primarily prevents infectious diseases such as diarrhea, Ebola and COVID-19 but relies on access to handwashing resources particularly in Sub Saharan Africa. We explored the feasibility of COVID-19 prevention through the promotion of handwashing by assessing the prevalence and correlates of access to handwashing facilities in nine West African countries. Data were drawn from recent (2018-2020) Demographic and Health Surveys (DHS) in Benin, Cameroon, Gambia, Guinea, Liberia, Mali, Nigeria, Senegal and Sierra Leone. Chi-square tests and multivariate regression analysis explored the correlates of household ownership of an observed place for handwashing. Covariates included hygiene factors (type of toilet facilities in the household and whether the household treated their drinking water) and demographic factors (residence, household wealth, age and sex of head of household). Access to hand washing facilities in West Africa ranged from 21% in Liberia to 95% in Cameroon. Prevalence of handwashing facilities was comparable across urban and rural households except in Liberia and Senegal. Hygiene factors significantly associated with handwashing access included type of toilet (adjusted odds ratio (aOR) ranging from 1.06 - 2.35) and treatment of drinking water (aOR ranging from 1.25 - 4.13), while demographic factors included household size (aOR ranging from 0.95 - 1.08), female sex of household head (aOR ranging from 0.82 - 1.21), and highest wealth quintile (aOR ranging from 1.28 - 12.42). Handwashing access was somewhat low across many countries in West Africa. Behavioral interventions cannot succeed without relevant structural solutions. Increased priority on the provision of commodities such handwashing stations, soap and water in order to improve hygiene and other health outcomes such as COVID-19. Once such commodities have been provided, health promotion or behavior change interventions are needed to promote the uptake of handwashing in these settings.

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WASTEWATER SURVEILLANCE SYSTEM TO EVALUATE SARS-COV-2 AND OTHER VIRUSES IN A CITY WITHOUT WASTEWATER TREATMENT PLANT FROM THE HIGHLANDS IN PERU

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The monitoring of raw sewage is considered as a tool to understand the spread of viral infections as produced by SARS-CoV-2. A wastewater surveillance system was implemented in Huancayo (Junin), Peru, a city with half a million inhabitants and no wastewater treatment plants available dumping contaminated water into the Mantaro River. Wastewater samples were collected each two weeks from August 2021 to the present, with the aim of monitoring viral indicators of human fecal contamination and correlating the number of genomic copies (GC) of SARS-CoV -2, human adenovirus (HAdV), norovirus genogroup II (NoV GII) and rotavirus (RoV) with the infected population. Each sample underwent the flocculation viral concentration method with skimmed milk, nucleic acid extraction and Quantitaive Real-Time Polymerase Chain Reaction (qPCR). All samples were positive for HAdV, NoV GII and RoV, finding an average concentration of 4.18E+08 GC/100 mL, 6.10E+06 GC/100 mL and 1.92E+07 GC/100 mL, respectively. In the case of SARS-CoV-2, 25% of the samples were positive and an average concentration of 2.45E+06 GC/100 mL was observed. The detection and increase in the concentration of SARS-CoV-2 in wastewater samples were between January and February 2022, while the third wave of omicron variant of SARS-CoV-2 occurred in Peru. The increase in the number of people with COVID-19 was confirmed directly with data from the Regional Health Directorate - Junin and the Ministry of Health. These findings imply a relationship between the number of people with COVID-19 and the concentration of GC of SARS-CoV-2 in wastewater, therefore, it is possible to design a predictive statistical model that allows us to anticipate outbreaks of SARS-CoV-2 and even for other pathogens that are excreted through feces. Furthermore, the results suggest that the monitoring of viral indicators of human fecal contamination in wastewater has the potential to provide relevant information to effectively manage water resources.

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FOOD POISONING AND DEATH LINKED TO MONOCROTOPHOS CONTAMINATION OF TRADITIONAL BEVERAGE- ZAMBIA 2021

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On 5th October 2021, a rural health facility in Choma District in the Southern Province of Zambia reported 16 cases of food poisoning, one resulting in death. We conducted a field investigation in order to confirm the existence and likely cause of the outbreak. We conducted a descriptive epidemiology study of food poisoning cases of Mbulumwiinga village. Patient records and line-list were used to confirm existence of the outbreak. 18 respondents present in the village from 3rd to 5th October 2021 were recruited, regardless of symptoms, and interviewed using a structured questionnaire. The questionnaire collected information

on participants' demographic characteristics, onset and duration of symptoms, food exposures and the health seeking behaviour. The descriptive analysis was conducted using RStudio. Munkoyo is a traditional non-alcoholic drink prepared by using cooked maize meal and fermented with rhynchosia heterophylla root extract. The munkoyo drink samples were collected for toxicological laboratory analysis and stool samples were collected for microbiological examination. Of the 18 participants, 10 (56%) were female and median age was 10 years (Interquartile range: 5-27). Attack rate among the respondents who took munkoyo drink was 100% and 0% among those who did not (Fisher's exact p-value 0.007). Of those who took munkoyo drink, one person died (Case fatality rate: 6%) after consumption while 15 (94%) recovered after treatment. The analysis demonstrates that, all the people who took the home brewed Munkoyo drink experienced food poisoning symptoms such as abdominal pains, diarrhoea, vomiting and fever. The stool laboratory results proved no presence of micro-organisms such as salmonella and shigella. Monochrotophos was detected by laboratory in the munkoyo sample. The presence of monochrotophos in the munkoyo drink may have contributed to the observed symptoms in the affected persons, but it's not clear how the contamination occurred. There is need to continue educating people in the communities on prevention and control measures of possible organophosphate pesticides ingestion as they are fatal to human health**.**

0548

GEOGRAPHIC VARIATION AND DETERMINANTS OF CHILD FECES DISPOSAL PRACTICES IN 42 LOW- AND MIDDLE-INCOME COUNTRIES: AN ANALYSIS OF STANDARDIZED CROSS-SECTIONAL SURVEY DATA FROM 2016-2020

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Despite considerable progress in coverage of water, sanitation, and hygiene access globally, disposal of child feces in contained latrines remains uncommon in many low- and middle- income countries (LMICs). Because young children often have underdeveloped immune systems and high rates of enteric infection, child feces not deposited in latrines represents an important risk for diarrheal disease transmission. We synthesized data on personal and household factors and child feces disposal practices from the nationally standardized Demographic and Health Surveys and Multiple Indicator Cluster Surveys from 42 LMICs from 2016-2020. We analyzed the period prevalence of child feces disposal practices within and across these LMICs globally, and used survey weighted Poisson regression to assess individual and household determinants associated with appropriate disposal practices. Data on 403,036 children (weighted n = 191 million) showed only 40.3% of childrens' feces are deposited into a toilet or latrine, and merely 29% in an improved sanitation facility. Prevalence of appropriate child feces disposal varied substantially by country and region, however once pooled, adjusted analysis demonstrated disposal of child feces in any type of latrine increased with age, wealth, urban living, and access to improved water and sanitation facilities. An analysis restricted to households with access to sanitation facilities found only about half of children with household access to any latrine or improved latrines had their feces disposed in these facilities. This restricted analysis also found similar associated determinants, indicating these associations are robust to infrastructure and facility access improvements. We will present results related to the geographical variation of practices across regions and LMICs, as well as factors associated with appropriate disposal into a latrine. Our findings highlight the importance of efforts to improve child feces disposal practices globally, and emphasize the importance of shifting the focus moving forward beyond just improving access and toward social and behavioral interventions.

0549

SPATIAL HETEROGENEITY OF NEIGHBORHOOD-LEVEL WATER AND SANITATION ACCESS IN INFORMAL URBAN SETTLEMENTS: A CROSS-SECTIONAL CASE STUDY IN BEIRA, MOZAMBIQUE

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Rapid urbanization, resulting in population growth within informal settlements, has worsened exclusion and inequality in access to water and sanitation (WASH) services in the poorest and most marginalized communities. In this study, we describe the heterogeneity in water service satisfaction and WASH access in low-income, peri-urban neighborhoods of Beira, Mozambique, and examine whether this heterogeneity can be explained by distance to water distribution mains. Using spatial statistics and regression analyses, we identify spatial heterogeneity in household WASH access, as well as consumer-reported satisfaction with water services (services, pressure, quality, and sufficient quantity). We find that as distance from the water main increased, both access to an improved water source at the household and satisfaction with water pressure decreases, and water supply intermittency increases, controlling for household density and socioeconomic status. The odds of a household having access to a water source at the household or on the compound decreases with every 100-meter increase in distance from a water main pipe (odds ratio [OR] 0.87, 95% confidence interval [CI]: 0.82, 0.92). Satisfaction with water services also decreases with every 100-meter increase in distance from a water main pipe (OR: 0.80; 95% CI: 0.69, 0.94). Days of availability in the past week decreases by a factor of 0.22 for every 100-meter increase in distance from the water main (95% CI: -0.29, -0.15). Findings from this study highlight the unequal household access to water and sanitation in urban informal settlements, even within low-income neighborhoods. Describing this heterogeneity of access to water services, sanitation, and satisfaction - and the factors influencing them - can inform stakeholders and guide the development of infrastructural solutions to reduce water access inequities within urban settings.

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INVESTIGATION OF FOOD POISONING OUTBREAK AT A TRADITIONAL INITIATION CEREMONY IN PETAUKE DISTRICT, EASTERN PROVINCE OF ZAMBIA, OCTOBER 2021

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Food-borne outbreaks related to consumption of locally-brewed non-alcoholic beverages (i.e., munkoyo/thobwa) are commonly reported in Zambia. On 9th October 2021, a suspected food poisoning outbreak was reported among people who attended an initiation ceremony in a small village of a rural district in Zambia. We conducted an investigation to confirm the outbreak, determine its source, magnitude and risk factors. We conducted a 1:1 unmatched case-control study and collected information on demographics, symptoms, and food consumption history through a semi-structured questionnaire and review of medical records. A case was any person who attended the initiation ceremony and developed diarrhoea, vomiting, nausea or abdominal pain between the 9th and 16th of October 2021. Controls were individuals who attended the ceremony but did not present with any symptoms. We inspected premises, collected food, water, and stool samples for laboratory analysis. We used Stata version14 with significance set at $p<0.05$ to calculate frequencies, attack rates and odds ratios. Out of 96 respondents, 48%(n=46) were cases with a median age 27 (IQR 27-40) and 37.5 (IQR 22-50) among controls

(p=0.128). Of the cases, 60.9% (28/46) were female. Consumption of a locally brewed non-alcoholic beverage (thobwa) had the highest (86%) attack rate (p<0.0001). In the multiple logistic regression, eating of food from the ceremony (aOR 109.39, 95% CI:11.26,1063.15, p<0.0001) and consumption of thobwa (aOR 41.66, 95% CI:8.31, 208.77, p<0.0001) were significantly associated with foodborne illness. Abamectin was detected in thobwa sample, and Escherichia coli was isolated in 83% (5/6) stool samples. Although preliminary lab evidence suggests potential causes of this outbreak, additional evaluations could provide a more definitive cause of the outbreak. Given the magnitude of outbreaks linked to traditionally-brewed beverages in Zambia, an in-depth investigation aimed at identifying cause(s) and prevent future outbreaks should be done.

0551

SEROEPIDEMIOLOGY AND HOUSEHOLD TRANSMISSION OF COVID-19 AMONG MIGRANT FOOD PROCESSING AND FARM WORKERS IN NORTH CAROLINA

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The US farming and food processing industry employs large numbers of Latinx immigrants, a population who has suffered disproportionately from COVID-19, and several outbreaks occurred in such industries early in the pandemic. We conducted an observational cohort study of North Carolina (NC) farming and food processing workers and their households to investigate SARS-CoV-2 seroprevalence and risk factors for transmission. In fall 2020, we recruited adults who worked in food processing facilities or commercial farms in NC and their household members > 12 months old. Participants completed a questionnaire to collect demographic, workplace, household, and behavioral data. A blood sample was collected for SARS-CoV-2 serology. We used univariate and multivariate logistic regression to investigate risk factors for SARS-CoV-2 seropositivity. Among the 118 index workers and 100 household members for whom results were available, 119 (56%) were female, median age was 34 years (IQR 14-47), 95% identified as Hispanic, and 75% spoke primarily Spanish. The seroprevalence of SARS-CoV-2 was 50%. Of 89 households, 49 had at least one seropositive member, and 35 had 100% seropositivity. Visiting church (aOR 13.5, 95% CI 1.09-166), having a prior history of COVID-19 (aOR 19.1, 95% CI 6.13-59.7), and having a seropositive household member (aOR 28.3 95% CI 12.1-66.2) were significantly associated with SARS-CoV-2 seropositivity. Age, sex, race, and preventive behaviors were not associated with seropositivity, although the latter may be affected by social desirability bias or less stringent adoption of preventive behaviors inside the home. SARS-CoV-2 seroprevalence was much higher than the prevalence of self-reported illness (23%) suggesting a high rate of asymptomatic infections and limited access to testing in 2020. Our findings highlight the disproportionate burden of COVID-19 in this vulnerable population, the potential role of commercial farms and food processing facilities in community spread, and the sizeable role of household transmission. Involving faith-based organizations in public health measures may help curb COVID-19 transmission.

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HIGH SARS-COV-2 SEROPREVALENCE AND RAPID NEUTRALIZING ANTIBODY DECLINE AMONG WORKERS AT A LARGE AGRIBUSINESS IN RURAL GUATEMALA, JUNE 2020-MARCH 2021

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Seroprevalence studies in agricultural workers in low-and-middle-income countries are underrepresented in the literature. Understanding occupational risk factors can help to inform targeted workplace mitigation strategies. Using data from the Guatemala AGricultural workers and Respiratory Impact (AGRI) study and anti-SARS-CoV-2 nucleocapsid IgG (anti-N, Roche Elecsys®) to estimate past infections, we analyzed risk factors associated with seropositivity at enrollment and subsequent lab-confirmed SARS-CoV-2 infection. We assessed the stability of neutralizing antibody (NAb) response using a lentivirus-based pseudovirion assay in a subset of samples (June 2020–March 2021), prior to vaccine roll-out. Prevalence ratios (PR) were obtained using a multivariable binomial regression model. From June 15-December 30, 2020, 1334 (93.2%) participants were enrolled. The majority were male (84%), young (mean 31 years), and healthy (<13% had comorbidity). At enrollment, 616 (46.2%) had anti-N IgG suggestive of prior SARS-CoV-2 infection. Cough ≤10 days prior to enrollment (OR=1.78, 95% CI: 1.20-2.64), working as a packer (OR=4.95, 95% CI: 3.36-7.27), and as a packing plant manager (OR=3.71, 95% CI: 1.23-11.19) were associated with increased odds of seropositivity at enrollment. Of 718 seronegative workers, 2.1% had lab-confirmed COVID-19 during follow-up compared with 0.3% of the 616 seropositive workers. COVID-19 incidence density for seropositive workers was 0.4/100 Person–Years (P–Y), lower than those who were seronegative (2.3/100 P–Y). At enrollment, anti-N IgG titers in serum correlated with neutralizing antibody titers (R^2=0.26, p<0.0001). Notably, in <6 months from enrollment, most workers with follow-up NAb testing (65/77, 84%) exhibited a 95% decrease in neutralizing antibody titers. In conclusion, seroprevalence among agricultural workers was substantial. Natural infection offered some protection against reinfection but was short-lived and underscores the need for multipronged SARS-CoV-2 infection prevention strategies, including vaccination.

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EXCESSIVE EXPOSURE TO SARS-COV-2 REVEALED THROUGH COMMUNITY SERO-EPIDEMIOLOGICAL SURVEYS IN SOTHERN MOZAMBIQUE, FROM MAY 2021 TO FEBRUARY 2022

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COVID-19 caused by SARS-CoV-2 has quickly spread all over the World resulting in a pandemic, and after two years facing it, data and knowledge have been accumulated. Despite the severe impact in the world, data from Africa still reveal an apparently less severe impact compared with the

other continents, which may be underestimated due to the challenges in testing capacities and access to health facilities in most of the countries, particularly for people living in rural areas. However, no excessive deaths have been reported due to COVID-19 in those areas, raising uncertainties regarding the hypothetical protective factors among African people. Seroepidemiological surveys can help to uncover the proportion of people exposed to SARS-CoV-2. We conducted 3 community cross-sectional studies to estimate the community age-specific seroprevalence of SARS-CoV-2 in a rural district in Southern Mozambique (Manhiça). The cross-sectionals took place between May to June, October to November in 2021 and January to February 18, 2022, each with a 1200 sample size. Participants were randomly selected for each cross equally distributed by age group (0-19, 20-39, 40-59 and ≥60 years). Blood samples were collected to perform serological tests using a commercial kit test (Wantai SARS-CoV-2 Ab Elisa) and nasopharyngeal swabs were collected in a subset of 600 participants to perform qRT-PCR for SARS-CoV-2 detection; a questionnaire was administered to collect socio-demographic data. A total of 3603 individuals were enrolled in all three crosses (1201 in each), and the seroprevalence tended to double between crosses: 1st (27.6%, 184/666), 2nd (63.6%, 595/936) and 3rd (91.1%, 700/768) while the prevalence of SARS-CoV-2 infection remained below 15% in all crosses (4%, 0.7% and 10.1%, respectively). The seroprevalence between age-groups followed the same trend, however, the only significant difference was from the 3rd cross (p=0.001). Altogether this data shows the importance of seroepidemiological studies and reveal that people in rural areas were exposed across all age groups, but are somehow protected from disease by factors that still remain elusive.

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MONITORING THE INCIDENCE OF ACUTE FEBRILE ILLNESS HOSPITALIZATION AND DEATH AMONG THE GENERAL POPULATION IN VELLORE DURING THE COVID 19 PANDEMIC A COHORT STUDY

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Acute Febrile Illness (AFI) hospitalization, and deaths spiraled significantly during the Covid-19 pandemic placing an unprecedented strain on the healthcare systems across the globe. WHO reports over 400 million cases and 6 million deaths due to COVID-19. Quantifying the impact of the pandemic on the general population helps to prioritize the necessary preventive strategies. From February 2021 to March 2022, a cohort of 5250 individuals aged 2 and above residing in urban Vellore were followed up fortnightly for one year telephonically for AFI illness as part of a COVID serial serosurvey. Any AFI symptoms, hospitalization, treatment history, and deaths if any, were captured using an electronic data capture platform. The incidence of AFI events, hospitalization, and deaths per 1000 person-years of follow-up were calculated. The incidence rate per 1000 person-years for fever is 178.5 (95% CI 167.8-189.5), 115.3 (95% CI 106.4-124.5) for cough, 11.8 (95% CI 8.9-15.2) for breathing difficulty, 211 (95% CI 199.6-222.7) for nasal congestion and 23.1 (95% CI 19-27.7) for sore throat. The incidence of hospitalization per 1000 person-years was 32.5 (95% CI 27.7-37.8) and the incidence of AFI hospitalization per 1000 person-years was 12.3 (95% CI 9.4-15.9). The crude death per 1000 person-years was 8.7 (95% CI 6.4 to 11.7) over the year. The observed incidence of acute febrile illness and the associated respiratory symptoms, febrile hospitalization, and deaths were more among the general population during the pandemic. AFI surveillance during a pandemic provides much-needed data on the actual incidence of febrile illness in the community, especially in developing countries like India where the testing for COVID-19 is low either due to the existence of stigma towards the disease or due to low testing rates because of strain on the existing healthcare system.

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COVID-19 VACCINE ATTITUDES AND ACCEPTANCE AMONG REFUGEES VERSUS LEBANESE NATIONALS PRE- AND POST-VACCINE INTRODUCTION IN LEBANON

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This study evaluated attitudes toward COVID-19 vaccines and factors associated with vaccine acceptance among refugees versus Lebanese nationals before and after vaccine introduction. Two anonymous cross-sectional surveys were conducted in February 2021 (Survey 1, pre-vaccine introduction) and June 2021 (Survey 2, post-vaccine introduction), using a convenience sample of adult refugees (Syrian/ Palestinian) and Lebanese nationals accessing International Medical Corps- supported primary health care centers. Survey items were mapped to domains from the Health Beliefs Model (HBM). Descriptive analysis was conducted, and comparisons made with chi-squared test. Logistic regression was used to assess associations of demographic data and HBM domains with the outcome of vaccine acceptance. 52.9% of respondents in Survey 1 (n=3,927) and 54.2% in Survey 2 (n=4,174) were refugees. While vaccine acceptance was low in both groups in Survey 1 (25.9% nationals vs. 23.1% refugees), by Survey 2 this had increased, with vaccine acceptance being higher in nationals versus refugees (57.6% vs. 32.9% respectively). Respondents reported greater perceived benefits of vaccination, higher perceived susceptibility to COVID-19, and lower perceived barriers to vaccination in Survey 2 versus Survey 1. In regression analysis in Survey 1, gender, nationality, and age were not associated with vaccine acceptance. However, in Survey 2, refugees had lower odds of vaccine acceptance compared to Lebanese nationals (OR 0.50, 95%CI 0.41-0.60) while older age (OR 1.37, 95%CI 1.06-1.78, ≥51 years vs. 18-30 years) was associated with greater odds of vaccine acceptance. Vaccine attitudes shifted differentially between Lebanese nationals and refugees post-vaccine introduction. While both groups had similarly low vaccine acceptance before vaccine roll-out, attitudes toward vaccines diverged following vaccine roll-out, with Lebanese nationals having higher vaccine acceptance compared to refugees. Targeted efforts to improve COVID-19 vaccine confidence specific to refugee populations in Lebanon are needed.

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TRENDS OF INFLUENZA ACTIVITY DURING THE COVID-19 PANDEMIC IN GHANA, 2020

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By the end of March 2020, almost every country had reported cases of SARS-CoV-2, causative agent of COVID-19, with more than 5 million deaths worldwide at the end 2021. Surges in the number of active COVID-19 infections resulted in the closure of borders and restriction-of-movement (ROM) policies in most countries. Though WHO and other health agencies had advocated for preparedness for emerging and re-emerging diseases, many health systems were taken by surprise leading to collapse of surveillance systems. This cross-sectional study used prospective influenza surveillance data from 29 sentinel sites received by the Ghana National Influenza Centre (Ghana-NIC). We sought to detect the presence and burden of influenza cases during the COVID-19

pandemic. A retrospective analysis comparing 2017 to 2019 against 2020 data was conducted. In 2020, there was a significant reduction (50%) in the number of samples received from the sentinel sites compared to the previous years (2017-2019). Influenza activity occurred in two waves during the 2020 influenza surveillance season, December 30, 2019, to March 8, 2020 (epidemiological weeks 1-10) and September 28 to December 28 (weeks 40-52). Between these two waves, there was no records of influenza activity. In the first wave, percentage positivity peaked from late February to early March (week 9) at 9% and declined to 0% by mid-March (week 11) with AH3N2 commonly detected amongst positive patients. Influenza percentage positivity peaked in weeks 48 and 52 at 20% and 21% respectively in the second wave, with influenza B Victoria dominating. Between weeks 10 to 42, samples were not received from the sentinel sites and therefore, 1,083 samples selected from the COVID-19 surveillance were tested for influenza with no positives recorded. In Ghana and US military installations alike, ROM policies, international COVID-19 protocols and adherence to community mitigation strategies reduced the transmission of SARS-CoV-2, and indirectly affected transmission of influenza viruses as well.

0557

IMPACT OF ANTIGEN TEST TARGET FAILURE AND TESTING STRATEGIES ON THE TRANSMISSION OF SARS-COV-2 VARIANTS

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Population testing and genomic surveillance remain central to controlling the COVID-19 pandemic and will also be important for future pandemic preparedness. During the pandemic, the use of rapid antigen diagnostic tests has expanded, coinciding with a decline in the use of molecular tests. Here we report the results of a hospital-based surveillance study conducted in the Italian region of Veneto, where we identified a pattern of disruptive amino-acid substitutions within a major B-cell epitope of the SARS-CoV-2 N antigen, which enabled variants to escape N antigen tests. By fitting a multistrain compartmental model linking genomic and epidemiological data, we found that the widespread use of antigen tests in Veneto favoured the undetected spread of the antigen-escape variant compared to the rest of Italy, where the use of antigen testing was lower for the duration of the study period. We also quantified the impact of a range of testing scenarios, including mass antigen testing in the absence of molecular testing, on the transmission dynamics, diagnostic test performance and genomic surveillance of escaping and concordant SARS-CoV-2 variants. Our results highlight how the widespread use of antigen testing could facilitate the transmission of novel SARS-CoV-2 variants with disruptive N antigen mutations. Critically, in the presence of a variant that escapes antigen testing, we found that molecular testing and genomic surveillance, independent of antigen testing, are critical for unbiased estimates of escaping and concordant variant prevalence. Given the high levels of SARS-CoV-2 incidence across the globe, novel variants of concern can be expected. Our findings therefore highlight the importance of global investment in molecular testing capacity and genomic surveillance, to facilitate the rapid detection and control of such SARS-CoV-2 variants.

0558

THE TRANSCRIPTION FACTOR MYB-M DRIVES MALE COMMITMENT IN THE PARASITE *CRYPTOSPORIDIUM*

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The apicomplexan parasite *Cryptosporidium* is a leading cause of diarrheal disease and infects millions of people worldwide each year. With no vaccine and inadequate treatment, a great need exists for new therapeutics. Related parasites have complex life cycles with multiple hosts, but *Cryptosporidium* infects a single host where its entire life cycle unfolds, making it a great model for the study of transcriptional regulators. Sporozoites excyst from an oocyst and invade intestinal epithelial cells, propagating asexually for three cycles before transitioning to male and female gametes. Sex leads to the production of new oocysts. Recently, we performed single-cell RNA-sequencing of 9,310 parasites to document the transcriptional changes that occur throughout the life cycle. We found an abrupt switch to male or female development and identified AP2 and Myb transcription factors associated with sexual stages, including Myb-M. Myb-M is expressed in the earliest males and was deemed essential *in vivo*. We developed a conditional overexpression system in *Cryptosporidium* to functionally characterize Myb-M and other essential transcription factors. Overexpression of Myb-M drove the direct development of males from asexual parasites and induced the expression of male-specific genes, including AP2-M and HAP2. Growth assays also showed that Myb-M overexpression halted parasite propagation *in vitro*, and induction of Myb-M *in vivo* led to reduced parasite burden, measured by fecal oocyst shedding. These findings indicate that Myb-M is sufficient to induce male fate, even at the earliest stages of the parasite life cycle, and is a master regulator of male commitment in *Cryptosporidium*. Current work is focused on using ChIP-seq to define the genes controlled by Myb-M as well as utilizing the Myb-M overexpression strain to study large populations of mature male parasites via microscopy and high-throughput sequencing.

0559

IN VIVO ASSESSMENT OF *PLASMODIUM VIVAX* CHESSON STRAIN LIVER STAGE INFECTION: NOVEL STUDIES TO ASSESS HYPNOZOITE FORMATION, PERSISTENCE, ACTIVATION, AND RELAPSE

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The main goal of Plasmodium vivax liver stage research is aimed at understanding the formation, persistence and activation of hypnozoite stages, which are the source of recurrent relapses. This research, however, is hampered by several challenges to studying P. vivax (Pv) liver stages in the laboratory, including the limited access to sporozoites (SPZ). Sporozoites are primarily obtained from mosquitoes fed on infected patient blood, causing significant variability in experimental outcomes. Here, we revisited the use of Chesson strain PvSPZ for analysis of hypnozoite biology. Pv Chesson blood stages were propagated in Saimiri monkeys and used for mosquito feeds to generate PvSPZ (Chesson) that then underwent cryopreservation. We used these to infect human liver-chimeric FRG huHep mice. Furthermore, single cell RNA-seq analysis of PvSPZ (Chesson) was undertaken. We observed robust liver infection of FRG huHep mice. Exo-erythrocytic schizonts matured normally over nine days, when primary exo-erythrocytic merozoites egressed from the liver into the blood. Strikingly, hypnozoites formed frequently and persisted. The hypnozoite:schizont ratio in the infected livers was consistently approximately 40%:60%, constituting the first quantitative determination of Chesson strain hypnozoite frequency. Hypnozoites were viable,

activated and caused first relapses after approximately three weeks. This model will allow for consistent profiling of both hypnozoites and schizonts as well as the infected host hepatocytes. To understand if the hypnozoite fate is predetermined in PvSPZ (Chesson), we performed single cell RNA-seq analysis of PvSPZ (Chesson). Preliminary analysis showed enrichment of genes associated with chromatin remodeling in a subset of sporozoites, possibly highlighting a role for epigenetic regulation in hypnozoite formation. Our Chesson strain liver stage model will allow us to gain a better understanding of hypnozoite biology and can aid in the discovery of novel interventions to prevent relapse.

0560

SICA-MEDIATED CYTOADHESION OF *PLASMODIUM KNOWLESI*-INFECTED RED BLOOD CELLS TO HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS

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Plasmodium knowlesi is a causative agent of zoonotic human malaria in Southeast Asia. Post-mortem examination of human *knowlesi* malaria cases showed sequestration of *P. knowlesi*-infected red blood cells (iRBCs) in blood vessels, which has been proposed to be linked to disease severity. This sequestration is likely mediated by the cytoadhesion of parasite-iRBCs to vascular endothelial cells, however, the responsible parasite ligands remain undetermined. In this study, we enriched *P. knowlesi*-iRBCs which bound to the human umbilical vein endothelial cells (HUVECs) by repeating panning selection. Transcriptome analysis revealed that the transcript level of one gene, encoding a Schizont Infected Cell Agglutination (SICA) protein, herein termed SICA-HUVEC, were more than 100 fold increased after the panning. The cytoadhesion activity of SICA-HUVEC to HUVECs was confirmed by reverse genetics approach: exogenous expression of SICA-HUVEC significantly increased cytoadhesion activity of the transgenic parasites in both monkey and human iRBCs. Transgenic *P. knowlesi* parasites expressing Myc-fused SICA-HUVEC increased cytoadhesion activity following infection of monkey as well as human RBCs, confirming that SICA-HUVEC conveys an activity to bind to HUVECs. In summary, this study revealed that SICA-HUVEC protein is a strong candidate ligand recognizing receptors on HUVECs and mediating the cytoadhesion in *knowlesi* malaria.

0561

DIFFERENCES IN GENE ESSENTIALITY BETWEEN *PLASMODIUM KNOWLESI* AND *P. FALCIPARUM* REVEALED BY *PIGGYBAC* SATURATION MUTAGENESIS

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Experimentally friendly attributes of *Plasmodium knowlesi* make it of increasing interest for systematic genetic studies of vivax-like malaria parasites. It is genetically very tractable, with much higher transfection efficiencies than *P. falciparum*, and while a cause of human malaria in only some malaria endemic regions, it is phylogenetically closely related to *P. vivax*, which causes the majority of malaria outside Africa but cannot currently be cultured *in vitro.* We have adapted the *piggyBac* mutagenesis approach to *P. knowlesi* using the A1-H.1 line that can be grown in human RBCs and is now widely adapted in many malaria research laboratories. The *pkef1a* promoter is used to drive transposase expression and the *pkhsp70* promoter drives hDHFR-GFP expression for selection of mutants. Approximately 33,000 insertions were identified randomly distributed throughout the genome to achieve a saturation-level of mutagenesis even though the available TTAA insertion sites in *P. knowlesi* is approximately half that of *P. falciparum*. However, the relative proportion of insertions within the UTR regions, especially the 5', is much higher in *P. knowlesi* along with a higher percentage of exon insertions (i.e. more dispensable genes). Based on this level of mutagenesis we can determine mutability or a mutagenesis index score of 5401 *P. knowlesi* genes. While the patterns of essentiality by GO classifications are similar between these species, the high proportion of non-mutable *P. knowlesi SICAvar* family genes is notably different than the high overall mutability of the orthologous *P. falciparum var* gene family. This successful application of the *piggyBac* methodology to *P. knowlesi* provides a robust scalable platform for experimental forward genetic screens to explore unique biology of vivax-like malaria parasites.

0562

A MODULAR CLONING SYSTEM FOR HIGH EFFICIENCY PRODUCTION OF *PLASMODIUM FALCIPARUM* TRANSFECTION VECTORS

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Genetic modification of *Plasmodium falciparum* through the transfection of DNA plasmids is an important tool for understanding the parasite›s biology. However, the extreme AT-bias and low complexity of the parasite›s genomic sequences makes traditional cloning in circular plasmids prone to spontaneous rearrangements and deletions. These issues can be avoided by using linear cloning vectors derived from the non-integrating prophage of the N15 coli phage. However, the only commercially available linear plasmid is large (~13 kb), and contains cut sites for nearly every common restriction enzyme, which limits flexibility during construction and modification of *P. falciparum* transfection vectors. To address this, we reconstructed the N15 linear plasmid from scratch, reducing its size by 5 kb and recoding the backbone to eliminate 85 restriction sites and render another 50 unique. We have used this new linear plasmid to develop a Modular Cloning (MoClo) system, a popular technique in the synthetic biology community given its speed, reliability and scalability. MoClo uses type-IIS restriction enzymes to perform multi-piece assembly of standard biological parts in a single reaction with high efficiency. We are creating a collection of standard parts for *P. falciparum* including promoters, terminators, epitope tags, reporters, effectors, and selectable markers. Using our linear plasmid, we can easily assemble these parts into large, complex, AT-rich plasmids. Our approach improves the predictability, reliability and speed with which new plasmid vectors for *P. falciparum* can be created and will accelerate the malaria community›s ability to address important biological questions.

0563

LIVER ULTRASOUND FINDINGS IN PRESCHOOL CHILDREN FROM THE PRAZIQUANTEL IN PRESCHOOLERS (PIP) TRIAL IN LAKE ALBERT, UGANDA

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Periportal fibrosis is recognized as a late-stage manifestation of chronic infection with the waterborne parasite *Schistosoma mansoni.* Praziquantel (PZQ), the only drug available for the treatment of schistosomiasis, has

limited effect on advanced morbidity at the current recommended 40 mg/kg given as a single dose annually. Preschool children (PSAC) less than 4 years of age are not considered to be an at-risk population for such severe morbidity. However, the prevalence of periportal fibrosis in PSAC in highly *S. mansoni* endemic settings is not known. As part of a phase II trial examining different dosing regimens for PZQ in children age 12-48 months in Uganda (PIP trial), we present the prevalence of schistosomiasis-related fibrosis as determined by liver ultrasound. PSAC from Lake Albert who were infected with *S. mansoni as* diagnosed by stool Kato-Katz were enrolled into the PIP trial. Infection intensity was classified by eggs per gram of stool (epg) as low (<100 epg), moderate (100 – 399 epg) and heavy (>400 epg). Standard measures following the WHO Niamey protocol for schistosomiasis-related periportal fibrosis were captured at baseline. Mean age was 34 months (std dev 9.1). Infection intensities were: light (56.9%), medium (24.0%) and heavy (19.1%). Of the 343 participants with recorded ultrasound data, 7 (2%) had evidenced of possible periportal fibrosis, 27 (8 %) evidence of incipient periportal fibrosis and 59 (17%) had evidence of periportal thickening. Older age (per month increase) and lower maternal education were associated with higher degree of periportal thickening (OR 1.03, CI: 1.00, 1.07) and (OR 2.72, CI: 1.37, 5.40) respectively. No other variable was found to be associated with the prevalence of periportal thickening or established fibrosis at baseline. Incipient schistosomiasis-related liver morbidity was detected in young children enrolled in the PIP trial. This trial presents a unique opportunity to identify optimal PZQ dose and frequency of dosing in a population that has been systematically excluded from control efforts. Earlier and repeated PZQ treatment may reverse or delay disease progression.

0564

GUT MORBIDITY AMONG PRE-SCHOOL CHILDREN WITH *SCHISTOSOMA MANSONI* INFECTION IN ALBERTINE REGION, WESTERN UGANDA

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Schistosoma mansoni causes intestinal inflammation as eggs from adult worms in the mesenteric blood vessels are passed in stool. Eggs transit the gut mucosa, eliciting a Th1 inflammatory process that has been demonstrated to contribute to Environmental Enteric Dysfunction (EED) among older children and adults. Calprotectin is a neutrophil cytoplasmic protein and its presence in stool denotes active intestinal inflammation. As part of an ongoing NIH-funded phase II trial of optimal PZQ dosing for PSAC ages 12-48 months in Uganda, we examined the relationship between baseline markers of gut morbidity and *S. mansoni* infection. Few if any studies have addressed gut morbidity among young children with schistosomiasis. At trial enrolment, children were screened for the presence of *S. mansoni* by duplicate Kato Katz, and included if they were infected. Infection intensity was classified by eggs per gram of stool (epg) as low (<100 epg), moderate (100 – 399 epg) and heavy (>400 epg). Age, household sanitation (any latrine), maternal education (no school vs some), and water source (lake vs other) were evaluated for inclusion in linear and logistic regression models Fecal calprotectin and occult blood (FOB) were measured in N = 348 PSAC. Mean age was 34 months (std dev 9.1). Infection intensities were: light (56.9%), medium (24.0%) and heavy (19.1%). Calprotectin level was associated intensity of schistosomiasis infection, (β=0.07; $P < 0.01$) and lack of latrine (β=86; ($P < 0.001$) after adjusting for age and maternal education. FOB was detected in 27% (95% CI 22.3 – 32.1). 22% of PSAC with FOB also had history of bloody stools. Moderate/high vs low intensity *S. mansoni* infection was associated with increased risk of FOB (OR=1.84; P =0.04) after adjusting for maternal education. The association between both calprotectin and FOB and *S. mansoni* infection suggests that young children may be less able to downregulate intestinal inflammation and are already accruing significant gut morbidity. The association between lack of sanitation and calprotectin is likely due to the presence of non-schistosomal causes of EED such as other parasitic, bacterial and viral infections.

0565

MULTILOCUS PCR-DNA SEQUENCE TYPING SCHEME TO INVESTIGATE HYBRIDIZATION IN *SCHISTOSOMA HAEMATOBIUM*

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Schistosomiasis is a parasitic disease caused by blood flukes in the genus *Schistosoma* that infect human and animal hosts. Reports of ongoing hybridization between human and animal species of schistosomes in many parts of Africa suggest that a species complex may exist within the Schistosoma haematobium group, comprised of *S. haematobium*, *S. bovis*, *S. currasoni*, *S. intecalatum*, *S. guineensis*, and *S. mattheei*. We investigated the occurrence of schistosome hybrids in three pastoral and two non-pastoral communities across Nigeria. In two of the pastoral communities, there was no evidence of schistosome infections detected. In the other three communities, eighty parasite isolates were obtained by urine filtration or hatched miracidia on FTA cards. Extracted DNA was PCR amplified at the gene markers rITS and mtCO1 and five haplotypes were resolved. Five isolates from a pastoral community possessed SNPs at the rITS locus that grouped them with either *S. bovis* or *S. haematobium-S. bovis* hybrids, suggesting that they might be hybids. However, the rITS and mtCO1 failed to provide sufficient genetic information to allow for robust differentiation between S. haematobium, S. bovis, and hybrids of both species. We therefore developed a multilocus sequence typing scheme based on newly identified markers to generate high-resolution data to study the genetic diversity of schistosomes. The new markers characterized field isolates and provided additional inference on the diversity and population genetic structure within this complex group of schistosome species related to *S. haematobium*. We propose this multilocus typing scheme as an alternative for distinguishing between *S. haematobium*, *S. bovis*, and hybrids from both species. The generated data also provided information for the assessment of genetic diversity, and phylogenetic relationships within and between schistosome species.

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RELATIONSHIPS BETWEEN *SCHISTOSOMA MANSONI* INTENSITY AND NUTRITIONAL STATUS AMONG PRESCHOOL-AGED CHILDREN IN UGANDA

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Schistosomiasis causes anemia and impaired linear growth among children. However, there is a paucity of evidence in pre-school age children (PSAC) because it was commonly held that they were not significantly infected, and studies addressing reversibility of morbidity with praziquantel (PZQ) are limited as PZQ has only recently been approved for children ages

1-4. As part of an ongoing NIH-funded phase II trial of optimal PZQ dosing for PSAC ages 12-48 months in Uganda, we present baseline findings assessing *Schistosoma mansoni* infection and nutritional morbidities. Children with *S. mansoni* infection, detected by Kato Katz in duplicate stool samples, were enrolled from the Lake Albert region in Uganda. Anemia was defined as hemoglobin <11.0 g/dL. Undernutrition categories of underweight (weight-for-age z score<-2), stunting (length-for-age z score<-2), and wasting (weight-for-length z score<-2) were defined using WHO Anthro. Statistical analyses included multivariate linear and log binomial regression models adjusting for age, malaria co-infection, and father's education level. Of the 348 participants included, the median infection intensity was 72 EPG (IQR 24-258). Sixteen percent of children had malaria and 56.6% were anemic. Higher infection intensity was associated with lower hemoglobin concentrations (ß=-0.0128, p=0.0015), an increased risk for anemia (RR=1.29, CI 1.10-1.50), and occult blood in stool (RR=1.21, CI 1.03-1.42). Infection intensity was not significantly associated with underweight (RR=0.75, CI 0.47-1.18), stunting (RR=0.83, CI 0.69-1.01), or wasting (RR=1.28, CI 0.66-2.48). This trial offers a unique opportunity to assess *S. mansoni*-associated morbidity in PSAC who received PZQ treatment and will be followed for 12 months. At baseline, infection burden was associated with an increased risk for anemia, which may be explained in part by occult blood loss associated with schistosome egg-induced intestinal damage. Evidence of PSAC experiencing schistosomiasis-related nutritional morbidities further demonstrates the need for PZQ mass drug administration campaigns to include young children in endemic areas.

0567

LIVER AND BLADDER MORBIDITY IN AN *SCHISTOSOMA MANSONI AND S. HAEMATOBIUM* CO-ENDEMICITY AREA IN THE DEMOCRATIC REPUBLIC OF CONGO

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Schistosomiasis is a chronic and devastating disease responsible for significant morbidity and a relative mortality. In endemic areas, chronic infection causing periportal fibrosis, for infection with *Schistosoma mansoni* (*S.m*) and squamous cell bladder diseases ending in carcinoma, for infection with *Schistosoma haematobium (S.h)*. The Democratic Republic of the Congo (DRC) is among the most affected countries by both *S.m* and *S.h*. However, little is known about the morbidity associated with infection, despite the considerable burden of the disease. The study aims to determine specific Schistosoma morbidity, and its correlation with species of Schistosoma. We conducted a community-wide study between November 2015 and March 2016 in a rural community of Kifwa 2 village, in western of the DRC. Ultrasound examinations were performed in a total of 899 individuals aged 1-85 years previously tested for *Schistosoma* infections. Indicators of morbidity were recorded accordingly to the Niamey protocol, and multivariate logistic regression analysis employed to identify predictors for *Schistosoma* morbidity. Ultrasonography findings revealed that 68% of the study participants had *S.h* specific bladder morbidity (0.6%, 50.1% and 17.3% respectively for score 1, 2 and ≥3), 64.9% had *S.m* specific liver morbidity (56.4%, 6.8%, 0.9%, and 0.8% for grade C, D, E and F, respectively), and 48.7% had both bladder and fibrosis morbidity. Bladder and fibrosis morbidity are common for all age, but increases with age peaking at 10-14 years (77%) for *S.h* specific bladder morbidity and ≥ 40 years (79%) for *S.m* specific liver morbidity. Risk factors for *S.h*-specific bladder morbidity was age ≥40 years (p=0.024), *S.h* infection (p=0.004), and *S.m* infection (p=0.049). However, sex female (p=0.030), age ≥40 years (p<0.001), and *S.m* infection (p=0.008) are risk factors for *S.m*-specific liver morbidity. There is an urgent need of chemotherapy and/or chemoprophylaxis and reevaluate this situation after a certain period such as 2 or 5 years. In the same time, the control vector of schistosomiasis could enhance the elimination of this disease as a public health problem.

0568

OPTIMIZING THE USE OF PRAZIQUANTEL FOR PLANNING PREVENTIVE CHEMOTHERAPY CAMPAIGN AGAINST SCHISTOSOMA INFECTION IN SENEGAL: RESULTS FROM COMMUNITY LEVEL ANALYSIS

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Preventive chemotherapy (PC) with Praziquantel is the major strategy for controlling schistosomiasis in Senegal. This community level data analysis was aimed at updating the endemicity of schistosomiasis for better targeting population requiring Praziquantel in Senegal. Demographic and epidemiological data from 1610 community health areas were analyzed using the WHO/AFRO schistosomiasis sub-district data optimization tool 2021. The tool applies a WHO/AFRO decision tree for areas without epidemiological data to determine if mass treatments should be continued at community level. Overall, the endemicity of the 1610 community health areas (CHA) were updated based on the data in JRSM form (40.5%) and the use of endemicity at implementation unit (IU) (33.5%). Up to 282 (17.5%) and 398 (24.7%) community health areas were classified as moderate and high endemicity. 41.1% of communities were non endemic. High endemicity was more important in Tambacounda, Saint Louis, Matam, Louga and Kedougou. A change in endemicity category was observed when data was disaggregated from district level to community level. The number of implementation units classified as non-endemic was higher at community level (n=666) compared to district level (n=324). Among 540 areas previously classified as high endemic by district level data aggregation, 392 (72.6%) remained high prevalence category, while 92 (17%) became moderate, 43 (8.0%) low and 13 (2.4%) non-endemics at community level. Number of IU requiring PC was more important at district level (1286) compared to community level (944). Number of SAC requiring treatment was also more important at district level compared to community level. The analysis to disaggregate data from district level to community level using the WHO/AFRO schistosomiasis sub-district data optimization tool has allowed to target schistosomiasis interventions, optimize use of available PZQ and exposed data gaps.

0569

NOVEL RESAMPLING METHOD TO STRENGTHEN ACCURACY AND PRECISION OF SCHISTOSOMIASIS DIAGNOSTICS TO GUIDE MASS DRUG ADMINISTRATION PROGRAMS

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Schistosomiasis affects 200 million people in low- and middle-income countries. New WHO guidelines for mass drug administration depend on estimation of infection prevalence to modify MDA strategies. However, conventional diagnostic techniques for schistosomiasis via egg-count

(stool microscopy for *Schistosoma mansoni*) have poor sensitivity, wide day-to-day variation, and overdisperson that make accurate and precise prediction challenging. In this study, we developed a new statistical methodology leveraging secondary datasets from large-scale control/surveillance studies in Africa (SCORE project) The SCORE dataset on *S. mansoni* contains 260,000 personal tests, from 1744 communities in 3 countries. A high proportion of SCORE tests had multiple screening (up to 3 days/person), and SCORE communities represent a broad cross-section of infection burden (ranging 0 - 100% prevalence). We leveraged these SCORE features to generate a comprehensive set of conditional empirical distributions (CED) for resampling single stool tests to predict their putative alternatives (e.g. second day test). Our procedure can adjust the observed prevalence values by bringing them close to the 'true' state via a consistent CED resampling. The relevant CEDs are drawn from the pool of SCORE communities comparable to a given raw data. An alternative approach to CEDs employs a classifier function based on inferred infection intensity (low, moderate, or heavy). To test the consistency and predictive skill of our methodology we run multiple simulations with SCORE and additional datasets. Our model reduced discrepancy between 'observed' and 'true' prevalence values from 20-35% (raw data) to the 2-5% range (CED resamples). We can also estimate infection intensity. In all cases (prevalence, intensity), we get confidence intervals to assess diagnostic uncertainty. The proposed method can improve estimation of schistosomiasis prevalence to better guide mass drug administration programs in endemic settings, with cost savings through reduced stool samples.

0570

GENOME-WIDE SNPS ANALYSIS FOR TRACKING THE SPREAD OF *ANOPHELES STEPHENSI* IN EASTERN ETHIOPIA AND SOMALILAND

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Anopheles stephensi invasion in the Horn of Africa poses a substantial risk of increased malaria disease burden in the region. Population genomic approaches can reveal population structure and demographic history to infer vector invasion and dispersal patterns, information essential for vector control. Here, we analyzed 13 populations of *An. stephensi* from eastern Ethiopia and Somaliland collected in 2018 and 2020, respectively. We used double digest restriction-site associated DNA (ddRADseq) to genotype 250 mosquitoes at 2300 genome-wide single nucleotide polymorphisms (SNPs). Principal component and ancestry analyses revealed clustering that corresponded to geographic region, differentiating populations in Ethiopia and Somaliland. *Anopheles stephensi* populations from the northeastern and central-eastern sites were separated from the southernmost populations in Ethiopia. Somaliland *An. stephensi* clustered with some northeastern and central-eastern Ethiopian *An. stephensi*. Furthermore, genetic relatedness was observed between the northeastern and central-eastern Ethiopian *An. stephensi* populations and the Somaliland *An. stephensi* populations. The southeastern Ethiopian *An. stephensi* population was also distinct from the other populations in the admixture analysis. Overall, these results confirm previous evidence of population differentiation and geographical structure within eastern Ethiopian *An. stephensi* populations and reveal potential gene flow between Ethiopian and Somaliland *An. stephensi* populations. In addition, these findings may also indicate that southeastern Ethiopian *An. stephensi* are the result of a separate introduction. These details on the gene flow between *An. stephensi* populations can be incorporated into environmental models for predicting *An. stephensi* spread and can inform planning of vector control strategies against this invasive malaria vector in the Horn of Africa.

0571

UNRAVELLING THE PHENOTYPIC AND GENOMIC DIVERGENCE WITHIN SUB-POPULATIONS OF THE MAJOR MALARIA VECTOR *ANOPHELES GAMBIAE*

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Malaria is a mosquito-borne disease which remains a huge threat to global human health. Vector control remains the most effective method in reducing disease transmission. However, increase in resistance to different vector control tools combined to increasing drug resistance and high costs of implementation, make malaria resurgence a grim reality. New strategies with novel tools that complement LLINs and IRS to target the major vectors could prevent the resurgence of disease and hasten malaria elimination. Despite the central role of oviposition preference in selecting suitable environments in blood-feeding insects, its contribution to ecological specialization and local adaptation remains elusive. Population studies at early stages or ecological/genetic divergence provide an excellent opportunity to assess the role of oviposition preference in local adaptation of mosquitoes. Combining laboratory dual choice experiments and whole genome sequencing, we conducted the first assessment of phenotypic variation among some of the subpopulations of the malaria mosquito *Anopheles gambiae* that are emerging along gradients of anthropogenic disturbance in sub-Saharan Africa. When offered the choice, gravid females released individually in 30x30 cm cages under standard conditions and provided with 10% sugar solution lay eggs almost exclusively in water collected from their locality of origin. This extreme source-specialization prevails in populations belonging to the same ecological biome and displaying very low levels of genome-wide divergence. Interestingly, females maintained in laboratory conditions using regular (clean) water for five generations retained water discrimination and were still able to choose between source water and exogenous water. We conclude that favourable aquatic oviposition sites though highly heterogeneous in form, space and time are strong enough to drive ecological specialization in the presence of extensive gene flow in mosquitoes and act as signature cues at early stages of divergence in gravid Anopheles mosquitoes seeking to lay.

0572

SPECIATION WITHIN THE MALARIA-TRANSMITTING *ANOPHELES GAMBIAE* COMPLEX: HIGH-THROUGHPUT WHOLE GENOME SEQUENCING OF ADULT FEMALES PROVIDES EVIDENCE OF A NEW CRYPTIC TAXON IN FAR-WEST AFRICA

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The western extreme of the range of the two major malaria vector species, Anopheles coluzzii (CO) and An. gambiae (GA), in Sub-Saharan Africa is considered an area of high hybridization between the two species, due to high reported frequencies of specimens characterized by a heterozygous pattern of rDNA IGS diagnostic markers. We took advantage of high-throughput Whole Genome Sequence data of 1,190 adult females made available by the Ag1000G project and focused our

analyses on chromosome-3 and -X euchromatic regions in 3 populations from far-west (hereafter FW-pops: 2 populations from the Gambia, GM1 and GM2, and one from Guinea Bissau, GW) and in 10 populations from western (5 CO and 5 GA) Africa. Evidence, so far, are as follows: i) PCA clearly separates GM2 and GW (characterized by GA-specific Ancestry Informative Markers) and to a lesser extent GM1 (characterized by CO-specific AIMs) from all other populations; ii) Bayesian clustering analyses (ADMIXTURE and TESS3r) identify a taxon genetically distinct from CO and GA present in all 3 FW-pops; iii) mean Fst values between all FW-pops and GA (0.027-0.035) are in the range of those between CO and GA western populations, while only GM2 is highly differentiated (0.028) from CO; iii) genome-wide Fst values show a highest peak of differentiation between FW-pops and GA and CO in the centromeric region of chromosome-2L; iv) F3 statistics does not support the hypothesis that FW-pops are the results of historical admixture between west-African CO and GA; v) Patterson statistics suggest gene-flow between FW-pops and CO (not with GA). Further analyses are in progress to better understand the nature of the FW-taxon and its phylogenetic relation with the other members of the gambiae complex. Nevertheless, it is relevant to note that this represent the first finding of adult mosquitoes with a distinct genetic background from the other species of the complex and that parallel studies have highlighted that the FW-pops do not share most of the genomic patterns associated to insecticide resistance typical of CO and GA across their range.

0573

CONTRASTING THE HERITABILITY AND GENETIC BASIS OF DENGUE AND CHIKUNGUNYA VIRUS SUSCEPTIBILITY IN *AEDES AEGYPTI*

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Aedes aegypti is the primary vector of the arboviruses dengue (DENV) and chikungunya (CHIKV). Viral susceptibility and transmissibility in mosquito populations depend in part on GxG interactions between the virus and the vector genotypes. We used modified full-sibling design to estimate and compare the contributions of mosquito genetic variation to DENV and CHIKV susceptibilities. We demonstrated significant genetic variation for both viruses, but heritability was much higher for DENV (40%) than for CHIKV (18%). The differences were largely driven by greater within-family variation for CHIKV. Interestingly, we also reveal a complete lack of genetic correlation between DENV and CHIKV susceptibility. We then explored the genetic basis of differences between high and low susceptibly families to CHIKV and found two key genes whose expression is higher in families with lower viral loads. While both genes encode for uncharacterized proteins, one of the genes is a distant family member of the Salivary Gland Surface proteins that interestingly has also been horizontally transferred into the endosymbiont, *Wolbachia*. Our data suggest that the mosquito is much better at controlling DENV infection, and that the mosquito responds to the viruses with two very different mechanisms. These disparities may result from different coevolutionary histories, with CHIKV only recently emerging and acting as a selective agent in mosquitoes.

0574

AGO2 REGULATES AUTOPHAGY TO CONTROL MOSQUITO DEATH DURING ARBOVIRUS INFECTION

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The yellow fever mosquito, *Aedes aegypti* transmits many human infectious diseases caused by arthropod-borne (arbo) viruses, including dengue virus and chikungunya virus. Infection with these arboviruses does usually not impose fitness cost to mosquitoes in nature. It has been demonstrated that the small RNA interfere (siRNA) represents the major antiviral defense system to control systemic arboviral infection in *Ae. aegypti* by degrading viral genome into virus-specific 21-nt vsiRNAs through an RNA-induced-silencing-complex (RISC). Argonaute2 (Ago2) is the core gene of the siRNA signaling and cleaves complementary RNA sequences, and subsequently degrades target viral RNA. Here we overexpressed *Ago2* in midguts under the control of a blood-inducing promoter *carboxypeptidase A,* and mutated *Ago2* through CRISPR/Cas9 genome editing. Our data shows that the infection of multiple viruses and mortality of mosquitoes are significantly increased in *Ago2* mutant mosquitoes after oral viral infection. Small RNA sequencing and transcriptome analysis indicate elevated expression of autophagy genes, and further experiments demonstrated that repression of the autophagy pathway results in mosquito death after viral infection. Our results suggest a mechanism of arbovirus-induced mosquito death.

0575

GENOMIC SIGNATURES OF SEXUAL SELECTION IN THE YELLOW FEVER MOSQUITO *AEDES AEGYPTI*

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Aedes aegypti mosquitoes are vectors of several arboviruses of public health concern. Promising new control methods involving the mass release of modified mosquitoes to induce sterility or pathogen resistance into wild populations critically depend on the ability of lab-reared males to successfully mate with wild-type conspecific females. A thorough understanding of the genetic basis of male mating success could help to increase efficacy of such control strategies and aid in the development of novel mosquito control interventions. In this study, we compare whole genome sequences from populations of recently colonised *Ae. aegypti* mosquitoes evolved in the presence and absence of sexual selection. Our data show that populations evolved under sexual selection retain greater genetic similarity to recently colonised field populations, and that populations evolving without sexual selection show greater genomic divergence from the ancestral population. We report that significantly diverging variants with functional impact on amino acid sequence were enriched for several gene ontology terms related to chemosensation. Further, we used RNAi to deplete expression of high-confidence candidate genes to determine a mating-related phenotype. Our results highlight the importance of sexual selection in mosquito rearing, and that sexual selection may be important in maintaining genetic similarity to field populations.

0576

AFRICAN CONVERSATIONS ABOUT GENE DRIVES: INSIGHTS FROM AFRICAN STAKEHOLDERS ON HOW GENE DRIVE MODIFIED MOSQUITOES CAN BENEFIT MALARIA CONTROL AND ELIMINATION EFFORTS

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Genetic bio-control tools, such as gene drive modified mosquitoes (GDMMs), have been demonstrated as promising new tools to improve malaria control and possibly accelerate elimination. Although still in early-stage development, there is a need to start critical conversations with key stakeholders in sub-Saharan Africa (SSA) regarding safe and responsible testing and use of these technologies. We conducted a series of focus group discussions (n=18) and surveys (n=192) with key stakeholders representing 20 countries and five (5) islands across SSA, to explore their opinions, concerns and recommendations regarding GDMMs for malaria control in the continent. The stakeholders were recruited from

research and academia, regulatory agencies, health and other government ministries, and the media and advocacy groups. This study revealed a broad desire by the stakeholders for potentially transformative tools such as GDMMs to enable malaria elimination in resource-limited settings in the continent. There was an overall high awareness of gene drive technologies for malaria control among the participants, however, the knowledge of how the technologies work to control malaria was low. When provided with a brief explanation of how the technologies work, the participants expressed their concerns and suggestions to be addressed before wide-scale evaluations and use. This study presents voices of key stakeholders in SSA on if and how GDMMs could improve malaria control.

0577

ASSESSING RISK FOR TICK-BORNE DISEASE UNDER THE CONTEXT OF THE MODIFIABLE AREAL UNIT PROBLEM

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The modifiable areal unit problem (MAUP) is a cause of statistical bias when aggregating data according to spatial units, particularly when spatial units may be changed arbitrarily. An example of the MAUP occurs during the gerrymandering process, when political units are purposefully changed to alter electoral outcomes. The MAUP is also a concern in vectorborne disease research when entomological metrics gathered from point-level sampling data are related to epidemiological data aggregated to political units like counties or ZIP Codes. Here, we assess the impact of the MAUP when comparing these two metrics from the context of tick-borne disease and ecology. Our study uses geocoded human cases of anaplasmosis in New York State during 2017 and a geostatistical layer of an entomological risk index for *Anaplasma phagocytophilum* from *Ixodes scapularis* ticks collected during the fall of 2017. We assess the impact of polygon scale by simulating random Voronoi polygons of increasing size and calculating the correlation coefficient between entomological risk and cases of anaplasmosis within these polygons. We also assess the impact of polygon orientation by repeating this procedure 10 times for each number of polygons simulated. Correlations were also calculated using county and ZIP Code Tabulation Area polygons from New York State for comparison. Results from these simulations indicate increasing the number of polygons decreases the correlation coefficient (β=-.0001168, p=<0.0001). Further, the variance of simulated correlation coefficients decreased as the number of polygons increased. The correlation coefficients using the county and ZIP Code Tabulation Area polygons were at or beyond one standard deviation from the mean of the simulated correlation coefficients. These results indicate that reducing polygon size may allow public health researchers to better estimate spatial risk for tick-borne disease. However, as polygon size decreases, other landscape and environmental features may need to be incorporated to best assess risk.

0578

TRANSMISSION OF POWASSAN VIRUS BY THE INVASIVE ASIAN LONGHORNED TICK, *HAEMAPHYSALIS LONGICORNIS*, UNDER LABORATORY CONDITIONS

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The Asian longhorned tick, *Haemaphysalis longicornis*, is a tick native to eastern Asia that was first detected in North America outside a port of entry in 2017. Established populations of this invasive species have since been detected in 17 states. As the invasive range of the tick continues to expand, the ability for *H. longicornis* to serve as a vector of pathogens native to North America is under investigation. Here, we evaluate the vector competence of *H. longicornis* for Powassan virus (POWV) under laboratory conditions. POWV is a North American tick-borne flavivirus that is typically transmitted through the bite of *Ixodes* species ticks. The invasive range of *H. longicornis* is expected to overlap heavily with the geographic range of *I. scapularis* and POWV cases, highlighting the potential for this invasive tick species to amplify POWV transmission in natural foci. In our studies, adult female *H. longicornis* ticks were infected with POWV via anal pore microinjection. Viral RNA and infectious virions were detected in tick tissues via q-RT-PCR and focus-forming assay, respectively. POWV-injected female ticks were infested on mice, and POWV was transmitted to the mice during tick feeding, as shown by clinical signs of disease and seroconversion in the tick-exposed mice, as well as the detection of viral RNA in various mouse tissues. A POWV-injected female tick transmitted virus to her larval progeny, indicating that *H. longicornis* can vertically transmit POWV. These naturally-infected larval ticks were also able to transmit POWV to the mouse on which they fed, further demonstrating that *H. longicornis* can horizontally transmit POWV to a vertebrate host. Additionally, this study provides the first report of POWV neuropathology based on a natural tick transmission model of POWV. Together, our results suggest that the invasive *H. longicornis* tick is a competent vector of POWV. These findings underline the growing danger this tick may pose to human health in the United States. On-going studies are investigating the extent by which non-viremic transmission of POWV occurs between native *I. scapularis* co-feeding on the same host with *H. longicornis*.

0579

THE ROLE OF TICKS AND RODENTS IN THE TRANSMISSION AND EXPANSION OF TICK-BORNE FLAVIVIRUSES IN NORTHWESTERN EUROPE

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Tick-borne encephalitis (TBE) is the most important arboviral disease in Europe with 2,000-3,500 human cases each year. The transmission of the TBE virus (TBEV) depends on a complex interplay between the virus, *Ixodes* ticks and small rodents. TBEV is endemic in large parts of Central and Eastern Europe but has recently been discovered in Northwestern European countries such as the Netherlands and the United Kingdom. The emergence of TBEV in these countries was not predicted according to existing TBEV distribution models, thus the factors that favor the geographical spread of TBEV remain poorly understood. In the current study, we sought to determine the vector competence of *Ixodes ricinus* ticks for different viruses within the TBEV complex. An artificial blood-feeding system was used to infect ticks with different viruses. Viral strains from different geographical origins than the tested tick populations showed lower infection success compared to viruses isolated from the same region as where ticks were collected. Furthermore, we investigated whether wild rodents, such as wood mice (*Apodemus sylvaticus)* and yellow-necked mice (*A. flavicollis),* differ in their reservoir competence for TBEV. The wood mouse is a very common and widespread species in Europe, whereas the distribution of the yellow-necked mouse is limited to small parts of the Netherlands and the United Kingdom. Captured rodents of both species were inoculated with 1000 $TCID_{50}$ of either a classical European subtype of TBEV (Neudoerfl) or TBEV-NL, a more genetically divergent TBEV strain from the Netherlands. Experiments with wood mice and yellow-necked mice showed that all animals survived the infection with TBEV and remained without disease symptoms. Nevertheless, TBEV was detected up to 21 days in the blood of both rodent species and TBEV infected the brain of the mice from 3 to 21 days after infection. Our study demonstrates that TBEV strains isolated from the Dutch ecosystem are efficiently transmitted by *I. ricinus* ticks. Further, wood mice and yellow-necked mice are viraemic for a longer period than previously thought, confirming their important role as reservoir hosts for TBEV.

0580

HOST BLOODMEAL PREFERENCES DIFFER BETWEEN LARVAL AND NYMPHAL DEER TICKS

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The enzootic cycle of *Borrelia burgdorferi*, the agent of Lyme disease, depends on infected nymphal deer ticks, *Ixodes dammini*, feeding on competent reservoir hosts each summer. These hosts then serve as the source of infection for the new cohort of larvae. The force of transmission depends on both immature stages focusing their bites upon the same kind of host. Mammal trapping studies suggest that subadult deer ticks mainly feed on white-footed mice, but the potential range of hosts is diverse. To determine whether subadult deer ticks differ in their host preferences, we identified bloodmeal remnants from host-seeking nymphal and adult ticks that had fed as larvae and nymphs in the same site during the same season. We thus compared ticks that had access to the same potential bloodmeal hosts. Bloodmeal hosts from adult ticks collected in fall 2019 and 2020 were compared with nymphal ticks collected in the summer 2020 and 2021, respectively. Six different sites were surveyed; bloodmeal analysis was conducted on 321 adult and 357 nymphal ticks using assays for hosts commonly found in New England enzootic sites. Using our retrotransposon targeted PCR assay for host bloodmeal identification, we found no difference in the utilization of white-footed mice, voles, rabbits, deer or opossum by subadult deer ticks. However, nymphs were significantly more likely to feed on birds and sciurids (OR=2.8 and OR=8.6 respectively, p=0.000), whereas larvae were significantly more likely to feed on shrews (OR=6.3 p=0.00). In fact, host-seeking nymphs infected with *Borrelia* were likely to have fed as larvae on mice or shrews (OR=2.6 and OR=3 respectively, p<0.003) but not birds or sciurids. The general paradigm for the enzootic transmission of *B. burgdorferi* is that nymphs infect white footed mice, which feed larvae and thus produce the majority of infected nymphs. The enzootic cycle appears to be more complex, with a large number of infectious nymphal bites diverted from the expected mouse host. We conclude that the local force of enzootic *B. burgdorferi* transmission may depend on the extent to which the bloodmeal host preferences of larval and nymphal deer ticks coincide.

0581

PERSISTENCE OF PLAGUE IN RODENTS AND FLEAS IN FOCI WITH WIDESPREAD ANTHROPOGENIC LAND USE IN THE CENTRAL HIGHLANDS OF MADAGASCAR

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Plague remains endemic in Madagascar. Under conditions where anthropogenic land use and habitat loss occurs, human-rodent-flea dynamics may be altered allowing transmission to persist year-round. To estimate risk of transmission to humans and to refine proactive plague prevention strategies, surveillance of small mammals (SM) was conducted during low and high plague seasons (LPS/HPS) in August 2021 and January 2022 in three active plague foci where deforestation associated to charcoal production and agriculture croplands dominate. Blood, spleen and fleas were collected to assess *Yersinia pestis* circulation using ELISA, diagnostic rapid tests (RDT), culture and also the flea index (FI). A total of 383 SM (*Rattus rattus, Rattus norvegicus, Mus musculus* and *Suncus murinus*) were captured during the two periods of study; 250 in LPS against 133 in HPS. Of the 383 SM, 489 fleas were collected and 430 were identified (76.0% *Xenopsylla cheopis,* 15.4% *Synopsyllus fonquerniei 7.7% Dinopsyllus* spp., 0.7% *Ctenocephalides felis* and 0.2% *Paractenopsyllus* spp.). The FI was higher during HPS (2.2) when compared to 0.8 in LPS. Two strains of *Y. pestis* were isolated from *R. rattus* during LPS and HPS. Three percent and 2.8% of SM were tested positive on RDT during the LPS and HPS respectively. Antibodies for *Y. pestis* were detected in 57 SM with more positive during LPS (16.8%) than HPS (11.3%). *Yersinia pestis* circulates in rodent populations during both HPS and LPS in these active foci, which provides an explanation for why plague persists year-round. *Dinopsyllus* and *Paractenopsyllus* species, known as forest fleas, were found from *R. rattus* inside houses in close proximity to deforestation which disturb their habitats. Land use alteration has the potential to create favorable environmental conditions for zoonotic transmission of this infectious disease to humans. These findings showed that environmental conditions should be considered when reinforcing plague control measures. Additional work is needed to elucidate the role of rodent and *Dinopsyllus* species, some of which are known plague vectors in continental Africa, in plague epidemiology in Madagascar.

0582

CARDIAC COMPLICATIONS OF HUMAN BABESIOSIS

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Human babesiosis is a worldwide emerging tick-borne disease caused by intraerythrocytic protozoa. Most patients experience mild to moderate illness, but life-threatening complications can occur. Although cardiac complications are common, the full spectrum of cardiac disease and the frequency, risk factors, and outcome of patients experiencing cardiac complications are unclear. Accordingly, we carried out a retrospective review of cardiac complications among babesiosis patients admitted to Yale-New Haven Hospital (YNHH) over the last decade to better characterize cardiac complications of babesiosis. We reviewed the medical records of all adult babesiosis patients admitted to YNHH from January 2011 to October 2021, confirmed by identification of Babesia parasites on thin blood smear and/or by polymerase chain reaction. The presence of Lyme disease and other tick-borne disease co-infections were recorded. Of 163 enrolled subjects, 32 (19.6%) had at least one cardiac complication during hospitalization. The most common cardiac complications were atrial fibrillation (9.4%), heart failure (8.6%), QTc prolongation (8.0%), and cardiac ischemia (6.8%). Neither cardiovascular disease risk factors nor preexisting cardiac conditions were significantly associated with the development of cardiac complications. The cardiac complication group had a greater prevalence of high grade parasitemia (>10%) (p<0.001), longer median length of both hospital (p<0.001) and intensive care unit stay (p<0.001), and higher mortality (p=0.024) than the non-cardiac complication group. Cardiac complications of acute babesiosis are common and occurred in approximately one fifth of this inpatient sample. Further investigation is needed to elucidate the relationship between babesiosis severity and cardiac outcomes.

0583

AN IMMUNOLOGICAL ATLAS OF *BABESIA MICROTI* PRIMARY INFECTION AND REINFECTION IMMUNITY IN BALB/C MICE

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Correlates of protective immunity to and pathogenesis of Human Babesiosis have not been clearly defined. *Babesia microti* (the most common cause of Human Babesiosis) causes an acute but self-resolving infection in Balb/c mice. We developed an immunological atlas of *B. microti* infection in Balb/c mice over the course of a primary infection and reinfection by performing histological analysis of multiple organs, in depth flow cytometry, and immune profiling of antibody isotypes and cytokines in serum. Histopathologic observations included hepatic vascular congestion, pulmonary vascular erythrocyte margination, clumping, and intrahistiocytic cytoplasmic parasite adherence to the endothelium. By

flow cytometry, we report 4 major findings. First, *B. microti* infection of Balb/c mice is associated with expansion of a novel population of $CD4^-$ $CD8^-$ T cells. Second, *B. microti* induces a potent Th2 $CD4^+$ T cell response characterized by 3.6 fold more Th2 associated GATA-3^+CD4^+ T cells compared to Th1 associated T-bet^+CD4^+ T cells on day 3 post-infection ($p<0.01$, Mann–Whitney *U* test). Third, naïve $CD4^+$ T cells differentiate into short lived $CD62L^-CD127^-$ effector cells during primary infection. Fourth, B cells undergo isotype switching and differentiate into $CD38^+CD138^+$ plasmablasts and $CD95^+GL7^+$ germinal center B cells. Among 23 cytokines analyzed, IL-13 was the most abundant cytokine produced during Acute Babesiosis in Balb/c mice. These results identify novel immune cells and cytokines associated with the acute and clearance phases of *B. microti* infection in a mouse model of Human Babesiosis.

0584

LINKS BETWEEN WATER, SANITATION AND HYGIENE INTERVENTIONS, ENVIRONMENTAL CONTAMINATION, CHILD ENTERIC INFECTIONS AND GROWTH: AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

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Recent trials of household- and community-level water, sanitation, and hygiene (WASH) interventions have found no or mixed effects on child health. Measuring pathogens and host-specific microbial source tracking (MST) markers in environmental samples can help explore if limited effects occur because interventions insufficiently reduce contamination or if measurable environmental pathogen exposure is not a strong determinant of child health. We conducted a systematic review and individual participant data meta-analysis to assess WASH intervention effects on pathogens/MST markers in environmental samples and associations between pathogens/MST markers and subsequent pathogen-specific infections, caregiver-reported diarrhea, and height-for-age Z-scores (HAZ) in children. We received data from 5 eligible WASH intervention studies. Environmental sampling was focused on onsite sanitation interventions and included drinking water, hand rinses, soil, and flies (pooled N=12,184 samples). Pooled across studies, interventions led to a small reduction in any pathogen presence in any sample type (prevalence ratio=0.94 (95% CI: 0.90, 0.99)) but had no overall effect on human/animal MST markers. Pathogen detection in environmental samples was consistently associated with subsequent child infection with the same pathogen, but not with diarrhea. Detection of any pathogen in any sample type was associated with slightly lower HAZ (pooled Δz=-0.08 (95% CI: -0.15, 0.00)). There were no consistent associations between MST markers and child health. Results for individual pathogens/MST markers were similar. Among the few WASH trials that measured pathogens or MST markers in the environment, effects of onsite sanitation on these targets were consistently small or null. Our findings are aligned with the limited impacts of onsite sanitation interventions on fecal indicator bacteria in the environment and on child health. The limited associations between advanced measurements of environmental contamination and child health highlight the limitations of current approaches in characterizing environmental exposure to pathogens.

0585

UNDERSTANDING THE DRIVERS OF THE WASH BENEFITS BANGLADESH TRIAL RESULTS: HYPOTHESES AND ESTIMATES FROM AN INFECTIOUS DISEASE TRANSMISSION MODEL

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Recent large-scale, well-powered intervention randomized controlled trials (RCTs) in low-income settings have not found the expected health benefits of water, sanitation, and hygiene (WASH) interventions, including on reduced diarrhea. There has been a robust discourse about the potential reasons for these underwhelming impacts, addressing issues of completeness, coverage, compliance, and baseline WASH/disease conditions, among others. However, an RCT, which evaluates a hypothesis in a specific context, cannot easily generalize to other contexts, so that counterfactual questions of "what would have happened if…" are hard to address. Mechanistic models are a widely used to generalize findings between contexts but have not been previously applied to RCTs. The purpose of this study was to 1) develop a modeling framework to explain relative risk outcomes in an RCT and 2) to generalize the RCT results to other contexts and conditions. Our model accounts for i) transmission across multiple environmental pathways, ii) multiple interventions applied individually and in combination, iii) adherence to interventions, and iv) the impact of individuals not enrolled in the study. A Bayesian sampling approach was used to obtain posterior estimates of mechanistic parameters and their uncertainties for the WASH Benefits Bangladesh RCT (n=17,187), reproducing reported diarrheal prevalence. The baseline estimate of the basic reproduction number R_0 for the control arm was 1.15, (95% CI: 1.09, 1.27) in the absence of intervention or preexisting WASH conditions. No single pathway—water, fomites, or all other pathways—was likely able to sustain transmission as pathway-specific R_0s were each below 1 (0.49 (95% CI: 0.07, 0.99), 0.26 (95% CI: 0.04, 0.57), and 0.40 (95% CI: 0.02, 0.88), respectively). In our counterfactual simulations, completeness and coverage, rather than compliance, efficacy, or baseline conditions, were most strongly associated with intervention effectiveness. Our approach can aid in understanding the contentious findings of the WASH-Benefits trial but also enhance analysis of empirical RCT data for program decision-making.

0586

REDUCED DIARRHEA PREVALENCE, IMPROVEMENTS IN HANDWASHING WITH SOAP AND STORED DRINKING WATER QUALITY ASSOCIATED WITH AWARENESS MEASURED BY INTERACTIVE VOICE RESPONSE (IVR) MESSAGES IN A WATER, SANITATION AND HYGIENE CHOBI7 MOBILE HEALTH PROGRAM

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The Cholera-Hospital-Based-Intervention-for-7-days (CHoBI7) mobile health program promotes WASH behaviors through voice calls and text messages to reduce diarrheal diseases in Bangladesh. The objective of this study was to investigate the relationship between responses to CHoBI7 WASH interactive voice response (IVR) quiz messages and diarrhea and WASH behaviors. Fourteen CHoBI7 IVR quiz messages were sent to 517 households during the 12-month program period for this intervention on handwashing with soap and water treatment. IVR message responses were classified as "correct answer", "incorrect answer",

"no response" (did not press 1 or 2), and "failed" (did not answer the phone). Diarrhea prevalence was assessed through monthly clinical surveillance. Handwashing with soap was assessed by 5-hour structured observation, and stored water quality was defined by *E.coli*. Households that correctly responded to a CHoBI7 mHealth program IVR quiz message had a significantly lower odds of diarrhea for all age groups (Odds Ratio (OR): 0.73; 95% Confidence Interval (CI): 0.54, 0.98), and significantly higher odds of handwashing with soap at stool related events (OR: 2.33; 95% CI: 1.09, 5.01) and *E. coli* <100 colony forming units /100 mL in the household stored water (OR: 2.04; 95% CI: 1.25, 3.33) compared to households that did not answer the IVR quiz. Correct responses to CHoBI7 mHealth IVR quizzes were associated with decreased diarrhea prevalence and improved stored drinking water quality and handwashing with soap. These findings suggest engagement in the CHoBI7 mHealth program and awareness of diarrheal disease prevention can reduce diarrhea and facilitate changes in WASH behaviors.

0587

RANDOMIZED CONTROLLED TRIAL OF THE CHOBI7 CHOLERA RAPID RESPONSE PROGRAM TO REDUCE DIARRHEAL DISEASES IN BANGLADESH

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Worldwide there are 2.9 million cholera cases annually. Effective targeted water, sanitation, and hygiene (WASH) interventions are urgently needed to reduce cholera globally. Individuals living within 50 meters of a cholera patient are at higher risk of developing cholera than the general population during the month after the index patient seeks care at a health facility. To build an evidence base on effective WASH interventions to reduce diarrheal diseases for this population, we developed the CHoBI7 cholera rapid response program. Once a cholera patient (confirmed by bacterial culture) is identified at a health facility, a health promoter delivers a targeted WASH intervention to the cholera hotspot (households within 50 meters of a cholera patient) through both in-person visits, and weekly WASH mobile messages for the 3-month program period. A randomized controlled trial of the CHoBI7 cholera rapid response program was conducted of 261 participants in 15 cholera hotspots in urban Dhaka, Bangladesh. This program was compared to the standard message in Bangladesh on the use of oral rehydration solution for dehydration. Five-hour structured observation of handwashing with soap practices, and diarrhea surveillance was conducted monthly for the 3-month program period. Delivery of the CHoBI7 cholera rapid response program significantly increased handwashing with soap throughout the 3-month program period (Odds Ratio: 3.96 95% CI: 2.35, 6.66, p=0.035) (54% in the CHoBI7 arm vs. 23% in the standard arm). Furthermore, there was a significant reduction in diarrheal prevalence for all participants (adults and children) (Prevalence Ratio (PR) 0.35: ,95% Confidence Interval (CI): 0.128 - 0.99, p = 0.049), and for children under 5 years of age (PR: 0.21, 95% CI: 0.06 - 0.74, p = 0.015) during the 3-month program. These findings demonstrate that the CHoBI7 cholera rapid response program is effective in lowering diarrhea prevalence and increasing handwashing with soap for a population at high risk of cholera.

0588

EFFECT OF A BEHAVIOUR CHANGE AND HARDWARE INTERVENTION ON SAFE CHILD FECES MANAGEMENT PRACTICES IN RURAL ODISHA, INDIA: A CLUSTER-RANDOMISED CONTROLLED TRIAL

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Poor child feces management (CFM) may be an important source of enteric pathogen exposure and contribute to a large disease burden. Yet, in many low- and middle-income countries households with a latrine often fail to safely dispose of their child's feces into the latrine. We conducted a cluster randomized trial (CRT) in 74 villages in rural Odisha, India to evaluate the effectiveness of an intervention aimed at improving caregiver safe disposal of child feces and child latrine use. The intervention was designed based on behavior change theory and novel CFM hardware was co-developed with caregivers following a user-centered design approach. The resultant CFM intervention consisted of six behavior change strategies together with provision of hardware: wash basin and bucket with lid to aid safe management of soiled nappies and a novel latrine training mat to aid safe disposal and latrine training. All households with a latrine and a child <5 years old were eligible. Following a baseline survey, 37 villages were randomly allocated to intervention arm and 37 to control arm. A community-based organization delivered the intervention and an endline survey was carried out four to six months after delivery among all eligible households. The primary outcome was safe disposal of child feces after last defecation as defined by the Joint Monitoring Programme (JMP), which encompasses two sub-behaviors: caregiver disposal of the child's feces into a latrine and the child using the latrine. Analysis included 662 caregivers (841 children) in the intervention arm and 631 caregivers (785 children) in control arm. We found the prevalence of JMP-defined safe disposal at endline was 1.15 times greater (95% CI 1.03 - 1.29) in the intervention arm compared to control. We separately examined the sub-behaviors and found the prevalence of caregiver disposal in latrine at endline was 1.76 times greater (95% CI 1.33 - 2.33) in the intervention arm compared to control but there was no difference observed in prevalence of child latrine use at endline (PR 1.05, 95% CI 0.94 - 1.17). The CFM intervention achieved increases in caregiver safe disposal of child feces but not child latrine use.

0590

SYSTEM PERFORMANCE OF A DECENTRALIZED NATURE-BASED APPROACH TO WASTEWATER TREATMENT IN LMIC INFORMAL SETTLEMENTS

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Increasing urbanization in low- and middle-income countries has led to the growth of informal settlements, a long-standing challenge for conventional water and sanitation management that is fundamental to health and wellbeing. Introducing interventions aimed at providing safe sanitation and disrupting multiple fecal-oral contamination pathways in the complex sociocultural and biophysical setting of an urban informal settlement poses many challenges. Revitalising Informal Settlements and their Environments (RISE) is a randomized controlled trial among 24 settlements in Makassar, Indonesia and Suva, Fiji to assess a novel "water sensitive cities" approach for managing wastewater and environmental fecal contamination in informal settlements through decentralized bioremediation. Systems are co-designed with community residents

with technology options that include communal septic tanks and drains, precinct scale pressure sewers, constructed subsurface and surface flow treatment wetlands, and biofilters to filter wastewater prior to release into the environment. A demonstration project was constructed in 2020 in Batua, South Sulawesi to optimize the intervention and confirm system performance. The system services 22 dwellings and includes 40m^2 of wetlands. A total of 317 water samples collected over 57 weeks indicates that, except for ammonia, the system met all Indonesian discharge standards for domestic wastewater, including pH, BOD, TSS, COD, oil and grease and total coliforms. Ammonia remained non-compliant (inflow 181.4mg/L, effluent 35.2mg/L, standard <10mg/L), possibly due to non-dilution with greywater and requiring additional aeration. Mean total coliforms were reduced by 99.3% (from 308,900 to 2,100 CFU/100ml) and *E.coli* by 99.7% (from 195,150 to 650 CFU/100ml). Performance suggests that this nature-based solution can substitute for conventional wastewater treatment while being appropriate for decentralized, low-income settings. The demonstration project also showed how nature-based solutions could be incorporated into high-density settings.

0591

EVALUATING TRADE-OFFS BETWEEN LOCAL AND GLOBAL PRIORITIES FOR THE CONTROL OF MALARIA

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Despite global efforts to reduce malaria transmission, the world remains offtrack to meet the goals set in the WHO Global Technical Strategy for Malaria. International donor funding for malaria interventions has plateaued and therefore difficult decisions need to be made regarding resource allocation. Currently, international donor funding is allocated between countries in proportion to disease burden as a measure of need. This can however lead to sub-optimal allocation at a broader regional level. We sought to quantify the tradeoffs between global and local perspectives for resource allocation. We extended a compartmental model of malaria transmission into a metapopulation model in which populations were stratified by their level of transmission. We used the model to evaluate the optimal distribution of insecticide bed nets strategies from two different perspectives; first minimising disease burden across all the populations aligned with the international donor perspective; and then minimising disease burden for each sub-population, aligned with the country perspective. Results show that the current allocation in proportion to disease burden is optimal in terms of reducing burden globally and therefore aligned with the international donor perspective. In contrast, for low transmission countries, an equal allocation of resources regardless of transmission levels is optimal from the country perspective, allowing a greater number of cases to be averted in the individual country provided that mixing levels with a high transmission country stay below 16%. As mixing between a low and a high transmission country increases, our results show that sharing resources proportionally to the level of connection with the high transmission country may be better than keeping resources locally. These findings highlight that international donor and individual country perspectives may not be aligned when considering allocation of limited resources for malaria control. Our findings also support current cross-border control initiatives, demonstrating the wider value to low transmission countries of controlling malaria across their borders.

0592

CHARACTERISTICS OF TRAVEL FROM ZANZIBAR TO TANZANIA MAINLAND AND THE ASSOCIATED RISK OF MALARIA INFECTION

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Zanzibar has made significant progress in malaria control as a result of rolling out interventions including vector control, improved diagnosis, and highly effective artemisinin-based combination therapy. However, imported infections from mainland Tanzania have been highlighted as an important contributor to sustained malaria transmission on the archipelago. This research aimed to understand the links between travel patterns to mainland Tanzania and malaria infections detected in people in Zanzibar. We did a rolling cross-sectional survey on Pemba and Unguja islands linked to the routine case-based surveillance-response system. We surveyed households of patients diagnosed with malaria at health facilities ('index cases') and tested all household members for malaria using rapid diagnostic tests (RDT) and highly sensitive qPCR. Interview questions elicited a detailed travel history of all household members who had traveled within the past two months. We recruited 17,891 participants of whom 2,788 respondents (16%) reported a recent trip, and 786 out of these (66%) had traveled to mainland Tanzania. Among those who traveled to the mainland, 54% and 21% reported traveling to high and moderate malaria-endemic districts, respectively. Of all travelers to the mainland, 165 (38%) reported never using a mosquito net during their recent travel. Of those who visited highly malaria endemic districts, 25 (9%) were positive by RDT and 83 (34%) by qPCR. Travelers to highly endemic districts had a 2.5-fold higher odds of being qPCR-positive than those who traveled only to districts where malaria-endemicity is lower (95% CI: 1.5-4.1, p=0. 001). Further risk factors of malaria infection among travelers will be presented alongside their travel destinations and recommendations for reducing malaria importation from mainland Tanzania to Zanzibar.

0593

SINGLE LOW DOSE TAFENOQUINE COMBINED WITH DIHYDROARTEMISININ-PIPERAQUINE TO REDUCE *PLASMODIUM FALCIPARUM* TRANSMISSION: A PHASE 2 SINGLE BLIND RANDOMIZED CLINICAL TRIAL IN OUELESSEBOUGOU, MALI

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Tafenoquine (TQ) was recently approved as prophylaxis and radical cure for *P. vivax* infection. Like its analogue primaquine (PQ), tafenoquine can kill *P. falciparum* gametocytes. This activity makes it a potentially valuable tool for malaria transmission blocking, particularly for the containment of drug resistant parasites. In the current trial, we aimed to establish the efficacy and safety of three single low doses of TQ in combination with dihydroartemisinin-piperaquine (DP) for reducing gametocyte density and transmission to mosquitoes. Eighty participants

(12-50 years of age) with normal glucose-6-phosphate dehydrogenase (G6PD) activity and asymptomatic *P. falciparum* gametocyte carriage were randomised to DP, or DP plus a single dose of TQ at 0·42mg/kg, 0·83mg/kg, or 1·66mg/kg. Clinical assessments, biochemical, and molecular gametocyte quantification assays were conducted throughout the 28 days of follow up, with additional samples at day 0, 2, 7 and 14 to test infectivity to mosquitoes. Participants were enrolled from 29th October to 25th November 2020. Before treatment, 66% (53/80) of individuals were infectious to mosquitoes, infecting on average 12·5% of mosquitoes (Interquartile range [IQR] 3·64-35). Within-arm percent reduction in mosquito infection rate on day 7 (primary endpoint) was 79·95% (IQR 57·15-100) following DP (p=0·0005), and 100% (IQR 98·36-100) following all treatments with DP and TQ (p<0·0005). Male and female gametocyte clearance following TQ suggests a different mechanism of clearance compared to PQ. No serious adverse events (SAE) occurred, and there were no significant differences in the incidence of all AEs (p=0.73) or drug-related AEs (p=0.62) observed between treatment arms. TQ was well tolerated at all doses and accelerated *P. falciparum* gametocyte clearance. All TQ doses demonstrated improved transmission reduction at day 7 compared to DP alone. Despite being slower to achieve blockade than PQ, PQ remains active for only a few hours whereas TQ has a half-life of more than 2 weeks. Future trials should focus on establishing the longevity of TQ's transmission blocking activity.

0594

ASSESSMENT OF PRIMAQUINE UTILIZATION IN FOUR ETHIOPIAN HEALTH FACILITIES IN THE CONTEXT OF ETHIOPIA'S MALARIA ELIMINATION STRATEGY

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Malaria is one of the major causes of morbidity and mortality in Sub-Saharan Africa. Appropriate use of antimalarial drugs is vital in the effective management of malaria, and it reduces the development of drug resistance and the cost of therapy. Effective supply planning of antimalarial drugs is integral to preventing stockouts or wastage. Based on Ethiopia's National Malaria Treatment Guidelines (NMTG) and malaria elimination strategy, radical cure with primaquine 0.25mg/kg for 14 days is recommended for all patients with *P. vivax* (Pv) and mixed malaria, and a single dose 0.25mg/kg of primaquine with Artemether-Lumefantrine (AL) is used for the treatment of *P. falciparum* (Pf). The U.S. President's Malaria Initiative funded the USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project to conduct a retrospective cross-sectional drug use evaluation (DUE) in four supported health facilities from August to December 2021 to assess the extent of primaquine utilization in malaria patients and treatment adherence to the NMTG in Ethiopia. The DUE reviewed 593 patient charts with malaria treatments from 2019 to 2021. Of these cases, 99% (588/593) had laboratory tests of which 93.7% (551/588) were malaria positive. Of the total malaria positive cases, 64% (353) were *Pf*, 24.7% (136) were *Pv*, 3.3% (18) were mixed species infections (507 in total), and 8% (44) had no specified species. The utilization rate of primaquine was 75.5% (379/507). A single dose of primaquine with AL was used in 77% of *Pf* cases, 14-day primaquine with chloroquine was used in 86% of *Pv* cases, and 14-day primaquine was used in 67% of mixed malaria cases. The use of primaquine in the studied facilities was found to be lower than the national recommendation. Interventions, including trainings and supportive supervision should be considered to improve the use of primaquine. Additional nationally representative primaquine utilization studies should be considered to better understand primaquine use more broadly and help identify causes of under-use.

0595

ACTIVE SCREENING AND TREATMENT SIGNIFICANTLY REDUCES THE INFECTIOUS RESERVOIR OF MALARIA IN BURKINA FASO

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The majority of malaria infections in endemic countries are asymptomatic and can remain untreated and potentially transmissible to mosquitoes for many months, posing a major obstacle to malaria elimination. Malaria burden and transmission could be reduced by detecting and treating these infections early using active methods to screen for infections. In an 18 month cluster-randomised intervention study in Burkina Faso we assessed the impact of two interventions on the prevalence and transmissibility of malaria infections. The interventions included (i) enhanced community case management (CCM), comprising active weekly screening for fever, with treatment of rapid diagnostic test (RDT) positive febrile individuals, or (ii) monthly screening and treatment (MSAT) using standard RDTs. 180 compounds with 906 subjects were randomized to: Arm 1 - control; Arm 2 - enhanced CCM; or Arm 3 - enhanced CCM combined with MSAT. Interventions were implemented over 16 months, with parasite and gametocyte prevalence and density monitored by qPCR in 4 start/end season cross-sectional surveys. At the start of the study, parasite prevalence by qPCR was 64%, and 61% of these infections carried gametocytes. Most infections in cross-sectional surveys were asymptomatic (98.6% [1336/1355]), and asymptomatic infections were as transmissible to mosquitoes in membrane feeding assays (4.5% [35/771]) as symptomatic infections (5.7% [7/123]). A total of 108 malaria infections were detected by CCM, and 534 infections detected by MSAT. There was a significant impact of CCM plus MSAT, with parasite and gametocyte prevalence and density being significantly lower in arm 3 in all end season surveys. Notably, gametocyte prevalence was up to 79.2 % lower and transmissible gametocyte prevalence (>1 p/uL) was up to 95.3 % lower, with only 0.73% (2/275) of participants in arm 3 carrying gametocytes at a transmissible density at the end of the dry season. This study could pave the way for a simple yet effective method to control malaria burden in areas of high transmission by abrogating infections before clinical presentation and the development of transmissible gametocytemia.

0596

EFFECTIVENESS OF REACTIVE FOCAL MASS DRUG ADMINISTRATION FOR MALARIA IN THAILAND DURING THE COVID-19 PANDEMIC

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Thailand has achieved dramatic success in reducing its malaria burden by implementing robust surveillance approaches including case investigation and active case detection, and has targeted malaria elimination by 2024. One active approach includes reactive case detection (RACD), where all cases confirmed through the health system are followed up at

the community level with testing of neighboring household members. However, neighborhood-targeted RACD has had limited effectiveness in the Greater Mekong Subregion (GMS) due to low diagnostic sensitivity and high rates of forest work exposure. Additionally, active case detection and treatment adherence for *Plasmodium vivax* is especially challenging. We conducted a pragmatic randomized controlled trial to assess the effectiveness of community-level reactive focal mass drug administration (rfMDA), or administration of an effective antimalarial to all neighborhood or forest work contacts of an initial confirmed case, including quantitative G6PD testing and radical cure for *P. vivax* with follow up by village health volunteers. Forty subdistricts were randomized to conduct rfMDA with artesunate-mefloquine or the standard of care control (RACD) from November 2020 - November 2021, and confirmed case incidence was measured through routine surveillance in each arm. An endline survey measuring parasite prevalence by PCR in 7,495 individuals across arms was conducted December 2021 - February 2022. Coverage of index case response was much lower in the intervention arm (29.4%) than control (87.7%) due to the COVID-19 pandemic, as intervention arm health staff were also frontline COVID-19 workers. Confirmed case incidence was reduced in the intervention arm from 4.0/1000 in 2020 to 3.0/1000 in 2021, while in the control arm incidence was 4.3/1000 in 2020 and 4.8/1000 in 2021. Adjusted incidence and endline parasite prevalence results will be presented. These results suggest that rfMDA, including radical cure for *P. vivax*, may be an effective strategy for reducing transmission in the remaining active foci in Thailand that can be feasibly implemented with supported village health volunteers.

0597

FEASIBILITY AND EFFECTIVENESS OF TARGETED MALARIA INTERVENTIONS FOR HIGH-RISK POPULATIONS IN SENEGAL

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Senegal has made significant progress in reducing malaria burden over the last decade. However, malaria remains a major cause of morbidity and mortality in some regions and key challenges exist among high-risk populations where access to malaria control tools is limited. Our preliminary study indicated that both gold miners and Talibés (Koranic school students) have high exposure to mosquito bites, but low coverage and use of vector control measures and limited access to health services. We conducted a controlled pre/post study to determine whether targeted malaria interventions, including expansion of community case management and distribution of LLINs, at mining sites and Koranic schools (Daaras) increased LLIN coverage and reduced malaria infection prevalence and clinical incidence during high transmission season in Senegal. We randomly assigned eight health facility catchment areas to intervention or control groups: four in Kaolack (a city with many Koranic schools) and four in Saraya (a district with gold mining sites). Surveys were conducted pre (Oct 2021; n=1740) and post (Feb 2022; n=2200) delivery of intervention to assess LLIN coverage and infection prevalence by rapid diagnostic test. In Kaolack, pre-intervention LLIN ownership was 44.7% in intervention and 70.6% in control areas, and post-intervention 100% and 73.1%, respectively. In Saraya, pre-intervention LLIN ownership was 62.8% in intervention and 64.4% in control areas, and post-intervention 73.1% and 68.6%, respectively. In Kaolack, prevalence of malaria infection increased from 4.9% to 12.9% in intervention areas, but from 5.9% to 24.7% in control areas; in Saraya, prevalence decreased from 27.6% to 6.3% in intervention areas, and from 31.6% to 6.4% in control areas. Multivariable results of impact on infection prevalence and clinical incidence will be presented. These results suggest that targeted malaria interventions are feasible and can effectively increase LLIN coverage and reduce prevalence in certain high-risk populations. Expansion to other unreached high-risk populations is essential for meeting malaria elimination goals.

0598

IL-11 REGULATES MUCOSAL RESPONSES IN ACUTE PULMONARY HELMINTH INFECTION

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Transient larval migration of helminth parasites in the host tissue during their life cycle drives an early neutrophil-associated inflammation before the establishment of an eosinophil-dominated type-2 response. Members of the IL-6 cytokine family, including IL-11, have been described to play a role in acute inflammatory responses. Investigating the role of IL-11 following *Ascaris spp*. infection in mouse models, we observed significantly elevated IL-11 levels in the lung tissue of *Ascaris*-infected mice (2,196 pg/mL *vs* 968 pg/mL, p<0.001 at 8 dpi) compared to uninfected mice. Flow cytometry and confocal imaging demonstrated that lung $EpCAM^+$ epithelial cells were the major source of IL-11 in the lungs of *Ascaris*-infected mice. Neutralization of IL-11 (using anti-IL-11 antibody intranasally) during *Ascaris* infection markedly impaired the influx of neutrophils to the lung, whereas intranasal administration of rIL-11, in contrast, increased neutrophil influx as a consequence of increased levels of G-CSF and CXCL1. *Ascaris* infection in IL-11Ra1 deficient mice was similarly associated with a marked reduction in lung neutrophil influx (20.3×10^5cells *vs* 51.2×10^5cells, p=0.030 at 8 dpi) and a significant decrease of neutrophil-associated mediators (e.g., CXCL-1 and G-CSF) when compared with WT *Ascaris*-infected animals. To further elucidate whether IL-11 production by lung epithelial cells is elicited directly or indirectly, a human bronchial epithelial cell line (HBEC3-KT) was shown to produce markedly increased (55% above baseline) amounts of IL-11 following exposure to *Ascaris* larvae. Moreover, HBEC3-KT cells, when stimulated *in vitro* with various recombinant cytokines, including IL-33, IL-1b, IL-1a, and TGF-b, only rTGF-b was capable of inducing IL-11 in a dose dependent manner. Indeed, pulmonary *Ascaris* larval migration drives a marked increase of TGF-b levels *in vivo* (1476.23 pg/mL vs 986.87 pg/mL, p<0.001). Taken together, our data suggests that IL-11 produced by epithelial cells regulates a neutrophil-dominated inflammation in response to epithelial damage and through TGF-b during acute helminth infection in the lungs.

0599

PHAGE SCREENING IDENTIFIED A NOVEL NEMATODE PAN ALLERGEN (NPA) RESPONSIBLE FOR IGE RESPONSES IN HUMAN FILARIAL TROPICAL PULMONARY EOSINOPHILIA (TPE)

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Tropical pulmonary Eosinophilia (TPE) is an allergic condition that occurs in individuals with Lymphatic Filariasis (LF), a tropical parasitic infection that affects over 120 million people in 82 countries. Parasite antigens responsible for triggering the IgE responses in TPE subjects is not fully identified. The main objective of this study was to identify IgE-specific allergens in TPE individuals. We screened a phage-displayed cDNA expression library of *Wuchereria bancrofti* microfilaria with pooled human monoclonal IgE antibodies isolated from B-cell hybridomas prepared from TPE individuals. After five rounds of biopanning, we analyzed 13 clones and the sequences obtained were blasted to identify the genes. Our results showed that the sequences belonged to two genes, Bm2855 and *Wb*TCTP.

Bm2855 (*Brugia malayi* RNA recognition motif domain-containing protein) gene is not yet annotated in the literature. Phylogenetic tree analysis on Bm2855 sequence showed that this gene is highly conserved in nematode parasites and showed over 95% similarity in several nematodes with no homology to human. Therefore, we named Bm2855 as Nematode Pan Allergen (NPA). The NPA gene sequence is now deposited in the NCBI GenBank (accession # ON023112). Further analysis showed that the NPA gene is highly expressed in the microfilaria stage and adult females compared to all other lifecycle stages of *W. bancrofti*. Similarly, sera samples from TPE, and microfilaremic subjects had high levels of antibodies against NPA compared to chronic pathology (CP) and endemic normal (EN) control subjects. *Wb*TCTP has already been described and characterized from our laboratory as a histamine releasing factor. Thus, in the present study, we report for the first time the NPA as a novel pan allergen that can induce IgE response in TPE individuals. Our study suggest that NPA and *Wb*TCTP may have a significant role in the pathology and allergic symptoms associated with TPE in filarial infected patients.

0600

INFLAMMASOME AND REACTIVE OXYGEN SPECIES (ROS) SIGNALING CASCADES DURING MICROFILARIAE- AND THIRD STAGE LARVAE-INDUCED NEUTROPHIL AND EOSINOPHIL ETOSIS

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Neutrophils and eosinophils as well as their cytotoxic granules are important for protective immunity against filariae. The release of those granules can be mediated through extracellular DNA trap cell death (ETosis), where intracellular DNA is explosively released, entrapping pathogens and supporting their killing. For neutrophils, reactive oxygen species (ROS) production and the non-canonical inflammasome pathway appears to be essential for PMA-induced ETosis. However, the exact signaling cascade for filaria-induced neutrophil and eosinophil ETosis is not known yet. Our *in vitro* results demonstrate that *Litomosoides sigmodontis* microfilariae (MF) and third stage larvae (L3) induce ETosis in bone marrow-derived neutrophils and eosinophils. However, the granulocytes vary in their ROS responses towards different stimuli. While neutrophils show faster and stronger ROS production towards stimuli such as PMA and zymosan, eosinophils generate more ROS in response to MF/L3 than neutrophils. Especially MF triggered intracellular ROS including mitochondrial ROS (mtROS) and extracellular ROS in eosinophils. Since MF primarily trigger the release of mtDNA in eosinophils and mtROS positively correlated with DNA release, a link between mtROS formation and ETosis is suggested. In addition, ROS generated by NADPH oxidase was shown to be important for the MF-induced ETosis, since granulocytes generated from NADPH oxidase knockout (ko) mice failed to generate DNA traps. Furthermore, experiments with eosinophils generated from AIM2 and caspase-1 ko mice indicate that AIM2 inflammasome activation, which detects double stranded DNA, followed by caspase-1 signaling is involved in the MF-induced ETosis suggesting a positive feedback-loop for ETosis in eosinophils. In summary, these results reveal the underlying signaling mechanism during granulocyte DNA release that is in part dependent on the stimuli. Our results further illustrate both conserved mechanisms as well as differences in ETosis and ROS production in eosinophils and neutrophils.

0601

PRE-EXISTING ALLERGIC SENSITIZATION RESHAPES THE TRANSCRIPTIONAL AND FUNCTIONAL PROGRAMMING OF CD4 T CELLS IN HUMAN FILARIAL INFECTION

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We have previously demonstrated that environmental house dust mite (HDM) allergic sensitization coincident with helminth filarial infection in humans drives a hyperreactive parasite antigen-specific Th2-dominated response. To further characterize the heterogeneity and function of these antigen-reactive Th2 cells, we analyzed 47 subjects' PBMCs [23 filarial-infected (Fil^+) with or without coincident HDM sensitization (Fil^+HDM^+ n=12; Fil^+HDM^-, n=11) and 24 subjects without filarial infection (Fil^-) (Fil^-HDM^+ n=12; and Fil^-HDM^-, n=12) multiparameter flow cytometry with 2 level clustering. The frequency of 3 memory $CD4^+$ T cell clusters, including $CCR4^+CCR6^+CRTH2^-$ (subset 1), $CCR4^+CCR6^-CRTH2^+$ (subset 2), as well as $CCR6^+CCR4^+CRTH2^+$ (subset 3) were markedly enriched among Fil^+ subjects. These 3 subsets were sorted and analyzed by multiomic single cell RNA profiling. This functional characterization indicated subset 2 and 3 as distinct Th2 cytokine producers, which together were responsible for the majority of IL-4, IL-5, or IL-13 produced among the Fil^+ subjects. Indeed, the gene set enrichment analysis (fine DICE) indicated that both $CCR4^+CCR6^-CRTH2^+$ and $CCR4^+CCR6^+CRTH2^+$ $CD4^+$ T cells as predominantly Th2 effector cells by their single cell molecular signature. When the Fil^+ subjects were divided by their allergic status, the Fil^+HDM^+ subject had an expansion of both $CCR4^+CCR6^-CRTH2^+$ (3.19% vs 1.28%, p=0.001) and $CCR4^+CCR6^+CRTH2^+$ (0.39% vs 0.15%, p=0.002) Th2 cells when compared with Fil^+HDM^-. Gene expression analysis further demonstrated that HDM sensitization in the presence of filarial infection reshaped the molecular program of both Th2 cells subsets of through the upregulation of GATA3, IL17RB, CLRF2, and KLRB1 mRNA. This distinct molecular and functional signature of Th2 cells subsets in Fil^+HDM^+ may explain their Type-2 associated hyperreactivity that sheds new light on Th2 effector cell diversity and their contribution to immune regulation in helminth infection.

0602

SINGLE-CELL APPROACHES TO DISSECTING *BRUGIA MALAYI* PARASITE-HOST-DRUG INTERACTIONS

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Lymphatic filariasis is a debilitating neglected tropical disease caused by filarial nematodes transmitted by a mosquito vector. Strategies to minimize parasite transmission rely on mass distribution of anthelmintics that are suboptimal and cannot be used in all locales. The precise mechanisms of action of these essential drugs remain elusive and the dynamics of the parasite-drug-host interface are unresolved. Harnessing single-cell sequencing approaches, we have successfully profiled gene expression patterns across over 48,000 *Brugia malayi* microfilariae-derived cells. We have leveraged these data to map the cellular origins of prominent antigens, resolve the distribution of putative anthelmintic targets, and identify informative markers for the annotation of discrete tissue types. We have used flow cytometry and single-cell sequencing experiments to measure the effects of the major anthelmintic classes (macrocyclic lactones, benzimidazoles, and nicotinic receptor agonists) on the viability and transcriptional trajectories of dispersed nematode cells. Given the importance of parasite ion channels as anthelmintic targets, we have generated predictions about the in vivo co-localization and physical association of channel subunits. Lastly, we have developed functional assays on cultured cell *B. malayi* populations to further resolve receptor-mediated drug perturbations at single-cell resolution. Together, this work

establishes a platform for the investigation of cell and tissue-specific processes relevant to drug action and secretory processes in filarial nematodes. We expect that these approaches can be readily adapted to other stages and species of parasitic nematodes.

0603

OCCURRENCE OF LYMPHATIC FILARIASIS INFECTION AFTER 15 YEARS OF MASS DRUG ADMINISTRATION IN TWO HOTSPOT DISTRICTS IN THE UPPER EAST REGION OF GHANA

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Lymphatic filariasis (LF) causes chronic morbidity, which usually manifests as lymphedema or hydrocele. Mass drug administration (MDA) with ivermectin and albendazole to control LF began in the Kassena Nankana East Municipal (KNEM) and Nabdam, two hotspot districts in the Upper East Region of Ghana, in 2000 and 2005, respectively. This cross-sectional study evaluated the impact of 15 years of MDA on the control of LF as determined by circulating filarial antigen (CFA) and microfilariae (MF) prevalence in the KNEM and Nabdam districts. 7,453 participants from 8 sub-districts in the two hotspot districts (KNEM: N = 4604; Nabdam: N = 2849) were assessed for CFA and MF in this study. The overall CFA prevalence as determined by the Filariasis Test Strip (FTS) was 19.6%/12.7% in the KNEM/Nabdam districts, respectively. Manyoro, a sub-district on the border with Burkina Faso, recorded the highest CFA prevalence of 26% in the KNEM. Assessment of MF and Og4C3 antigen was done for 1009 (KNEM: N = 799 (79.2%); Nabdam: N = 210 (20.8%)) randomly selected FTS-positive (N = 885) and FTS-negative (N = 124) individuals. The Og4C3 antigen was detected in 22.6%/23.0% of individuals in KNEM/Nabdam, whereas night blood revealed MF in only 0.7%/0.5% of individuals, respectively. Using the WHO-approved FTS, CFA prevalence exceeded the <2% threshold. Surprisingly, the Og4C3 ELISA showed positive results in only about one-fifth of the FTS-positive samples. However, even the relatively less sensitive Og4C3 ELISA would still not have met the <2% CFA criteria for LF elimination. In contrast, the MF results revealed a halt in LF transmission. This calls for a revision of the long-standing stringent WHO recommended <2% CFA threshold especially after more sensitive diagnostic kits such as the FTS has been introduced for post-treatment surveillance. This may reduce the risk of continual CFA pre-TAS failure in endemic countries trying to reach elimination goal, which has now been extended to 2030. Intensification of focused MDA interventions for seasonal migrants and regular MDA non-compliers, and adoption of alternative treatment strategies are required for the elimination of LF.

0604

BAYESIAN NETWORK ANALYSIS PREDICTS ADDED VALUE OF LYMPHATIC FILARIASIS ANTIBODY TESTING IN POST-MDA SURVEILLANCE IN MANDALAY REGION, MYANMAR

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Lymphatic filariasis (LF) is eliminated through mass drug administration (MDA) of anti-filarial medications over multiple years which interrupts transmission and prevents new infections. Accurate transmission assessments are critical to deciding when to stop MDA. Current methods for evaluating transmission may be insufficiently sensitive, resulting in post-MDA resurgence. We therefore evaluated potential testing scenarios for post-MDA surveillance. Data were used from two surveys (a household cluster and a case-control) conducted in an area of Mandalay Region, Myanmar with ongoing transmission following several rounds of MDA. First, an age- and sex-adjusted seroprevalence was estimated for the area from the household survey. Next, three Bayesian networks were built from the combined datasets to compare antigen (by ICT and/or Og4C3), Wb123 antibody (Ab) and Bm14 Ab respectively. The networks were checked for validity, and then used to compare testing scenarios. The adjusted prevalence from the household survey for antigen, Wb123 Ab and Bm14 Ab were 4.4% (95% CI 2.6 - 7.3%), 8.7% (5.96 - 12.5%) and 20.8% (16.0 - 26.6%) respectively. For the three networks, the Area Under the Receiver Operating Characteristic Curve and True Skill Statistic ranged from 0.80 - 0.97 and 0.54 - 0.79 respectively. In the Bayesian sample, the probability of a positive result prior to any testing scenario was 17.4%, 16.8% and 26.6% for antigen, Wb123 Ab and Bm14 Ab respectively. When only antigen was tested and negative, the probability of a missed LF positive result was 5.2% for Wb123 Ab and 15.6% for Bm14 Ab. The testing combination of antigen plus Bm14 Ab was the most sensitive, with the probability missed LF positive result detected by Wb123 Ab of 0.88%. Meanwhile the combination of antigen plus Wb123 Ab yielded a probability of a positive result by Bm14 Ab of 11.5%. These findings suggest that addition of Wb123 Ab testing does not add increased sensitivity if Ag tests are already being used, but the addition of Bm14 Ab testing should be considered for inclusion in post-MDA surveillance to detect transmission more accurately, and prevent the premature cessation of MDA.

0605

GLOBAL ENVIRONMENTAL SUITABILITY OF LYMPHATIC FILARIASIS TRANSMISSION

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Despite the global progress in reducing the lymphatic filariasis (LF) burden, LF is endemic in 47 countries and around 51 million individuals were estimated to be infected with LF in 2018. LF is caused by filarial parasites that infect human lymphatic vessels. Three filarial species are linked to LF and transmitted via *Anopheles, Culex, Aedes*, and *Mansonia* mosquito vectors. Delineating the environmental limits of these vectors will help to identify areas under potential LF transmission risk. We compiled 15,760 georeferenced LF prevalence data points covering 74 countries from 1990 to 2018. The data sources included both published scientific literature and program monitoring data. We studied the relationship between LF prevalence and environmental and climate covariates including, temperature, precipitation, evaporation, land use types, enhanced vegetation index, elevation, distance from water bodies, and population density. To understand these relationships, we first generated randomly

sampled background points from outside of a 100-km buffer from occurrence locations to represent LF absence since reported absence can include false negatives. Then we extracted corresponding covariate values for both LF presence and background locations. We used separate boosted regression tree models to estimate the relationship between LF presence/background data and covariates in Africa, South Asia, South East Asia, and the island of Hispaniola. Finally, we produced environmental suitability maps of LF transmission limits at a 5 X 5 km resolution. The results indicated substantial heterogeneity in LF transmission risk. Particularly, geographic locations with no reported cases were estimated to have substantial environmental suitability for LF, suggesting potential risks of LF transmission. The widespread environmental suitability of LF emphasizes the importance of ongoing mass drug administration campaigns and transmission assessment monitoring efforts. These high-resolution maps can aid decision-makers to identify high transmission risk locations and prioritize resource mobilization to successfully eliminate the disease.

0606

CHARACTERIZATION OF AN IGG4/OV16 RAPID TEST TO DETECT EXPOSURE TO *ONCHOCERCA VOLVULUS* INFECTIONS

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The Onchocerciasis v1.0 Rapid Diagnostic Test (RDT) is a serological lateral flow assay indicative of exposure to *Onchocerca volvulus* infective larvae and detects IgG4 antibodies specific for the Ov16 antigen. The test was created to mitigate procurement risks for onchocerciasis national public health programs, which rely on a single source of RDTs (SD BIOLINE Onchocerciasis IgG4 Rapid Test). The clinical sensitivity of the Onchocerciasis v1.0 RDT was determined to be 83.8% (95% CI 74.1-90.3 %, n = 80) based on an independent evaluation at NIAID using serum samples. Its specificity was 100% (95% CI 88.7-100.0%, n=30) when using sera from presumed uninfected US volunteers as a comparator group, and 99.1% (95% CI 94.9-100.0 %, n = 105) when using sera from other filarial infections (60 LF samples provided by the CDC and 45 other infections tested at NIAID). Having demonstrated that the RDT is both a sensitive and specific tool, we characterized its analytical sensitivity and verified its suitability for field-use in tropical climates. When using a recombinant, humanized IgG4 antibody specific for Ov16, the limit of detection (LOD) is 50 ng/mL in serum and 25 ng/mL in whole blood. Heparinized whole blood and heparinized plasma are by and large comparable matrices. The test appears to be suitable for point-of-care use in that it tolerates a variation of ± 50% in sample volume and a variation of ± 1 drop of chase buffer, as may unwillingly happen in the field. Test performance is temperature dependent, and the analytical sensitivity further increases when the test is run at 40°C compared to 21-25°C; if operating close to the limit of detection, temperatures below 21°C should be avoided. The test is 100% stable after 6 months at 40°C, and therefore a shelf life of > 2 years can be projected. Furthermore, the test tolerates excursions to 50°C for > 2 weeks, providing additional peace of mind while the tests will be in transit.

0607

SIGNIFICANT PROGRESS TOWARDS ELIMINATING LYMPHATIC FILARIASIS AS A PUBLIC HEALTH PROBLEM IN SOUTHEASTERN NIGERIA

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Nigeria has the second highest burden of lymphatic filariasis (LF) in the world. Elimination efforts began in seven states supported by The Carter Center in 2014 with mass drug administration (MDA) using ivermectin and albendazole. We report significant progress in stopping MDA through transmission assessment surveys (TAS) in districts with baselines ranging from 1% to 58% antigen prevalence. In 2019, 19 local government areas (LGAs) undertook Pre-TAS in 3 southeastern states: Anambra, Ebonyi, and Imo. Filariasis test strips (FTS) were used to test 11,720 people aged ≥ 5 years in one sentinel and one spot-check site per LGA. All but 3 LGAs passed (84% success), with antigen prevalence less than 2% in each village. Follow-up investigations in the 3 LGAs that failed showed very low usage of bed nets; 88% antigen-positive individuals were negative upon later retesting. Sixteen LGAs, grouped into 13 evaluation units (EUs), proceeded to stop-MDA TAS in 2021. One EU could not complete its sample due to insecurity and will continue treatment until it can be re-evaluated. Of 17,765 children tested in primary grades 1 and 2 across 12 EUs, only 2 children were antigen positive. The number of antigen-positive children in each EU (range 0-1) was less than the critical threshold (range 8-18), meaning all 12 EUs pass TAS and now enter post-treatment surveillance for LF. Approximately 3.4 million people in 15 LGAs no longer require MDA. These studies represent major achievements for the Nigeria national LF elimination program.

0608

DETECTION OF *BRUGIA MALAYI* ELEVEN YEARS AFTER STOPPING MASS DRUG ADMINISTRATION TO ELIMINATE LYMPHATIC FILARIASIS IN BELITUNG DISTRICT, INDONESIA

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The filarial parasite *Brugia malayi* is the major cause of lymphatic filariasis (LF) in Indonesia. Belitung district consists of a part of Belitung Island with some adjacent islands in the south-east of Sumatra and was formerly highly endemic for *Mansonia*- transmitted *B. malayi*. Mass drug administration (MDA) with DEC and albendazole to eliminate LF was ceased after five annual rounds in 2010, the district passed three transmission assessment surveys (TAS) and the Ministry of Health certified the district in 2018 as free of LF. As part of post-MDA surveillance of the LF elimination program in Indonesia, we collected in 2021 night blood

samples for the detection of microfilariae (Mf) from 1,911 subjects aged 5 years and older residing in 7 villages. Mf were detected by 60 uL Giemsa-stained three-line blood smears and microscopy. While no Mf-positive subjects were detected in two villages, an Mf prevalence ranging from 1.7 to 5.9% was found in five villages. All 40 Mf-positive subjects were adults or teenagers aged 16 years and older, who were not targeted by TAS. Mf densities in infected individuals were mostly low, with 60% of the subjects having less than 167 Mf/ml. Our results indicate that in areas endemic for *B. malayi* post-MDA surveillance of the entire community may be needed despite the fact that the area passed TAS that is based on antibody detection using the Brugia Rapid tests in school children. It can also not be excluded that an animal reservoir caused re-introduction of infection into the human population. Further monitoring and evaluation studies together with improved MDA strategies in areas endemic for brugian filariasis are needed to support the elimination of LF.

0609

REPURPOSING CANINE HEARTWORM RAPID DIAGNOSTIC TESTS FOR HUMAN LYMPHATIC FILARIASIS

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Lymphatic filariasis (LF) is a neglected tropical disease caused by *Wuchereria bancrofti* and *Brugia spp*. The success of the World Health Organization's (WHO) Global Programme to Eliminate Lymphatic Filariasis relies on diagnostic tools for mapping disease and monitoring the progress of mass drug administration (MDA). The only test recommended by WHO for stopping MDA in *W. bancrofti* areas is the Filariasis Test Strip (FTS) (Abbott) which detects circulating filarial antigen (CFA). Although the test is used widely, there are recognized limitations: procurement risk due to a single manufacturer, requirement of a relatively large amount of blood (75 µL) per test, and a narrow time window to read the result. Based on the early discovery that monoclonal antibodies developed for *Dirofilaria immitis* cross-reacted with *W. bancrofti* antigen, we investigated if rapid diagnostic tests (RDT) for canine heartworm can be repurposed for human LF and used as potential alternatives to the FTS. Performance characteristics for three commercial canine heartworm RDTs: Anigen (Bionote), Vetscan (Abaxis), and Witness (Zoetis) were evaluated. Clinical sensitivity was determined by *W. bancrofti* sera (n=100, Haiti) that had been confirmed positive by microscopy and CFA tests. Clinical specificity was determined by a panel comprised of uninfected U.S. volunteers (n=120), uninfected individuals from an LF endemic country (Haiti) (n=50) and persons with other helminth infections (n=125). All 3 RDTs required 10 µL of sample per test. Clinical sensitivity and specificity for Anigen, Vetscan and Witness were 98.0% (95% confidence interval [CI]: 93.0-99.8) and 99.3 % (95% CI: 97.6-99.9); 96.0% (95% CI: 90.1-98.9) and 99.0% (95% CI: 97.1-99.8); and 100% (95% CI: 96.4-100) and 98.0% (95% CI: 95.6-99.3), respectively. Differences between tests were minor but the Bionote Anigen test was the leading alternative to the FTS as it had the highest specificity, withstood storage for 12 months at 40 °C without compromising sensitivity and test results were stable for 90 minutes. Our results suggest canine heartworm tests may be suitable alternatives to the FTS.

0610

RISK FACTORS ASSOCIATED WITH EXTENSIVELY DRUG-RESISTANT (XDR) TYPHOID IN AN OUTBREAK SETTING OF LYARI TOWN KARACHI, PAKISTAN

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Typhoid fever is endemic in Pakistan, with high annual incidence rates. An outbreak of extensively drug-resistant (XDR) typhoid fever that first started in the Hyderabad district of Sindh province in November 2016 immediately spread to the whole province. The associated organism *Salmonella* Typhi (*S.* Typhi) H58 strain was resistant to five classes of antimicrobials (chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins). This strain of XDR *S.* Typhi was sensitive only to azithromycin and meropenem which threatened the role of antibiotics in typhoid control. We conducted an age-matched case-control study to identify the risk factors associated with typhoid fever in the XDR typhoid outbreak setting of Lyari, Town, Karachi. This study targeted the population of children from 6 months to 15 years of age as children younger than 15 years of age comprise more than 90% of the XDR typhoid cases. We enrolled 82 blood culture-confirmed *S.* Typhi cases between August 2019 to December 2019. Out of total enrolled culture-confirmed typhoid cases, 28 were enrolled from Lyari General Hospital, 28 were enrolled from Kharadar General Hospital and 26 were enrolled from Jan Bai Aga Khan Secondary Care Hospital. A total of 164 community age-matched controls and 82 hospital controls were enrolled as well. Participant ages range was from 6 months to 15 years, the mean age of culture-confirmed typhoid case patients was 54.6 months, community control was 58.9 months and hospital controls was 55.1 months. Out of enrolled cases, 68.3% were males, 51.8% of community controls were males and 56.1% of hospital controls were males. In a matched conditional logistic regression model, consumption of meals outside the home more than once per month was significantly associated with the development of culture-confirmed XDR typhoid fever compared to no food consumption outside (Odds Ratio: 4.11; 95% Confidence Interval: 1.77, 9.54; p-value < 0.05). Hygiene of the environment in which food is prepared, access to clean water and food legislation play a significant role in the spread of typhoid fever.

0611

ASSOCIATION BETWEEN WASH INDICATORS AND SELF REPORTED CHILDHOOD DEATHS IN RURAL COMMUNITIES OF THE PERUVIAN AMAZON BASIN

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Improved water access, sanitation, and hygiene (WASH) has the potential to reduceannual deaths by 6.3% worldwide. We evaluated whether improved WASH wasassociated with lower frequency of self-reported child deaths in indigenous villages inthe Peruvian Amazon. Twenty-one villages in the Peruvian Amazon were chosen byprobability-proportional-to-size, and cross-sectionally surveyed 387 mothers with ≥1child under 5 years of age in ~30 randomly selecting households in each village. Questionnaires were adapted from the Peruvian Demographics and Health Survey andWASH questions from the World Health Organization's (WHO) WASH monitoring corequestions. Access to drinking water, sanitation and hygiene practices weredichotomized following WHO recommendations. A generalized linear model regressionwas fitted with significance set at p<0.05. The mean±SD mother's age and the numberof live births were 37.2±13.4 and 4.9±2.5, respectively. Sanitation was primarilyunimproved (88%, n=340) and hygiene practices inadequate (78%, n=301). Nearly athird (31%) of women reported a child death in their lifetime and the mean±SD child'sage at death was 8.2±13.0 months. After adjusting for sanitation, hygiene practices,mother's age, number of live births, drinking water, and having a health facility in thevillage, the frequency of having had a child dying was 1.75 times higher in mothersliving in households with unimproved versus improved sanitation (95% CI: 1.29-2.38,p<0.001). Older maternal age (PR 1.02, 95%CI: 1.01-1.03, p=0.001) and having hadmore children (PR 1.18, 95%CI: 1.11-1.25, p<0.001) were both positively associatedwith childhood mortality, but no association was observed for improved drinkingwater, inadequate hygiene practices and having a health facility in the village (p>0.25for all). Unimproved sanitation was the only WASH variable associated with infantmortality in indigenous

villages in the Peruvian Amazon. Further studies shoulddetermine whether improvement of sanitation in similar settings can reduce childhoodmortality.

0612

INFLUENCE OF COMMUNITY-LEVEL SANITATION COVERAGE AND POPULATION DENSITY ON ENVIRONMENTAL FECAL CONTAMINATION AND CHILD HEALTH IN A LONGITUDINAL COHORT IN RURAL BANGLADESH

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Household-level sanitation interventions have had limited effects on child health or environmental contamination, potentially due to low community coverage. Higher coverage can reduce opportunities for pathogen transmission throughout the community. We estimated associations between community-level sanitation coverage, environmental fecal contamination, and child health among 360 compounds in the control arm of the WASH Benefits trial in rural Bangladesh. We enumerated *E. coli* in environmental samples and recorded the 7-day prevalence of caregiver-reported diarrheal disease and acute respiratory infections (ARI) among children under five. We observed indicators of latrine access and quality among all neighboring compounds within 100 m of each study compound. We defined community coverage as the proportion of neighboring compounds with (1) at least one latrine and (2) exclusively hygienic latrines (improved facility observed to safely contain feces), within both 50 m and 100 m of study compounds. We assessed effect modification by population density and season. Adjusted for confounders, study compounds surrounded by 100% coverage of at least one latrine per compound within 50 m had slightly lower $\log_{10}$ *E. coli* counts in stored water ($\Delta\log_{10}$ = -0.13, 95% CI -0.26, -0.01), child hand rinses ($\Delta\log_{10}$ = -0.13, 95% CI -0.24, -0.02), and caregiver hand rinses ($\Delta\log_{10}$ = -0.16, 95% CI -0.29, -0.03) and marginally lower prevalence of diarrheal disease (prevalence ratio [PR] = 0.82, 95% CI 0.64, 1.04) and ARI (PR = 0.84, 95% CI 0.69, 1.03). Effects were similar but less pronounced at 100 m. At higher population densities, community latrine coverage was associated with larger reductions in *E. coli* on caregiver hands and prevalence of diarrheal disease. Coverage with exclusively hygienic latrines was not associated with any outcome. Our findings indicate that higher community coverage in highly local areas was associated with reduced pathogen transmission, with stronger effects at high population densities, but more research is needed to uncover complex relationships between sanitation coverage and health across multiple scales of community.

0613

HOW FREQUENTLY DO COMMUNITY LATRINES NEED TO BE CLEANED? A STUDY IN KATHMANDU, NEPAL

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The United Nations Sustainable Development Goals (SDGs) currently do not count community toilets as "improved" sanitation. Cities with poor sanitation coverage are growing at an astounding pace, and often there is inadequate space and resources to equip households with individual latrines, therefore community sanitation needs to be a viable option. One key criticism of community latrines (among others) is that they are not clean and cannot be adequately maintained. This study examined the cleanliness of community latrines implemented by Aerosan Toilets in 2018 in Kathmandu, Nepal. We did one cleaning study in 2018 and then revisited the same toilets ~22 months later after the latrines were transferred over to a private operator to see if cleaning practices were maintained. The goals of the study were to understand 1) if cleaning protocols were maintained by private operators and 2) how usership affects cleanliness of latrine surfaces to make recommendations on the frequency of cleaning. In 2019, after oversight of the latrines was transitioned to private operators, we conducted a second cleaning study where we swabbed latrine surfaces for *E. coli* (EC) and Total Coliforms (TC) (n= 230). Swabbing occurred in "clean" conditions - before the latrine was opened- and "dirty" conditions - during operating hours. We also collected data on the number of latrine users. The TC concentration averaged for each type of latrine surface differed significantly among surface types (slab, wall, doorknob, handle and rim of anal cleansing bucket, sink tap) during dirty ($p<0.05$) but not clean conditions ($p = 0.077$). For EC, we observed significant differences in the average concentration across latrine surface types in both dirty and clean conditions ($p<0.05$). The number of users was significantly correlated with the microbial contamination on dirty latrine surfaces. This study demonstrated that cleaning practices were effective at reducing microbial contamination and the protocols in place by Aerosan were sustained after nearly two years. We also recommend that latrines are cleaned after every 25-50 users.

0614

DIARRHEAL DISEASE AWARENESS IS ASSOCIATED WITH CAREGIVER HANDWASHING WITH SOAP IN THE DEMOCRATIC REPUBLIC OF THE CONGO (REDUCE PROGRAM)

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Diarrhea is one of the leading causes of childhood illness and a major cause of infant and child mortality globally. In the Reducing Enteropathy, Undernutrition, and Contamination in the Environment (REDUCE) prospective cohort study, we investigated the association between diarrheal disease awareness and handwashing with soap among caregivers of children under 5 years of age. A total of 259 caregivers of children under 5 years of age in Walungu Territory, South Kivu, Democratic Republic of the Congo (DRC), were administered an open-ended questionnaire assessing awareness of diarrheal disease transmission and prevention, and key times to wash hands with soap. An overall diarrhea awareness score was developed based on the responses to these items. Five-hour structured observation of handwashing behaviors was conducted at the 6-month follow-up. Diarrheal disease awareness among caregivers was low. Only 32% of caregivers were able to correctly identify a method of diarrhea prevention. The median diarrhea awareness score was three out of 10 (SD: 1.7, range: 0-9). During structured observation, 9% of caregivers washed their hands with soap at a food-related event and 9% washed their hands with soap at a stool-related event. Higher diarrheal disease awareness was associated with an increased odds of handwashing with soap at food-related events (odds ratio: 1.40, 95% confidence interval: 1.03, 1.90). Our findings emphasize the need for targeted water, sanitation, and hygiene interventions to increase diarrhea awareness to facilitate handwashing with soap among caregivers of children under 5 years in rural DRC.

0615

INVESTIGATING THE EFFICACY OF VARIOUS HANDWASHING METHODS AGAINST ENVELOPED AND NON-ENVELOPED VIRUSES

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Respiratory infections and diarrheal diseases are two leading causes of death worldwide. Handwashing with soap and water is a well-established intervention, and has been proven to reduce both pathogen concentration on hands and the incidence rate of many diseases, including respiratory diseases like COVID-19. Despite this, limited resources among people in low- and middle-income regions, people in remote areas, refugees, internally displaced people, and those experiencing homelessness, may prevent individuals from using handwashing methods recommended by the CDC or WHO (soap and water for 20+ seconds). The aim of this study is to evaluate handwashing alternatives for use when handwashing with soap and water for 20s is not feasible, including washing with water only, washing with soapy water, washing for a short duration, using alcohol-based hand sanitizer (ABHS), and washing with towels. To evaluate the efficacy of the handwashing methods, we seeded MS2 (a non-enveloped virus) and Phi6 (an enveloped virus) onto the hands of volunteers who then used a handwashing method. Viruses remaining on the hands after washing were recovered and the log reduction value (LRV) of viruses was quantified using culture-based methods and molecular methods. Results indicated that washing with water only and with soapy water were similar to washing with soap and water for 20s for both viruses studied. Overall, towel alternatives did not perform as well as washing with soap and water for either virus. The impacts of ABHS and timing were mixed: results for ABHS and soap and water for 5s were similar to soap and water for 20s for Phi6, but less than soap and water for 20s for MS2. Additionally, results determined using molecular methods were in agreement with those obtained using culture-based methods. This study provides foundational data to ensure handwashing promoted in humanitarian crises is effective for important outbreak diseases. These results inform handwashing method recommendations and future research on handwashing effectiveness in low resource settings to both prevent disease transmission and promote dignity.

0616

DETECTING SARS-COV-2 LINEAGES IN BANGLADESH: LESSONS FROM WASTEWATER-BASED EPIDEMIOLOGY

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Wastewater-based epidemiological surveillance has been considered a powerful tool for early detection and monitoring of the dynamics of SARS-CoV-2 and its lineages circulating in a community. This study collected 504 wastewater samples across different treated and untreated sanitation points in the capital city, Dhaka, Bangladesh, from September 2020 to February 2021. We used a modified calcium flocculation-citrate dissolution method to concentrate microparticles and the Norgen Soil Total RNA Purification kit to extract and purify the SARS-CoV-2 viral RNA. The detection of SARS-CoV-2 was performed using the iTaq Universal Probes One-Step kit for the RT-qPCR amplification of the SARS-CoV-2 ORF1ab and N gene targets. Out of 504 samples, 185 (36.7%) were tested positive for SARS-CoV-2. To further reveal the genetic diversity of SARS-CoV-2, ten samples having ORF1ab cycle threshold (Ct) values ranging from 28 to 32 were subjected to next-generation sequencing using nanopore technology. According to clade classification, sequences from wastewater samples were grouped into 4 clades: 19B, 20A, 20B, 21A, and the Pango lineage: B.1, B.1.1.25, B.1.1.315, coverage was >73% and 50% belonged to clade 20B; 30% belonged to clade 20A. The clades 19B, 21A were less prevalent (10%). Also, the sole sample within clade 21A (B.1.617.2) had genome coverage of 43.22%. The lineage B.1.1.25 was predominant in Bangladesh and phylogenetically related to the sequences from India, the USA, Canada, the UK, and Italy. The Delta variant (B.1.617.2) was first identified in clinical samples at the beginning of May 2021, whereas we found the Delta variant circulating in wastewater in September 2020. The findings of this study supported the use of wastewater-based epidemiology and provided the baseline data of SARS-CoV-2 variant dynamics in Dhaka, Bangladesh. We conducted a study on complex sanitation systems that can be reproducible in areas of low sanitation coverage worldwide. These findings imply that monitoring wastewater can be a useful tool to identify symptomatic and asymptomatic COVID-19 patients in the community and act as an early alert system.

0617

HISTIDINE-RICH PROTEIN DELETION: TEMPORAL PREVALENCE IN UK TRAVELLER MALARIA PATIENTS AND GENOMIC STRUCTURE OF THE *PFHRP/3*-DELETED PARASITES

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Plasmodium falciparum that can evade detection by rapid diagnostic tests (RDT) have emerged globally. Parasites become undetectable due to deletion of two loci encoding histidine-rich proteins (HRP2 and/or HRP3). The emergence of *P. falciparum* lacking *hrp2* and *hrp3* genes (*pfhrp2/3*) is causing major malaria public health concern and threatens malaria control and case management efforts. *P. falciparum* lacking histidine-rich proteins are on the increase in Africa. The rate of such increase is unknown. It is also not clearly understood how the deletions occur, or what the consequence of such deletions are to the parasite genome. In this study, we report the prevalence of *pfhrp2* and *pfhrp3* in UK travellers who visited malaria endemic countries in Africa from 2018 to 2022. We also report, using high-quality short- and long-read genomic sequencing and custom-made bioinformatic tools, the genome structure of two culture-adapted *P. falciparum* parasite isolates with *pfhrp2/3* deletions. We identified the chromosomal points that delimit each deletion event, which typically as also remove several hundred adjacent genes on chromosome 8 and 13, respectively. We also investigated the genomic structural variation of the *pfhrp2/3*-deleted *P. falciparum* parasites before and after culture-adaptation to understand whether the parasites acquire any further variation during culture-adaptation.

0618

ADDITION OF HUMAN SERUM OR ALBUMAX TO GLYCEROLYTE BEFORE CRYOPRESERVING *PLASMODIUM FALCIPARUM* INCREASES PARASITE YIELD AFTER THAWING

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Cryopreservation of *Plasmodium falciparum* enables important laboratory investigations of malaria, but methods have not been optimized. We compared three different methods for cryopreserving *P. falciparum* infected red blood cells (RBCs) directly from patient samples, using glycerolyte, glycerolyte + human serum, or glycerolyte + 10% Albumax. Blood samples were collected from individuals with documented *P. falciparum* infections. RBCs were then prepared either by washing the RBC pellet from an EDTA tube three times to remove buffy coat or by collecting the RBC pellet after PBMC isolation from blood samples collected in heparin or acid citrate dextrose tubes. Pellet volume of 1500 µl was aliquoted to three tubes,

500 µl each, to the tubes labeled serum and albumax, 500 µl of serum and albumax was added respectively. Glycerolyte was then added to each aliquot in ratio of 1:2 (pellet:glycerolyte). Aliquots where then freezed at -80°c for 18hrs then transferred to liquid nitrogen. After 30 days samples were then thawed based on protocol and cultured at 37°c in complete RPMI. Pellet volume was measured and smears prepared and read at 36hrs, 48hrs and 72hrs, these were stained using giemsa. Pellet volume at thaw was significantly lower following cryopreservation with glycerolyte alone (median= 70.0 µl; IQR= 61.25-170.0), than Glycerolyte + serum (median= 127.5 µL; IQR= 95.0-201.3) or Glycerolyte + Albumax (median = 127.5µL; IQR= 107.5-195.0), p-value <0.05 for both comparisons. Parasite growth was observed with all three methods of cryopreservation across a range of parasitemia (0.2-3.0%). Median parasitemia was comparable across all three treatments at 36, 48, and 72 hours. (36hrs; glycerlote alone = 1.9%, glycerolyte+serum = 1.9%, glycerolyte+albumax = 2.25%: 48hrs; glycerlote alone = 1.5%, glycerolyte+ serum = 2.05%, glycerolyte+albumax= 1.5%: 72hrs; glycerlote alone= 1.6%, glycerolyte+ serum = 2.2%, glycerolyte+albumax = 1.8%) These findings suggest that addition of human serum or 10% Albumax during cryopreservation improves parasite yield when clinical isolates of *P. falciparum* are freezed, thawed and cultured.

0619

THE MILAB™ PLATFORM, A FULLY AUTOMATED ON-SITE DIAGNOSTIC SYSTEM WITH ARTIFICIAL INTELLIGENCE FOR MALARIA

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The miLab™ platform is a fully automated on-site diagnostic system that determines the infection of malaria parasites in human EDTA-anticoagulated whole blood (or capillary blood) of individuals with signs and symptoms of malarial infection. It produces consistent, high-quality thin blood smears, stains blood cells with a novel solution-free method based on hydrogel-based stamping and reads out by digital optical scanning in combination with highly efficient embedded artificial intelligence (AI) based morphological analysis for malaria diagnosis. The clinical performance of the miLab™ platform for malaria detection was evaluated by comparing with the reference test - the manual microscopy - using total 502 whole blood samples collected from fever patients visiting clinical sites in Malawi (Kamuzu; n=323, and Mzuzu; n=179) between December 2020 and April 2021. All samples were tested by both the manual microscopy and the miLab™ platform. Of those samples, 142 samples (28.5%) and 161 samples (32.1%) were determined as positive for malaria infection by manual microscopy and the miLab™ platform, respectively. The clinical sensitivity was 89.51% (95% CI; 83.41% - 93.54%) and the specificity was 90.81% (95% CI; 87.37% - 93.38%). Forty-eight samples that were discordant between both tests were confirmed by quantitative PCR (qPCR). Noteworthy, the miLab™ platform results indicated 93.75% (95% CI; 83.16% - 97.85%) agreement with the results from qPCR. Furthermore, in one of two samples which were positive by the miLab™ platform but negative by the qPCR, the digital images of malaria-infected cells confirmed by expert microscopists were shown from the miLab™ platform. The results suggest that the miLab™ platform can replace manual microscopy while having more sensitive performance.

0620

PARASITAEMIA THRESHOLDS FOR DIAGNOSING PATIENTS WITH *PLASMODIUM VIVAX* MALARIA

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Optimal parasitaemia thresholds for diagnosing *Plasmodium vivax* malaria are defined by the relationship between parasitaemia and fever. We conducted an individual patient data meta-analysis of *P. vivax* clinical trials in the WorldWide Anti-Malarial Resistance Network (WWARN) repository and used parasitaemia centiles of febrile patients at enrolment to derive the proportion of patients who would have been diagnosed at different parasitaemia thresholds ("capture thresholds"). Febrile and afebrile patients with recurrent infection during follow-up were selected to determine pyrogenic densities using receiver operating characteristic curve analysis and risk factors for fever at recurrence were identified using logistic regression. In total 13,263 patients from 50 studies were included in the analysis. In the 27 studies that did not apply a parasitaemia threshold as an inclusion criterion, the median parasitaemia of 8,378 febrile patients at enrolment was 3,280/µL (IQR 968 - 8,320). 90% of patients had a parasitaemia above 278/µL (10^{th} centile or 90% capture threshold), and 95% above 120/µL (5^{th} centile or 95% capture threshold). Compared to adults, children presented with higher parasitaemias. 2,270 patients from 41 studies had at least one episode of recurrent *P. vivax* parasitaemia, of whom 57% (1,134/1,983) were febrile at their first recurrence. The *P. vivax* pyrogenic density at first recurrence was 1,063/µL, giving a positive predictive value for fever of 61% and a negative predictive value of 77%. The pyrogenic density was lowest in children. After accounting for confounders, high parasitaemia and living in an area of low relapse periodicity were associated with an increased risk of fever at first recurrence. These parasitaemia capture thresholds inform the design of novel tests to diagnose patients with symptomatic vivax malaria. Variations in thresholds with age and location should be taken into account when selecting diagnostic thresholds and interpreting results.

0621

AISCOPE: CREATING THE BIGGEST OPEN CROWDSOURCED DATASET OF MICROSCOPY IMAGES FOR MALARIA AND OTHER INFECTIOUS DISEASES TO TRAIN ARTIFICIAL INTELLIGENCE ALGORITHMS

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Microscopy is still the gold standard for diagnosing numerous communicable diseases worldwide, in particular in low-resource settings.

For malaria, reliable Malaria rapid diagnosis tests (mRDTs) or molecular techniques are not always available in endemic countries and their performance can be low in low transmission settings or those where HRP2/3 deletions are present, and thus diagnostic confirmation relies on optical microscopy. Manually discriminating subtle differences on a stained slide under the light microscope is a labor-intensive, time-consuming, error-prone, and somehow subjective process. Artificial intelligence (AI) and, particularly, computer vision may allow automation of this process using trained algorithms, saving time and reducing human errors and the need for trained personnel. Although AI is progressively gaining importance in medical diagnosis, its application is still limited by the availability of large, high-quality datasets to train algorithms. Thus, building a reliable training dataset represents a strategic asset to deploy all AI potential for diagnostic applications. AiScope is a non-profit organization developing an open-source smart, low-cost microscope to diagnose infectious diseases in low-resource settings. AiScope uses AI running on a cellphone to automatically diagnose infectious diseases, without the need of highly trained personnel. Since large public open infectious diseases datasets are lacking, AiScope is building a collection of open-access datasets of microscopy images of several pathogens, such as *Plasmodium* spp, *Mycobacterium tuberculosis*, and intestinal parasites among others. Besides, AiScope has developed an open-source easy-to-use platform to ensure correct labeling of microscopy images. The database is being built thanks to the collaboration of universities, research and medical institutions, and companies worldwide. This crowdsourced project provides the opportunity to develop affordable smart diagnostic systems essential in low-resource settings, while offering an open collection of microscopy images for research, training and education purposes.

0622

STATUS OF *PFHRP2* AND *PFHRP3* GENES DELETIONS IN *PLASMODIUM FALCIPARUM* PARASITES FROM A LARGE HEALTH FACILITY SURVEY: TANZANIA, 2021

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Plasmodium falciparum which has deleted the histidine-rich protein 2 gene (*pfhrp2*, and paralog *pfhrp3*, *pfhrp2/3*) can escape detection by HRP2 rapid diagnostic tests (RDTs), leading to false negative diagnostic results. Deletions of these genes have been found in *P. falciparum* populations worldwide, and the WHO recommends non-HRP2 RDTs for case management when *pfhrp2* deletion prevalence exceeds 5% in a region. Therefore, *pfhrp2* deletion surveillance is essential for national malaria programs to assess reliability of HRP2-RDTs in different settings. Tanzania is a country of heterogenous malaria transmission, with some regions approaching elimination and others at different levels of control phase. In concordance with the current recommended WHO surveillance strategy, 100 health facilities encompassing 10 regions of Tanzania were used as sites for enrollment of treatment-seeking persons to provide estimates for *pfhrp2/3* gene deletion prevalence. The survey was conducted from February to July 2021 and enrolled 7,865 persons of all ages who were tested with two RDTs: pLDH/HRP2 combo and pLDH only. Of these, 3,777 (48.0%) were positive by either type of RDT, and 57 (1.6% of all infections) were positive for the pLDH band only. Multiplex antigen detection by laboratory assay (n=7,847) found 135 (1.7%) of all blood samples positive for *Plasmodium* antigens but very low or absent for HRP2. These were selected for further DNA extraction and PCR assays. Of these 135 selected samples, 8 (5.9%) were found to be *P. ovale* infections, and 109 (80.7% of selected) were *P. falciparum* infections appropriate for *pfhrp2/3* genotyping. One sample did not amplify *pfhrp2* (0.03% of all *P. falciparum* infections), and six (0.16%) were unable to amplify the *pfhrp3* gene. Of the 3,777 *P. falciparum* infections identified, a very low percentage (0.19%) showed deletions of *pfhrp2* or *pfhrp3* genes, and no dual deletions found. This large health facility survey conducted in Tanzania in 2021 provides strong evidence for the overall absence of *pfhrp2* gene deletion and continued utility of HRP2-RDTs in the country for confirmatory diagnosis of symptomatic *P. falciparum* infections.

0623

DEVELOPMENT AND EVALUATION OF A SIMPLIFIED MOLECULAR PLATFORM FOR THE DIAGNOSIS OF MALARIA

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Current needs for the diagnosis of malaria include tests that avoid false negative results (due to issues with limit of detection or mutations in genes encoding for diagnostic targets) or false positive results caused by persisting *Plasmodium* antigen after successful treatment. Molecular biology based tests avoid the limitations of currently used diagnostics (microscopy and rapid diagnostic tests), but implementation in resource limited malaria endemic countries is hampered by their complexity and infrastructural needs. The miniaturised direct-on-blood PCR nucleic acid lateral flow immunoassay (mini-dbPCR-NALFIA) is an innovative, easy-to-use molecular assay for the diagnosis of malaria in these particular settings. Unlike other simplified molecular methods, such as LAMP, the mini-dbPCR-NALFIA does not require DNA extraction and utilises a handheld, portable thermal cycler powered by a solar-charged power pack enabling to perform the test without any laboratory infrastructure. Reading of results is done using a rapid lateral flow strip enabling differentiation of *Plasmodium falciparum* and non-*falciparum* malaria infections. Laboratory validation was performed to assess the performance of this innovative platform. Diagnostic accuracy was determined by testing a set of confirmed *Plasmodium*-positive blood samples from returning travellers, and confirmed *Plasmodium*-negative blood samples from returning travellers with suspected malaria, Dutch Blood Bank and intensive care patients at our centre. Overall sensitivity and specificity of the assay were determined at 96.6% (95% CI, 82.2% - 99.9%) and 96.8% (95% CI, 89.0% - 99.6%) compared to expert microscopy. The limit of detection for *P. falciparum* was 2 parasites/µl blood, as measured in dilution series of three *P. falciparum*-positive clinical blood samples. The repeatability and reproducibility of the assay is determined to be over 90%. A phase-3 field trial is now being performed to evaluate the potential implementation of this assay in malaria control programmes in both high- and low-transmission settings.

0624

CLINICAL EVALUATION OF THE BIOFIRE® GLOBAL FEVER PANEL PLUS

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BioFire Defense has developed the BioFire® Global Fever Panel, in collaboration with the U.S. Department of Defense and NIAID (contract Nos. W911QY-13-D-0080 and HHSN272201600002C), as an in vitro diagnostic test for the simultaneous identification of viral, bacterial, and protozoan pathogens directly from whole blood in under an hour using

the BioFire® FilmArray® platform. The BioFire Global Fever Panel has been granted De Novo classification by the US FDA for the detection of chikungunya virus, dengue virus (serotypes 1-4), *Leptospira* spp., and *Plasmodium* spp. from individuals with signs and/or symptoms of AFI and known or suspected exposure to target pathogens. The BioFire Global Fever Panel Plus is a modified version of the Global Fever Panel, which, in addition to the pathogens described above, contains assays for the detection of 13 additional pathogens: Crimean-Congo hemorrhagic fever virus (CCHFV), *Ebolavirus* spp., Lassa virus, Marburg virus, West Nile virus (WNV), yellow fever virus (YFV), Zika virus, *Bacillus anthracis*, *Francisella tularensis*, *Salmonella enterica* (ser. Typhi and Paratyphi A), *Yersinia pestis,* and *Leishmania* spp. BioFire Defense performed a prospective clinical evaluation for the Global Fever Panel Plus at eleven geographically distinct sites across the globe. A total of 2139 prospective whole blood specimens were tested between March 2018 and March 2021. The Global Fever Panel Plus detected at least one analyte in 34.1% of specimens (730/2139). The most prevalent analyte was *Plasmodium*, followed by dengue virus. Chikungunya virus, *Leptospira* spp., *Leishmania* spp., CCHFV, WNV, Zika virus, and *S. enterica* ser. Typhi were detected in fewer than 5% of specimens. All other analytes were not detected by the Global Fever Panel Plus. Positive percent agreement between the Global Fever Panel Plus and comparator testing ranged between 50.0-100%, and the negative percent agreement ranged between 99.2-100%. The results show that the BioFire Global Fever Panel Plus could aid in rapid and actionable AFI diagnosis caused by multiple, sometimes co-occurring, pathogens.

0625

TAQMAN ARRAY CARD MULTIPLEX PCR PANEL TO DETECT PATHOGENS IN WHOLE BLOOD OF FEBRILE INPATIENTS IN NORTHERN TANZANIA, 2016-2019

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Acute febrile illness (AFI) is a common reason for seeking healthcare in low- and middle-income countries; yet determining etiologies of febrile illness remains a challenge. Here, we deployed a multiplex TaqMan-Array Card Acute Febrile Illness panel (TAC AFI) to describe causes of febrile illness among pediatric and adult inpatients in Tanzania. TAC AFI was run on total nucleic acid from whole blood samples from patients who reported a history of fever within 72 hours or had tympanic temperature ≥38.0°C. The panel was designed to detect 20 bacteria, 19 viruses, 2 fungi, and 3 protozoa. TAC AFI detections were compared to available conventional diagnostics undertaken by the study, which included blood culture, blood parasite smear, and, for persons with a positive rapid HIV antibody test, serum cryptococcal antigen. Of 1,132 participants enrolled in the prospective etiologic cohort study, 697 (61.6%) were selected for TAC AFI analysis. Median (IQR) age was 29.6 (4.6-46.4) years, and 378 (54.2%) were male. In-hospital and 30-day mortality occurred in 41 (5.9%) and 74 (10.6%), respectively. TAC AFI detected 191 pathogens from 167 (23.9%) participants. This included four viruses: enterovirus (n=7), Rift Valley Fever virus (n=3), dengue (n=1), and measles (n=1). Eight bacteria species were detected, including fastidious bacteria, such as *Bartonella* spp. (n=2), *Brucella* spp. (n=3), *Coxiella burnetii* (n=2), *Leptospira* spp. (n=1), and *Rickettsia* spp. (n=9). *Plasmodium* spp. and *Schistosoma* spp. were detected in 77 (11.4%) and 49 (7.2%) participants, respectively. Conventional diagnostics detected 98 pathogens in 97 (13.9%) participants. Excluding *Schistosoma* and *Plasmodium* spp., TAC AFI detected an etiology in 51 (7.3%) participants with no etiology by conventional diagnostics. In the context of AFI surveillance, TAC AFI increased the proportion of febrile inpatients with an etiologic pathogen detected compared to conventional methods. TAC AFI provided clinically actionable results, such as detections of fastidious bacterial pathogens, and epidemiologically important results, such as Rift Valley Fever virus and dengue detections.

0626

ETIOLOGY OF FEBRILE ILLNESSES ASSOCIATED WITH SEIZURES IN CHILDREN FROM LOW- AND MIDDLE-INCOME COUNTRIES: RESULTS FROM THE FIEBRE STUDY

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Fever is a common symptom resulting in health care seeking worldwide. There is limited evidence of the epidemiology and underlying etiology of seizures associated with fever in children in low- and middle-income countries (LMICs). They can vary from mild conditions (benign febrile seizures) to more serious life-threatening diseases such as bacterial meningitis and cerebral malaria. This analysis aims to provide a description of children with fever and seizures in the FIEBRE (Febrile Illness Evaluation in a Broad Range of Endemicities) observational study.Child in- and outpatients were recruited and systematically investigated in Mozambique, Zimbabwe, Malawi and Lao PDR from 2018 to 2021. Clinical description, treatment and outcome were recorded for each participant. Point-of-care tests (including blood culture, urine dipstick and culture, and HIV and malaria tests) were systematically performed, and further samples were shipped to reference laboratories for gold standard testing for a broad range of infectious agents. Lumbar puncture was only performed when clinicians considered it necessary.Across all sites 389 /3718 (4.9%) children aged 2 months to 14 years presented with seizures. The frequency among inpatients was uneven across the sites: 112/345 (32.4%) in Malawi, 122/533 (22.9%) in Mozambique, 46/355 (13%) in Zimbabwe, and 51/414 (12.3%) in Lao PDR. The frequencies in outpatients were 0.3%, 0.6%, 1.5% and 12.7% respectively. Of the 58 outpatients with seizures, 63.7% were categorized as "fever of unknown origin" by clinicians, 53.4% were prescribed with antibiotics and all of them who completed follow-up were alive by day 28. However, of 331 inpatients with seizures, 42.9% were diagnosed with malaria and 12.4% with suspected sepsis and/or meningitis. Among the 301 who completed D28 follow-up, mortality was 5%. We will present microbiology results stratified by clinical phenotypes, countries, and age groups.Seizures on presentation are very frequent among febrile child inpatients in LMICs. Detailed etiological diagnoses are crucial to better target the scarce therapeutic interventions available and improve survival.

0627

SIXTEEN YEARS OF PRIMARY CARE OBSERVATIONS REVEAL CASES OF AFEBRILE DENGUE AND DISTINGUISHING CHARACTERISTICS OF DENGUE, CHIKUNGUNYA, AND ZIKA

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Dengue, chikungunya, and Zika are diseases of high global health concern with overlapping clinical features, making differential diagnosis difficult without laboratory testing. Small sample sizes and characterization of these diseases in adults have compounded this problem. Here, we analyze 16 years of data from the Nicaraguan Pediatric Dengue Cohort Study to identify distinguishing features among these diseases. We assessed >8,000 primary care medical records of laboratory-confirmed cases aged 2-17 over the first 10 days of illness. Generalized additive, linear, and mixed-effects models; hierarchical clustering; and principal component analyses (PCA) were used to characterize the clinical features of 881 dengue, 519 chikungunya, and 524 Zika cases. We describe 43 RT-PCR-confirmed dengue cases without any evidence of fever. Afebrile dengue cases, constituting ~12% of the last major dengue epidemic, resembled mild cases of afebrile Zika. The prevalence of many clinical features differed across pediatric age, particularly fever, rash, and arthralgia. Peri-articular edema was almost never observed in dengue and Zika cases, and papular rash was never observed in chikungunya cases. The temporal dynamics of fever, rash, and arthralgia prevalence differed most across diseases. The average temperature of dengue and chikungunya cases seen at the primary health clinic were similar over the first 10 days of illness, while temperatures of Zika cases were noticeably lower. The classic biphasic fever of dengue was only observed for 8% of uncomplicated dengue cases. Dengue, chikungunya, and Zika cases exhibited distinct patterns in PCA space, with appetite loss being a major factor distinguishing chikungunya. Clinical differences were noted by dengue virus (DENV) serotype, with DENV1 and DENV3 cases exhibiting a similar, diffuse, and bimodal clinical profile that differed from DENV2 cases in PCA space. We are developing an interactive web app based only on clinical data that can be used to better inform arboviral differential diagnosis. Overall, our results substantially update the clinical epidemiology of pediatric arboviral diseases.

0628

METAGENOMIC NEXT-GENERATION SEQUENCING OF NASOPHARYNGEAL SWABS IN ACUTE FEBRILE ILLNESS IN CAMBODIA

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There is growing recognition of metagenomic next-generation sequencing (mNGS) as a valuable diagnostic tool capable of providing unbiased pathogen detection, but data on performance in low-resource settings remains scant. Here, we use mNGS of nasopharyngeal (NP) swabs taken from subjects in Cambodia to identify potential pathogens causing acute febrile illness. Febrile subjects aged 2 months to 65 years were enrolled in a cross-sectional study conducted across 4 tertiary hospitals in Cambodia. NP swabs were collected at hospital presentation. Depending on reported symptom constellations, sera was also taken in a subset of subjects for comparison of mNGS results. RNA was isolated from biosamples, converted to cDNA libraries, and sequenced on a NextSeq2000 (Illumina). Raw sequence reads were stripped for host reads and aligned to NCBI nucleotide and protein databases using a cloud-based bioinformatics platform (CZID). NP swabs were collected from 97 subjects between April 2020 and June 2021. Subjects were predominantly male (53.6%) and young (median age 3 years [IQR 1-25]). Pathogens were identified in 42 (43.2%) NP swabs; of these, 26 (61.9%) were respiratory viruses including 9 rhinovirus, 7 coronavirus (1 SARS-CoV-2), and 5 respirovirus cases. Co-infection was identified in 3 subjects with coronavirus and respirovirus (N=2) and coronavirus and rhinovirus (N=1). Of subjects with paired sera and NP samples (N=61), 18 (29.5%) had positive NP swabs but negative sera, 7 (11.5%) had negative NP swabs but positive sera, 12 (19.7%) had positive NP swabs and sera, and 24 (39.3%) had negative NP swabs and sera. Pathogen hits correlated in NP swabs and sera in 10 of 12 subjects, including six subjects with chikungunya. mNGS can be successfully implemented in low-resource settings to identify emerging pathogens and common respiratory pathogens, including co-infecting pathogens, from NP swabs of febrile patients. mNGS may also be able to detect chikungunya from NP swab alone, raising the possibility of non-invasive diagnostics for infections associated with high viremic states.

0629

BUILDING DIAGNOSTIC CAPACITY FOR HIGH-CONSEQUENCE PATHOGENS: USE OF MULTIPLEX DIAGNOSTIC PLATFORMS FOR PATHOGEN DISCOVERY FROM BIOREPOSITORY SAMPLES IN THE DEMOCRATIC REPUBLIC OF CONGO

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During disease outbreaks it is common for patients presenting with clinical symptoms consistent with the causative etiology to test negative for the agent of interest. Reasons for this include sample integrity, low-sensitivity tests, and pathogen diversity. However, when these patients test negative, the true etiology of the disease often remains undiagnosed. In an effort to increase diagnostic capabilities and improve the capacity of the country to respond to outbreaks, we used the BioFire platform to identify the etiology of disease in negative samples from the biorepository at the Institut National de Recherche Biomédicale (INRB) in Kinshasa, Democratic Republic of Congo (DRC). Blood samples collected during a 2019 Chikungunya virus (CHIKV) outbreak in Kinshasa, a 2022 Monkeypox outbreak in Maniema, and Ebola virus outbreaks from Komanga, Beni, and Mangina in 2018 - 2020 were analyzed using the BioFire Global Fever (GF) or Bio Threat (BT) pouches. Respiratory virus surveillance samples

from Kinshasa that tested negative for SARS-CoV-2 and Influenza were tested using the BioFire RP2.1 pouch. In total 41 samples were tested, and among those 20 were tested on the GF pouch, 14 on the BT pouch and 7 on the RP2.1 pouch. Five out of five (100%) samples that had been previously diagnosed were used as positive controls and tested positive on the BioFire (2 CHIKV, 2 Monkeypox, and 1 SARS-CoV-2). Of the samples that had previously been undiagnosed, 21/36 (58%) tested positive for at least one target on the pouch. The most common positive result among blood samples was *Plasmodium* spp. (9 samples), followed by *Plasmodium falciparum* (7 samples), CHIKV (2 samples), Orthopox genus (2 samples), and Dengue serotype 2 (1 sample). Among the respiratory samples, Adenovirus (5 samples), Coronavirus NL63 (4 samples), Parainfluenza virus 3 (1 sample), parainfluenza virus 4 (1 sample), and SARS-CoV-2 (1 sample) were detected. These data suggest that supplementing outbreak investigations in the DRC with screening for other causes of disease, such as those used in this study, could improve accuracy of diagnosis and clinical management of cases.

0630

PLASMODIUM SPP., SARS-COV2, DENV AND CMV HAVE THE HIGHEST POPULATION ATTRIBUTABLE FRACTION FOR ACUTE FEBRILE ILLNESS USING MULTIPLEX PCR DIAGNOSTICS IN A HEALTH-FACILITY BASED CASE-CONTROL STUDY IN IQUITOS, PERU DURING THE COVID-19 PANDEMIC

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Numerous emerging and endemic pathogens circulating in the tropical regions of South America, count among the etiologies for the clinical syndrome Acute Febrile Illness (AFI). In the Peruvian Amazon, these diseases, which are often clinically undifferentiable, include malaria, dengue, Zika, Chikungunya, leptospirosis, and others. Modular quantitative PCR diagnostic devices like the TaqMan Array Card (TAC) can detect dozens of pathogens in a single biological specimen. To demonstrate the feasibility of implementing etiology specific AFI surveillance using TAC, this study enrolls adult patients presenting with the syndrome and matched controls at two hospitals and five health posts spanning the urban-rural gradient of the greater Iquitos Metropolitan Area. TAC diagnostics are performed on blood samples, and medical, symptom and travel history data are collected upon enrolment. Concurrently, SARS-CoV-2 presence in saliva and nasopharyngeal samples is tested for using a separate PCR assay. During the first year (March 2021 - February 2022) 578 cases and 572 controls were recruited and tested for a panel of 26 pathogen targets. Epstein-Barre virus (EBV) had high positivity in both cases and controls (34.5% and 34.8% respectively) but no association with AFI, while 14 pathogen targets had zero detections. Excluding EBV, 17.8% of subjects (27.7% of AFI cases) were positive for at least one other pathogen, while just 5 subjects (0.4%, 2 cases, 3 controls) were coinfected with multiple non-EBV pathogens. The odds of *Plasmodium* spp. positivity were 12 times higher in cases than controls (OR = 12.12 [4.83, 39.00, p&lt0.001]), while the equivalent associations were 2.57 (1.51, 4.50, p&lt0.001) for SARS-CoV-2, 2.95 (1.38, 6.86, p=0.002) for Dengue virus and 3.81 (1.20, 15.87, p=0.011) for cytomegalovirus. Population attributable fractions for AFI of the 9 prevalent pathogens totaled 22.3%. AFI cases had 6.17 (3.57, 910.67, p&lt0.001) higher odds of having traveled in the preceding 15 days. Consistent with previously reported findings, this study found a high burden (77.7%) of AFI with etiology that is unattributable by multiplex PCR diagnostics.

0631

DEFINING RATIONAL ASSAY CUT-OFFS DOCUMENTING HUMORAL IMMUNE RESPONSES TO SEVERAL FILOVIRUSES IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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In the Democratic Republic of the Congo (DRC), the extent of human filovirus exposure remains unclear. While filovirus antibody response is classically detected using ELISA, we utilized a multiplex microsphere immunoassay (MIA) which produces simultaneous readouts of multiple analytes allowing for greater range and sensitivity in a limited laboratory resource setting. This study explores potential cutoff values for human antibody response to a specific MIA to better understand serologic immune profile against multiple filovirus proteins in various Congolese populations. Healthcare workers and members of the general population reporting no current illness were eligible for study participation. Serum samples were collected from consenting participants (N=1,813). The Luminex-based MIA was used to detect human IgG binding to recombinant filovirus antigens. Two potential response cut-offs for exposure indication were used: 1) mean +3 SD of MFI values recorded among Kinshasa participants reporting no contact with a confirmed or suspected Ebola case and no involvement in an Ebola outbreak, or 2) mean +3 SD of 1/3rd serum samples with lowest MFI values among the sample. Overall, 8.2% of samples were identified as having elevated EBOV GP reactivity defined by the Kinshasa-derived cutoff as opposed to 51.9% using the lowest 1/3rd cutoff. Similarly, 2.2% had elevated reactivity for EBOV VP40 and 2.4% for EBOV NP using the Kinshasa cutoff compared to 53.9% and 55.8% using the lowest value cutoff, respectively. Using the Kinshasa cutoff, 2.5% of samples had elevated BSA levels, 5.1% for SUDV GP, 2.3% for MARV VP40, 6.2% for MARV GP, and 2.5% for BDBV. Alternatively, the lowest 1/3rd cutoff identified 53.2% of samples had elevated BSA levels, 58.1% for SUDV GP, 56.2% for MARV VP40, 57.6% for MARV GP, and 53.5% for BDBV. Dramatic disparity in determination of possible filovirus exposure using different methodology indicates the importance of appropriate cut points for specific study population. Multiplex assays can be important tools in better monitoring changes in filovirus antigen reactivity in the general population absent of identified outbreaks.

0632

INSIGHTS INTO FILOVIRUS VIRUS GLYCOPROTEIN FROM EPITOPE MAPPING AND INFECTIVITY ANALYSES

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Recent disease outbreaks highlight the need to characterize the immune response to filoviruses to develop vaccines and therapies. We have used extensive GP mutation libraries to map the epitopes for >200 monoclonal antibodies (MAbs) targeting the EBOV surface glycoprotein, GP. We have extended these studies to Marburg virus (MARV) by generating an Ala-scan library of MARV Dmucin GP (Uganda strain). Initial maps of anti-MARV MAbs include those of two non-neutralizing MAbs MR228 and MR235, targeting the wing region of MARV GP, that showed therapeutic

protection in animal models (MR228) or that increased binding (MR235) by neutralizing MAbs. The variety of EBOV MAbs mapped, many from survivors of ebolavirus infection, include cross-neutralizing MAbs targeting the GP membrane-proximal external region (MPER); a broadly cross-reactive MAb that blocks GP interaction with its endosomal receptor Niemann-Pick C1; GP binding activity in sera of mice injected with DNA encoding MAbs (DMAbs), and MAbs who synergistically transform a non-neutralizing MAb into a potent neutralizer. The epitope maps have expanded our understanding of how the immune system recognizes EBOV GP, and allow correlation of epitopes with MAb neutralizing capabilities, to develop anti-EBOV therapeutics and vaccines. Mapping also identified mutations that increase the exposure of neutralizing epitopes, impacting future anti-ebolavirus vaccine strategies. To identify GP residues important for EBOV infectivity, we performed infectivity assays with the full GP mutation library, using a lentivirus pseudotype system. We identified critical residues whose mutation abrogated infectivity without affecting GP conformational integrity. Their locations suggest crucial roles in GP conformational changes that cause virus-host membrane fusion. Additionally, to identify uncharacterized EBOV cellular receptors, we assayed wild-type GP infectivity in non-permissive cells individually expressing 6,000 unique human membrane proteins of our membrane proteome array (MPA). This has identified candidate membrane proteins that enable EBOV infectivity.

0633

SEROLOGIC PROFILING OF THE HUMORAL IMMUNE RESPONSE TO EBOLA VIRUS AMONG VACCINATED SUBJECTS IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Antibody profile analysis is critical for the development and monitoring of vaccines and therapeutics. Antibody response profiles in individuals who have received the recombinant vesicular stomatitis virus-Zaire Ebola virus (rVSVΔG-ZEBOV-GP) against Ebola virus (EBOV) infection is limited. In the Democratic Republic of the Congo (DRC), Ebola vaccinations have been given in response to active outbreaks using a ring-vaccination strategy. This study investigates the serologic profile of antibodies against the vaccine antigen, EBOV GP as well as other filoviral proteins, in vaccinated individuals in Mbandaka, where participants received the rVSVΔG-ZEBOV-GP vaccine in 2018 during an Ebola outbreak. Individuals who received Ebola vaccination and reported no current illness were eligible for study participation. Serum samples from all consenting participants with a baseline and at least one follow-up measure were included in analysis (N=386). A multiplex Luminex-based microsphere immunoassay was used to detect human IgG binding to recombinant EBOV antigens as well as other filovirus antigens in serum. Change in MFI value from pre-vaccination to 21 days post, 6 months post, and 2.5 years post was computed. Median Ebola antibody response at pre-vaccination, 21 days post, 6 months post, and 2.5 years post was: EBOV GP: 1481, 4863, 6514, 5645 MFI; EBOV VP40: 193, 2487, 2737, 2613 MFI; EBOV NP: 756, 544, 707, 563 MFI. Median change in EBOV GP was 2260, 3570, and 2630 ΔMFI by 21 days post, 6 months post, and 2.5 years post vaccination, respectively. Similarly, median change in EBOV VP40 was 2320, 2520, and 2450 ΔMFI at the follow-up time points. Smaller changes post-vaccination were generally observed in other analytes (i.e., EBOV NP, SUDV GP, MARV VP40, MARV GP, and BDBV GP). To date, only the FANG Ebola virus immunoassay has been FDA approved to determine change in antibody response after rVSVΔG-ZEBOV-GP vaccination. This study suggests that additional assays could be used to detect changes in Ebola-specific antibody responses over time and provide additional information on potential durability of immunity to EBOV GP as well as other filovirus antigens.

0634

SAFETY OF THE AD26.ZEBOV, MVA-BN-FILO EBOLA VIRUS VACCINE IN PREGNANT WOMEN IN AN OPEN-LABEL CLINICAL TRIAL CONDUCTED DURING THE 2018-2020 EBOLA VIRUS OUTBREAK IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Pregnant women and their offspring experience disproportionally high mortality from Ebola virus disease (EVD). During the 2018-2020 EVD outbreak in North Kivu and Ituri provinces in the Democratic Republic of Congo, pregnant women were included in a clinical trial to assess the safety and effectiveness of the EVD vaccine regimen dose 1 (Ad26.ZEBOV) at day 0 and dose 2 (MVA-BN-Filo) at day 56 in adults and children aged ≥1 year. Women pregnant at time of vaccination or who notified a pregnancy during the study were followed for the collection of serious adverse events (SAEs) and pregnancy outcomes. Among 20,408 participants who received dose 1, 1221 women reported 1238 pregnancies. Pregnancy outcome was recorded for 1169 pregnancies (69 lost to follow up). Of the 1221 women ever pregnant during the study, 371 (38%) experienced an SAE. SAEs in pregnant women were predominantly related to pregnancy outcome; 260/1169 (23%) pregnancies with a known outcome resulted in a caesarian section delivery, primarily due to uterine scarring, fetal distress syndrome and cephalopelvic disproportion and 55 (4.7%) ended in miscarriage. Other SAEs occurred in less than 2% of women ever pregnant. No SAEs recorded for pregnant women were considered related to either vaccine. Of 1169 pregnancies with a known outcome, 1084 resulted in a live birth with 1100 babies born alive due to some twin pregnancies. Preterm birth occurred in 21% (188/891) of babies born alive and low birth weight in 8% (79/1032), amongst those with known gestational age and birth weight. Neonatal death up to 7 days occurred in 1% (11/1100) of babies born alive and 0.5% (5/1100) had congenital abnormalities. Congenital abnormalities included one inguinal hernia, one umbilical hernia, one congenital anomaly of the tongue, one cleft lip, one exomphalos. The Ad26.ZEBOV/MVA-BN-Filo vaccine appeared to be well tolerated in pregnant women and, although this trial did not have a control arm, trial data did not suggest worse adverse birth outcomes compared to a systematic review of pregnancy outcome data in this setting. If possible, these findings should be confirmed in randomized studies.

0635

EXPANDED USE OF THE RVSVΔG-ZEBOV-GP EBOLA VACCINE

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The Merck Ebola vaccine, rVSVΔG-ZEBOV-GP (Ebola Zaire Vaccine, live), is indicated for the prevention of disease caused by *Zaire ebolavirus* in

individuals 18 years of age and older and approved in over 40 countries including the United States, the European Union, and a number of countries in Africa. Post-approval non-clinical and clinical trials, including ongoing studies in pediatric and HIV positive participants, have continued to generate additional information on the performance of the vaccine. The studies in pediatric participants are focused on the safety and immunogenicity of the vaccine and include characterization of vaccine viral shedding. One of the pediatric studies, the Partnership for Research on Ebola VACcination (PREVAC V920-016), also includes evaluation of a second dose of rVSVΔG-ZEBOV-GP administered on Day 56 and is evaluating the durability of the immune response following one or two doses through five years postvaccination. Data available out to one year postvaccination in V920-016 showed that one and two doses of rVSVΔG-ZEBOV-GP were generally well tolerated and induced robust and durable immune responses in both adults and children as measured by a validated *Zaire ebolavirus* glycoprotein enzyme linked immunosorbent assay and Plaque Reduction Neutralization Test. Vaccine virus shedding was evaluated in a subset of children in V920-016. Vaccine virus RNA was detected in the saliva of less than 40% of the children within the first 28 days postvaccination. In addition to the ongoing clinical studies, rVSVΔG-ZEBOV-GP has been used extensively in the context of outbreak response with more than 380,000 individuals vaccinated in the Democratic Republic of the Congo, neighboring countries, and Guinea. Few breakthrough cases have been documented, consistent with a high level of efficacy/effectiveness and durable protection. The rVSVΔG-ZEBOV-GP vaccine is being stockpiled by UNICEF under the governance of the International Coordinating Group on Vaccine Provision in accordance with the World Health Organization Strategic Advisory Group of Experts recommendations.

0636

NIPAH VIRUS DIVERSITY ACROSS DIFFERENT SPATIAL SCALES IN SOUTH AND SOUTHEAST ASIA

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Nipah virus (NiV) is a bat-borne zoonotic pathogen with high fatality when it infects humans. It has been identified in bats throughout South and Southeast Asia. While infections in humans are rare, Nipah infection in bats appears to be widespread throughout the region, and its genetic diversity remains poorly understood. Here, we compiled a comprehensive dataset of all known genomes for NiV and associated location and host species information (N=209 from India, Bangladesh, Thailand, Cambodia, Indonesia, and Malaysia, sampled between 1999 and 2018). We reconstructed a time-resolved phylogeny and organised the sequences into distinct lineages. We then developed statistical approaches that tracked the spatial spread of lineages, accounting for the biased approach undertaken to collect NiV isolates. We also explored the distribution of human cases across the phylogeny. Finally, we implemented a rarefaction model to investigate cluster saturation in specific geographic regions and considered correlates as drivers of diversity. We found existing NiV sequences could be divided into 4 major lineages and 12 clusters. Within any bat roost there were an average of 2 distinct lineages circulating, rising to 4.6 lineages within a division. The probability that a pair of sequences came from the same lineage ranged from 0.5 (95%CI 0.4-0.62) when the sequences were sampled within 10km of each other to 0.28 (95%CI 0.18-0.46) when they were 500-1000km apart. Overall, we found the geographic spread has been slow. The mean spatial distance between viruses rose from 99km (95%CI: 52-179km) when viruses were separated by %lt;5years in evolutionary time to 895km (95%CI: 840-951km) when viruses were separated by 20 years. Finally, we estimate that cluster saturation has been reached at four divisions, while the viral diversity in other regions remains unknown. These findings suggest widespread and entrenched viral diversity in NiV and that different areas across the region have different circulating viruses, which could eventually be observed with extensive, uniform sampling.

0637

CHARACTERIZING INCIDENT ACUTE LASSA VIRUS INFECTION IN SOUTHERN NIGERIA

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Lassa fever is a viral hemorrhagic disease caused by the Lassa virus (LASV). First described in Nigeria in 1969, LASV is now endemic across West Africa. Roughly 80% of LASV infections present with mild or asymptomatic disease; the true burden of LASV infection in endemic regions is not well understood, leaving a knowledge gap that is critical for epidemic preparedness and outbreak response. Knowledge gaps in LASV distribution outside of West Africa and the dynamics of disease transmission also exist. Since April 2021, the Walter Reed Army Institute of Research Emerging Infectious Disease Branch and the African Center of Excellence for Genomics of Infectious Diseases have been carrying out a population-based, longitudinal cohort study, designed to determine the incidence and background prevalence, as well as risk factors for and transmission dynamics of acute LASV infection at two Lassa-endemic locations in Southern Nigeria: Owo and Abakaliki. Participants are followed weekly during peak transmission season to test for LASV by RT-PCR and serology. Detection of symptomatic LASV infection triggers more frequent blood sampling to characterize the early immune response and viral kinetics of acute LASV infection and their correlation to clinical outcomes. The study includes concurrent zoonotic surveillance of targeted (LASV-affected households) and non-targeted (households without history of LASV infection) rodent and non-rodent reservoirs. To date, 380 participants have been enrolled with 7086 follow-up visits completed, yielding 33 (8.68%) total LASV positive cases, of which 6 (18.18%) were asymptomatic and 27 (81.81%) were symptomatic with one death reported. 4,351 samples isolated from 1,030 trapped rodents (47.7% were *Mastomys natalensis*) and 661 samples isolated from 310 non-rodent animals (from 829 households) are being analyzed for the presence of LASV. Of the 336 rodent tissue samples so far analyzed by RT-PCR, 79 tissues (from 42 rodents, 37.5%) were positive for LASV. Ongoing analyses on human and animal specimen are underway. Enrollments will continue through the 2022 LASV season.

0638

TRENDS OF MORTALITY AND MORBIDITY BURDEN RELATED TO NEGLECTED TROPICAL DISEASES (NTDS), 1990-2020

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There has been significant progress in reducing the burden related to neglected tropical diseases (NTDs) due to control and elimination programs, improved sanitation, vector control, and treatment availability. We aim to compare the differences of burden and trends attributed to a group of NTDs from 1990 to 2020. We selected 12 NTDs that contribute

both morbidity and mortality to the Global Burden of Disease (GBD) Study. In order to assess the distribution of this burden, we estimated years lived with disability (YLDs), years of life lost (YLLs) and their sum, disability-adjusted life years (DALYs), based on global, super-region and age categories. Counts and age-standardized rates (ASRs) were calculated from 1990 to 2020. Estimated differences and percent change were used to quantify changing trends. We present preliminary GBD 2020 results here. Global DALYs for this group are estimated to have decreased by 51.9% from 1990 to 2020. Global YLDs and YLLs for this group decreased by 765,000 (95% UI 551,000-1.21million) and 7.29 million (95% UI 4.86-15.6), respectively. The largest reduction in ASRs of YLDs and YLLs were in sub-Saharan Africa. Larger percent changes in ASRs were observed for YLLs compared to YLDs in all super-regions except Southeast Asia, East Asia, and Oceania. The highest decrease of total YLDs was estimated in ages 5 to 9, from 543,000 (95% UI 293,000-917,000) in 1990 to 204,000 (95% UI 99,100-368,000) in 2020. Total YLLs had the highest decrease in ages 2 to 4 [-2.20 million (95% UI -4.70 to -1.23)]. Rates of YLDs and YLLs for dengue, Ebola and Zika increased across every age group. Across age groups, ascariasis in ages 5 to 9 years had the largest decrease in YLD rate [-52.9 (95% UI -90.4 to -28.9) per 100,000], whereas visceral leishmaniasis in ages 2 to 4 years had the largest decrease in YLL rate [-389 (95% UI -1,130 to -102) per 100,000]. Our estimates demonstrate that morbidity and mortality burden due to NTDs are largely decreasing, with more substantial reductions shown in mortality. These estimates can be utilized as a resource for future interventions and targeted strategies to reduce the impact of NTD burden.

0639

BURDEN OF DECLARATION VS NON-DECLARATION NEGLECTED TROPICAL DISEASES (NTDS)FROM 1990-2020

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The London Declaration on Neglected Tropical Diseases (NTDs) placed a focus on 10 NTDs for reducing or eliminating attributable burden. Several factors of the program, including increased treatments, funding and collaboration, all contributed toward progress in reducing the selected NTDs. However, progress on NTDs not included could be declining more slowly. We aim to estimate the progress of declaration NTDs in comparison to a subset of NTDs not selected. We used preliminary 1990-2020 burden estimates for 20 NTDs from the 2020 Global Burden of Disease (GBD) study. To estimate fatal and non-fatal burden, we estimated deaths and disability-adjusted life years (DALYs), calculated as the sum of years lived with disability (YLDs) and years of life lost (YLLs). Age-standardized rates and counts were estimated at 5-year intervals spanning 1990 to 2020. Percent change and differences were used to compare the varying trends. We present preliminary GBD 2020 results here. Global DALYs of declaration NTDs (d-NTDs) and non-declaration NTDs (nd-NTDs) were estimated to be 6.60 million (95% UI 4.69-9.15) and 5.90 million (95% UI 4.33-7.70) in 2020, reductions of 65.7% (95% UI 65.6%-68.7%) and 4.87% (95% UI 2.12%-10.2%) since 1990, respectively. Among these 20 NTDs, nd-NTDs accounted for 32.9% of DALYs in 1990 and 47.2% in 2020. Total deaths of d-NTDs were estimated to be 31,700 (95% UI 25,700-43,600) in 2020, a 74.6% reduction since 1990. Total deaths of nd-NTDs decreased from 55,800 (95% UI 44,200-72,400) in 1990 to 48,700 (95% UI 32,300-64,000) in 2020, a 12.8% reduction. The results of our analysis showed higher decreases in burden of deaths and DALYs attributable to declaration NTDs in comparison to non-declaration NTDs. This indicates a need for updating strategies and encompassing a focus on a broader range of NTDs, similar to the approach taken by the World Health Organization (WHO) NTDs Roadmap. Doing so will be critical to ensuring that countries can shift to the cross-cutting approaches needed to ultimately reach prevention, control, elimination, or eradication targets.

0640

DENGUE FORECASTING MODELS FOR THE AMERICAS

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Forecasting dengue can enable timely preventative measures, like vector control and hospital surge preparation. However, forecasting dengue is challenging. We developed and assessed regional indicators of dengue virus transmission across the Americas to identify potential drivers of transmission dynamics and evaluate forecasting capability. We used historical monthly dengue case data ranging from 1985 to 2019 from 241 jurisdictions in fourteen countries in the Americas to forecast monthly cases of dengue. Log-linear regression models were developed using dengue and climate (temperature, precipitation, and El Niño South Oscillation (ENSO)) data up to 2011 and incorporating short-term correlation, lags, and spatial correlation and forecasted monthly dengue cases at one- to six-months ahead for 2011 onward. Regional and national logarithmic scores (aggregated over time and across subnational locations) were used to assess model skill at each lead time. We applied regression models to the logarithmic scores to assess potential factors (forecast lead time, amount of historical data available, country, and location population size) associated with forecast skill. Increased surprisal was associated with longer lead times ($p<0.01$), less available training data ($p<0.01$), and varied by country ($p<0.01$). Accounting for these factors, a model including autoregressive and seasonal terms had the lowest surprisal estimates at one- and six-months ahead. Models incorporating the autoregressive component had more skill at the one-month horizon than all others. However, at six-months ahead, models that also included either seasonal and ENSO terms or seasonal and regional dengue terms had higher forecast skill. The autoregressive model with seasonal terms had the best average forecast skill across all horizons, suggesting that this model may serve as a base model to forecast dengue across the region. While forecast skill marginally increased with the inclusion of ENSO and regional dengue terms, that increase suggests those factors may contribute to long-term regional dengue dynamics.

0641

INTERPRETATION OF SYMPTOMS AND EXAM FINDINGS BY HUMAN OR MACHINE TO DETECT DENGUE VIRUS IN KENYAN CLINICS

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Clinicians in Kenyan public health clinics lack access to diagnostic testing for emerging infections such as dengue virus (DENV) and must rely on clinical history and physical exam observations when evaluating febrile patients. We investigated whether the use of machine learning algorithms to develop diagnostic models based solely on clinical observations could enhance detection of DENV and form a valuable approach to aid in the surveillance for emerging infectious diseases in resource-limited settings. We extracted symptoms and physical exam data from 6,208 pediatric febrile illness visits to four clinic sites in Kisumu and Kwale Counties, Kenya, between 2014 and 2019, and created a data set with 138 clinical features. Malaria testing was available at the clinics. DENV testing was later performed in our labs. 485 subjects (7.8%) had acute DENV infection based on RT-PCR detection of viral RNA or anti-DENV IgG seroconversion (ELISA) by 1-month follow-up. 3,145 subjects (50.7%) had malaria

detected by light microscopy or rapid detection tests. 220 (3.5%) subjects had co-infection with both DENV and malaria. Clinicians diagnosed 83.9% (sensitivity, Sn) of malaria cases with 79.7% specificity (Sp), but only identified 13% (Sn) of DENV cases (85.5% Sp). We randomly sampled 70% of the dataset to train DENV and malaria prediction models using boosted logistic regression, decision trees and random forests, support vector machines, naïve Bayes, and neural networks with 10-fold cross validation, tuned to maximize accuracy (Ac). In the reserved 30% test dataset, clinician diagnosis of malaria outperformed all models (82.4% vs. range of 56.4-68.7% Ac for the models). In contrast, clinicians detected only 21 of 145 cases of DENV (79.7% Ac, 14.5% Sn, 85.2% Sp). Of the six models, only logistic regression identified any DENV case (8 cases, 91.1% Ac, 5.5% Sn, 98.3% Sp). Thus, without diagnostic testing, interpretation of clinical findings by humans or machines cannot detect DENV with a prevalence of up to 8%. Greater access to point-of-care diagnostic tests must be prioritized to address the global disparity in surveillance of emerging infectious diseases.

0642

EXPANDING XENOSURVEILLANCE CAPABILITIES USING LONGITUDINAL DATA COLLECTED FROM HOUSEHOLDS IN RURAL GUATEMALA

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Rapid detection of established and emergent human pathogens is necessary for efficient implementation of public health response. This is often inhibited by barriers to acquisition of high-quality samples and lack of infrastructure for sample testing and analysis in resource-limited communities. Previously, we demonstrated use of blood-fed mosquitoes as tools for human pathogen surveillance (xenosurveillance) in resource limited regions of West Africa. A recent pilot study in Guatemala compared household-matched mosquito and human blood samples to reveal circulating pathogens, including Epstein-Barr virus. Leveraging an expanded cohort in the same rural Guatemalan community, we hypothesized that mosquitoes could be used as a non-invasive, self-supported sampling sources for xenosurveillance. We enrolled 107 individuals across 40 households in two communities of southwestern Guatemala for one year of weekly syndromic surveillance. Households with individuals reporting symptoms of fever, arthralgia, and/or rash were activated for a four-week intensive follow-up period wherein blood was collected from enrolled subjects, domestic animals, and replete mosquitoes. Blood was preserved on FTA cards and used for targeted PCR screening of human pathogens and next-generation sequencing. Twenty-one households, representing 64 individuals, were activated during the study. The most frequently reported symptoms were fever and arthralgia. Replete mosquitoes belonged to the genera *Culex* (n = 1,191), *Aedes* (n = 540), *Mansonia* (n = 51), and *Anopheles* (n = 23). Molecular analysis including NGS and confirmation of mosquito bloodmeal and species identification are ongoing. Data collected throughout this study will allow for comparison between samples (i.e. mosquito versus domestic animal versus mosquito), demonstrating the untapped potential for mosquitoes to be used in pathogen surveillance. This work will also create infrastructure for disease monitoring in rural and resource-limited communities that are particularly vulnerable to the burden of disease.

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COUNTRY OWNERSHIP OF NEGLECTED TROPICAL DISEASES IN TANZANIA: RESOURCE MOBILIZATION THROUGH COMPREHENSIVE COUNCIL HEALTH PLANS

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Historically, Neglected Tropical Disease Control Programs (NTDCPs) have been donor funded for interventions like Mass Drug Administration and surveys. The WHO NTD 2021-2030 Road Map puts forward three foundational pillars namely: accelerate programmatic action, intensify cross-cutting approaches, and change operating models and culture to facilitate country ownership. Country ownership focuses on leadership and domestic resource mobilization (DRM) for NTD programming. In Tanzania, among 158 councils assessed by the President's Office, Region Authority and Local Government (PORALG), 18.4% and 48.7% respectively did not allocate funds for NTDs in 2019/20 and 2020/21. The aim was to increase DRM by building capacity for planning and budgeting to 15 selected councils through regular Comprehensive Council Health Plan (CCHP) cycle. Selection was done based on the disease burden (high and near elimination). Ten of the 15 had zero allocation in 2020/21. National CCHP master trainers capacitated key council planners during the CCHP pre-planning stage. Planning and budgeting were done through planning and budgeting system (PlanRep) using DHSI2. Funding allocations were done across cost centers and fund sources. District Medical and Planning officers signed their plans as a commitment for integration into the CCHP. The budget was done in TZS, equivalent to 159,594 USD for all councils, at an average of 10,640 USD per council. Allocation per cost centers: Council Health Management Teams (CHMTs)-44,865 USD, Council Hospitals- 12,872 USD, Health Centers-27,105 USD, Dispensaries- 32,290 USD. CCHP interventions included case detection and management, early diagnosis, health promotion and prevention, medicine, medical equipment, medical supply and diagnostic supplies, preventive chemotherapy, vector control, safe healthcare waste management and practices. DRM for sustainable NTD programming depends on integration of NTD interventions into the CCHPs. Timing, data availability, and capacity of council NTD coordinators are keys for effective planning. Post CCHP assessment analysis is required to inform guidance for DRM scale up.

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ASSESSING COMMUNITY HEALTH WORKERS' TIME ALLOCATION FOR A CERVICAL CANCER SCREENING AND TREATMENT INTERVENTION: A TIME AND MOTION STUDY

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Community health workers (CHWs) are increasingly used to delivery priority maternal child health interventions to achieve Universal Health Coverage (UHC). Existing literature allude to the potential for detrimental effects of multi-tasking CHWs. We assessed the impact of integrating cervical cancer screening and prevention therapy (CCSPT) with family planning (FP) on time utilization among CHWs. A time and motion study was conducted in 7 health facilities in Malawi. Data was collected at baseline before CCSPT between October-July 2019, and 12 months after CCSPT implementation between July and August 2021. CHWs trained to deliver CCSPT were continuously observed in real time while

their activities were timed by independent observers. We used paired sample t-test to assess differences in mean hours that CHWs spent on key activities: clinical and preventive care; administration; FP and non-work-related tasks. Regression models were used to ascertain the impact of CCSPT on the average duration of key activities. Thirty-seven (n=37) CHWs were observed. Of these, 35% were females. Their mean age and years of experience were 42 and 17, respectively. Overall, 323 hours (inter quartile range 2.8-5.5) of CHWs observations took place. Compared to the period before CCSPT, the proportion of hours CHWs spent on clinical and preventive care, administration and non-work-related activities were reduced by 13.7, 8.7 and 34.6%, respectively. CHWs spent 75% more time on FP services after CCSPT implementation relative to the period before CCSPT. The provision of CCSPT appeared to result in less time that CHWs devoted towards clinical and preventive care but this association was not significant. Following CCPST, CHW spent significantly few hours on non-work-related activities. Introduction of CCSPT was not very detrimental to pre-existing community services. CHWs managed their time ensuring additional efforts required for CCSPT were not at the expense of essential activities. The programming and policy implications are that multi-tasking CHWs with CCSPT will not have substantial opportunity costs.

0645

DEEP CHARACTERIZATION OF THE IMMUNOGENICITY INDUCED BY NEXT GENERATION YELLOW FEVER VACCINE IN PHASE 1 DOSE-RANGING STUDY

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vYF is a next-generation live-attenuated yellow fever (YF) vaccine candidate grown in serum-free Vero cells, free of allergens and of raw material from animal or human origin, developed to ensure a more robust worldwide supply. vYF preclinical testing demonstrated equivalence with licensed YF vaccines before its evaluation in humans. We conducted a Phase I randomized, observer-blind, active-controlled (YF-VAX), dose-ranging clinical trial to assess in 72 healthy adults of 3 dosages of vYF (4.0, 5.0 or 6.0 Log CCID50/dose) in a 1:1:1:1 allocation (NCT04142086). Immunogenicity was followed during 6 months after vaccination through the longitudinal evaluation of neutralizing antibody titers, detection of serum cytokine and chemokine levels by Luminex®, immune-profiling by focused transcriptomics analysis by RT-qPCR and evaluation of YF-specific memory B cell frequency by Fluorospot. All YF-naive vaccinees seroconverted 28 days after vaccination with both vYF and YF-VAX. Neutralizing antibody geometric mean titers increased from D10 to D28 and slightly decreased at 6 months post-vaccination but stayed far above the surrogate of protection threshold of ≥10 (1/dilution). No increase of inflammatory markers in sera was observed in all groups except a slight increase of IP10 at D7. The focused transcriptomics analysis allowed to identify induction of a strong antiviral innate response with activation of blood transcriptional modules linked to interferon response, viral sensing and dendritic cell activation followed by the initiation of adaptative T- and B-cell responses. Finally, a strong YF-specific memory B cell response with both IgM and IgG secreting cells was detected at D28 post-vaccination and IgG memory B cell response was maintained for at least 6 months. Overall, no difference was observed between the 3 doses: 4, 5 and 6 Log CCID50 and no difference was observed between vYF groups and YF-VAX vaccinees. Together these results show that vaccine take is similar for vYF and YF-VAX and it may suggest that the immune response to vYF could provide the same immune response over time and longevity as that induced by the reference vaccine.

0646

SOFOSBUVIR OFF LABEL TREATMENT OF YELLOW FEVER PATIENTS DURING AN OUTBREAK IN BRAZIL, 2018

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In 2018 a huge yellow fever (YF) outbreak took place in Southern Brazil, causing 2,166 confirmed human cases and 752 deaths. Among the patients hospitalized at Eduardo de Menezes Hospital (MG, Brazil) and diagnosed with YF, 46 patients were selected for a off label, non-randomized treatment with Sofosbuvir (approved antiviral against HCV), based on the days after disease onset (up to 5 days post symptoms onset-DPS). Previous studies had already shown the Sofosbuvir antiviral activity against YFV in vitro and experimentally infected mice. Selected patients were presenting severe symptoms and were at great risk for fatal YF disease. Patients or their legal responsible consented to the use of Sofosbuvir during acute YF phase. This study was approved by the Ethics Committee on Human Research at René Rachou Institute/FIOCRUZ on CAAE 65814417.0.0000.5091 and CAAE 43000815.7.0000.5091. Patients had serial serum samples collected during Sofosbuvir use (up to 10 DPS), followed by RNA extraction and qRT-PCR. We analyzed the YFV genomic viral load (VL) of treated patients and compared them with those of untreated YF patients who either survived (NT-S) or died (NT-D) during hospitalization. Serum samples were collected between the 4th to the 10th day after symptoms onset (DPS). The average genomic VL was higher for the NT-D group (2.04x10^{7}GC/mL), followed by the treated one (1.25x10^{5}GC/mL), and last the NT-S (5.93x10^{4}GC/mL). Comparing genomic VL for each day, differences were observed at all analyzed time points (4,5,6,7,8 and 9 DPS), with higher values for the NT-D group followed by the treated group and lastly the NT-S ($p=0.002$ for NT-SxTreated, and $p<0.0001$ for the pairs NT-SxNT-D and NT-DxTreated). The treated group showed an intermediary YFV VL at the beginning, and, after treatment, suggesting that Sofosbuvir could be able to reduce the YFV load at levels similar to the NT-S group. There is no specific therapy against YF, reinforcing an urgent need for antiviral treatment. Further studies are needed, considering controlled and randomized circumstances, to better investigate the role of Sofosbuvir and its impact on YFV infection in human patients.

0647

MAPPING ZIKA VIRUS-SPECIFIC NEUTRALIZING IMMUNITY FOR OPTIMAL VACCINE DEVELOPMENT

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Zika virus (ZIKV) has been reported in 87 countries since 2015. Although most infections are mild or asymptomatic, ZIKV can cause infantile Guillain-Barré syndrome, brain or eye defects, low birth weight, and even pregnancy loss. Vaccines are urgently needed to prevent ZIKV, but current understanding of humoral responses to ZIKV is incomplete, and tools to assess candidate vaccines' immunogenicity are lacking. Here, we examine whether vaccination and natural infection elicit ZIKV-specific antibodies (Abs) that target the same epitopes as potent ZIKV-neutralizing monoclonal antibodies (mAbs) via blockade of binding (BOB) assays. We also use standard measures of binding and neutralizing antibody (NAb) titers. We hypothesize that vaccines which elicit NAb responses similar in quality to natural infection - particularly Abs that recognize quaternary epitopes - will be most likely to provide durable protective immunity. We find that two vaccine candidates, a DNA vaccine (VRC) and a purified inactivated virus vaccine (ZPIV), elicit distinct antibody responses to ZIKV. One month after completing the three-dose ZPIV regimen, samples produced a 45.70% mean BOB response using MZ4 as the mAb probe; two months post-third dose of VRC 320, samples produced <10% BOB. Importantly, although MZ4 was isolated from a dengue-immune individual vaccinated with ZPIV, convalescent sera from individuals with prior ZIKV infections consistently compete with it. This supports our hypothesis that the ZPIV antigenic structure closely recapitulates the native ZIKV virion (including the MZ4 epitope). We also found that dengue-immune sera exhibited minimal BOB activity against MZ4 and other mAbs such as A9E, G9E, and Z004. This suggests that our mAb probes were specific for ZIKV-induced immunity. Ongoing experiments seek to quantify total ZIKV-binding Ab across sample sets to discriminate between quantitative and qualitative Ab reactivity and to expand the probed ZIKV antigenic regions. This project demonstrates the importance of assessing Ab response quality beyond a single measure (such as NAb titer) and may help optimize ZIKV vaccine development.

0648

HUMORAL AND T-CELL-MEDIATED RESPONSES TO A PRE-CLINICAL ZIKA VACCINE CANDIDATE THAT UTILIZES A UNIQUE INSECT-SPECIFIC FLAVIVIRUS PLATFORM

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Vaccination is critical for the control and prevention of viral outbreaks, yet conventional vaccine platforms may involve trade-offs between vaccine immunogenicity and safety. Insect-specific flaviviruses (ISFVs) are emerging as a novel method to overcome this challenge. ISFVs are safe; they neither replicate nor cause disease in vertebrates, and hence also don't require traditional inactivation methods that can result in antigenic degradation. Previously, we used a novel ISFV called Aripo virus (ARPV) to create a promising recombinant Zika virus (ZIKV) vaccine candidate (called ARPV/ZIKV) that consists of ZIKV precursor membrane and envelope (prM-E) genes expressed on an ARPV backbone. Previously, ARPV/ZIKV showed no pathogenicity, including in suckling mice injected intracranially. Immunocompetent and immunocompromised mice immunized with a single unadjuvanted dose were also completely protected from lethal ZIKV challenge. Given ZIKV's propensity to evade key innate antiviral responses in humans, and in order to assess correlates of protection and adjuvant selection in the future, a better understanding of the balance between vaccine-induced humoral and T-cell responses is required. Here, we explore these responses for both developing immunity post-immunization and for providing protection post-challenge. Passive transfer of antibodies from APRV/ZIKV-immunized mice to naïve IFNAR$^{-/-}$ mice prior to challenge emphasized neutralizing antibodies as an important correlate of protection. However, circulating antibodies post-transfer were not sufficient for full protection. Follow-up *in vivo* T-cell depletion studies of CD8^{+} or CD4^{+} T-cells in IFNAR$^{-/-}$ mice at the time of challenge indicated the potential importance of vaccine-induced T-cell responses for protection. Vaccine efficacy studies in Rag1 KO, Tcra KO, and muMt^{-} mice also demonstrated the importance of T-cell responses for developing immunity after ARPV/ZIKV immunization. Overall, ARPV/ZIKV induces robust responses in both branches of the adaptive immune system, meaning that ISFV platforms continue to be a promising method for vaccine development.

0649

THE EFFECT OF OBESITY ON PEDIATRIC DENGUE VIRUS INFECTION, DISEASE, AND IMMUNE RESPONSE

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Obesity is an important risk factor for poor outcomes of multiple infectious diseases and has been associated with reduced antibody responses and a faster antibody waning rate; however, whether obesity increases the risk of dengue virus (DENV) infection or affects DENV antibody responses has not be explored. Given that obesity and dengue both pose a substantial and increasing burden in children, we sought to investigate whether and how pediatric obesity modulates DENV infection and immune responses to infection. Data were derived from the Pediatric Dengue Cohort Study (PDCS) in Managua, Nicaragua, following ~3,800 children 2-15 years old. To study the effect of obesity on anti-DENV antibody responses, serum samples from a subset of 90 selected PDCS participants (n=30 each normoweight, overweight, and obese, defined by BMI z-score) at ~6, ~18, and ~30 months post-infection are being tested for anti-DENV antigen-specific antibody binding profiles, neutralizing capacity, and temporal dynamics. To do so, we have developed a novel multiplex Luminex system to measure the magnitude and binding characteristics of antibodies that target the envelope (E) protein, E domain III, and nonstructural protein 1 from the four DENV serotypes. We found that between 2011 and 2019, the incidence rate of obesity in the cohort increased from 2.1 to 3.9 per 100 population, and the prevalence of obesity increased by 86% (from 7 to 13%). Participants with obesity had a 1.27 (95% confidence interval [CI] 1.08, 1.49) greater risk of DENV infection when compared to normoweight individuals in univariate analysis. Further, participants with obesity had a 1.86 (95% CI 1.36, 2.53) higher risk of developing dengue symptoms given infection and had an adjusted (for age, sex, infection history and cohort year) higher risk of 1.63 (95% CI 1.16, 2.30). Our results suggest that obesity is a risk factor for DENV infection and disease and may modulate DENV antibody responses over time.

0650

OBESITY ALTERS IMMUNE RESPONSES TO DENGUE VIRAL INFECTION IN CHILDREN AND YOUNG ADULTS

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Obesity, an increasing global health problem, is a potential risk factor for the development of severe dengue. Individuals with obesity may possess an altered cellular metabolism which could impact anti-viral immunity,

however the mechanisms underlying these alterations in dengue are unknown. Our study investigates the phenotype/functionality of T, NK and B cells and their association with body mass index (BMI) and dengue outcomes in children and young adults. The phenotypic/functional features of T, NK and B cells were evaluated by multiparameter flow cytometry in a Vietnamese cohort of acute severe and non-severe dengue patients with obesity/overweight (n=75) or normal weight (n=75), matched by age, sex, and illness phase. Magnitude, phenotype and multifunctionality of dengue-specific T cells targeting DENV1-4 were assessed by intracellular cytokine staining. We identified robust T (CD4+ and CD8+), NK, and B cell activation in all patients analyzed (day 8 illness onset), which was decreased in patients with obesity. Obesity also associated with reduced cytotoxic potential and more dysfunctional phenotype of CD8+ T and NK cells, suggesting altered immune responses with potentially impaired capacity to clear dengue virus. Moreover, these altered cellular phenotypes were more marked in severe disease and strongly correlated with increasing BMI and serum leptin levels. In both patient groups (obesity and normal weight), DENV2-specific CD8+ T cells expressed high levels of MIP-1β and CD107a, and variable levels of IFN-γ, TNF-α and IL-2 cytokines. The multifunctionality of DENV2-specific T cells was decreased in secondary infection in patients with obesity compared to patients with normal weight. We are currently analyzing the metabolic profiles and phenotype/function of T/NK cells in these patients early in infection (days 3-5). We identified alterations in immune responses of dengue patients with obesity/overweight compared to patients with normal weight, which were more marked in severe disease. Our data suggest obesity may potentially impact on the anti-viral capacity of T, NK and B cells, particularly during severe dengue.

0651

TAK-003 ELICITS TETRAVALENT, ROBUST, AND SUSTAINED NS1 AB RESPONSES SPANNING POPULATION AGE AND BASELINE SEROSTATUS

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Dengue (DENV) is a *Flavivirus* which causes significant disease burden worldwide. Exposure to DENV can lead to asymptomatic dengue, dengue fever, or potentially deadly dengue hemorrhagic fever/dengue shock syndrome, characterized by endothelial dysfunction and vascular leakage. Non-structural protein 1 (NS1) is the only secreted viral protein from DENV-infected cells and is involved in viral replication and immune evasion. The antibody response to NS1 may play a role in protecting against severe disease. Takeda's dengue vaccine candidate TAK003 consists of an attenuated DENV-2 virus, and three chimeric viruses containing the pre-membrane and E protein genes of DENV-1, -3, and -4, genetically engineered into the attenuated DENV-2 backbone. The DENV-2 backbone of TAK-003 includes the NS1 from DENV-2. We developed an indirect ELISA to measure anti-dengue NS1 IgG antibodies in pre-and post-vaccination samples from TAK-003 recipients. We tested samples from two different Phase 3 clinical trials conducted in dengue-endemic and non-endemic regions (DEN-301, NCT02747927; DEN-304, NCT03423173, respectively) to assess the magnitude and persistence of DENV-2 NS1-specific, and DENV-1, -3 and -4 NS1 cross-reactive IgG responses in pediatric, adolescent and adult participants. Our data indicate that anti-NS1 IgG responses peak post-vaccination at day 120 (30 days post-second dose), followed by a sustained response above baseline through Day 450 (360 days post second dose) in both seropositive and seronegative participants. The anti-NS1 IgG response in seronegative participants follows a hierarchy of magnitude, with the highest antibody responses to DENV-2 NS1, followed by cross-reactive responses to DENV-1, 3 and 4 NS1 respectively. Pre-vaccination, the anti-NS1 antibody responses in baseline seropositive participants are higher than seronegative participants, and remain higher post-vaccination. These data indicate that TAK-003 elicits tetravalent, robust and sustained NS1 IgG responses in pediatric, adolescent and adult participants from endemic and non-endemic countries, irrespective of baseline serostatus.

0652

SPOROZOITE IMMUNIZATION FOLLOWED BY ANTIMALARIAL CHEMOPROPHYLAXIS TARGETING PLASMEPSINS IX AND X CONFERS STERILE IMMUNITY AGAINST MALARIA

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Naturally acquired immunity to malaria only develops after repeated cases and does not prevent reinfection. The licensed malaria vaccine RTS,S/AS01 offers moderate efficacy that wanes with time, resulting in rebound *Plasmodium* infections. Efficacious protection from malaria has been achieved with chemoprophylaxis vaccination involving controlled infection with live sporozoites and chemoprophylaxis targeting liver or blood stage parasites. Malaria parasites have evolved resistance to most antimalarials, and few treatments effectively kill pre-erythrocytic liver stages. A new antimalarial that arrests late liver stages before blood infection takes hold may aid the development of a next generation malaria vaccine. Previously, we showed that a new class of antimalarials targeting plasmepsins IX and X inhibit liver merosomes from establishing the first wave of erythrocytic infection. This liver merozoite arrest occurred after sporozoite inoculation, preventing detectable blood stage parasitaemia and malaria (chemoprophylaxis). Here, we have investigated whether liver merozoite arrest using plasmepsin IX/X-specific antimalarials confers protective immunity. Immunization of two mouse strains with sporozoites under antimalarial prophylaxis targeting plasmepsins IX and X elicited sterilizing immunity against mosquito-borne malaria with a half-life of up to 24 months. Protective immunity involved robust antibody and T cell responses. These results have implications for malaria vaccination involving immune priming and/or boosting with locally circulating, heterologous, mosquito-borne malaria parasites in endemic regions using a new class of antimalarials that arrests very late liver stages.

0653

ALTERED Vδ2+ γδ T CELL CHROMATIN ACCESSIBILITY AND IMMUNE FUNCTION FOLLOWING REDUCED IN *VIVO OR* IN *VITRO* MALARIA EXPOSURE

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A major component of incomplete natural immunity to *Plasmodium falciparum (Pf)* malaria is attenuation of cytotoxic, pro-inflammatory responses by innate immune cells following repeated malaria exposure. In order to identify mechanisms underlying Vδ2+ γδ T cell dysfunction and to characterize the longevity of this response, we obtained repeated samples from a longitudinal cohort of children living in Tororo, Uganda, before and after a district-wide insecticide campaign that dramatically reduced malaria transmission. Paired ATAC-Seq and RNA-Seq experiments utilizing sort-purified Vδ2+ cells from Ugandan children (n=20) at 3 timepoints revealed differential chromatin accessibility and gene expression based on prior incidence of clinical malaria. We identified differential chromatin and transcription factor motif accessibility between samples

from 2016 (reduced transmission) vs. 2013 (high malaria transmission) at sites associated with immune signaling (e.g. IL-19, CD8, CXCR6, STAT1) and regulation (e.g. BCL2, KLRC1). Analysis of RNA-Seq data is ongoing. In addition to defining transcriptional and epigenetic changes underlying altered cell function following repeated malaria or reduced malaria transmission, we established an *in vitro* system to simulate the *in vivo* context. Vδ2+ T cells from malaria-naïve individuals stimulated for 6 days with *Pf*-infected red blood cells (iRBCs) or the phosphoantigen HMBPP produced less TNFα and IFNγ and degranulated less in response to secondary stimulation compared to unstimulated cells; however, rest following stimulation partially rescued the decreased responsivity to iRBCs. Similar results were obtained using cells from malaria-uninfected Ugandan individuals, but responses from recently infected individuals were more variable. Ultimately, this work could deepen our understanding of mechanisms driving inefficient acquisition of antimalarial immunity—including potential reversibility of functional changes following repeated malaria—and could have applications for novel therapeutic approaches targeting innate immune responses in addition to adaptive responses.

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THE ACQUISITION OF HUMORAL IMMUNE RESPONSES TARGETING *PLASMODIUM FALCIPARUM* SEXUAL STAGES IN CONTROLLED HUMAN MALARIA INFECTIONS

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Anti-gametocyte immunity is the foundation-stone of malaria transmission blocking vaccine development. Individuals infected with *Plasmodium falciparum* develop antibody responses to intra-erythrocytic gametocyte proteins and gametocyte proteins exported to the surface of infected erythrocytes, but our knowledge of the immunogenicity of gametocyte antigens and the specificity of gametocyte-induced antibody responses is very limited. In this study, we assessed antibody responses in participants of two controlled human malaria infection (CHMI) studies by ELISA, multiplexed bead-based antibody assays and protein microarray. By comparing antibody responses in participants with and without gametocyte exposure, we aimed to disentangle the antibody response induced by asexual and sexual stage parasites. We showed that after a single malaria infection, a significant anti-sexual stage humoral response is induced in malaria-naïve individuals, even after exposure to relatively low gametocyte densities (up to ~1,600 gametocytes/mL). In contrast to antibody responses to well-characterised asexual blood stage antigens that were detectable by day 21 after infection, responses to sexual stage antigens (including transmission blocking vaccine candidates Pfs48/45 and Pfs230) were only apparent at 51 days after infection and were correlated with the intensity of prior exposure. Sixty-four antigens were identified as eliciting higher antibody responses exclusively in individuals with significant gametocyte exposure, among which antigens previously associated with early gametocyte or anti-gamete immunity were highly represented. Our data provide detailed insights on the induction and kinetics of antibody responses to gametocytes and identify novel antigens that elicit antibody responses exclusively in individuals with gametocyte exposure. Our findings provide target identification for serological assays for surveillance of the malaria infectious reservoir, and support vaccine development by describing the antibody response to leading vaccine antigens after primary infection.

0655

PLASMODIUM INFECTION IS ASSOCIATED WITH CROSS-REACTIVE ANTIBODIES TO CARBOHYDRATE EPITOPES ON THE SARS-COV-2 SPIKE PROTEIN

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Sero-surveillance can monitor and project disease burden and risk. However, SARS-CoV-2 antibody test results can produce false positive results, limiting their efficacy as a sero-surveillance tool to estimate population-level SARS-CoV-2 exposure. False positive SARS-CoV-2 antibody results have been associated with malaria exposure, and understanding this association is essential to interpret sero-surveillance results from malaria-endemic countries. In this study, pre-pandemic samples from eight malaria endemic and non-endemic countries on four continents were tested by ELISA to measure SARS-CoV-2 Spike S1 subunit reactivity. Pre-pandemic individuals with acute malaria infection generated substantial IgG and IgM reactivity to SARS-CoV-2. People with acute malaria infection had significantly higher rates of SARS-CoV-2 reactivity compared to uninfected people in malaria-endemic areas (t-test log IgG and IgM p-values<0.0001), with reactivity peaking 2-4 weeks after malaria infection. Peptide and protein arrays showed that cross-reactivity to S1 Spike of SARS-CoV-2 was not associated with reactivity to other human coronaviruses or other SARS-CoV-2 proteins (no significant associations, except with malaria epitopes). In investigating the mechanism of cross-reactivity, ELISAs with deglycosylated and desialated Spike S1 subunits revealed that cross-reactive antibodies target sialic acid on N-linked glycans of the Spike protein. The functional activity of cross-reactive antibodies measured by neutralization assays showed that cross-reactive antibodies did not prevent viral entry to neutralize SARS-CoV-2 in vitro. Routine use of heavily glycosylated or sialated assays could result in false positive SARS-CoV-2 antibody results in malaria endemic regions, causing serological surveillance tools to overestimate SARS-CoV-2 exposure and possible population-level immunity, and in turn underestimate the risk of continued COVID-19 transmission. These findings emphasize the importance of developing assay approaches that minimize cross-reactivity to improve serological surveillance.

0656

A SINGLE FULL-LENGTH VAR2CSA ECTODOMAIN VARIANT PURIFIES CROSS-INHIBITORY ANTIBODIES AGAINST PLACENTAL MALARIA ISOLATES

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Placental malaria (PM) is a deadly syndrome that results from accumulation of *Plasmodium falciparum*-infected erythrocytes expressing surface antigen VAR2CSA and binding to chondroitin sulfate A in the placenta. VAR2CSA is the leading PM-vaccine candidate, as anti-VAR2CSA antibodies have been associated with naturally acquired PM-resistance over successive pregnancies. The cysteine-rich ectodomain is formed by an N-terminal sequence (NTS), followed by six and sometimes more Duffy-binding-like (DBL) domains interspersed with interdomain (ID) regions. The first subunit VAR2CSA-based vaccines (called PAMVAC and PRIMVAC) failed to induce strain-transcending anti-adhesion antibody in clinical trials. Similarly, VAR2CSA fragments (single or double domains) fail to purify the broadly neutralizing activity of sera from PM-resistant multigravidae. Although VAR2CSA fragments (including constructs similar to PAMVAC vaccine) purified antibodies with CSA-binding inhibitory activity against homologous parasites, broadly neutralizing activity was neither purified nor depleted after passing sera over several VAR2CSA domains and variants. Here, we sequentially purified IgG on five full-length VAR2CSA variants from PM-resistant multigravidae sera and assessed the antigen-specific IgG as well as the flow through IgG for functional activities on several placenta-binding isolates. We show that a single full-length VAR2CSA purifies strain-transcending CSA-binding inhibitory activity. IgG remaining after depletion on all five variants showed significantly reduced binding-inhibition activity compared to initial total IgG. These observations support the hypothesis that functional antibodies to VAR2CSA may target conformational epitopes not displayed by VAR2CSA subunit in comparison to the full-length VAR2CSA exposed to host immune system during natural infection. Our data suggest a broadly effective PM-vaccine may be achieved with a limited number of full-length VAR2CSA variants and provide a basis to design improved PM vaccines.

0657

HOST TARGETED KINASE INHIBITORS AS A DRUG CANDIDATE WITH DUAL ANTI-PARASITIC AND PROTECTIVE BLOOD BRAIN BARRIER ACTIVITY AGAINST CEREBRAL MALARIA

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Cerebral malaria (CM) caused by *Plasmodium falciparum* infection continues to be a major concern worldwide. Brain swelling associated with blood brain barrier (BBB) dysfunction is a main factor underlying CM pathogenesis. While fast-acting artesunate-based combination therapies improve patient survival, emerging parasite drug resistance may compromise this benefit and anti-malarials are not designed to treat inflammatory injury to blood vessels. Recent work suggests that imatinib, an FDA-approved kinase inhibitor, targets asexual blood stage parasite growth and improves parasite clearance rates when used in a triple-combination therapy in uncomplicated malaria cases. Kinase signaling plays a key role in hyper inflammatory pathways that leads to endothelium dysfunction and targeting these kinases may offer new host-targeted therapies for preventing excessive inflammation. To identity new drug compounds with dual activity against parasite growth and host inflammatory pathways, we screened 28 FDA-approved kinase inhibitors targeting various signaling cascades for regulating barrier pathways in primary human brain microvascular endothelial cell (HBMEC) monolayers and in asexual parasite growth assays. Notably, we found two classes of drugs (BCR-ABL and MEK inhibitors) that were dual-acting with both barrier protective against thrombin, the main clotting enzyme elevated in inflammatory conditions and implicated in endothelial dysfunction, and the ability to inhibit intraerythrocytic *P. falciparum* growth. Our work demonstrates a novel dual role of kinase inhibitors in maintaining BBB integrity and targeting malaria parasite development. Thus, kinase inhibitors dual benefit for CM by targeting parasite growth and as an adjuvant novel therapy to restore the BBB after excessive inflammation.

0658

ROSIGLITAZONE ADJUNCTIVE THERAPY FOR CHILDREN WITH SEVERE MALARIA

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Despite the widespread use of effective anti-malarials, the case fatality rate of severe malaria (SM) remains unacceptably high. Adjunctive therapies that target the host response to malaria infection may decrease mortality over that of anti-malarial agents alone. Rosiglitazone, a peroxisome proliferator-activated receptor-gamma (PPARg) agonist, has been shown to act on pathways implicated in the pathogenesis of SM including reducing inflammation and enhancing endothelial stability, as determined by decreased levels of angiopoietin-2, a surrogate maker of malaria severity and mortality. To test the hypothesis that rosiglitazone plus IV artesunate would improve outcome in SM over IV artesunate alone, we conducted a randomized, double-blind placebo-controlled trial in a rural hospital in Manhiça, southern Mozambique. The primary objective was to determine whether supplemental rosiglitazone (0.045mg/kg/dose) twice daily for 4 days, in addition to standard of care anti-malarial treatment (IV artesunate), accelerates the rate of decline in angiopoietin-2 from admission levels in children with severe malaria compared to standard of care plus placebo. We previously determined the safety and tolerability of rosiglitazone in children with uncomplicated malaria before proceeding to examine its efficacy in children with SM. Children with SM were enrolled between March 2016 and December 2019. We screened 203 children for eligibility and 180 children were enrolled: 91 children were assigned to rosiglitazone and 89 to placebo (all received IV artesunate). 85 were females (47.2%) and 95 were males (52.8%). 141 out 180 were younger than 5 years (78.3%) and 39 out of 180 were older than 5 years (21.6%). Secondary objectives included: comparing clinical outcomes between groups, quantifying the changes in biomarkers of disease severity and host response to treatment as well as assessing neurocognitive outcomes. Analysis of primary and secondary objectives is currently underway. We will present the results of this clinical trial.

0659

STRUCTURAL CHARACTERIZATION OF PHOSPHATIDYLSERINE DECARBOXYLASE A PROMISING THERAPEUTIC TARGET OF *PLASMODIUM FALCIPARUM* AND PREDICTION OF ITS POTENTIAL INHIBITORS

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Plasmodium falciparum is a protozoan parasite responsible for the most severe and deadly form of malaria. The resistance of this parasite to

last resort antimalarial drugs has been reported, so there is an urgent need to identify new therapeutic candidates for the development of new drugs. Bioinformatics is the most appropriate approach to predict therapeutic candidates in a reasonable time and at low cost. In this work, we propose *Phosphatidylserine Decarboxylase* (PSD) as a promising new target of *P. falciparum*. It is an enzyme extracted from the TDR Target database which facilitates the identification and prioritization of drugs and drug targets of neglected pathogens according to specific criteria. It is a member of the lyase family, more precisely the carboxy-lyases, which cut carbon-carbon bonds. *Phosphatidylserine decarboxylases* (PSDs) catalyze the decarboxylation of phosphatidylserine to generate phosphatidylethanolamine, a critical step in phospholipid metabolism in prokaryotes and eukaryotes moreover, phospholipid biosynthesis is essential for the development, differentiation and pathogenesis of several eukaryotic pathogens including *P. falciparum*. The model of this protein not previously characterized, structurally opens the way to the design of new potential inhibitors for the development of future antimalarial drugs.The main objective of this work is to build the 3D structure of PSD and to identify new inhibitors of this promising new therapeutic target. The 3D structure of the target protein was predicted using the Alphafold server and the ligands extracted from the zinc DB chemical library. The molecular docking was performed using autodock-vina. At the end of this study, we have identified ten (10) PSD inhibitors that should be studied experimentally to evaluate their antimalarial activities.

0660

APOPTOSIS INDUCING ANTI-MALARIA DRUGS TARGETING PFGARP

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Previously, we discovered that anti-PfGARP kills up to 99% of trophozoite stage parasites in the absence of immune effector molecules or cells-antibody binding alone leads to parasite apoptosis. We reason that PfGARP is a high value druggable target based on: **1)** its surface expression on iRBCs, **2)** the absence of amino acid homology with host proteins, **3)** the absence of significant sequence variation in over 3,000 field isolates sequenced to date, and **4)** the ability of antibody binding to PfGARP to kill essentially all parasites within 12-24 hours. To develop drugs based on PfGARP binding, we screened 6,400 compounds from a small molecule library to identify compounds that inhibit the binding of anti-PfGARP to bead-immobilized rPfGARP protein. We idenitifed a single compound with anti-parasite activity in parasite growth assays. We performed a limited structure-activity relationship campaign of 48 structurally related analogs and identified two compounds with enhanced parasite killing activity with an IC_{50} of 1.8 - 4.8 uM in 3D7 parasites and no activity in PfGARP-KO parasites, indicating specificity for PfGARP. Treatment of *P. falciparum* with either drug results in rapid loss of mitochondrial membrane polarity, caspase-like activation, release of Ca^{++} from the food vacuole and DNA fragmentation- all hallmarks of apoptosis seen in anti-PfGARP treated parasites. Toxicity assessments in human monocytes, lymphocytes and BeWo cells show no loss of viability or proliferative capacity at up to 400 uM- the highest concentration tested. SPR studies demonstrate specific binding of both drugs to PfGARP (K_D = 29.9 and 24.8 nM) and this direct binding was confirmed in 2D-NMR studies. Following toxicology and PK studies in mice, we evaluated one compound in the NSG/*P. falciparum* humanized mouse model. Mice treated with our compound had a rapid and complete clearance of their parasitemia. Evaluation of these two compounds in freshly isolated field parasites is ongoing. These results validate a novel drug target (PfGARP) and screening approach (inhibition of antibody binding), and represent lead compounds for further anti-malarial development.

0661

THE POTENTIAL PUBLIC HEALTH IMPACT OF NOVEL MALARIA MONOCLONAL ANTIBODY INTERVENTIONS

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The first candidate malaria monoclonal antibodies (mAbs) are undergoing clinical trial testing, yet the potential public health impact of these novel prevention tools is not well understood. Modelling can provide quantitative evidence linking mAb intervention characteristics to population-level impact and help identify minimum criteria for candidate selection to accelerate development. We use an individual-based mathematical model of malaria transmission coupled with analytical approaches to explore the multi-dimensional space of mAb characteristics, deployment factors, and population-level outcomes. Modelled mAbs characteristics are informed by pharmacokinetics (PK) and pharmacodynamics (PD) data from the first human mAb candidates CIS43LS and L9LS. We explore drivers of impact by modelling a range of efficacy characteristics, including duration of protection, and deployment strategies, including a range of coverage, in both seasonal and perennial transmission settings. For a single seasonal deployment of an anti-infective mAb co-administered with a blood-stage clearance drug given to children under five years old, we identified protective efficacy decay over time and half-life duration as crucial drivers of impact. Implementation factors such as coverage, access to care, and timing of deployment across transmission settings will greatly impact predicted reductions in clinical infections, severe disease, and mortality. For a single administration with at least 80% coverage among eligible children, mAb interventions that can achieve 80% efficacy against infection and 90-days protection can lead to 50% clinical incidence reduction. Candidates with rapidly decaying protection are likely to achieve less impact and a single deployment in perennial settings may not be sufficient to reduce incidence by 50%. While early mAb candidates have demonstrated safety and protection against infection in early clinical trials, our modelling highlights the need to understand better their PK/PD properties and implementation factors for different use-cases and standard of care comparators to best inform candidate selection.

0662

REDUCING THE RISK OF *PLASMODIUM VIVAX* AFTER *P. FALCIPARUM* INFECTIONS IN CO-ENDEMIC AREAS - A RANDOMIZED CONTROLLED TRIAL

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Plasmodium vivax forms dormant liver stages that can reactivate weeks or months following an acute infection. There is an increased risk of *P.*

vivax parasitaemia following falciparum malaria suggesting radical cure (killing dormant stages) could be beneficial in patients presenting with *P. falciparum* as well as *P. vivax* malaria. We conducted a multicentre, randomized, controlled, open label trial in Bangladesh, Indonesia and Ethiopia. Patients with uncomplicated falciparum malaria, ≥70% G6PD activity and hemoglobin levels ≥8g/dl were enrolled and randomized in a 1:1 ratio to either receive standard blood schizonticidal treatment plus 7-day high dose primaquine (total dose 7mg/kg) or standard blood schizonticidal treatment alone. Patients were followed up weekly until day 63. The primary endpoint is the incidence risk of any *P. vivax* parasitemia at day 63. Secondary outcomes include the proportion of adverse events and serious adverse events, the incidence risk of severe and very severe anaemia (Hb<5g/dl and <7g/dl) and/or the risk for blood transfusion and the incidence risk of a ≥ 25% fall in haemoglobin with and without hemoglobinuria. The trial is registered at clinicaltrials.gov (NCT 03916003). Between 18th August 2019 and 14th March 2022 a total of 500 patients were enrolled and followed for up to 63 days. The study has generated important data with policy and practice implications for countries co-endemic for both *P. falciparum* and *P. vivax*. The full results of the trial will be presented including a discussion on the need to expand the indications for radical cure of hypnozoite stages to facilitate *P. vivax* elimination.

0663

MECHANISTIC MODELLING OF PRIMAQUINE PHARMACOKINETICS, GAMETOCYTOCIDAL ACTIVITY, AND MOSQUITO INFECTIVITY

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Numerous clinical studies have shown that adding a single dose of 0.25 mg/kg of primaquine to standard antimalarial regimens rapidly sterilizes *Plasmodium falciparum* gametocytes. However, the mechanism of action and overall impact on malaria transmission is still unknown. Using data from 81 adult Malians with *P. falciparum* gametocytemia who received the standard dihydroartemisinin-piperaquine treatment course and were randomized to receive either a single dose of primaquine between 0.0625 and 0.5 mg/kg or placebo. Nonlinear mixed-effects modeling and simulation were used to characterize the pharmacokinetic-pharmacodynamic relationships for transmission blocking activity. Both gametocyte clearance and mosquito infectivity were assessed. A mechanistically-linked pharmacokinetic-pharmacodynamic model adequately described primaquine and carboxy-primaquine pharmacokinetics, gametocyte dynamics, and mosquito infectivity at different clinical doses of primaquine. Primaquine showed a dose-dependent gametocytocidal effect that preceded clearance. *In silico* simulations, based on data from these presumably chronically gametocytemic adults, suggested that approximately 70% of patients were predicted to be non-infectious within one day of administering a single primaquine dose of 0.25 mg/kg. These observations provide strong support for the current low dose recommendation. Adding a single dose of 0.25 mg/kg of primaquine to the standard ACT treatment for *P. falciparum* infection reduces transmissibility substantially, and should be recommended to accelerate malaria elimination.

0664

*WOLBACHIA W*ALBB INHIBIT DENGUE AND ZIKA INFECTION IN AUSTRALIAN *AEDES AEGYPTI* MOSQUITOES

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Biological control of mosquito-borne arboviruses using insect-specific *Wolbachia* bacteria is an emerging strategy for the management of human arboviral diseases. We recently described the development of a new strain of *Aedes aegypti* mosquitoes (referred to as *w*AlbB2-F4 strain) infected with the *w*AlbB strain of *Wolbachia* using simple backcross mating of a *w*AlbB infected *Ae. aegypti* from the USA with wild type mosquitoes from Australia. Mass releases of male *w*AlbB2-F4 mosquitoes at trial sites resulted in substantial suppression of wild populations of mosquitoes through the strain's *Wolbachia*-induced cytoplasmic incompatibility. Here we show that the strain is resistant to infection with dengue and Zika viruses and is highly genetically similar to the Australian wild type strain. There was a highly significant reduction in the percentage of *w*AlbB2-F4 mosquitoes that become infected after feeding on a blood meal containing dengue 2 virus (16.7%) compared the wild type mosquitoes (69.2%). After feeding on an epidemic strain of Zika virus, there was a 6.7 fold reduction in the percentage of mosquitoes with virus in saliva. Further, there was a reduction in the intensity of dengue and Zika virus infection in *w*AlbB2-F4 mosquitoes, demonstrated by molecular detection and by immunofluorescence analysis of *Wolbachia* and the arboviruses in mosquito histological sections. We also showed that *w*AlbB2-F4 mosquitoes have 98% Australian ancestry though Restriction-site Associated DNA (RAD) sequencing and that the strain has equivalent insecticide resistance genotype and phenotype, critical attributes for successful strain establishment for biological control. The ease of which *Wolbachia w*AlbB can be transferred to a target mosquito population, installing virus inhibition and maintaining the target mosquito genetic background, demonstrates the great potential of this strain for biological control of mosquitoes and the pathogens they transmit.

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TARGETING MOSQUITO HYDROXYPHENYLPYRUVATE DIOXYGENASE (HPPD) AS A NOVEL STRATEGY FOR PREVENTING MALARIA TRANSMISSION

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Progress in reaching the global malaria elimination targets requires investment in strategies to reduce disease transmission. One approach to blocking insect-borne disease transmission that is successfully employed in veterinary medicine, is the use of endectocides that render vertebrate blood toxic to blood-feeding insects. Recent studies have identified that an enzyme involved in the tyrosine detoxification pathway, 4-hydroxyphenylpyruvate dioxygenase (HPPD), is essential for blood-feeding arthropod survival. Using an FDA-approved HPPD inhibitor called nitisinone, we demonstrate that the malaria-transmitting mosquito, *Anopheles gambiae,* is rapidly killed upon ingesting nitisinone-containing bloodmeals. Furthermore, both insecticide-susceptible and insecticide-resistant mosquito strains likewise perish in a dose dependent manner. Proof-of-concept pharmacokinetic-pharmacodynamic (PK/PD) modelling of the dose-exposure-response relationship of nitisinone, administered at recommended doses for adults and children (3 x 1 mg/kg), shows improved efficacy against young, adult and insecticide-resistant mosquitoes compared to the current gold-standard ectoparasitic drug,

ivermectin. These data demonstrate that targeting *Anopheles* HPPD is a viable strategy for the development of new malaria transmission-blocking interventions.

0666

THE ROLE OF NOVEL IMMUNE MODULATORS AND ANTI-CTL4 NANOBODIES IN *ANOPHELES GAMBIAE* ANTI-*PLASMODIUM* IMMUNITY

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Anopheles gambiae is considered the main vector of the malaria parasite *Plasmodium falciparum*. However, the transmission of this parasite through the mosquitoes does not go unnoticed. On the contrary, *Anopheles gambiae* mosquitoes mount a potent immune response against the parasite. This immunity is characterized by a complex interaction between agonistic and antagonistic immune effector mechanisms and factors. Among these mechanisms is melanization that was recently shown to be an important immune effector mechanism against *P. falciparum* infections. Additionally, the C-type lectin 4 (CTL4) was shown to be an important factor that is recruited by *P. falciparum* to evade malanization. To gain insight on CTL4 function in mosquito immune responses, we have utilized a combination of *Plasmodium* ookinete interactome screening, genome editing and transient gene-silencing to identify factors that modulate CTL4-mediated protection of the malaria parasite. We have identified novel candidates belonging to the serine protease and thioester containing protein families in addition to other previously unknown factors as potential modulators of anti-*P. falciparum* immunity. Moreover, since CTL4 is considered a major transmission blocking target for malaria control, we have identified several anti-CTL4 nanobodies that that are explored for their *P. falciparum* transmission blocking activity.

0667

LIFE HISTORY AND INFECTION CHARACTERISTICS OF *ANOPHELES STEPHENSI* MOSQUITOES FOLLOWING CRYOPRESERVATION

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Sanaria has developed a unique method for the cryopreservation of *Anopheles* eggs, allowing the long- term, stable storage of anopheline mosquitoes at minimal cost and effort. We have successfully and repeatedly cryopreserved many batches of *An. stephensi* eggs and successfully revived them from storage in Liquid Nitrogen Vapor Phase after periods of at least 5 years. Here we examine the life history characteristics of *A. stephensi* following thawing. We optimized conditions for small scale rearing of mosquitoes that matched life history traits - larval growth, pupation, eclosion, wing length, mating success, blood feeding success and fecundity - of *A. stephensi* reared in Sanaria's main insectary. Different batches of cryopreserved eggs were thawed, the hatch rates determined and L1 larvae transferred to the optimized rearing conditions side-by-side with L1 mosquitoes from the insectary. Cryopreserved eggs hatched over a longer period compared to insectary derived eggs, and this was reflected in a similar spread timeline at pupation. However, the adult mosquitoes resulting from cryopreserved eggs were able to mate, feed on blood and produce fecund eggs at rates similar to insectary-derived mosquitoes. We will present a detailed comparison of these life history traits and the capacity for offspring of cryopreserved mosquitoes to be infected with *Plasmodium falciparum*. Our data demonstrate clearly that cryopreservation of *A. stephensi* is sufficiently robust to enable generation of a new colony when needed, and adds an important element of security to Sanaria's vaccine manufacturing process.

0668

PATTERNS THAT DRIVE MOSQUITO-FUNGUS ASSEMBLIES ARE MAINTAINED ACROSS MOSQUITO SPECIES

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Microbial interactions in the larval environment provide nutritional value and cues that are critical for mosquito development to adulthood, and thus contribute to vector fitness. While the bacterial community assembly has been elucidated in several mosquito species, little is known about the interactions between fungal communities and mosquito larvae in their aquatic habitat. In this study, we used metabarcode sequencing of the fungal Internal transcribed spacer 2 (ITS2) marker to characterize the fungal communities associated with field-collected *Aedes albopictus*, *Culex pipiens*, and *Culex restuans* larvae and their breeding water. Reads were assigned to operational taxonomic units (OTUs) and amplicon sequence variants (ASVs) using the mothur (v.1.44.3) bioinformatics pipeline. Alpha diversity analyses of the water samples revealed diverse fungal communities in the aquatic habitats on a fine geographic scale. Comparisons of the Bray-Curtis dissimilarity matrices between the breeding water and larval tissues revealed that the gut-associated fungal communities were most similar to the aquatic environment and highly enriched in plant-associated fungi. In contrast, mosquito carcasses harbored fungal communities enriched in animal pathogens, revealing that in addition to mosquito feeding behavior, fungal substrate use is an additional driver of fungal community assembly in mosquito larvae. The observed differences between gut- and carcass-associated fungal communities were more evident in *Ae. albopictus* and *Cx. pipiens* than in *Cx. restuans* larvae. Taken together, our results show for the first time that the larval breeding water is the key determinant of fungal community assembly across taxonomically distant mosquito species, with little evidence for environmental filtering by the larval guts. The assembly of fungal communities in mosquito larvae is further influenced by fungal life history, and potential species-specific variations among mosquito species may be best explained by differences in larval feeding behaviors.

0669

THE EFFECT OF SUBLETHAL DOSES OF IVERMECTIN ON *ANOPHELES GAMBIAE* MIDGUT MICROBIOTA

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Ivermectin (IVM) is a safe endectocide commonly used in mass drug administrations for controlling neglected parasitic diseases. The drug also exhibits mosquitocidal efficacy, particularly against anopheline mosquitoes when they bite people given standard doses, and so it is now being assessed in clinical trials with the objective of reducing malaria transmission and clinical episodes in treated communities. It is well known that IVM affects mosquito physiology in different ways depending on the concentration ingested in the bloodmeal, but the effects of sublethal doses of IVM are not well understood. This study aimed at determining the effects of two sublethal IVM concentrations on the midgut microbiota of laboratory-reared *Anopheles gambiae*. *Anopheles gambiae* female mosquitoes were fed with a control bloodmeal (containing the vehicle dimethyl sulfoxide alone) or a bloodmeal spiked with IVM (5ng/ml or 15 ng/ml), and the microbiota analyzed at different timepoints post bloodmeal. The bacteria load was quantified by qPCR and also analyzed through NGS amplicon sequencing of the V4 region of 16S rDNA. Results from both approaches were consistent: the midgut microbiota is altered after a bloodmeal, but there is only a limited effect of sublethal concentrations of IVM on the overall composition of the midgut microbial community. The bacterial communities in IVM-treated

and control mosquitoes were dominated by three families; Weeksellaceae, Enterobacteriaceae, and Pseudomonadaceae, but alpha and beta diversity analysis showed that the midgut microbiota of treated mosquitoes was not significantly different from controls at most time points. However, a few bacteria genera were found to be present only in IVM-treated mosquitoes or only in controls. In the field, these modest changes due to IVM exposure may be amplified in certain mosquito populations which could impact their fitness, survival, or *Plasmodium* infection status.

0670

ZOOPROPHYLAXIS-AIDED IVERMECTIN-BASED VECTOR ELIMINATION (ZAIVE), A RANDOMIZED VILLAGE-BASED ENTOMOLOGICAL TRIAL, CENTRAL VIETNAM

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Treating cattle with ivermectin (IVM) has been proposed as an important contribution to malaria vector management, yet the impacts of IVM are untested in field trials. Through a randomized village-based trial, this study aimed to quantify the effect of IVM-treated cattle on the anopheline populations in treated vs. untreated villages in central Vietnam. Local cattle in three rural villages were treated with IVM and the cattle in three other rural villages were included as controls. The mosquito populations in all villages were quantified using cattle-baited traps for ten-days before and after the 2-day treatment administration period. The impact of the intervention was analyzed using a difference-in-differences (DID) approach with generalized estimating equations (negative binomial and robust sandwich errors). Secondary analyses assessing the impact of the dose/density of treated cattle were also examined. Across the intervention villages, 1112 of 1527 censused cows (73% overall; range 67% and 83%) were treated with IVM. In both control and intervention villages, there was a marked decrease in total anophelines captured in the pre- vs. post-treatment period of 30-40% during the study. In the control villages, 1873 vectors were captured pre- and 1079 were captured post-treatment. Corresponding numbers for intervention villages were 1594 and 1101 respectively. In preliminary model results for the primary DID analysis there is no evidence for a difference in the change in trapping between intervention and control villages (IRR = 1.2; 95% CI; 0.60-2.4; $p = 0.61$). In preliminary secondary analysis including total doses administered and treated animal density as covariates we found evidence for a significant decrease in trapped anopheline density in intervention villages relative to control villages (IRR = 0.34; 95% CI: 0.18 - 0.65; $p < 0.001$) in DID analysis. In order to more fully assess whether zooprophylaxis-aided ivermectin-based vector elimination (ZAIVE) may serve as a vital tool in village-level elimination initiatives, additional studies less impacted by temporal trends should be implemented.

0671

POPULATION ANALYSIS OF EASTERN EQUINE ENCEPHALITIS VIRUS DERIVED FROM INFECTED HUMAN BRAIN TISSUE: WITHIN- AND BETWEEN-HOST VARIATION

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Eastern equine encephalitis virus (EEEV) is a mosquito-borne, neuroinvasive alphavirus in the family Togaviridae. Although reported human cases have remained low since it was first formally described in the 1930s, Eastern equine encephalomyelitis represents one of the most severe viral encephalitides in the Western hemisphere. Thus, it is critically important to understand EEEV evolution, particularly as it pertains to emergence and neuroinvasion. To this end, we sequenced EEEV RNA obtained from formalin-fixed, paraffin-embedded brain samples from discrete brain regions of three human patients that had succumbed to infection. We constructed consensus sequences for all patients, as well as from discrete brain regions (including the frontal lobe, thalamus, and midbrain) for one patient, which were used for phylogenetic analyses; interestingly, some consensus-level changes were noted between different brain regions for one patient. Further, for this same patient, intrahost single nucleotide variant (iSNV) analyses revealed differential minority variant populations and diversity between discrete brain regions, suggesting the potential for intrahost evolution of EEEV as it traverses different brain regions. Together, these data provide novel and important insights into both inter- and intrahost evolutionary dynamics of EEEV.

0672

A RETROSPECTIVE GENOMIC SURVEILLANCE OF CHIKUNGUNYA TRANSMISSION IN MINAS GERAIS STATE, SOUTHEAST BRAZIL

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Brazil accounted for a total number of 1,276,194 notified cases of Chikungunya fever between 2014 and in 2022. Additionally, since 2015 the country is also showing an increasing death toll in which the northeast and southeast regions appear to report the worst scenario. Although the CHIKV transmission dynamics have been studied in many parts of the country after its introduction in 2014, little is still known about the CHIKV transmission and genetic diversity in the state of Minas Gerais, located in southeast Brazil. Moreover, no studies have been published characterizing CHIKV genomic surveillance in this state. Thus, to retrospectively explore the CHIKV epidemic in Minas Gerais we generated 40 genomes by nanopore sequencing from clinical samples. Phylogenetic analysis indicated multiple introductions of CHIKV occurred likely from northeastern Brazilian states, with the most recent common ancestral dated to early March 2016, which is in agreement with local epidemiological reports. Additionally, epidemiological data revealed a decline in the number of reported cases over 2017-2021 indicating that population immunity to CHIKV decreases waves of infections. Together, our results shed a light on the dispersion dynamics of CHIKV and showed that infections decreased from March 2017 to January 2021 despite of multiple introductions in Minas Gerais state. In conclusion, our study highlights the importance of combining genomic and epidemiological data in order to assist public health laboratories in monitoring and understanding the patterns and diversity of mosquito-borne viral epidemics.

0673

CHIKUNGUNYA: PHASE 3 CLINICAL DEVELOPMENT OF A SINGLE-SHOT LIVE-ATTENUATED VACCINE

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VLA1553 is a live-attenuated chikungunya virus (CHIKV) vaccine candidate designed for active immunization as a prophylactic measure. Due to the sporadic epidemic occurrence of chikungunya, an immunological surrogate to assess clinical efficacy was accepted by regulators. A double-blinded, multicenter randomized, pivotal phase 3 study enrolling 4115 healthy adult volunteers, aged 18 years and above, randomized in a 3:1 ratio to receive VLA1553 or placebo was performed across 43 study sites in the United States (US) (NCT04546724). The primary objective of the study was to evaluate the immunogenicity and safety of VLA1553 28 days after immunization and as secondary objective participants were followed up to 180 days. Immunogenicity evaluations were analyzed in a pre-selected subset of 501 participants at 13 study sites across the US. The pivotal trial met its primary endpoint with 98.9% of subjects achieving seroprotection (263 of 266 participants in the per-protocol immunogenicity subgroup). The immunogenicity profile was maintained over time. Geometric mean titers peaked at day 29, then decreased subsequently, however stayed well above the seroprotective level of antibodies in 96.3% of participants until day 180 (233 of 242 participants in the per-protocol subset tested for immunogenicity). The vaccine was also confirmed to be highly immunogenic in older adults (≥ 65 years), who achieved equally high seroprotection rates and neutralizing antibody titers as younger adults (< 65 years). VLA1553 was also well tolerated with a favourable safety profile. The generation of protective titers in nearly 100% of vaccinated participants analyzed indicates VLA1553 is an effective candidate for the prevention of disease caused by the CHIKV.

0674

A PHASE 2 OPEN-LABEL STUDY TO ASSESS THE SAFETY AND IMMUNOGENICITY OF AN ALUM-ADJUVANTED CHIKUNGUNYA VIRUS-LIKE PARTICLE (VLP) VACCINE IN PRIOR RECIPIENTS OF OTHER ALPHAVIRUS VACCINES VERSUS ALPHAVIRUS NAÏVE CONTROLS

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Immune responses to alphavirus vaccines may be impaired when heterologous alphavirus vaccines are administered sequentially. The purpose of this Phase 2 open-label study was to evaluate the safety and immunogenicity of CHIKV VLP vaccine in prior recipients of heterologous alphavirus vaccines. Adults 18-65 years with prior receipt of an investigational alphavirus vaccine (N=30) and gender/age matched alphavirus vaccine-naïve controls (N=30) were administered 1 dose of 40 µg alum-adjuvanted CHIKV VLP vaccine. The primary immunogenicity endpoint was the CHIKV SNA seroconversion rate (defined as 4-fold rise over baseline) at Day 22. Immunogenicity was assessed by luciferase-based serum neutralizing antibodies (SNA) and safety was assessed by solicited/unsolicited adverse events (AE) and serious adverse events (SAE). The majority of solicited AEs were of mild/moderate severity, with two grade 3 solicited events, both in alphavirus vaccine-naïve subjects (2/30). The most common systemic solicited AEs were headache, occurring in 7/30 and 4/30 subjects, and myalgia occurring in 4/30 and 7/30 subjects in the prior alphavirus vaccine and alphavirus vaccine-naïve groups, respectively. Injection site pain was reported by 13/30 prior alphavirus vaccine recipients and by 9/30 subjects in the alphavirus vaccine-naïve group. There were no vaccine-related SAEs. The anti-CHIKV SNA seroconversion rate at Day 22 was 100% in both groups. A higher percentage of prior alphavirus vaccine recipients (93.3%) had a 4-fold SNA rise at Day 8 than alphavirus vaccine-naïve controls (66.7%, p=0.021). The GMTs peaked in both groups at Day 22 and were similar between the groups on Day 22 and all subsequent visits. Prior alphavirus vaccine recipients also exhibited a significantly stronger and more rapid anti-CHIKV total IgG antibody response by ELISA as compared to the alphavirus vaccine-naïve controls. This alum-adjuvanted CHIKV VLP vaccine was well tolerated and immunogenic in both alphavirus vaccine-naïve and prior recipients of a heterologous alphavirus vaccine; there was no significant difference in the incidence of AEs between the groups.

0675

IMMUNOLOGICAL INSIGHTS BASED ON ANTIBODY BINDING EPITOPES ON THE CHIKUNGUNYA VIRUS ENVELOPE

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To identify Chikungunya virus (CHIKV) structures that elicit a protective immune response, we have epitope mapped over 70 monoclonal antibodies (MAbs) against the CHIKV envelope glycoprotein E2/E1, using a comprehensive shotgun mutagenesis library of 910 E2/E1 alanine-scan mutants. Published studies used epitope maps to characterize broadly cross-reactive and ultrapotent neutralizing MAbs that blocked post-attachment steps, and that bound to functionally-important E2 domains A or B, suggesting that MAbs inhibit virus-host membrane fusion by preventing exposure of the E1 fusion loop. Additional studies characterized MAbs that induce structural changes on E2 A and B. Other mapped MAbs included human E1-specific MAbs cross-reactive across alphaviruses, isolated from survivors of equine encephalitis virus infection. MAb binding and epitope mapping identified differences in E1 reactivity based on exposure of epitope on E1 through pH-dependent mechanisms or presentation on the cell surface prior to virus egress. We also used CHIKV E2/E1 mutants to map the binding site on E2 A and B domains of cell adhesion molecule Mxra8, identified as enhancing attachment and internalization into cells of CHIKV and other alphaviruses, by infectivity screens of cells targeted by CRISPR/Cas9 gene knockouts. We also isolated human MAbs against CHIKV E2/E1. Our most potent MAb, IM-CKV063, was highly neutralizing (50% inhibitory concentration, 7.4 ng/ml), showed high-affinity binding (320 pM), and gave therapeutic and prophylactic protection in animal models up to 24 h post-exposure. Epitope mapping identified an inter-subunit conformational epitope on E2 domain A. Subsequent studies demonstrated that IM-CKV063 blocks both virus entry and virus release. To provide critical reagents for analyses of MAb or serum immune responses to CHIKV infection, we developed a pseudotyped lentiviral reporter virus system for CHIKV, using reporter virus particles (RVPs) displaying E2/E1. The replication-incompetent RVPs perform one round of infectivity and enable safe (BSL-2), reproducible virus neutralization assays with luminescent or fluorescent readout.

0676

IL2/ANTI-IL2 COMPLEX FOR THE TREATMENT OF CHRONIC CHIKUNGUNYA VIRUS ARTHRITIS IN A MOUSE MODEL

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Chikungunya virus (CHIKV) is an alphavirus characterized by disabling joint pain that causes persistent arthritis in one-fourth of patients. Foot pad CHIKV inoculation in a mouse model causes localized swelling and systemic infection, with histologic evidence of arthritis, synovitis, periostitis and myositis. Preliminary data suggest that altered regulatory T cell (Treg) function may play a role in CHIKV arthritis. Interleukin-2 (IL2) therapies for autoimmune disease have been shown to up-regulate Tregs. We hypothesized that chronic CHIKV arthritis is associated with deficient Treg levels; thus, we tested the therapeutic effects of IL2, an anti-IL2 monoclonal antibody (mAb), and an IL2/anti-IL2 mAb complex in a mouse model. Our aims were to 1) describe the role of IL2 in Treg expansion and CHIKV arthritis severity, and 2) determine the role of IL2 in the treatment of CHIKV arthritis. In our study, mice inoculated via foot pad injection were confirmed CHIKV-positive by qRT-PCR at 2 days post infection (dpi) and CHIKV-negative by 16 dpi. Mice were then treated for 3 days with placebo, IL2, anti-IL2 mAb, or complex. Tarsal joint measurements showed an increase in swelling of infected tarsal joints that peaked at 6 dpi and returned to baseline by the end of the study, with the complex treated group showing the steepest drop in swelling at 17 dpi. IL2 levels increased significantly at 19 dpi compared to 2 dpi, with a 349% increase in IL2 mice, 821% in anti-IL2 mAb mice, and 3990% in complex mice. Flow cytometry determined a large increase in Treg numbers and activity in complex-treated mice, but a decrease in IL2-treated mAb mice and no significant change in IL2-treated mice. Tarsal joint histology showed more mice with severe arthritis in the PBS and IL2 groups compared to the anti-IL2 mAb and complex groups. The data suggest that complexing IL2 with the anti-IL2 mAb makes it more biologically available, resulting in a greater impact on Tregs, and decreasing overall inflammation and joint degradation. These findings indicate the need for clinical studies using an IL2/anti-IL2 complex to treat chronic CHIKV arthritis.

0677

PATHOGENESIS OF CHIKUNGUNYA VIRUS ASSOCIATED WITH FATAL OUTCOMES

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Chikungunya virus (CHIKV) is a mosquito-borne virus that can cause acute, subacute, or chronic human diseases. Recently, CHIKV has caused over 10 million reported cases in more than 125 countries. Since 2004, CHIKV has been associated with increased deaths in Asia and America. However, the host response mechanisms associated with these fatal outcomes remain poorly understood. Here, we combined molecular, genomic, and metabolomic approaches to investigate potential mechanisms that could contribute to fatal CHIKV outcomes. Our data show that CHIKV-fatal cases are characterized by multiple infected organs and a median viremia ~13-fold higher than that measured in CHIKV-survivors. CHIKV-fatal patients exhibited significantly elevated serum levels of pro-inflammatory cytokines compared to CHIKV-survivors, such as IL-6, MCP1, IFN-α, and TNF-α. Notably, serum and CSF levels of IFN-λ3(IL-28b) were higher in CHIKV-fatal than those detected in CHIKV-survivors. Phylogenetic analysis confirmed that patients with both outcomes were infected by the East/Central/South African genotype. A high proportion of CHIKV-fatal cases sequenced were infected with a CHIKV variant carrying one amino acid change at residue 243 in the E2 protein (E2-R243H). This single mutation increases the surface area and interaction of the CHIKV trimeric E1/E2 spike heterodimer with the MXRA8 receptor, and also stabilizes the spike. Metabolomic analysis revealed that metabolite signatures following CHIKV infection overlap with those of hemodynamic shock, implying that reductions of vasopressin (essential for cardiovascular homeostasis), chondrosine (critical for connective tissue and extracellular matrix), and isoxanthopterin (indicative of oxidative stress) could explain hallmarks of fatal CHIKV infection. Collectively, our data suggest that the CHIKV-fatal outcomes result from multi-systemic infection altering endothelial cell integrity, hemodynamic shock, and inflammation resulting in multiple failure organs, leading to death. Overall, this study reveals insights into CHIKV pathogenesis and suggests potential biomarkers for CHIKV outcomes.

0678

PROVINCIAL UNDER-FIVE MORTALITY AND KEY CHILD HEALTH POLICY INDICATORS IN THE CONTEXT OF PROTRACTED CONFLICT: SECONDARY ANALYSIS OF HOUSEHOLD AND FACILITY DATA IN THE DEMOCRATIC REPUBLIC OF CONGO

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Considerable provincial variation in under-five mortality has been observed in the Democratic Republic of Congo, but the relationship with conflict is unclear. We compared provincial coverage of key child health policy indicators, and explored their association with under-five mortality rates and conflict. We performed secondary analysis of the: 2017-18 Service and Provision Assessment; 2018 Multiple Indicator Cluster Survey; and Uppsala Conflict Data Program Georeferenced Event Dataset. Indicators, taken from three global action plans, were generated at the provincial level and collapsed into combined mean scores for: newborn health, pneumonia, diarrhoea, malaria, and safe environment. Negative binomial regression compared scores with provincial mortality rate. Binary logistic regression at the individual level compared indicators (outcome) with living in a conflict affected province (exposure), defined as >25 battle related deaths/year. All coverage scores demonstrated substantial provincial variation: newborn health: 20—61%, pneumonia: 30—86%, diarrhoea: 25—63%, malaria: 22—53%, safe environment: 4—53%. Diarrhoea score demonstrated the strongest association with mortality (coeff: - 0.026; 95% CI: -0.045, -0.007). Conflict-provinces both had the highest and lowest mortality rates and indicator coverages. Children in conflict-provinces had higher odds of being covered by 13 out of 23 indicators, compared to non-conflict provinces (1/23). Conflict alone is a poor predictor for child health. It is important to ensure that children in non-conflict provinces do not get neglected whilst addressing the needs of the most vulnerable in conflict settings. Prevent, protect, and treat strategies for diarrhoeal disease could help improve equity in child survival.

0679

THE IMPACT OF FAMILY PLANNING UTILIZATION AMONG ADOLESCENTS GIRLS ON MATERNAL AND CHILD HEALTH OUTCOMES

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Adolescent pregnancy and motherhood are associated with an increased risk of numerous poor maternal and child health outcomes. The majority of adolescent births are within the context of girl child marriage (before age 18). The health-seeking behaviors of adolescent girls and young women are different from the behaviors of women in older age groups. Exploring the compounding effect of pre-pregnancy and postpartum contraceptive use, as a proxy for accessing health services, on improving maternal and child survival rates can help optimize the timing and location of maternal, newborn, and child health (MNCH) interventions that incorporate family planning. We use Demographic and Health Surveys (DHS) data in Sub-Saharan Africa (SSA) and South Asia to examine the spatiotemporal heterogeneities in girl child marriage and childbearing patterns as well as adolescent girls and adolescent mothers health-seeking behaviors. Our analysis shows that the risk of mortality among children born to adolescent mothers who had a history of using any type of contraceptive method before was lower, and overall, a risk gradient by maternal age appeared in different regions even after adjusting for the health-seeking variables. Using family planning services could represent a proxy for accessing health services overall. Interventions focused on expanding contraceptive access and use could help women to increase choice and spacing in their fertility decisions.

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BRINGING TOGETHER CIVIL SOCIETY AND ACADEMIA IN RESPONSE TO COVID-19 VACCINE INEQUITY: EARLY LESSONS FROM THE VACCINE ADVOCACY ACCELERATOR — UGANDA PROJECT

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Inequitable global access to COVID-19 vaccines remains a public health and moral crisis. Our objective was to join local activists affected by COVID-19 vaccine shortages (who best understand community needs and perspectives) and academic institutions (which offer scientific authority and other assets) for evidence-based advocacy demanding COVID-19 vaccines for lower-income countries. Together, the Global Health Collaborative at Mbarara University of Science and Technology (an academic partnership in Uganda supported by Massachusetts General Hospital) and the Coalition for Health Promotion and Social Development (a health advocacy organization in Uganda) formed the Vaccine Advocacy Accelerator — Uganda (VAX-Uganda) project, spotlighting vaccine shortages and delivery challenges in Ugandan communities via activities in Uganda and the US. Using academia's grant-writing experience, we applied for and received donor funding for 12-months of advocacy. From activist connections, we recruited 29 Ugandan organizations to form a coalition focused on COVID-19 vaccine access. Other partnership accomplishments include: an investigative report aired on Ugandan national news calling for transparency in government funding for COVID-19 vaccination; pieces in The New York Times and STAT News countering claims of widespread "vaccine hesitancy" in African countries; and a letter sent by 32 Ugandan organizations to the US Agency for International Development in response to misleading COVID-19 vaccination claims, leading to regular accountability meetings between US agencies and Ugandan civil society. Activities will continue through 2022, including an inter-ministerial meeting in Uganda to accelerate COVID-19 vaccination for children and a study of COVID-19 vaccine supply at four Ugandan vaccination sites. While the ultimate impact of VAX-Uganda on COVID-19 is to be determined, the project has created new platforms for Ugandan voices to reach key decision-makers, grounds US academic science and advocacy on global vaccine equity in authentic partnership, and provides one model for partnership between activists and academia.

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INNOVATION AND JUDICIALIZATION OF HEALTHCARE: USING DESIGN-THINKING TO SECURE THE RIGHT TO HEALTH IN COLOMBIA

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From 2018-2021, Colombians filed 954 554 tutelas (judicial actions which enable citizens to seek protection of their rights) with roughly 30% of them health-related. Rights-based litigation can result in plaintiffs receiving medical needs or structural remedies redistributing health resources. In countries where judicialization of healthcare is a means of health systems reform, judges are integral to the health system. Ensuring that judges can make equitable decisions in dynamic environments, such as pandemics, can present a complex challenge. Design thinking, increasingly used in healthcare, offers solutions that respond to people's needs through empathy, intuition, creativity, and the generation of innovative ideas. We sought to use design methodology to innovate how Colombian judges access information on science, health equity, and legal precedent to make decisions on the right to health. In 2020, we conducted a two-semester design-challenge at the Universidad de los Andes on health-tutelas. Forming interdisciplinary teams, design, engineering, and law students used design thinking for their projects. Core design thinking principles such as contextualization of the problem, information analysis and counter-proposal, ideation and prototyping, and definition and specification were introduced. Students were able to contextualize the problem and identify practices around tutela decision-making. They determined that judges rely on the claimant's proof and lacked time to extensively research medical conditions or existing resource constraints. Using this information, students developed a prototype that was tested with justices. From this prototype, a minimal viable product is being developed and will be tested in the Colombian judicial system. To our knowledge, this is the first course to approach the burden of health tutelas through design thinking and demonstrates the feasibility of using this methodology to tackle problems at the interface of law and medicine. Further research is needed to determine the optimal means of introducing design methodology into legal and medical workplaces outside of the academic setting.

0682

ENGAGING NATIONAL STAKEHOLDERS IN THE CO-DESIGN OF A NOVEL CHEMOPREVENTION MALARIA INTERVENTION: THE EXPERIENCE OF THE IPTI+ PROJECT IN BENIN, CAMEROON, COTE D'IVOIRE, AND MOZAMBIQUE

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Since 2010, WHO has recommended the delivery of SP to infants through routine EPI services at 10 weeks, 14 weeks, and 9 months in areas of moderate-to-high transmission. Intermittent Preventive Treatment in infants (IPTi) reduces clinical malaria by 30% and anemia by 21%, but prior to 2022 only Sierra Leone had implemented IPTi at scale. Updated WHO chemoprevention guidance in 2022 will move away from prescriptive limits on number of doses, geographies, age ranges and drug types. Anticipating this change, the IPTi+ Project is supporting countries to adapt and expand IPTi coverage by increasing the age range, delivery channels and number of doses, building on a country's existing systems. In late-2021 we conducted 4-day intervention co-design workshops in Benin, Cameroon, and Cote d'Ivoire (with Mozambique scheduled for May 2022) with stakeholders from malaria and immunization programs, the MOH HMIS team, maternal, child health and community programs, WHO, CSOs, health workers from a range of channels and other stakeholders. Project staff prepared a master agenda, presentations, and facilitation guide, which were adapted to each country context during a two-day pre-meeting with country teams and malaria program representatives. Workshop facilitation used adult learning techniques and small group work to develop country-designed and owned expanded IPTi models. Project staff played a facilitation role only and final decision-making was through consensus by country participants. Agreed models were responsive to existing country plans and dialogues for chemoprevention. Benin and Cameroon adopted an eight-dose model reaching children up to two years, leveraging vaccination and Vit A contacts. Cote d'Ivoire selected a five-dose model building on EPI and Vit A contacts though 18-months of age. CHWs played an important role in all designs: supporting sensitization and community mobilization in all countries and SP delivery in Cameroon. Building on the relationships and trust engendered through the co-design workshops, the project is now collaborating with MOHs to execute their IPTi+ models through pilot implementation.

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HIV CARE, PREVENTION, AND SEXUAL AND REPRODUCTIVE RIGHTS OF MIGRANT FEMALE SEXUAL WORKERS FROM VENEZUELA LIVING IN THE DOMINICAN REPUBLIC

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This study aims to identify the elements of vulnerability of Venezuelan female sex workers (FSW) and the existing obstacles in their search for sexual and reproductive health care in Santo Domingo and Puerto Plata. A mixed-methods study design was employed consisting of four focus group discussions with 2-7 participants per group. A cross-sectional quantitative survey was administered to a small sample (n=40) of Venezuelan female sex workers. Focus group discussions were analyzed using thematic content analysis to identify key themes related to the study objectives. Quantitative data were analyzed using univariate frequency and descriptive analysis. Key themes that emerged from the focus group discussions included legal status and its implication on access to health services and formal employment, mental well-being and quality of life in the DR, navigating sex work, perceptions of sex work, sexual and reproductive health knowledge, and limited social support. Results from the quantitative analysis indicated that the majority of participants struggled with depression (79%), loneliness and isolation (75%), and difficulty sleeping (88%). Participants reported an average of 10 sexual partners in the past 30 days, 55% engaged in sexual practices while under the influence of alcohol, and only 39% had used a condom when performing vaginal, anal or oral sex in the past 30 days. Seventy-nine percent had taken HIV-test in the past 6 months and 74% knew where to seek HIV services. Most participants sought care from the public sector (68%), whilst reporting that confidentiality (100%) and receiving integrated health services (100%) were the most important factors for deciding where to seek care. This study contributes with the knowledge of migrant experiences and social exclusions by several health determinants. Results offer key insights for researchers, advocates, and policymakers working with migrant population and the development of structural and behavioral interventions. In all, aiming towards a health policy design structural and behavioral interventions to reduce HIV risk factors and improve well-being of women in the DR.

0684

NEURAL TUBE DEFECTS: MAKING SENSE OF THE UNEXPECTED

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Neural tube defects (NTD) can result in severe disability, child death and stillbirth. The biomedical causes for NTDs have been explored widely and there is ample evidence of how NTDs can be prevented through folic acid supplementation. In rural communities in low-income countries, with limited access to healthcare, however, babies born with malformations and stillbirth have often been explained in terms of "God's will". In eastern Ethiopia, we conducted focus group discussions and interviews with mothers of children born with NTDs, health workers, traditional birth attendants, and other community members identified a wider range of perspectives on the underlying causes of NTDs. Unsurprisingly, health workers provided explanations of NTDs that were based on biomedical perspectives. Mothers of babies with NTDs suggested that hard work or accidents during pregnancy could possibly have been the causes, but more commonly referred to the will of Allah will to make sense of giving birth to babies with NTDs. Their explanations emphasized Allah as a force that made choices they had no control over, whereas other people in the communities, who had no experience of having children with NTDs, suggested that Allah was punishing parents for having sinned or behaved badly towards people with malformations. Although some provided explanations of NTDs related to natural phenomena, narratives of why some people gave birth to NTD cases were more commonly based on ideas that Allah gave people what they deserved. As a result of the perceived connection between behavior and NTDs many mothers hesitated to share

their experiences. These findings of how people in different positions explained the causes illustrate that people could be at risk of stigma and rumors through association with NTDs, which highlight the importance of taking into account and being sensitive to local perceptions when trying to reduce the cases of NTDs in Ethiopia and elsewhere.

0685

VULNERABILITY AND AGENCY IN RESEARCH PARTICIPANTS' DAILY LIVES AND THE RESEARCH ENCOUNTER: A QUALITATIVE CASE STUDY OF PARTICIPANTS TAKING PART IN SCRUB TYPHUS RESEARCH IN NORTHERN THAILAND

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Health researchers have a responsibility to conduct locally important research and protect participants especially "vulnerable" participants from harm. Group based vulnerability has been increasingly challenged, and vulnerability is increasingly understood to be context specific, yet limited guidance is available.This study aims to explore research participants' daily vulnerability and agency, and how these interact with their research experiences. A qualitative case study was conducted around two ongoing scrub typhus research studies in Chiangrai, northern Thailand (NCT03083197-clinical trial, NCT02915861- observational study). We conducted 42 semi-structured interviews with research participants, their families, researchers and key informants. The majority of the research participants belonged to a hill tribe ethnic minority group and some did not speak Thai or have Thai citizenship. We found that common challenges participants faced when participating in research were related to Thai language barriers, uncertain legal status, unstable employment, living remotely, lack of education and healthcare. Despite these challenges people demonstrated agency in their daily lives and were often supported in this by family members. People's daily challenges could be hidden from researchers such as participants' long journey to the research facilities, the need for family members to accompany them due to travelling concerns or language barriers. This could result in higher costs, family members missing work and burdens on family members' as well as the research participant's time. Despite these challenges, the majority of research participants perceived research to be beneficial. These were related to increased access to healthcare and gaining knowledge about their own health. We conclude that definitions of research vulnerability should consider participants' situations. Our data support the growing call to redefine the concept of research vulnerability away from group-based classifications to more nuanced definitions that take into account participants' situations and abilities.

0686

EVALUATING THE EFFECTIVENESS OF GLOBAL HEALTH PARTNERSHIPS FOR DISEASE ELIMINATION - A SYSTEMATIC REVIEW

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There is limited evidence on the critical success factors for global health partnerships. Yet, despite the limited evidence, donors have increased their support of such partnerships in the last 20 years. There is hence a need to understand the different types of partnerships in global health and identify factors contributing to the efficiency and effectiveness of partnerships. I conducted a systematic review of literature on coalition-building in global public health to identify criteria under which global health partnerships are considered essential for the success of global disease elimination efforts and reviewed the methods used to evaluate the efficiency and effectiveness of global health partnerships. I included studies from searches on databases such as Pubmed using search terms and criteria established a priori. I analyzed the studies that met the inclusion standards and synthesized study findings using a scoring mechanism that scored the studies on evaluation metrics and conceptual frameworks. Findings from 22 studies met the criteria for inclusion. Of these, three studies included metrics to assess both global health partnership processes and impact. Seventeen studies included a conceptual framework to analyze the efficiency or effectiveness of global health partnerships. Of the 35 global health partnerships that were reviewed in the selected studies, 13 partnerships supported drug and vaccine development, and 12 promoted access to pharmaceutical products to advance disease elimination. One philanthropic donor either directly or indirectly supported fifty percent of the studies included in the review. Transparency, communication, governance, inclusion, and representation were the process measures that most studies used to review the operational performance of global health partnerships. None of the studies established a causal linkage between partnership performance and disease outcomes. This review found that a multi-disciplinary approach to evaluating global health partnerships addresses the dynamic contexts within which such partnerships operate.

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ENUMERATING THE CHANGING BURDEN OF ALL-CAUSE FEBRILE ILLNESS IN INFANTS AND YOUNG CHILDREN IN LOW- AND MIDDLE- INCOME COUNTRIES

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Fever is a nonspecific symptom of a many tropical pathogens, including potentially deadly malaria infections, dengue fever, and severe bacterial or virile infections. Even in the absence of severe illness, febrile episodes are likely to prompt care-seeking. As such, changes in all-cause fever burden will have downstream impacts on health-system utilisation, including demand for diagnostic testing and treatment. To understand spatial and temporal trends in fever incidence we developed a spatio-temporal model of all-cause fever prevalence in 151 low-and-middle-income countries using a generalised additive mixed model based 279 nationally-representative surveys conducted between 1990 and 2020. This period prevalence (enumerated by the answers to the survey question 'has [child's name] been ill with a fever at any time in the last two weeks?') was converted to incidence using a rigorous mathematical formula which respects the censoring inherent in the survey question, and so is more accurate than naïve approaches extrapolating fortnightly period-prevalence to incidence, even when accounting for introduced uncertainty in the mean duration of febrile episodes. We found that between 2000 and 2019 the incidence of fevers decreased from an average of 7.22 (6.30-8.16 95% CI) episodes per child per year to 5.17 (4.53-5.81), corresponding to a decline in the mean period prevalence of fevers from 0.26 (0.23-0.28) to 0.19 (0.18-0.21). The largest declines were observed in Sub-Saharan Africa, with all-cause fever period prevalence in under-fives decreasing from 0.39 (0.36-0.41) in 1990 to 0.21 (0.20-0.22) in 2019. In 2019 we predicted an incidence of 5.56 billion (4.85-6.23 billion) distinct febrile episodes in under-fives, with the highest incidence rates in the Middle East, North Africa and Sub-Saharan Africa. Our results show a shift in geographic burden of fevers: in 1990 infants in sub-Saharan Africa experienced 66% more febrile episodes per year than the global average, falling to 14% in 2019, whilst in North Africa and the Middle East fever burden has remained steadily above the global average since 1990.

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COST EFFECTIVENESS ANALYSES OF THREE METHODS TO TRAIN HEALTH WORKERS IN ANGOLA: IN-CLASSROOM TRAINING, SELF-LEARNING, AND BLENDED LEARNING

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In 2020, the Angolan Ministry of Health launched an innovative e-learning platform called Kassai in 6 provinces to build Malaria Case Management capacity among health workers (HWs) and address challenges with in-classroom traditional training, such as variation in quality of materials and delivery, staff absence from facilities for training, limited individual tailoring for knowledge and learning pace. By March 2022, Kassai had over 3,500 enrolled learners, using two approaches: (1) fully digital self-learning, or (2) a blended learning mix of face-to-face training and digital tools on the Kassai platform, targeting HWs with less access to technology and fewer digital skills, often in distant communities. Using 2020 baseline data, we conducted a cost-effectiveness analysis of the two Kassai approaches compared to in-classroom traditional training, for the period 2021-2025, to inform policy discussions on the scale-up potential and associated cost. Average and marginal costs were estimated using the ingredients approach and included costs for staff, contractors, venue, lodging, transportation, per diem, equipment, fees, and opportunity costs. Effectiveness was measured as the number and proportion of HWs successfully completing trainings (scoring > 75% in post evaluation test). We assumed successful completion rates of 80% (blended learning), 50% (self-learning) and 42% (traditional in-classroom), based on project records. Cost-effectiveness was measured as the average cost per successful trainee. The Kassai self-learning approach was the most cost-effective of the three training methods, followed by Kassai blended learning. The marginal cost of successfully training one HW using self-learning was 13 times more cost-effective than in-classroom training (projection to 2025), and 7 times more cost-effective than blended learning. Future training approaches should consider a combination of self-learning and blended learning, to cater for differential HW Internet access and required level of support. Both methods are less expensive to scale up compared to in-class traditional training.

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DETERMINING SAFE NPI RELAXATION STRATEGY IN INDIA DURING THE DELTA AND OMICRON WAVES OF COVID-19: FINDINGS FROM A TWO-STRAIN COVID-19 TRANSMISSION MODEL

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The use of non-pharmaceutical interventions (NPIs) has been a critical strategy to slow and prevent the spread of SARS-CoV-2 during the COVID-19 pandemic. Dynamic transmission models have been developed to project the course of the pandemic under various assumptions. This study aimed to (1) validate a two-strain SEIR transmission model by comparing COVID-19 cases and deaths for the Delta wave and (2) project the course of the pandemic during the time period where transmission is driven by the Omicron variant, comparing different strategies of NPI relaxation. We compared model-projected and reported COVID-19 cases and deaths in India over 180 days starting from July 27th, 2021. The difference (projected - reported) and percent error were calculated to assess the degree of agreement between model projections and the reported data. We then updated model parameters with the best estimates corresponding to the Omicron wave and projected the number of COVID-19 cases and deaths over 180 days beginning from November 26th, 2021. While incidence increased slightly during the Onam festival, the model-projected cases for the Delta wave otherwise aligned with reported number of cases in India until late November 2021, with a mean percent error of 1.67% assuming a 12-week inter-dose interval and sustained NPIs throughout the simulation. This finding is consistent with NPI policies and the inter-dose interval used in India during the Delta wave, with larger differences beginning to emerge in late November 2021, when the Omicron variant emerged. Projections for the Omicron wave suggest that cases will peak earlier but at a lower level than they did in the Delta wave, with a smaller second peak occurring later during the simulation period due to the expected relaxation of NPIs once high vaccine coverage is reached. Overall, external validation of the two-strain SEIR model suggests that the model was consistent with cases in India. Moreover, our models suggest that NPIs might be able to be safely relaxed in late April as high vaccine coverage is achieved in India without large resurgences in cases.

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COVID-19 ASSOCIATED EXCESS MORTALITY IN BALIAKANDI, A RURAL DEMOGRAPHIC SURVEILLANCE SITE IN BANGLADESH

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The Covid-19 has been associated with excess mortality in many countries. However, due to poor testing coverage in many lower and middle-income countries (LMIC), the number deaths caused by Covid-19 is likely underreported. Assessing whether total deaths were in excess of expected deaths can serve as a proxy for the number of deaths associated with the pandemic. In this study, we used data from a demographic and health survey in Baliakandi, Bangladesh (population 236,488 living in 261 villages) to estimate the excess deaths that occurred in 2020 and 2021 compared to 2019 and 2018, by age; in total, officials count of Covid-19 related deaths were only 25. We counted all deaths from every household during our regular visits to households ranging from once every 2-4 months. We examined the weekly number of deaths from January 2018 to December 2021 among all residents. To identify the excess deaths, we calculated the rolling average deaths for each calendar week, by taking the mean of that week, the prior and the following weeks. We calculated weekly all-cause excess mortality by deducting the observed count of deaths in 2021 and weeks 13-52 of 2020 (Covid-19 started to transmit from week 13 in 2020) with the expected weekly estimated deaths for that same calendar week and stratum. There were an average of 1364 deaths per year during 2018 and 2019. But in 2020 we observed 1516 deaths and in 2021, 1446 deaths in total. During 2020 (13 weeks and onwards) and 2021, there were 230 excess deaths (9.8/10,000 population) in the Baliakandi. We estimated 121 excess deaths among males and 109 among females. Residents aged 45-64 years had 68 additional deaths, 65 to 79-year age group had suffered highest with 126 additional deaths. The 80+ age group had an additional 64 deaths. There were no excess deaths in younger age groups. In our observed data and weekly analysis methods we found excess in all-cause mortality in the Baliakandi DSS area in 2020 and 2021, many of which were likely due to with Covid-19, given the age distribution of the excess deaths.

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DEVELOPMENT AND VALIDATION OF MANUALLY MODIFIED AND SUPERVISED MACHINE LEARNING CLINICAL ASSESSMENT ALGORITHMS FOR MALARIA IN NIGERIAN CHILDREN

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It is estimated that 67% of malaria deaths occur in children under-five years. To investigate improving the accuracy of Integrated Management of Childhood Illness (IMCI) point-of-care clinical risk assessment protocols for malaria in febrile children, a malaria rapid diagnostic test (mRDT) workflow was embedded into THINKMD's clinical risk assessment platform

to support a comparative analysis of THINKMD-generated malaria risk assessments with mRDT data. Assessments using the THINKMD mHealth tool were performed by 7 Community Health Workers (CHWs) on 555 children 2-59 months of age who presented with fever or history of fever (>37.5° C) to 5 participating clinics in Kano State, Nigeria over a 4-week period from July to August 2018. Among 480 children identified as at risk of malaria, 66.7% had positive mRDT results and 33.3% had negative mRDT results. THINKMD then manually modified its original malaria-risk algorithm to increase sensitivity by removing more strict criteria for clinical severity as a requirement for malaria risk. For the modified versus the original THINKMD algorithms, we observed a +44% in PPV for (+) mRDT and +44% in NPV for (–) mRDT when applying the original field-based data. To test our ability to improve both sensitivity and specificity of our algorithms, we utilized additional mRDT data to generate supervised machine learning (ML) algorithms using random forest models applying 80% of clinical data captured as the ML training set and 20% to test the new ML logic. Compared to the original logic, ML significantly improved THINKMD malaria risk assessment specificity (36-64%) and PPV (43-67%) for (+) mRDT with a minimal increase in both sensitivity and NPV. For (-) mRDTs, ML significantly improved THINKMD malaria risk assessments for specificity (70-98%), PPV (63-87%) and NPV (43-75%) with a decrease in sensitivity from (36-29%). Results demonstrate that combining mRDT "truth" data with digital mHealth platform clinical assessments and clinical data can improve identification of children with malaria/non-malaria attributable febrile illnesses and enable rapid, cost-effective modification of acute febrile illness logic.

0692

THE COORFAMILY APP: FEASIBILITY OF A 10-DAY LOCATION HISTORY CONTACT TRACING SMARTPHONE APPLICATION FOR FEBRILE PATIENTS IN CAMBODIA

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Travel history data are important for controlling infectious disease transmission. For example, travel history data are often used as part of contact tracing for respiratory and sexually transmitted diseases. The most common approach to collecting travel history data is through interviews, meaning that the data depend on patients to accurately report locations they have visited. Such data are prone to several types of bias (e.g. recall bias). Having a measure of travel history that does not rely on patient memory could therefore be valuable for public health efforts. In this project we have developed a mobile phone app (named "CoorFamily") to collect retrospective locational metadata that are stored in photos on mobile phones for a specified period of time (currently 10 days). The app is available on the Google Play store in English and Khmer. The "CoorFamily" name underlines users' contribution to community health. We have implemented this software as part of a project that aims to characterize the infectious disease landscape in Cambodia using metagenomic next-generation sequencing on samples from febrile subjects at 4 enrollment sites in Phnom Penh and Kampong Speu. Here we report on the beta phase of the software and operational challenges of its use. We tested the implementation of CoorFamily in a 10-week pilot study involving 295 volunteers. Of 295 subjects approached, 142 had compatible phones; of these, 141 agreed to participate, 44 successfully downloaded the app and sent data, and 6 provided usable geolocation data. The primary obstacles we encountered were incompatible phones and lack of photos with locational metadata. We identified one case where an individual had traveled outside of their home but reported no movement during the enrollment interview. Preliminary results suggest that CoorFamily could be a valuable supplement to current data collection practices, but that it needs further development. Alternative sources of location data (e.g. Google accounts) may be more comprehensive but are also more difficult to access. Additional feasibility and data quality analyses are ongoing and will be available at time of presentation.

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RESEARCH CAPACITY MONITORING AND EVALUATION SYSTEM: A ROBUST DYNAMIC WEB-BASED APPLICATION FOR MEASURING THE IMPACT OF RESEARCH CAPACITY STRENGTHENING INITIATIVES

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Developing national research capacity is considered an essential tool in increasing socio-economic development and population health. To support this, global development partners invest large amounts of funding yearly to support capacity building initiatives in Low- and Middle-income countries (LMIC's). However, the lack of generalizable monitoring and evaluation system poses a drawback to assess and/or initiate timely and impactful capacity building initiatives. Hence, there is a need to establish a dynamic tool to monitor and evaluate the impact of such initiatives based on well-established indicators. Here, we have developed a research capacity monitoring and evaluation web-based application (ReCAMES) that can be used across several research capacity strengthening initiatives. The evaluation metrics used by ReCAMES are given by points and grouped across the three indicator groups, i.e., Outcome, Output, and Impact. The indicators being skills attained and their application, their collaboration with other initiatives and/or stakeholders, knowledge translation done and recognition received from other institutions/parties. A graphical presentation of the progress achieved for each indicator is displayed on the dashboard for all participating individuals. An assessment of the impact of the program is also calculated and displayed on the system based on the same identified indicators. In addition, the system allows the principal investigator to provide access to all required stakeholders on different access levels to ensure data security. ReCAMES provides a dynamic framework with the ability to measure impact for research capacity strengthening initiatives performed in different settings. It can be used by diverse research capacity strengthening initiatives to assess their impact in the short and long term. ReCAMES can be used by a wide range of stakeholders such as research institutions, universities, funders, program evaluators and implementing partners.

0694

MULTIMODAL VITAL SIGN DEVICES FOR SPOT-CHECKING: A LANDSCAPE REVIEW

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Monitoring of vital signs (pulse, blood pressure, body temperature, respiratory rate, oxygen saturation) can be a useful screening and triage tool for early severity assessment and informing referral decision at the first point of contact in low-resource settings. However, vital signs are often not measured or measured incompletely due to various reasons including lack of appropriate devices, lack of training of health care providers, cost of devices, and patient load. Therefore, multimodal devices (measuring >1 vital sign) suited for low-resource settings could be critical for improving early severity assessments at presentation ("spot-checks") to impact care and outcome of patients. A comprehensive review was conducted to document existing multimodal devices and assess the current and emerging landscape. Device selection criteria based on a preliminary target product profile, an assessment matrix, and definition of relevant use

cases were also developed and used to prioritise existing devices. A total of 150 devices were identified through database searches - Crunchbase, FierceBiotech, Google, Google Scholar, and ClinicalTrials.gov. Of 150 devices identified, 66% (99/150) were monitors, 28% (42/150) wearables, and only 9 (6%) handheld devices. The devices were scored and ranked using 20 predefined device attributes including device usability, design, performance and validation, and regulatory approval. Only a relatively small proportion of all available devices were deemed suitable based on pre-defined use cases (e.g. Checkme Pod Wireless Oximeter and Checkme Suit (Wellue, USA), Capnoxiplus (Capnoxi, China), Intellivue (Philips, Netherlands), Portable Multiparameter (Quirumed, Spain) and Neopenda (USA)). The landscape review revealed some promising devices for spot-checking patients at first presentation. Further, selected devices have limited validation data from LMICs. This review highlights that dedicated efforts to shape existing technologies for use in low resource settings remains critical. Moreover, targeted data generation is needed to inform procurement decisions and implementation efforts.

0695

PREDICTING INFECTIOUS DISEASE SPREAD WITH FLIGHT PASSENGER DATA: THE IMPLICATIONS OF USING HISTORIC MOVEMENT DATA

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The modern international flight network provides multiple routes by which pathogens can spread widely and quickly across the globe. During outbreaks of emerging or re-emerging pathogens, analyses using flight passenger data to identify countries at risk of importing the disease are common and can help inform disease control efforts. One challenge faced is that the latest aviation statistics are not always immediately available, either because the datasets can be slow and expensive to purchase, or the real-time data are unavailable. Therefore, flight patterns from a previous year or the average over multiple years are often used. Use of historic data may be a reasonable assumption if travel patterns are relatively stable but should human travel behaviour change, either voluntarily or due to the enforcement of travel policies, then use of historic movement data may introduce substantial errors into the modelled epidemic spread. In this work we retrospectively analyse the extent to which historic flight data are a good proxy for recent flight volumes and explore the level of bias that these proxies can introduce when predicting the spatial spread of epidemics. We use flight passenger data from the International Air Transport Association (IATA) from 2012 to 2021 to assess how baseline air travel patterns were affected in international infectious disease outbreaks over the past decade, including SARS-CoV-2, Zika, Ebola, MERS-CoV and Yellow Fever. We then explore the impact of using historic data compared to the true movement data in models of international infectious disease spread by comparing the predicted transmission hotspots. Our work highlights the importance of accessible and regularly updated measures of passenger flows between countries to aid the prevention and control of infectious disease outbreaks.

0696

COMPARATIVE ASSESSMENT OF METHODS FOR SHORT-TERM FORECASTS OF COVID-19 HOSPITAL ADMISSIONS IN ENGLAND AT THE LOCAL LEVEL

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Forecasting healthcare demand is essential in epidemic settings, both to inform situational awareness and facilitate resource planning. Ideally, forecasts should be robust across time and locations. During the COVID-19 pandemic in England, it is an ongoing concern that demand for hospital care for COVID-19 patients in England will exceed available resources. We made weekly forecasts of daily COVID-19 hospital admissions for National Health Service Trusts in England between August 2020 and April 2021 using three disease-agnostic forecasting models: a mean ensemble of autoregressive time series models, a linear regression model with 7-day-lagged local cases as a predictor, and a scaled convolution of local cases and a delay distribution. We compared their point and probabilistic accuracy to a mean-ensemble of them all, and to a simple baseline model of no change from the last day of admissions. We measured predictive performance using the Weighted Interval Score (WIS) and considered how this changed in different scenarios (the length of the predictive horizon, the date on which the forecast was made, and by location), as well as how much admissions forecasts improved when future cases were known. We found that assuming no change in current admissions is rarely better than including at least a trend, although forecasting accuracy varied by forecast date and location, depending on the trajectory of the outbreak. Using confirmed COVID-19 cases as a predictor can improve admissions forecasts in some scenarios, but this is variable and depends on the ability to make consistently good case forecasts. However, ensemble forecasts can make forecasts that make consistently more accurate forecasts across time and locations. Given minimal requirements on data and computation, our admissions forecasting ensemble could be used to anticipate healthcare needs in future epidemic or pandemic settings.

0697

ENHANCING FIELD SUPERVISION IN RURAL MOZAMBIQUE: TAKING ADVANTAGE OF THE GLOBAL POSITION SYSTEM (GPS) TO MONITOR FIELD WORKER PERFORMANCE IN REMOTE COMMUNITIES WITHOUT NETWORK CONNECTIVITY

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The supervision, tracking, and optimization of field work can be challenging when implementing health research projects in remote rural areas. Multiple factors can affect field worker performance and data quality, such as logistics, training, and incentives, but with the widespread use of electronic data collection methods, the limited network connectivity is the most challenging one. A demographic census using offline electronic data collection tool (ODK) was conducted in Mopeia district, Mozambique, in preparation for the BOHEMIA clinical trial, which aims at assessing the impact of ivermectin mass drug administration on malaria transmission. Due to the need to simultaneously monitor the performance of more than 300 field workers throughout the district, we developed a method to oversee the field activities in an offline environment. In addition, a mobile app that periodically captured and compacted the positions of the device using the global positioning system was installed on the tablets. This allowed supervisors to assess the routes taken by field workers, as well as the time they took to travel from one area to another, locate households, and fill out the electronic questionnaire. This system revealed that a large proportion of the fieldworkers spent the majority of their time in transit, traveling throughout the district and locating households, rather than carrying out the demographic census interview. This led to action, deploying field workers to be based in different areas of the district rather than traveling from the district headquarters. Moreover, the GPS monitoring tool showed that understanding the geography and other elements that affect the fieldworker's performance such as road conditions and distances between households, are crucial to plan and evaluate the quality of the field work at an individual level. Tools such as GPS can provide crucial support and strengthen field workers' productivity in the context of global health research and interventions.

0699

ESTIMATING TIME-VARYING REPRODUCTION NUMBERS FROM TEMPORALLY AGGREGATED INCIDENCE DATA

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The time-varying reproduction number (R_t) is an important measure of transmissibility during outbreaks; it can directly inform policy decisions and is critical for the optimisation of control measures in real-time. The R package EpiEstim is a widely used opensource tool that uses the incidence of new cases combined with a serial interval distribution (SI: time between symptom onset in a case and their infector) to estimate R_t. However, applications of EpiEstim can be limited by the fact that the incidence data and SI distribution need to be supplied on the same timescale. This currently precludes the use of EpiEstim (and other similar methods for estimating R_t) for pathogens with a mean SI shorter than the temporal aggregation of the incidence data. The routine reporting of many diseases, such as Influenza, is typically temporally aggregated (e.g., on a weekly basis), and as the SARS-CoV-2 pandemic persists, many systems are moving towards less frequent reporting. Therefore, routine estimation of transmissibility for these pathogens is not feasible with existing tools. Here, we address this issue by applying an expectation-maximisation algorithm approach to reconstruct daily incidence from temporally aggregated data, from which R_t can then be estimated using EpiEstim. We assess the validity of our approach using an extensive simulation study and apply the method to SARS-CoV-2 case and death data and a historical Influenza epidemic. We compare the R_t estimates obtained using data on different timescales and demonstrate that R_t can be accurately estimated from temporally aggregated incidence data and the estimation accuracy may even be improved by reducing the impact of prominent weekend effects in reported data. This extended version of EpiEstim is applicable to a wider range of diseases and data sources, which should enhance its use in pandemic and epidemic response globally.

0700

THE ETIOLOGY OF MESOAMERICAN NEPHROPATHY: ENVIRONMENTAL V. TOXIC V. INFECTIOUS?

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Mesoamerican nephropathy (MEN) is a regional form of chronic kidney disease of unknown etiology (CKDU) confined to the Central American Pacific lowlands that afflicts young male agricultural and mining workers in areas without access to renal replacement therapies. Unrelated to common causes of CKD, such as diabetes and hypertension, MEN has several other regional risk factors. In order to identify and stratify the most significant risk factors for MEN to support epidemic-control interventions, a convenience sample survey queried Internet search engines with key words (MEN + CKDU) in order to identify case-control and cohort studies of MEN during the study period, 1990-present. Environmental risk factors for MEN included strenuous labor in high temperatures with inadequate rehydration. Toxic risk factors included agrochemical exposures, arsenic and cadmium in drinking water, high-purine-containing diets causing uricosuria, and abuse of NSAIDs and herbal pain remedies containing diethylene glycol or aristolochic acid for occupational musculoskeletal pain. Infectious risk factors included rodent-borne leptospirosis and hantavirus infections causing renal syndromes. Case-control studies that matched male coffee workers in the Central American highlands as controls with MEN cases in sugarcane workers in the lowlands did not detect MEN in controls. Both groups had similar agrochemical exposures, diets, and analgesic use eliminating toxic exposures as risk factors. In addition, another case-control study in a Nicaraguan mining community found no causal links between leptospirosis and hantavirus seroprevalence and MEN. Strenuous labor in high temperatures and inadequate hydration with beer or soda were the most significant risk factors for MEN. MEN-like clusters of CKDU have also occurred in India and will continue to occur among outdoor laborers throughout the tropics until agricultural and mining industries in developing nations are completely mechanized. Only occupational heat stress monitoring, evaluation, and prevention programs will curtail the current epidemic of MEN in young male workers in Central America.

0701

MAJOR CAUSE OF STILLBIRTHS AND NEONATAL DEATHS AND PREVENTIVE MEASURES: FEEDBACK FROM PREGNANT WOMEN AND MOTHERS OF YOUNG CHILDREN IN RURAL BANGLADESH

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Child Health and Mortality Prevention Surveillance (CHAMPS) Program in Bangladesh analyzed pathological and multiple organ tissue sample reports from 82 stillbirths and early neonatal deaths. The determined major cause of these deaths was 'intrauterine hypoxia' and the recommended preventive measure to reduce high risk pregnancies is quality antenatal care (ANC). Communities need to be informed about the findings and evidence-based recommendations for preventive measures to improve use of ANC. We diffused the information among pregnant women, their family members, and mothers of young children in Baliakandi, a rural sub-district of Bangladesh and assessed their level of understanding and feedback. From March-December 2021 we conducted 26 courtyard sessions with pregnant women, their family members and neighboring women. Our team invited the them to a courtyard session when visiting households. A female team member facilitated each session and at the end of the session collected participants' feedback on the delivered messages through open and interactive conversations. All responses from participants were sorted and categorized. In total, 160 pregnant women, 244 family members and 263 neighboring women attended the courtyard sessions. According to them (~65%), 'intrauterine hypoxia', as the major cause of stillbirths and neonatal deaths in Baliakandi, was new to them and explanations of the preventive measures helped them to understand the importance of receiving quality ANC services. However, most common barriers to receive quality ANC were family conflict, lack of family support, financial incapability, delayed decision making and preference of taking alternative remedy during pregnancy complications. Pregnant women stated that following the recommended preventive measures is challenging because quality ANC services are not available in their area. The evidence-based etiology of stillbirth and neonatal death information and prevention messages could be integrated in health education programs and can be widely disseminated to all pregnant women in the CHAMPS catchment area including improving quality ANC services.

0702

COPING STRATEGIES OF HOUSEHOLDS DURING THE COVID-19 LOCKDOWN IN RURAL BANGLADESH

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Due to an increase in COVID-19 cases, the Bangladesh government implemented the first countrywide lockdown from March 27 to May 30, 2020. The resulting restrictions challenged people's livelihoods;

rural households adopted strategies to cope with reduced income. This study examined coping strategies across low, medium and high wealth households. A cross-sectional survey was conducted from November 7 to December 13, 2020 through a standing Demographic Surveillance System (CHAMPS-DSS, Baliakandi) with population=239,353. 1302 households were selected using simple (n=299) and stratified (n=1003) random sampling. A structured questionnaire was used to collect information on livelihood losses and coping strategies. Results show that 77% of households either lost their livelihood or experienced disruptions. Among the affected households, 31% did not use any coping strategies, 26% relied on savings, 14% sold assets, 14% and 10% borrowed and received financial support from friends and family, and 11% obtained a bank loan; only 4% received assistance from the government. Among households involved in farming, 10% had to sell their harvest in advance. Households' coping strategies were associated with their wealth; households with low wealth were less likely to have no coping strategies or to rely on savings compared to high wealth households (26% with no coping strategy and 21% relying on savings vs. 38% and 31%, p<0.05). Households with low wealth were more likely to have borrowed or received financial support from family and friends or to have taken bank loans than high-wealth households (17% borrowing, 14% receiving support, 15% took bank loan vs. 9%, 7%; and 6%, p<0.05). Households in the medium wealth group were more likely to have sold their harvest in advance compared to high wealth households (14% vs. 8%, p<0.05). Overall, the rural population of Bangladesh had to rely heavily on informal channels to cope with the financial losses resulting from lockdown; households with low and medium wealth were more involved in coping strategies. Thus, the study offers policy recommendations to enhance formal channels to mitigate such financial shocks.

0703

ACCEPTABILITY AND PERCEIVED FACILITATORS AND BARRIERS TO THE USABILITY OF BIOMETRIC REGISTRATION AMONG INFANTS AND CHILDREN IN MANHIÇA DISTRICT, MOZAMBIQUE: A QUALITATIVE STUDY

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In low-and middle-income countries, many infants and children remain unregistered in both civil registration and healthcare records, limiting their access to essential rights-based services, including healthcare. A novel biometric registration prototype, applying a non-touch platform using smart phones and tablets to capture physical characteristics of infants and children for electronic registration, was tested in rural Mozambique. This is the first study to date to assess acceptability and perceived barriers and facilitators to the usability a biometric registration prototype in Mozambique. The study followed a qualitative design consisting of semi-structured interviews with healthcare providers (n=5), focus group discussions (FGDs) with caregivers of infants aged between 0 and 5 years old (n=7), and FGDs with data collectors involved in the implementation of the biometric registration pilot project (n=2) in Manhiça district, southern Mozambique. Data were thematically analysed. This study showed a high level of acceptability of the biometric registration prototype among healthcare providers and caregivers. We identified the following two acceptability factors: the biometric registration prototype was perceived to solve the inefficiency of paper-based registration, and the community perception of biometric registration as "healthcare norm". Despite this, participants expressed some reservations: myths and taboos, lack of information, lack of time, lack of father's consent, and potential additional workload among healthcare providers. In conclusion, the biometric prototype was widely accepted due to its perceived benefit and usefulness. These findings anticipate reasons for acceptability and advances recommendations to overcome the perceived barriers that are important to take into account prior to any future implementation of biometric registration.

0704

FACTORS ASSOCIATED WITH LOW ONE MINUTE APGAR SCORE IN PERI-URBAN GAMBIA

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The Apgar score is a rapid assessment of the health condition of a newborn baby just after birth. At 1-minute, the score determines how well the baby tolerates the birthing process and establishes the needfor immediate resuscitation. A low Apgar score is associated with poor short and long-term healthoutcomes. This study aims to evaluate risk factors associated with a low 1-min Apgar score (Apgar score<7). This was an ancillary study of a cohort of newborns nested to a phase III, double-blind, placebo-controlled randomized clinical trial (PregnAnZI-2) conducted in two public health facilities situated inwestern Gambia. Data includes 6734 mothers and their 6773 live births (51 stillbirths excluded from theanalysis) enrolled in the trial, from Oct 2017 to May 2021. Analysis was done using R version 4.1.2.Multivariable logistic regression including variables associated with the outcome (low 1-min Apgar score)in the bivariate analysis (p-value<0.100) was performed. The analysis presented here is not stratified bytrial arm as the trial is still blinded. The prevalence of low 1-min Apgar score was 3.8% (258/6773). Up to80% (20/25) of neonatal deaths occurring within 24h after birth, and 43% (29/68) of overall neonataldeaths happened among newborns with low 1-min Apgar score. In the multivariate analysis, low 1-minApgar score was associated with primiparity [Adjusted odds ratio (aOR) 1.78; 95% CI 1.31-2.50), P<0.001],previous stillbirth [aOR 3.23; 95% CI (1.64-5.85), P<0.001], macrosomia (birth weight> 4kg) [aOR 2.33; 95%CI (1.01-4.76), P=0.03], and cesarean delivery [aOR 3.03; 95%CI (1.82-4.76, P< 0.001]. Results from thisstudy highlight that almost half of neonatal deaths happened among newborns with low 1-min Apgarscore. Therefore, effective interventions to decrease the prevalence of low 1-min Apgar score along witheffective clinical management of these newborns are urgently needed to contribute to the sustainabledevelopment goal target 3.2 of decreasing neonatal mortality to <12 or fewer deaths per 1,000 live births,by 2030.

0705

QUANTIFICATION OF FOETAL HAEMOGLOBIN (HBF) LEVELS IN HYDROXYUREA MONITORING THERAPY FOR CHILDREN WITH SICKLE CELL DISEASE (SCD) IN GHANA USING A NEW POINT-OF-CARE DIAGNOSTIC

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Sickle cell disease (SCD) is associated with extensive morbidity and early mortality. The majority of patients with SCD live in sub-Saharan Africa. SCD is a significant public health burden in Ghana affecting about 2% of newborns. Foetal hemoglobin (HbF) is a strong modifier of the severity of SCD. Elevated levels of HbF are associated with relatively mild clinical manifestations of SCD. HbF is also used as a marker of

compliance and response to disease modifying (hydroxyurea) therapy. Standard hemoglobin electrophoretic techniques are unable to quantify HbF. In resource-constrained settings such as Ghana, the use of high-performance liquid chromatography (HPLC) for HbF quantification is often challenging due to high cost and unavailability of laboratory equipment and skilled healthcare personnel. Here, we report the performance of a low-cost, point-of-care, microchip based cellulose acetate electrophoresis "GazelleTM" compared to HPLC for HbF quantification in Ghanaian children with SCD. GazelleTM is a fast (<8 minutes), easy-to-use test which can be performed by personnel with minimal training and using only a finger-prick volume of blood. This study was conducted at the paediatric SCD Clinic in Korle Bu Teaching Hospital, Accra, Ghana. Children of ages ≥ 1 year to 16 years who are known to have sickle cell disease, are about to commence hydroxyurea therapy, and followed at the paediatric sickle cell clinic were enrolled in the study. This study is currently ongoing. A total of 110 children were included in the analysis. Gazelle showed a correlation of 0.93 when compared to HPLC with an average error of 3.52%. Haemoglobin variants are quantified by Gazelle offering the ability to monitor disease modifying therapy in SCD such as hydroxyurea, where quantification of HbF levels is the key to assessing treatment adherence and monitoring response to therapy. Gazelle has the potential to be utilized as a point-of-care test for quantification of foetal haemoglobin (HbF) levels in monitoring hydroxyurea therapy for children with SCD.

0706

IMPLEMENTING A GROUP-BASED MULTICOMPONENT EARLY CHILD DEVELOPMENT INTERVENTION THROUGH THE GOVERNMENT HEALTH SYSTEM IN RURAL BANGLADESH: A FEASIBILITY STUDY

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Children in low- and middle-income countries face an increased risk of poor cognitive development due to contaminated environments poor nutrition and a lack of stimulating and responsive interactions with their caregivers. Implementation of multi-component, community-level interventions may reduce these risks; however little evidence supports implementing integrated interventions at scale. To address this research gap in 2019-2020 we implemented a group-based intervention that was delivered by government health workers and included responsive stimulation, maternal and child nutrition, water sanitation and hygiene, maternal mental health, and childhood lead exposure prevention in rural Bangladesh. We aimed to assess the feasibility of implementing this multi-component intervention through the government health system. After the intervention, we conducted 17 in-depth interviews with government frontline health service providers and 12 key informant interviews with supervisors and managers at the local and national levels to explore the facilitators and difficulties of implementing such intervention. Factors facilitating implementation included high-quality training for the providers for conducting sessions, level of provider's skill, support from the community, family and supervisors, and trustworthy relationships with community residents. Notable difficulties were increased workload of the providers, lack of proper readiness of the health care centers and difficulties managing intervention commodities. Key informants suggested solutions to facilitate scale-up of integrated interventions through the government health system engaging relevant NGOs as partners, identifying feasible ways to produce and distribute low-cost commodities, encourage intervention participants to make child stimulation toys from recycle materials on their own, and offering providers monetary or non-monetary rewards. These findings can be used to shape the design and implementation of multicomponent child development interventions to be delivered through the government health system.

0707

USABILITY AND ACCEPTABILITY EXPERIENCE OF VIRTUAL INTERVIEWS AMONG RESEARCHERS AND PARTICIPANTSIN A LMIC SETTING DURING AMID OF COVID-19: A QUALITATIVE STUDY

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Recently, qualitative researchers implemented virtual strategies to collect data to comply with the COVID-19 SOPs. Similarly, we also used virtual platforms to conduct FGDs(n=7) and IDIs(n=60) among participants and key informant interviews (KII n=4) with research team to identify the end user experience of Zoom and connect call's usability and acceptability. This exploratory qualitative study was an integrated part of a larger funded study about role of mHealth and social media during COVID pandemic. We used connect call system for conducting IDIs and KII with caregivers and researchers, further we used ZOOM for FGDs with healthcare providers and data was analyzed by using thematic approach. We explored that virtual platforms including connect call and ZOOM application as acceptable tools for qualitative data collection among urban and rural population. However, parents/caregivers were not aware of ZOOM application and half of the population had no smart phones. Due to lack of digital literacy among participants, researchers were struggling to make them understand the entire process of the interviews. However, this was managed through pre-scheduled discussions. The end users found these mediums user friendly, convenient and accessible during the time of pandemic. In addition, researchers revealed it as a cost and time effective tool for data collection. Researchers preferred ZOOM for FGDs as it provides data confidentiality as well as opportunity for a larger group discussion over connect call. Technical issues identified were mike issue, sound quality and networking issues specially in a rural setting. We conclude that virtual platforms like ZOOM and connect call are usable and acceptable among urban and rural population; however, unavailability of mobile phones and lack of digital literacy were found as a major barrier. Thus, we advocate user-friendly Apps and virtual platforms capable of increasing the use and accessibility of virtual instruments for enhancing research techniques.

0708

EVALUATING THE LANDSCAPE OF COMMUNITY HEALTH IN THE DEMOCRATIC REPUBLIC OF CONGO TO PROVIDE RECOMMENDATIONS FOR A STRENGTHENED COMMUNITY HEALTH APPROACH

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Strengthening community participation in the fight against major endemics like malaria remains a MOH priority in the Democratic Republic of the Congo (DRC). Prompt diagnosis and treatment is the most effective way to prevent a mild case of malaria from developing into severe disease and death. Yet, despite having more than 15,000 community health workers (CHWs) providing health services across the country, only 9% of all malaria infections were detected by CHWs in 2021. To better understand the challenges to the successful implementation of the community health approach in the DRC, CHAI and PATH on behalf of the MOH, conducted a desk review of current strategic policy documents and held semi-structured interviews with key stakeholders, including government, health care workers and civil society, at both the central and provincial levels, with 26 individuals across 5 provinces. Barriers pertaining to community health implementation fidelity were assessed. First, we

found that 37% of interview respondents cited a lack of funding for the CHW program as the main challenge to strengthening community health in the DRC. Second, 33% of respondents discussed the need for a community health information system that produces disaggregated data to support program M&E and supply chain management. Respondents also highlighted the importance of quality data for decision-making, with 78% stating that data collected from CHWs are used to inform strategy. We also found gaps in health coverage. Official health policy documents state that there should be a ratio of 1 CHW for every 500 individuals in a community. In practice, there is just 1 CHW for every 1,000 individuals. The results of the landscape report will inform the design and implementation of priority case management interventions, such as the implementation of a community health information system, as well as enhanced coverage to satisfy at least 50% of the needs. Ultimately, the results will aim to strengthen the community health system as well as support the planning of multisectoral coordination for the upcoming revision of the National Community Health Strategic Plan (NCHSP) in the DRC.

0709

PHARMACEUTICAL SERVICE DELIVERY IN MEDICINE RETAIL OUTLETS IN HARD-TO-REACH COMMUNITIES IN LOW-MIDDLE-INCOME COUNTRIES (LMICS)

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Community pharmacies and Over-the-Counter Medicine Sellers (OTCMS) outlets are an integral part of the healthcare system of Low-Middle-Income Countries (LMICs). This study examines the pharmaceutical service ecosystem and gaps in delivery in hard-to-reach communities in terms of patterns, practices, and regulations to optimize universal health coverage in LMICs. Using the Upper West Region of Ghana as a case study, Global Positioning System (GPS) devices were employed to determine the location of pharmaceutical service delivery points in six districts. A structured questionnaire was administered to evaluate the availability of specific medicines and services including antibiotics, family planning, rapid diagnostic test kits for malaria, and provision of National Health Insurance. Out of the districts surveyed, there were 4 registered pharmacies and 136 Over-the-Counter Medicine Sellers (OTCMS) outlets. About 50% of these facilities were operating without a license from the pharmacy regulator. Averagely, each facility had a staff strength of 4, with 3 out of each 4 staff having no formal training to dispense medicines or offer pharmaceutical services. Neither the community pharmacies nor OTCMS outlets were National Health Insurance Scheme accredited service providers, culminating in100% out-of-pocket payments for all clients. The findings of this study have significant implications for policy formulation aimed at addressing gaps in pharmaceutical care delivery and consequently improving the quality of services offered, both in community pharmacies and OTCMS outlets in rural and hard-to-reach communities in LMICs.

0710

RAISING THE VISIBILITY OF NTDS IN THE DISCUSSION OF DOMESTIC HEALTH RESOURCE ALLOCATION: LESSONS FROM COLOMBIA, GUATEMALA, AND THE PHILIPPINES

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Investing in efforts to combat neglected tropical diseases (NTDs) is considered one of the "best buys" in public health. These investments are cost-effective and have the potential to return significant long-term health and economic benefits, thus breaking the cycle of poverty and disease for those affected by NTDs. However, NTD programs remain largely underfunded in many countries and are highly dependent on external donor funding. This multi-country study examines common enabling factors that have contributed to enhanced domestic financing for NTDs and ensured their prioritization within integrated planning processes in Colombia, Guatemala, and the Philippines. To understand where NTDs fit within the countries' health finance landscape, we conducted a literature review of published papers, program and policy documents, and country reports. Secondary data collection to assess the status of domestic mobilization and current financing for NTDs comprised gathering publicly available information from the ministries' financial systems. Primary data collection included 28 semi-structured interviews with key informants, including representatives from the ministries of health, implementing partners and donors. Countries' experiences demonstrate that NTD programming can be domestically resourced through political commitment, effective advocacy and governance, and integration within broader health system budgeting and planning processes. Moreover, the integration of NTD services into existing healthcare service delivery models and platforms has evidenced an opportunity to increase efficiency and ensure continuity of both population-based and clinical services. Enabling factors that have contributed to enhancing domestic financing for NTD programming in Colombia, Guatemala, and the Philippines will provide session participants with clear examples of how endemic countries can situate NTDs within the broader political narrative and health financing reforms, including those devoted to the advancement of universal health coverage and its objectives for ensuring equitable access and financial protection.

0711

A SYSTEMATIC REVIEW ON LIGHTNING FATALITIES IN BANGLADESH WITH SPECIAL REFERENCE TO EPIDEMIOLOGY OF DEATHS AND INJURIES

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Lightning is a leading cause of weather-related deaths after tornadoes, flash floods and hurricanes. Annually, it causes about 24,000 deaths and 240,000 injuries worldwide. In Bangladesh, lightning related deaths and injuries have become a public health concern and the government has already declared it as a natural disaster in 2016. This systematic review attempted epidemiology of lightning injuries and deaths since 2000-2021 in the context of Bangladesh. All published (English) quantitative, qualitative and mixed method studies were searched using a three-step process from electronic databases. An analytical framework was developed to use PubMed, Scopus, Web of Science, Google Scholar electronic databases. Meta-analysis was utilized to identify key concepts. The studies were coded into related non-mutually exclusive themes. We then synthesized each theme by comparing each study. Emergent themes were determined based on the meticulous and systematic reading. Coding and interpreting the data were refined during the analysis. The search criteria included and analysis of 55 full-text articles, resulting in the understanding of situations relevant to lightning deaths and injuries in Bangladesh. Annual mortality rate was 3.661 per 1,000,000 million. The incidence of lightning caused injury was 19.89 per 100,000 people. Among victims, males were particularly vulnerable, in fact 1.46 times higher at risk compared with females. Rural populations were more vulnerable, 8.73 time riskier than urban. About 43% of injuries occurred between 12 noon and 6 pm local time. Results further revealed that lightning injuries need to be taken as a public health problem and a national strategy needs to develop through an integrated approach which can address this emerging public health issue. Also, national and regional level policy planning including the identification of most lightning-prone areas and implications for developing national strategy, targeted interventions for highly risky locations can be planned based on the findings of this work.

0712

THE CONTRIBUTION OF HUMAN MOVEMENT AROUND AN URBAN NETWORK TO THE EXPANSION OF THE DENGUE TRANSMISSION ZONE IN BRAZIL

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Dengue is one of the most important mosquito-borne diseases in the world with over half of the world's population living in areas at risk of infection. The past 20 years has seen a rapid expansion of dengue into areas of Brazil that were previously protected, including temperate zones in the South and remote areas in the Amazon rainforest. Previous geographical barriers to dengue outbreaks have been eroded and very few areas are now considered protected from frequent outbreaks. Our previous study found that temperature suitability, connectedness to the urban network, and urbanisation were important drivers of dengue spread. However, the contribution of human mobility over long distances, from metropoles with endemic transmission into the Amazon region, is still not fully understood. Here, we apply Bayesian spatial models which can account for multiple sources of spatial connectivity to dengue data from Brazil between 2001 - 2020 to quantify the relative importance of human mobility as a driver of dengue spread across different regions of Brazil. Preliminary results show that this method can accurately quantify the relative contribution of multiple sources of connectivity in simulated data but found human movement was not an important factor in dengue expansion within South Brazil. This framework will allow us to monitor the spread of dengue between connected regions and identify areas at future risk of expansion in previously protected areas of Brazil.

0713

ASSOCIATION OF AMBIENT TEMPERATURE WITH HYPOHYDRATION & URINARY BIOMARKERS AMONG THE SALTWATER-INTRUSION-AFFECTED TROPICAL COASTAL POPULATIONS OF BANGLADESH

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High ambient temperature is associated with an increased risk of kidney diseases and nephrolithiasis (kidney stones) in tropical regions. Possible mechanistic pathways include dehydration and increased calciuria, but limited population-based studies have explored this. We investigated the relationship between ambient temperature with 24-hour urinary volume, electrolytes, and kidney damage markers among ≥ 20-years population in coastal Bangladesh. We used 5,550 person-visits data from a stepped-wedge cluster randomized controlled trial conducted between December 2016 to April 2017 in Bangladesh. We repeatedly measured the participant's 24-hour urinary volume, electrolytes, urine total protein, and creatinine excretions. Daily ambient temperature data of local stations were obtained from the Bangladesh Meteorological Board. We used linear mixed models with participant, household, and community-level random intercepts to evaluate the association between daily average ambient temperature with,24-hour intra-individual changes in urine volume and biomarker. Models were adjusted for socio-demographic (e.g., age, sex, religion, household wealth), chronic disease risk factors (e.g., body mass index, physical exercise, smoking status, alcohol consumption, and sleep hours), and time and proxy for participants' drinking water concentration.Each 5 °C increase in daily ambient average temperature was associated with-0.03 (95% CI: -0.07, 0.03) liter change in urine volume; 1.01 (95% CI: 0.99, 1.04) geometric mean ratio(GMR) of 24hrs urine sodium, 1.04 (95% CI: 1.01, 1.07) GMR of 24hrs urine potassium, 0.94 (95% CI: 0.89, 1.00) GMR of 24hrs urine magnesium;1.09 (95% CI: 1.09, 1.14) GMR of 24hours urine calcium; 1.64 (95% CI: 1.27,2.00) GMR of 24hours creatinine; and 0.89 (95% CI: 0.84,0.94) gm/24hours in urine total protein, and no significant change 1.00 (95% CI: 0.97, 1.03) GMR of 24hours urine chloride. Ambient temperature is associated with electrolyte-concentrated urine and high urinary protein excretion among the study population.

0714

THE SURGICAL COMPLICATIONS OF NEGLECTED TROPICAL DISEASES AND THEIR LINK TO CLIMATE CHANGE

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Neglected tropical diseases (NTDs) predominantly affect the poorest communities worldwide; the same populations most affected by climate change. NTD burden will likely increase due to several climate change-related mechanisms, including human and vector migration and access to water. Several NTDs have surgically treated complications. We studied the nexus of climate change, NTDs and their surgical treatment, a neglected focus with important ramifications for providers and patients as climate change plays out across the globe. A review of relevant literature with searches pertaining to NTDs, surgery and climate change was conducted on PubMed. A collection of 7 NTDs with documented surgical treatments were identified and further studied including trachoma, lymphatic filariasis (LF), the leishmaniases, cystic echinococcosis (CE), cysticercosis, snakebite, and schistosomiasis. Their global burden and, if available, estimates of their surgical burden, were gathered and followed by a review of the climate factors related to their pathogenesis and epidemiology. Trachoma and LF were most closely tied to surgical care. Trachoma causes trichiasis, an in-turning of the eyelid resulting in corneal abrasion and blindness, affecting 2.5 million globally in 2019. Water access and hygiene are core components of prevention, making control of Trachoma prone to drought and flooding. LF causes hydrocele in chronically infected males, amounting to 19.43 million cases in 2012. The causal parasite is spread by mosquitoes, meaning the disease's reach will be influenced by the migration of these vectors in response to changing climates, causing infections within naïve populations. Other NTDs require surgical care to a lesser extent. It is unclear how climate change will impact future prevention and treatment programs of NTDs with surgically treated presentations. Surgical care, therefore, should be included in packages aimed at addressing NTDs in the era of anthropogenic climate to care for communities with a surgical burden of NTDs.

0715

PLANETARY HEALTH IN URBAN INFORMAL SETTLEMENTS: ASSESSING THE EFFECT OF WATER STORAGE PRACTICES ON THE RELATIONSHIP BETWEEN MOSQUITO EXPOSURE AND FEVER

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Globally, over 1 billion people live in urban informal settlements that lack proper water infrastructure. Residents of these settlements may be more likely to store water, including in ways that could promote mosquito proliferation and the spread of vector-borne diseases. This study aimed to evaluate the association between exposure to mosquitoes and fever, stratified by water storage practices, in urban informal settlements in two countries. Survey data were collected through Revitalizing Informal Settlements and their Environments (RISE), a randomized control trial working in 24 urban informal settlements in Suva, Fiji and Makassar, Indonesia. The main survey items of interest were self-reported fever in the last week, self-reported frequency of exposure to mosquitoes in the last six weeks, and whether respondents stored drinking water. Multi-variate

logistic regression models were used to analyze associations between fever and exposure to mosquitoes in the total sample and in a sub-sample of households that stored water. Models were adjusted for settlement-level clustering and relevant covariates, including wall materials, garbage disposal practices, water source, water access, and household wealth. We observed a positive association between daily mosquito exposure and having a fever in both Makassar [(adjusted OR 1.45, 95% CI: 0.24-8.67)] and Suva [(AOR 1.88, 95% CI: 1.18-3.02)]. A sub-analysis restricted only to respondents that stored water produced similar results for both Makassar (AOR 1.46, 95% CI: 0.27-7.78) models] and Suva (AOR 1.53, 95% CI: 0.99-2.34)]. Our study demonstrated that with the increased rate of mosquito encounters residents had a higher chance contracting a fever, suggesting a viral infection, including when stratified by water storage. Furthermore, our study provides impetus that socio-environmental factors that increase people's vulnerability need to be included in vector-mosquito and infectious disease analyses. With the rapid growth of urbanization and climate change, this relationship merits further attention.

0716

PROJECTIONS OF CLIMATE CHANGE ATTRIBUTABLE WATERBORNE DISEASE BURDEN: A SYSTEMATIC REVIEW

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Climate change threatens recent advances in reducing incidence and mortality of waterborne diseases, which contribute significantly to global public health burden, especially in children. It has been well documented that meteorological factors, like temperature and precipitation, impact waterborne disease incidence. There is growing interest to characterize the potential future waterborne disease burden associated with climate change to support adaptation planning, but to date there has been no synthesis of future modeling studies. We conducted a systematic review of research and methods for projecting waterborne disease burden under climate change scenarios. We screened the literature as of November 2021 for papers including a quantitative estimate of future waterborne disease using the electronic databases PubMED and EMBASE. We identified 1,908 unique studies, of which 29 met the inclusion criteria. Projections were available in each WHO region. Most studies indicated an increase in future waterborne disease burden, with severity varying by region and climate scenario. Authors used a variety of methods to obtain waterborne disease projections under exposure-response, climate model and risk metric dimensions. Most studies incorporated local health and climate data; however, spatial scale varied by study. Over half the studies utilized novel estimation of exposure-response functions, while the rest relied on published reviews. Notably, 17 studies included assumptions on future population exposure, vulnerability, and adaptation, but few incorporated more than one metric. Because of the different modeling approaches applied and regions evaluated, we could not synthesize future burden into a single summary estimate. Climate-attributable waterborne disease projections could benefit from establishment of best practices to bolster utility and comparability of findings and better serve adaptation planning efforts. In particular, since waterborne disease risk is highly dependent on demographic factors and development pathways, uncertainty in these metrics should be incorporated in all projections.

0717

SELF-ASSESSED HEALTH STATUS AND ACUTE COVID-19 SYMPTOMS IN URBAN INFORMAL SETTLEMENTS IN MAKASSAR, INDONESIA

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The COVID-19 pandemic has had enormous global impact, but has particularly affected vulnerable populations, including the more than one billion people living in densely populated informal settlements with inadequate basic infrastructure and services, and heightened exposure risks inherent to crowded conditions and poor hygiene infrastructure. This study aims to describe the self- or carer-reported health impacts of COVID-19 among people living in urban communities in Makassar, Indonesia that are part of the Revitalising Informal Settlements and their Environment (RISE) trial. Household survey data from two time points were collected: Feb/Mar 2021 (telephone survey) and Mar-April 2022 (face-to-face data collection, ongoing). Based on the government data, the highest reported COVID-19 cases in Makassar in 2021 were 71.1 per 100,000 population 1, and 91.2 in 2022. Self- or carer-assessed health status was measured by asking respondents if, within the last week they, or their children, had experienced any of 8 possible acute COVID-19-related symptoms: cough; trouble breathing; fever; loss of sense of taste or smell; nasal congestion; headache/dizziness; muscle aches; fatigue//nausea/vomiting/reduced appetite. Respondents were also asked about COVID-19 vaccination status of household members (2022 only). A count of the number of reported symptoms was determined, as was the proportion of people reporting any possible COVID-19-related symptoms at each survey period (grouped by age: a=<5 years, b=5-15, c=adult). The 2021 results showed that cough was reported as follows: a=11.3%; b=7.1%; c=8.5%; breathing difficulties: a=1.3%; b=0.51%; c=3.1%; and at least 2 of the 8 potential COVID-19-related symptoms: a=19.1%; b=12.6%; c=28.5%. Although 2022 data collection is ongoing, preliminary results suggest increases in symptom prevalence. The vaccination status (at least one dose) across all settlements is 62.4%, which is lower than the vaccination status 94.6% nationally. These findings suggest both high prevalence of self-reported symptoms and poor penetration of COVID-19 vaccination among residents of informal settlements.

0718

THE AFRICAN LEISHMANIASES CONSORTIUM AS PARADIGM FOR NTDS ELIMINATION

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Contextual and full knowledge of leishmaniases epidemiology and harmonization of available tools are needed to achieve the goals of VL elimination and CL control in Africa. Despite significant scientific advances and increasing research competencies, impact on public health and communities is limited in Africa. Critical data is not often available because of lack of tools to support activities and decisions towards elimination and control. Contextually, available knowledge, tools and R&D products are not sufficient. The tools need to be translated to innovations to support decision and select effective policy options maximizing health and development impact, and be implemented. The African Leishmaniases Consortium (ALC) was created to address these challenges and needs towards control and elimination of Leishmaniases in tandem with the 2021 WHO NTDs road map. We present here the vision and strategic approach of ALC, which brings together 7 African institutions in 7 countries with an international partner in Spain, to represent Africa leishmaniases

context- inc. diseases diversity, neglect levels, country and global underreporting, morbidity and mortality. ALC leverages on its partners' complementary expertise and strengths. The vision is to establish platforms for developing human capital, research innovations for control tools, policy imperatives, and to foster commitment, dedication, and strategic support for the elimination of leishmaniases in Africa. Nexus between research, implementation science and policy options gives opportunity to develop effective frameworks for NTDs elimination paradigm, and spurred the creation of ALC to apply these advances to diseases affecting the poorest of the poor in North, West, and East Africa countries. The ALC is a valuable platform to enroll international partners for collaborations and utilization of capacities and competencies in the endemic countries. Through its thematic networks, ALC will train a cohort of next generation leaders in Africa, address relevant scientific questions on the elimination and deliver knowledge, data, tools, maps, models, and policies.

0719

VACCINE CONFIDENCE AND ATTITUDES TOWARDS COVID-19 AMONG ADULT EMPLOYEES OF A LARGE AGRICULTURAL COMPANY IN GUATEMALA: A CROSS-SECTIONAL SURVEY

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COVID-19 mitigation in essential workers depends, in part on vaccine acceptance. Little is known about COVID-19 vaccine acceptance among agricultural workers, represent 35% of the Guatemala labor force. We sought to assess attitudes, beliefs and vaccine confidence towards COVID-19 vaccines offered (but not mandatory) at no charge, at the workplace in Guatemalan banana plantations. During August/September of 2021 we conducted a cross-sectional survey among a sample of banana plantation workers participating in a larger prospective cohort of respiratory disease among agricultural workers. All workers (n=1,586) were invited to respond to a validated Spanish-language questionnaire about demographics, vaccination status, prior vaccines access and refusal, reasons for vaccination, concerns about COVID-19, and trust in vaccines. Descriptive statistics were used to summarize findings. Among participants completing the survey (n=1,578), the average age (SD) was 31 (9.3) years. At the time of the survey, 1576 (99%) of respondents had accepted the first dose of Moderna COVID-19 vaccine. Twenty percent of respondents (320) reported encountering barriers to earlier COVID-19 or other types of vaccination due to the inability to leave their job (n=177 55%) or the unavailability of a vaccine at the public clinic (n=132 41%). The most common reasons for agreeing COVID-19 vaccination were to protect their families (835 53%) or themselves (621 39%). Only 16% (254) of respondents reported to be concerned about developing COVID-19. While 574 (36.51%) of workers trusted public health agencies promotion of COVID-19 vaccines, another 577 (36%) reported little to no trust. Most workers (1255 80%) also had trouble discerning genuine from fake COVID-19 information as presented in our instrument. Few our sample of rural Guatemala workers worried about COVID-19, and most were unable to readily distinguish between credible and fake COVID-19 information, nonetheless we documented high vaccine uptake in workplace setting. Free COVID-19 vaccination in the workplace may be a key strategy to increase coverage among essential workers in other rural communities.

0720

SAFE RESUMPTION OF COMMUNITY SOCIAL AND BEHAVIOR CHANGE ACTIVITIES DURING THE COVID 19 PANDEMIC: THE ROLE OF INTERACTIVE VOICE RESPONSE IN NIGERIA

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The COVID-19 lockdown in Nigeria interrupted community interventions such as house-to-house visits and community dialogues on malaria. Changes were made to safely restart them; however, early supervision visits found that calls and WhatsApp chats to introduce these changes were insufficient; community volunteers (CVs) and supervisors needed additional orientation on how to implement them and how best to integrate malaria and COVID-19 messages. Given widespread access to mobile phones among supervisors and CVs, Breakthrough ACTION-Nigeria developed trainings for supervisors through Interactive Voice Response (IVR). Trainees only required a simple feature phone to receive free, automated calls and quizzes at designated times. If trainees missed a call, they could retrieve the module through a call-back mechanism. Trainings covered prevention and care-seeking for malaria and COVID-19 and rumor management. All 76 supervisors completed the 13 modules in 13 weeks, then led one-on-one trainings for CVs during supervision visits. CVs then conducted household visits outdoors and dialogues in open spaces with fewer than 20 people. CVs used masks and sanitizers and encouraged community members to do the same. In a post-training survey, 90% of supervisors said they found the IVR orientation very useful, and 91% felt confident they could step down the material to CVs. The number of activities conducted in the 3 months after the CV trainings were similar or higher than the 3 months before lockdown (11,533 activities before vs. 23,083 after; 51,910 persons reached before vs. 98,671 after; and 7,409 referrals before vs. 5,467 after). The referral completion rate improved; 48% of individuals completed referrals after the reset vs. 22% before lockdown. IVR cost $5,188 less than in-person training. Combined with one-on-one supervision and modifications to community activities, IVR allowed supervisors and CVs to resume critical community-level malaria and COVID-19 messaging. After the pandemic, the IVR approach can be replicated for cost-effectively sharing technical updates with CVs and supervisors who are widely distributed across the country.

0721

METAGENOMIC NEXT-GENERATION SEQUENCING TO CHARACTERIZE ETIOLOGIES OF NON-MALARIAL FEVER IN A COHORT LIVING IN A HIGH MALARIA BURDEN AREA IN UGANDA

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Metagenomic next-generation sequencing (mNGS) allows for broad genomic-level detection of infectious agents in a biological sample, and has played a key role in areas such as microbiome characterization and outbreak detection. Here, we used mNGS to investigate the potential

causes of acute, non-malarial febrile illness in 212 participants enrolled in an ongoing cohort study of malaria infection in eastern Uganda. Between December 2020 and August 2021, 297 nasopharyngeal swabs and 294 plasma paired samples were collected from participants who presented with fever, but were negative for malaria by microscopy. Samples were extracted, reverse-transcribed, and sequenced using short-read Illumina sequencing. Data were analyzed using CZ ID, a web-based platform for microbial detection using mNGS data. Applying stringent criteria to call the microbes present in each sample, we identified bacterial, eukaryotic and viral sequences in both sample types and closely examined the latter two. Submicroscopic malaria infections were detected in 54 (18%) plasma samples of which 27 (50%) were qPCR positive. SARS-CoV-2 was detected in 11 of the nasopharyngeal swabs, and full genomes were recovered from 9 of the samples, consistent with circulation of the Delta wave in Uganda. Other viral pathogens identified included rhinoviruses (n=40), influenza A virus (H3N2 subtype, n=14), human orthopneumovirus (RSV, n=12) and seasonal coronaviruses (HKU1, n=1; NL63, n=1; OC43, n=4). We performed phylogeny exploration on recovered genomes to relate these samples to published viral genomes from Uganda and other parts of the world. Notably, 11 cases of influenza were detected between May and July 2021, coinciding with the period when Delta was circulating in this population. These data revealed co-circulation of multiple pathogens, primarily viruses, likely associated with fever in this cohort. More broadly, this pilot study demonstrates the power of mNGS in elucidating the multiple causes of febrile illness, which could aid in surveying and responding to pathogenic microbes circulating in a region.

0722

BUILDING CAPACITY AND CREATING TOOLS TO SUPPORT INTERNATIONAL HEALTH REGULATIONS IMPLEMENTATION AND COMPLIANCE IN IRAQ

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The International Health Regulations (IHR), requires State Parties to develop capacities and capabilities to adequately detect, report and respond to infectious disease threats with the potential to cross national borders. In Iraq, implementation of this legal framework is challenged due to continued destabilizing factors and unique governmental structures. The aim of this project is to develop an adequate framework to support the detection, assessment, and reporting of disease events in Iraq consistent with the obligations of IHR. In coordination with stakeholders at the Federal Government (GoI) and the Kurdistan Regional Government (KRG), we have expanded the scope and range of IHR awareness and oversight in country. In partnership with the Ministries of Health we have supported the development of inter-ministerial IHR Technical Committees, consisting of relevant ministry focal points, across the two governments and have established IHR units across GoI provincial health departments. Through a series of IHR stakeholder meetings aimed to strengthen Iraq's IHR core competencies, we have developed and finalized action plans to improve communication between ministries and departments at the national and sub-national levels and provided recommendations to the IHR Technical Committees on required resources, practices, and sustainability considerations to achieve IHR compliance. In addition, we are working across relevant sectors to prepare for the States Party Self-Assessment Annual Report (SPAR) reporting requirement under IHR. Outcomes of this project continue to support Iraq in IHR compliance while building formal and lasting networks between GoI and KRG stakeholders across a variety of ministries and directorates. This effort will help Iraq meet its IHR commitments by supporting sustainable IHR engagement in a whole-of-country approach. Ultimately, the project increases public health information sharing and cooperation between the two governments, improving detection and response to national notifiable diseases and reporting under the IHR.

0723

CAPTURING HOME DEATH TO CONDUCT MINIMAL INVASIVE TISSUE SAMPLING (MITS): A COMMUNITY BASED NOTIFICATION SYSTEM

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In 2020, the estimated mortality rate in sub-Saharan Africa among children under the age of five years (U5) was 74 deaths per 1000 live births, and mostly from preventable causes of death . In rural Ethiopia, U5 children often die without being seen by medical personnel, without a documented medical history and are often buried before their cause of death can be determined. The Child Health and Mortality Prevention Surveillance Network (CHAMPS) established a community-based mortality notification system, which aims to report potentially eligible deaths (U5 deaths and stillbirths) within 24 hours where minimal invasive tissue sampling (MITS) can be conducted quickly after death and analyzed to determine the cause of death. In eastern Ethiopia, lay people were trained as Community Health Volunteers to report potentially eligible deaths to counsellors and health officers who checked the eligibility criteria, asking for consent, enrolling consented cases for MITS procedures, and sharing results with the families of the deceased child and the community after the identification of the cause of death. From February 4th 2019 to February 3rd 2022 the site received 3665 of which, 329 (9%) were home deaths. Of these, 85/329 (26%) were eligible for MITS. CHAMPS counsellors have approached 77 MITS eligible families, and 39 (51%) consented for MITS. Consent for home deaths increased from 48% in 2019 to 59% in 2021 and has improved until 88% in the first months of 2022 after the implementation of different strategies to improve notifications and acceptability. The site developed an efficient death notification system tailored to the cultural and religious norms as well as the geographical setting. The community-based notification system can inform the development and improvement of similar platforms to engage the community in mortality surveillance, and share findings with communities and local health officials to inform immediate public health actions.

0724

SUSTAINING HEALTHCARE SEEKING IN WESTERN KENYA DURING COVID-19 PANDEMIC

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The COVID-19 pandemic disrupted care-seeking and healthcare delivery in sub-Saharan Africa. Patients avoided hospitals due to fear of COVID-19. Health care providers were inadequately trained to manage COVID-19 patients and had insufficient personal protective equipment (PPE). In April 2021, we implemented a project to sustain healthcare seeking during COVID-19 through creating community awareness on the adherence to recommended infection prevention and control (IPC) measures in Kisumu and Siaya counties in western Kenya. Interventions in 100 project-supported level 2 and 3 facilities, selected for attendance >20 visits per month in the outpatient department (OPD) and >20 visits per month at antenatal care (ANC), included provision of PPE, hand sanitizer, disinfectant, screening booths, handwashing stations, training, and monthly supportive supervision. All facilities in the two counties received job aids, guidelines on ANC, malaria, IPC, and COVID-19, and information, education and communication (IEC) materials on COVID-19, malaria, and ANC. In addition, social and behavior change messaging was disseminated

in the two counties. We monitored care-seeking in 100 project supported facilities pre (Jan- Dec 2019) and during COVID-19 (Jan 2020 to Dec 2021). We abstracted data on the number of OPD visits, ANC visits, and suspected malaria cases reported in the District Health Information System-2 to determine the changes from pre- and during COVID-19. OPD visits/month declined by 9.7% in 2020 relative to 2019, from an average of 1143 to 1032, and in 2021 remained depressed at 18.9% with a mean of 927 relative to 2019. New ANC visits/month increased by 5.0% in 2021 relative to 2019, from an average of 31 to 32 visits/ month. The number of monthly cases of suspected malaria declined by 11.4% from 2019 to 2020 from an average of 646 to 572 and remained lower than the 2019 baseline in 2021 by 14.2% lower, at 554 visits. Despite efforts to ensure that healthcare workers had the supplies they needed, felt safe, and reached communities with correct information during the pandemic, overall care seeking remained depressed through 2021, compared to 2019.

0725

FEBRILE ILLNESS AND MALARIA DIAGNOSIS IN SIAYA AND KISUMU COUNTIES, WESTERN KENYA

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Malaria remains a major public health threat, with an estimated 241 million cases and 627,000 deaths worldwide in 2020. Approximately 47,000 deaths were linked to disruptions in the provision of malaria prevention, diagnosis, and treatment during the Covid-19 pandemic. As disease can progress rapidly to severe malaria or death, early detection and treatment is critical. Though malaria often presents as a febrile illness, some infected people, particularly older children and adults in endemic areas, may have other malaria symptoms (headache, body aches, and joint pains) while remaining afebrile. We collected data on fever cases and malaria testing from patients who sought care at 28 and 20 selected health facilities in Kisumu and Siaya Counties, respectively, in western Kenya from February to March 2022. Screeners tallied the number of patients presenting with fever and abstracted data from laboratory registers on the number of patients tested using rapid diagnostic tests (RDTs) or microscopy and treated for malaria. These were stratified by those under 5 years old (U5) and those 5 and above (5+). Facilities recorded a mean of 7.6 sick visits among U5 per health facility per day (range 0-29) and on average 3.7 U5 reporting fever per day (range 0-22). On average 5.7 U5 were tested for malaria per facility per day (range 0-21); the test positivity rate was 38.5%. Among clients 5+, there were a mean of 18.0 sick visits (range 0-77) per facility per day, and 6.5 reporting fever per facility per day (range 0-40). On average, 13.6 clients 5+ were tested for malaria per facility per day (range 0-55); the test positivity rate was 45.6%. Even as health care providers apparently used broad criteria to define suspected malaria, the test positivity rate remained high, both among children under 5 years and patients 5 years and older. To ensure that all patients with malaria are diagnosed and treated early, diagnostic tests must be widely available.

0726

COMMUNITY PERCEPTIONS ABOUT COVID-19 VACCINE ACCEPTANCE: A QUALITATIVE RAPID ASSESSMENT IN BALIAKANDI, A RURAL COMMUNITY OF BANGLADESH

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Since launching of the nationwide COVID-19 vaccination program on 7 February 2021, Bangladesh has vaccinated more than 75% of the population with at least one dose, although in a cross-sectional survey only 25% of rural respondents had been vaccinated. We conducted a qualitative rapid assessment in September 2021, to understand perceptions about COVID-19 vaccines among rural residents in Baliakandi sub-district, Bangladesh. We interviewed 19 key informants, including residents who had COVID-19 infection, vaccinated residents; general residents, community and religious leaders; local administrator; and healthcare providers. Data were analyzed by framework analysis. Respondents said that because the vaccines were developed in a short time, did not have adequate information to rely on them and wanted to wait first and observe others' experience before receiving the vaccine themselves. Besides, respondents shared some initial concerns about perceived adverse effects of the vaccines, such as infertility and death that prevented some people from being vaccinated. Respondents said that they would receive this vaccine to protect from infection; if it was mandated for people who wanted to go abroad; or if the government restricted movement for those who had not been vaccinated. They reported that many residents who were formally registered but could not get a vaccination on scheduled time due to insufficient supply of vaccines. They also noted most of the vaccinated residents were not practicing any precaution (i.e. wearing mask) as perceived once vaccinated, they would not need to take any measures. They suggested that to increase the vaccine uptake and encourage people practicing preventative measures, community level vaccination locations should be established, the registration system should be easier, and community leaders should be involved in the government's initiatives for sensitization about vaccines and side effects. The findings could aid in government and international community to fine-tune the strategies for addressing gaps (i.e. access, risk perceptions) in COVID-19 vaccine administration in similar rural settings.

0727

EXPANSION OF THE LASSA FEVER TESTING NETWORK IN NIGERIA

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Lassa fever (LF) is an acute viral illness caused by Lassa virus (LASV), affecting 300,000 persons per year in West Africa, with annual outbreaks occurring in Nigeria. LF is probably underreported, primarily due to its non-specific presentation which makes clinical diagnosis difficult. Laboratory confirmation of LASV infection can be achieved by virus culture, molecular detection, or antigen detection but these tests are not widely available, especially considering that LASV is a Category A pathogen requiring special training and precautions when handling specimens. The Nigeria National LASV program was created in 2016, initially with only three testing laboratories in the country. Here we describe the process of increasing LASV testing capacity in Nigeria to improve surveillance and outbreak response. Laboratories were selected based on regional representation and epidemiologic data indicating high LF incidence. A baseline assessment was conducted on the safety and infrastructural capacity to conduct LASV testing using a checklist developed by experts at the National Reference Laboratory in Abuja. Only labs with a BSL-3 glovebox were selected. We then conducted onsite training on the testing and reporting protocol, training an average of 7 staff per laboratory. Staff then undertook blinded testing of LF panels as a proficiency test, requiring them to score 100% before the laboratories could be activated. Since 2017, five new laboratories have been added to the network. The first three laboratories were activated in the southern part of the country, which is a hotspot zone for LASV, one in the South East in 2018, and two in the South West in 2019 and 2021. After the 2020 outbreak, where more cases were detected in the North zone, two more labs were activated in 2021, one in the North West where cases were seen for the first time, and one in the North East, which is becoming a new hotspot. The addition

of new labs has led to enhanced surveillance and geographical coverage, improved turnaround times from 72hrs to 48hrs, and reduced the burden at the three initial laboratories.

0728

ESTABLISHMENT OF A LASSA FEVER BIOBANK AT THE FEDERAL MEDICAL CENTER OWO, ONDO STATE, NIGERIA

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Lassa virus (LASV) is a biosafety level 4 priority pathogen under the World Health Organization R&D Blueprint. LASV infects up to 300,000 persons annually across West Africa, causing a potentially severe viral hemorrhagic fever known as Lassa fever (LF). Timely access to high-quality biological samples through standardized processes is critical in accelerating the development of urgently needed fit-for-purpose diagnostics, medical countermeasures, and research on LF. However, limited in-country collection, coordination, and service capacity, as well as a disconnect between demand and supply, among many other factors, pose major challenges. To address this need, as part of the FIND Integrated Biobank Network, we established a LF biobank at the Federal Medical Center Owo (FMCO) in Nigeria to prospectively collect, process and store high quality, well-characterized samples from LASV-infected persons. Within the framework of this project, we set out to enroll 200 (100 LASV RNA positive [LASV+] and 100 LASV RNA negative [LASV-]) eligible participants presenting at FMCO within one year. Individuals aged 18 years or older with suspected LF who tested either LASV+ or LASV- using the RealStar LASV qRT-PCR Kit 2.0 (Altona Diagnostics, Hamburg, DE) were enrolled. Whole blood, serum, and plasma were collected at baseline from each participant and at weeks 4 and 8 from LASV+ individuals, immediately processed and stored at -80^{0}C. Clinical data and sample information (baseline and follow-up visits) were captured in OpenClinica and OpenSpecimen, respectively. Creation of the biobank facility began in March 2020 and enrollment of participants started in October 2021. As of April 2022, we have enrolled a total of 145 participants (78 LASV+ and 67 LASV-) with a total of 2,769 sample aliquots (198 whole blood, 1,222 serum & 1,349 plasma). Participant enrollment and follow-up are ongoing. Samples from this biobank are currently being used for the evaluation of commercial LASV serologic assays and a LASV antigen rapid test.

0729

GENOMIC CHARACTERIZATION OF MULTIDRUG RESISTANT TRAVEL-ASSOCIATED *E. COLI* IN U.S. INTERNATIONAL TRAVELERS

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Antimicrobial resistance (AMR) is a global public health threat, and its frequency is increasing. International travel has been associated with the acquisition of antimicrobial- resistant organisms. Antimicrobial consumption, destination, and travelers' diarrhea (TD) are risk factors for acquiring an AMR organism during travel. In this study, we sought to understand the characteristics of AMR *E. coli* acquired by U.S. international travelers. Stool samples from U.S. international travelers recruited through the Global Travelers' Epidemiology Network were screened on selective media before and after travel to isolate extended beta lactamase (ESBL) producing, carbapenemase producing-carbapenem resistant (CP-CR), and colistin resistant (carrying *mcr*) gram-negative bacteria. Isolates were phenotyped for antimicrobial susceptibility, and 273 were subjected to whole genome sequencing. We found that 38% of travelers acquired an AMR bacterium following international travel, and 97% of those were *E. coli.* The most common resistance was against beta-lactam antibiotics, but there were also 26 isolates carrying an *mcr* gene conferring colistin resistance. Based on sequencing analysis of *E. coli* isolates using strainGST, we found that phylogroup A isolates comprised 45% of acquired *E. coli* post-travel, a shift from the majority phylogroup B2 isolates found in US-associated pre-travel samples. There were no significant differences in phylogroup across travel regions. Most ESBL-producing isolates carried a CTX gene, and the most common CTX allele found in post-travel and pre-travel isolates was CTX-M-15; however, CTX-M-27 predominated in those visiting South and Southeast Asia. In addition to ESBL carriage, 150 isolates were phenotypically resistant to levofloxacin. In summary, we identified strain-level genomic differences between travel-acquired and U.S.-associated *E. coli*, with an enrichment of phylogroup A isolates in association with travel and majority acquisition of the CTX-M-15 allele alongside widespread resistance to other antimicrobials.

0730

ACCESS AND UTILIZATION OF INSECTICIDE TREATED MOSQUITO NETS IN CONFLICT-AFFECTED FRAGILE STATES: ANALYSIS OF SUBNATIONAL CONFLICT EFFECT IN DEMOCRATIC REPUBLIC OF CONGO AND NIGERIA

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Studies highlighted the potential impact of conflict and displacement on malaria prevention and mitigation efforts, but few investigated the effect of subnational conflict intensity on access and utilization of mosquito nets in fragile countries. This study bridges the gap by applying a conflict intensity lens to the analysis of access and utilization of Insecticide Treated Nets (ITN) in two conflict-affected fragile states (Nigeria and Democratic Republic of Congo (DRC)), where at least 45 % of global malaria deaths occur. We used the Demographic health survey (DHS) and the Uppsala Conflict Data Program for information on access and utilization of nets and conflict events respectively. Access was defined as the percentage of population with at least one ITN per 2 household members, while utilization was defined as the percentage of population who slept under an ITN the night before the survey in households with at least 1 ITN. To define conflict intensity, we linked household clusters to conflict events within a 50 km distance using ArcGIS. Conflict intensity was then categorized into medium or high intensity conflict and no or low intensity conflict using a cut-off of 2 or more deaths per 100, 000 population per cluster. Access and utilization of ITNs was compared by conflict intensity at the household cluster level. Analysis of data from 281,689 individuals living in 58,183 households revealed that 42.8% (CI: 42.3 - 43.3%) and 39.9% (CI: 39.5 - 40.1%) of members living in neighborhoods with medium and high intensity conflict in DRC and Nigeria respectively had access to ITNS compared to 47.9% (CI: 47.6 - 48.1%) and 51.0% (CI: 50.8 - 51.2%) in no or low intensity conflict. Similarly, 65.1% (CI: 64.3 - 65.9%) and 62.8% (CI: 62.3 - 63.3%) of those living in medium or high intensity conflict in DRC and Nigeria respectively utilized ITNS compared to 69.2 % (CI: 68.8 %-69.6 %) and 65.7% (CI: 65.4-66.0%) in no or low intensity conflict. National malaria control programs must consider that access and utilization of ITNS are statistically significantly lower in neighborhoods with medium or high intensity conflict and target supporting interventions accordingly.

0731

DETECTION AND SEQUENCING OF A MONKEYPOX VIRUS OUTBREAK IN MANIEMA PROVINCE, DEMOCRATIC REPUBLIC OF THE CONGO

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Since 1970, the Democratic Republic of the Congo (DRC) has been facing repeated outbreaks of Monkeypox virus, which causes a pox-like disease in humans. The disease is endemic in the Equator forest zone, affecting the Sankuru, Tshuapa, and Equateur Provinces. On September 27th, 2021, the provincial health authorities in Maniema Province, which borders Sankuru, sent a health alert to the Ministry of Health. A cluster of cases with fever and skin eruptions had been detected and linked to bushmeat consumption. Samples were sent to the National Institute for Biomedical Research (INRB) and were positive by Orthopoxvirus PCR. On December 9th, 2021, an epidemic of Monkeypox virus was declared, with 191 cases, including 24 deaths. Samples were referred to the INRB Pathogen Genomics Laboratory for viral characterization as Monkeypox-positive samples from humans in the DRC had not been sequenced and publicly released since 2008. The Illumina DNA Prep with Enrichment protocol was used to generate enriched libraries for dual-indexed pairwise sequencing, using a custom Twist Biosciences probe panel designed against high consequence viruses, including Monkeypox virus. Enriched libraries were loaded onto an Illumina iSeq for 2 x 151 cycles. Sequencing reads were trimmed to remove adapter and low-quality bases, deduplicated, and aligned to a Monkeypox virus genome collected in Yambuku in 1985. We obtained two genomes with 99.9% and 99.7% coverage, excluding the repetitive terminal ends. Phylogenetic analyzes demonstrated that these cases of Monkeypox from Maniema were linked to historical genomes from Kolé and Lodja villages, located in the Sankuru Province close to the Maniema border, which share the same forest. The geographical expansion of this re-emerging virus underscores the threat that Monkeypox virus presents to the local and global population. The experience strengthened the INRB capacity for Monkeypox detection and sequencing and enabled preparedness for real-time tracking of future reemergence. In addition, further research should be conducted at the animal-human interface to understand the determinants of such a dangerous disease.

0732

HESITANCY IN COVID-19 VACCINE UPTAKE AMONG PREGNANT WOMEN IN KISUMU AND SIAYA COUNTIES, WESTERN KENYA AUGUST 2021- FEBRUARY 2022

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Vaccine hesitancy is defined as the reluctance to accept or agree to be vaccinated irrespective of the availability and accessibility of the vaccine. WHO attributes this reluctance to three major factors: convenience, confidence, and complacency. Vaccine hesitancy is a critical barrier in achieving high uptake of COVID-19 vaccines. In Kenya, COVID-19 vaccination was rolled out to the general population in March 2021. ANC based surveillance involving a questionnaire administered to all consenting women attending ANC1 in selected facilities starting in August 2021 to assess COVID-19 vaccine uptake among pregnant women was used . Data on COVID-19 vaccine uptake and reasons for the vaccine reluctance were collected using ScanForm software. Stata used to perform descriptive analyses. Additionally, a qualitative evaluation to further explore reasons for vaccine hesitancy and trusted data sources was conducted; analysis is in process. Between August 2021 and February 2022, 2,691 pregnant women were interviewed regarding their COVID-19 vaccination status and perceptions. The median age was 25.5 years (IQR 12-49) years and approximately half had attained secondary education. The vast majority (2,318; 86.1%) had not received the vaccine. Among these, 817/ 2,318 (35.3%) stated that they would decline the COVID-19 vaccine if offered, with 721/ 817 (88.3%) citing concern about the side effects of the vaccine as the reason. A small proportion 22/ 817 (2.7%) stated they would decline the vaccine if offered because they were not worried about getting COVID-19, and one person had already had COVID-19 and felt vaccination was unnecessary. A third of pregnant women surveyed at ANC were hesitant to receive the COVID-19 vaccine, primarily due to fear of side effects; this will substantially hamper vaccination uptake. There is a need to address concerns about the safety of COVID-19 vaccines in order to increase the uptake. Understanding how best to respond to peoples' concerns most effectively is critical to reach high vaccine coverage.

0733

EDUCATION AND OCCUPATION ARE THE BASIC FACTORS CONTRIBUTING TO INEQUITY IN COVID VACCINATION COVERAGE OVER TIME AMONG PEOPLE AGED 40 YEARS AND OLDER: FINDINGS FROM A RURAL COHORT IN BANGLADESH

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Bangladesh began offering vaccines against COVID-19 on January 27, 2021, to those aged ≥40 years. Our objective was to assess the sociodemographic factors associated with vaccination of the population aged ≥40 years who received at least one vaccination dose between February 2021 to January 2022 in Baliakandi, a rural sub-district of Bangladesh. Since 2017, the Child Health and Mortality Prevention Surveillance (CHAMPS) network has been collecting demographic surveillance data from the Baliakandi population, with prospective COVID-19 vaccination information beginning in April 2021 through interviews and vaccination cards. We classified the first dose of vaccination dates into four quarters from February 1, 2021, to January 31, 2022. The relationships between participant demographics and vaccination timing were examined using bivariate multinomial logistic regression. Only 6% of the population received vaccinations in the first quarter, 12% in the second, 44% in the third, and 13% in the fourth quarter. By the end of January 2022, 75% of the population aged ≥40 years and 64% of the population aged >65 years had been vaccinated. Males were 1.5 times more likely to receive vaccines in the first quarter. In the first two quarters, 60% of the population who had more than 12 years of schooling received vaccinations, compared to only 10% of the population with no or only non-formal education. By July 2021, 38% of healthcare and administrative workers, groups targeted early for vaccination, had received doses, and these groups had 10.7 times higher odds (95% CI: 8.7-13.1) of receiving vaccination in the first quarter compared to others. Preliminary data indicates people aged ≥40 years with higher education and working in healthcare or administrative offices, who make up only 12% of the rural population, started receiving vaccinations earlier than others. A particular focus should be given to educating people without formal education about the importance of vaccination and encouraging them to receive it early. Education based interventions, outreach vaccination centers, community leaders, and the media may all be of assistance in this initiative.

0734

COMMUNITY-BASED SURVEILLANCE AND MINIMALLY INVASIVE TISSUE SAMPLING (MITS) FOR RSV-ASSOCIATED INFANT MORTALITY IN KARACHI, PAKISTAN

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A community-based infant mortality surveillance study was conducted in low-income peri-urban catchment areas of Karachi, Pakistan (2018-21), to establish the burden of respiratory syncytial virus (RSV) in recently deceased infants. In the first phase of the study, 589 nasopharyngeal swab specimens were collected, of which 15 were RSV positive and 1 was positive for Bordetella pertussis. In the next phase (2020-21), minimally invasive tissue samples (MITS) of the lungs/thorax were collected from 24 recently deceased infants from the same community, with the aim of improving the classification of upper respiratory tract infections via histopathology analysis. Interviews, focus group discussions, study advocacy and ongoing community engagement with key community stakeholders (parents of deceased infants, religious and community leaders, graveyard administrators) facilitated and enabled the challenging process of obtaining consent from bereaved parents in a critical time window of an hour between an infant's death and burial. A van was customized to mobilize for specimen collection within the community, and local health workers and mobilizers from the community were able to effectively counsel bereaved families regarding the study procedure, and later provide grief support to the bereaved parents. While RSV was not detected in the MITS cases, remarkable pathology findings from 11 cases included bacterial pneumonia, pyogenic pneumonia, hyaline membrane disease, mild focal chronic interstitial inflammation, aspiration pneumonia, diffused alveolar damage, and bronchopneumonia in the lungs. These findings indicate the significance of MITS in identifying causes of death in infants, which can be helpful in prioritizing strategies for determining causes of death and reducing infant mortality in developing regions.

0735

QUALITY MANAGEMENT SYSTEMS IMPLEMENTATION IN ANIMAL HEALTH LABORATORIES FOR IMPROVED DETECTION OF PRIORITY ZOONOSES IN UGANDA

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Emerging and re-emerging zoonotic diseases pose an ever-increasing threat to public health. Implementation of Quality Management System (QMS) in laboratories is critical for detecting and responding to disease threats. Uganda has 34 human health laboratories accredited to ISO standards. However, the animal health sector lacks any ISO accredited facility. Therefore, USAID's Infectious Disease Detection and Surveillance (IDDS) project and the Ministry of Agriculture, Animal Industry and Fisheries initiated QMS implementation in April 2021, to improve laboratory service delivery and set regional animal health laboratories on the path toward accreditation based on ISO/IEC 17025:2017 structure. From October 2020, the IDDS project conducted a multi-sectoral consultative meeting to develop a QMS mentorship tool kit based on ISO 17025:2017, in addition to Training of Trainers (TOTs). The certified TOTs then supported training for staff at four regional animal health laboratories in Gulu, Mbale, Mbarara, and Moroto, with each regional veterinary laboratory supporting between 7 to 11 districts in the catchment area. These facilities were enrolled in a mentorship program, and audits were conducted to gauge policy documents' impact, standardizing, and alignment. IDDS supported the development of a QMS mentorship tool kit and 8 veterinary and 12 laboratory staff training at the respective regional animal health laboratories. Four regional facilities were enrolled in the QMS mentorship program. Pre-audit results indicated that these facilities had no QMS-related documentation. Post-audit results showed that relevant SOPs and Quality Manuals were developed. We conducted mandatory trainings for QMS implementation and developed SOPs and policy documents required by the standard. The pre and post test scores during the trainings indicated an average increment in knowledge from 33.2% in the pre-test to 81.8% in post scores.

0736

DESIGN OF EFFECTIVE OUTPATIENT SENTINEL SURVEILLANCE FOR COVID-19 DECISION-MAKING: A MODELING STUDY

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Decision-makers impose COVID-19 mitigations based on public health indicators such as reported cases, which are sensitive to fluctuations in supply and demand for diagnostic testing, and hospital admissions, which lag infections by two weeks. Imposing mitigations too early has unnecessary economic costs, while imposing too late leads to uncontrolled epidemics with too many cases and deaths. To overcome bias and lag in conventional indicators, the city of Chicago, USA, implemented sentinel surveillance of recently-symptomatic individuals in outpatient testing sites by collecting data on symptom status and symptom onset date. Even with few participating testing sites, Chicago found that sentinel cases were more timely than hospital admissions, although trends were less certain due to low sampling rate. To characterize the minimal outpatient sentinel surveillance system needed for reliable trend estimation, we use a stochastic compartmental model and evaluate the performance of various surveillance indicators at reliably triggering an alarm in response to, but not before, a step increase in transmission rate. We find that outpatient sentinel surveillance that captures at least 20% of incident mild cases results in mitigative action median of 3 to 5 days earlier, triggers fewer false alarms (5% vs 39%), and averts more deaths per day spent in mitigation than surveillance based on hospital admissions. Because hospitalization rates are lower in younger populations, we tested whether sentinel surveillance was especially beneficial when transmission surges happened first in younger populations, as was observed in several epidemic waves in the USA. When older populations lag younger populations in experiencing transmission surges by 20 days, sentinel surveillance extends its lead in acting against an incoming wave by an additional 4 days over hospital admissions. Sentinel surveillance of mild symptomatic cases is a feasible and effective tool for guiding decision-makers in an epidemic like COVID-19.

0737

SHARING MINIMALLY INVASIVE TISSUE SAMPLING (MITS) RESULTS WITH MOTHERS AND ITS IMPACTS ON HEALTH-SEEKING BEHAVIOR AND DELIVERY OUTCOMES IN SUBSEQUENT PREGNANCY: FINDINGS FROM HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) BANGLADESH

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The Child Health and Mortality Prevention Surveillance (CHAMPS) network conducts minimally invasive tissue sampling (MITS) and data collection to determine the causes of stillbirths and under 5 child deaths in a rural area Baliakandi, Bangladesh. An expert panel identifies causes of death and preventive measures after reviewing laboratory reports, clinical records, and verbal autopsies. The results and recommendations, such as using quality antenatal care (ANC) and future health-seeking behavior, are shared with the mothers. This study aimed to assess the impact of sharing MITS results and recommendations with mothers on their health-seeking behavior and delivery outcomes in subsequent pregnancies. From September 2017 to February 2022, we conducted 121 MITS of babies of 118 mothers and shared results with 99 mothers in the Baliakandi catchment area. Among them, 36 women had subsequent pregnancies and delivery outcomes. For the pregnancy associated with the MITS procedure, 13 women had stillbirths, 21 died in the early and 2 in the late neonatal periods. Sixty percent (15/25) of women sought ANC services during their MITS-associated pregnancy, which increased to 85% (28/33) in subsequent pregnancies with known ANC status. Previously only one woman (1/25) had ≥ 4 ANC visits, compared to 33% (11/33) of women in the subsequent pregnancies. During their MITS-associated pregnancy, the median gestational age at the first ANC visit was 18 weeks (IQR: 8-26), compared to 13.5 weeks (IQR: 9.5-17.5) in the subsequent pregnancy. The median birth spacing was 7.5 months (IQR: 3-14). However, 53% (19) of mothers' last menstrual period (LMP) of subsequent pregnancy was before the result sharing date, and their mean inter-pregnancy interval was 3 months. Pregnancy outcomes included 29 (81%) live births, 5 (13%) miscarriages, 2 (6%) induced abortions, and 79% (23/29) chose to deliver their babies at a health facility. Our preliminary findings highlight the increased coverage and timeliness of ANC in subsequent pregnancies. Further exploration of barriers to ANC visits, early result sharing within 3 months may improve their further health-seeking behavior.

0738

IMPROVING COMMUNITY DEATH NOTIFICATION IN A HEALTH AND DEMOGRAPHIC SURVEILLANCE SYSTEM: LESSONS LEARNT FROM 5-YEAR OF A TOLL-FREE IN MANHICA DISTRICT, MOZAMBIQUE

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In some low and-middle income countries, health and demographic surveillance systems (HDSS) are established to provide accurate and timely reported demographic data for biomedical research, but the increasing demand on timely reported events forces the constant innovation in their methods. This paper describes the Manhica HDSS the toll-free introduced to report deaths and stillbirths in 24 hours of occurrence, evaluating the usefulness of this toll-free for improving the HDSS timely report. The toll-free was implemented in 2017 to respond to the Child Health and Mortality Prevention Surveillance (CHAMPS) network study, which require the report of under five years deaths and stillbirths within 24 hours to perform minimally invasive tissue sampling in the corpses for ascertaining the causes of death. All the calls received are recorded in a database that report the time of the call, category of the notifier, type of event, place and date. The analysis consists of descriptive statistics of who reports what from where, and whether the time-to-report events has improved during the 5-year period of toll-free compared to 5-period prior to the toll-free. Challenges for a correct functioning of this call center include low network coverage, scarcity of mobile phones within the community, and the lack of electricity in many households. The analysis shows that the time to report events has sharply decreased after the introduction of toll-free, compared to the period prior to the toll-free from an average of 69.8 days to 48.3 for reporting under-five deaths and from 64.9 to 2.7 days for reporting stillbirths. The percentage of child deaths and stillbirths reported within 24 hours has increased from an average of 43.7% before toll-free to 67.6% after in stillbirths, and from 15.2% to 34.1% in child deaths. Delays in reporting remain significant, particularly with community deaths, where only 26% were reported within 24h. Community engagement remains critical to foster faster reporting of community deaths. The toll-free number needs to be distributed to all the households rather to be given to community key informants who cannot capture all the information.

0739

LYME SERO-CONVERSION SURVEILLANCE AMONG U.S. MILITARY PERSONNEL IN HONDURAS

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Lyme disease is caused by the spirochete *Borrelia burgdorferi sensu lato*. Transmission is through the bite of infectious ticks, primarily the hard tick from the genus Ixodes. Within the US active duty members, Lyme disease is the most frequently reported vector-borne disease with an incidence rate of 292 cases per 100,000 person years in in fiscal year 2016-2018 in a study in West Point. There has been no report about Lyme disease in Central America but there are reports of a traveler that contracted rickettsia after his trip to Honduras. This highlights the need for better surveillance of Lyme disease in Honduras. The aim of this study is to determine the prevalence of Lyme disease in U.S. military personnel deployed to Honduras using serological assays. A cohort of pre- and post-deployment sera from the most recent 1,000 U.S. military personnel stationed in Honduras for at least six months between 2000 and 2016 was used for this study. All post-deployment serum samples were screened at a dilution of 1:100 for the presence of IgG antibodies against *Borrelia burgdorferi* with ELISA. The pre-deployment sera from those individuals with seropositive post-deployment samples were tested to determine seroconversion. Seroconversion was defined as conversion of an optical density value from below the cutoff in a pre-deployment specimen to above the cutoff in a post-deployment specimen. The post-deployment seropositivity in U.S. military personnel for antibodies against *Borrelia burgdorferi* was 5.2% (52/1,000). Among them, seroconversion occurred for 11 (1.1%) persons during their assignment to Honduras. In conclusion, this is the first study for risk assessment of Lyme disease among U.S. military personnel deployed to Honduras. Additional testing of potential vectors for *Borrelia burgdorferi* in the regions could inform effective vector control counter measurements to prevent exposure.

0740

HYPERSENSITIVITY REACTIONS TO *IXODES SCAPULARIS* BITES

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Tick salivary proteins introduced into mammalian hosts during a blood meal result in an array of complex immune reactions. Previous studies

have suggested that hypersensitivity reactions following *Ixodes scapularis* bites, including itch, may interfere with the transmission of tick-borne pathogens, including *Borrelia burgdorferi* (the Lyme disease agent). There are few studies in humans regarding the spectrum of hypersensitivity reactions that occur following *I. scapularis* bites and their effect on *B. burgdorferi* transmission. We analyzed data obtained from the prospective enrollment of 102 people who reported acute tick bite to a medical practice in Mansfield, Connecticut and from serosurvey participants on Block Island Rhode Island from 2005-2018. Ticks brought in by study subjects were speciated. Clinical responses from these patients and those who participated in the serosurvey were recorded and subject based diaries were used to classify hypersensitivity reactions and to determine whether they reduced Lyme disease transmission. None of the 102 subjects developed systemic reactions following tick bite. The most common localized reactions were type I hypersensitivity reactions, including local erythema (88%), swelling (64%), and itch (48%). About a quarter of study subjects experienced swelling that was consistent with a delayed type hypersensitivity reaction. Of these reactions, only tick bite itch was associated with the frequency of tick bites. Those with 3 or more tick bites in the previous 12 months were 6 times more likely to report a current tick-associated itch than those who experienced 1 bite in the previous 12 months. Hypersensitivity responses were not associated with the presence or absence of a history of Lyme disease. A third (308) of the 919 serosurvey participants reported itch following tick bites.In conclusion, hypersensitivity reactions to *I. scapularis* bites were common in residents of a Lyme disease endemic region in the Northeast. Tick bite-associated itch was positively associated with the frequency of tick bite but not with a past history of Lyme disease.

0741

LONGITUDINAL STUDY OF *IXODES SCAPULARIS* ABUNDANCE AND PATHOGEN BURDEN IN CONNECTICUT, U.S.A.

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Ixodes scapularis are the primary vector for numerous human pathogens, including *Borrelia burgdorferi*, *Borrelia miyamotoi*, *Anaplasma phagocytophilum*, *Babesia microti*, and Powassan virus lineage II. Understanding the spatial and temporal distribution of *I. scapularis* and its associated pathogens is paramount to implementing necessary control strategies and public health interventions. Consequently, in 2019, we began an active tick surveillance program to better monitor tick presence and tick-borne pathogen prevalence in Connecticut. Between 2019 and 2021 a total of 1561 female and 1787 nymphal *I. scapularis* were collected from all 8 counties across the state. Individual *I. scapularis* were tested with a RT-qPCR multiplex assay against the five aforementioned pathogens. Statewide pathogen prevalence rates were 56.6% in females (833/1561) and 26.8% in nymphs (478/1787), with the most common being *B. burgdorferi*, 49.7% (776/1561) and 18.6% (332/1787) in females and nymphs, respectively. Year-to-year analysis of pathogen prevalence revealed a significant increase in the percentage of pathogen positive ticks. While pathogen presence at the county level fluctuated year-to-year, significant differences were witnessed between counties when examining total pathogen presence over the three-year period. Our multiplex assay allowed us to observe significant increases in co-infection with *B. burgdorferi* and at least one other pathogen at the state level since 2019. Results from the active tick surveillance program gives both a better grasp of tick abundance as well as the burden of tick-borne pathogens throughout the state at the county level.

0742

PRE-CLINICAL EFFICACY AND CORRELATES OF IMMUNITY FOLLOWING VACCINATION WITH FOUR IMMUNODOMINANT *BABESIA MICROTI* ANTIGENS IN MICE

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Babesia microti, an intraerythrocytic apicomplexan parasite, is the primary causative agent of human babesiosis and an emerging threat to public health in the United States and elsewhere. In addition to natural transmission by *Ixodes* ticks, *B. microti* can also be transmitted in blood and blood products. In spite of its global presence and geographical expansion, very little investment has been made to develop novel therapeutics, including drugs and vaccines, against this pathogen. Here we report on immunogenicity, protective efficacy and immunological correlates of immunity following vaccination with four recombinantly-produced immunodominant *B. microti* antigens—Serine-repeat antigen 1 (SERA1), Maltese cross form-related protein 1 (MCFRP1), piroplasm β-strand 1 (PiβS1), and *Babesia* α-helical cell surface 1 (BAHCS1). BALB/c mice were immunized with purified *E. coli*-expressed protein with Montanide ISA 51/CpG adjuvant delivered subcutaneously. Protective efficacy was measured as reduction in peak parasitemia and in total parasite burden throughout the course of infection following challenge with asexual blood form *B. microti* parasites. Vaccination-induced immune response against each *B. microti* antigen was assessed by antigen-specific total IgG and IgG subclass ELISA, multiparameter flow cytometry, and Bio-Plex Pro Mouse Cytokine 23-plex assay. Results showed that that immunization with BAHCS1 led to highest reduction in peak parasitemia (70.2%), followed by SERA1 (43.5%) and MCFRP1 (41.9%). While all four antigens demonstrated a capacity to stimulate strong antibody and cellular responses, early activation of a Th2-type response was generally associated with a protective immune response. Our data suggest that BAHCS1 warrants further evaluation in preclinical studies. Details of immunization/challenge and correlates of vaccination-induced immunity against these antigens will be presented.

0743

FLEA-BORNE TYPHUS CAUSING FATAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Flea-borne typhus (FBT) is increasing in incidence in multiple global locations and usually has a benign course. Herein, we present a fatal case of hemophagocytic lymphohistiocytosis (HLH) ascribed to FBT. A 71-year-old diabetic woman presented with confusion, weakness, nausea, and urinary frequency. She was lethargic, with vitals significant for tachypnea and BP 163/63 mm Hg. Lab evaluation revealed WBC 9.84 K/μL (reference range (RR) 3.4-10.4 K/μL), Hgb 14.2 g/dL (RR 11.5-14.9 g/dL), platelets 125 K/μL (RR 140-370 K/μL), bicarbonate 13 mmol/L (RR 20-29 mmol/L), anion gap 22 mmol/L (RR 8-12 mmol/L), glucose 148 mg/dL (RR 60-100 mg/dL), AST 153 U/L (RR 13-39 U/L), ALT 55 U/L (upper limit of normal (ULN) <36 U/L), alkaline phosphatase (AP) 48 U/L (RR 45-117 U/L), and albumin 3 g/dL (RR 3.2-5.0 g/dL). She was diagnosed with euglycemic diabetic ketoacidosis and was started on ceftriaxone, IV fluids, and insulin drip. On day-2 (D2), anion gap normalized. She was persistently febrile; blood, urine culture were negative, and CT showed lingular consolidation. Viral respiratory and hepatitis panels as well as HIV test were negative; C-reactive protein was 247 mg/L (ULN 10 mg/L). On D4, she had increasing AST, ALT, and AP. On D5, she developed worsening mental status, lactic acidosis, hypotension, and respiratory failure. She was intubated and started on norepinephrine and broad-spectrum antibiotics including doxycycline. Testing on D5 showed WBC 23.2 K/μL, Hgb 11.3 g/dL, platelets 74 K/μL, and procalcitonin >200 ng/mL. On D6, AST 3361

U/L, ALT 392 U/L, AP 403 U/L, and bilirubin 2.4 mg/dL (RR 0.2-1.2 mg/dL). Bronchoalveolar lavage cultures were negative. She had worsening lactic acid to 20.3 and increasing pressor requirements. Later, she transitioned to comfort care. Final lab tests showed Hgb 8.1 mg/dL, platelets 64 K/μL, and elevated lactate dehydrogenase (3374 U/L); d-dimer (58,663 ng/mL (< RR 500 ng/mL)), and hypertriglyceridemia. *Rickettsia typhi* serology sent on D5 returned later with IgM 1:256, IgG <1:64. Autopsy revealed hemophagocytic histiocytes in lymph nodes and bone marrow. With these findings, the cause of death was ascribed to HLH due to FBT.

0744

DEVELOPMENT OF A RECOMBINASE POLYMERASE AMPLIFICATION LATERAL FLOW (RPA-LF) ASSAY TO DETECT *EHRLICHIA CHAFFEENSIS*

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Human Monocytic Ehrlichiosis (HME) is an emerging and potentially fatal tick-borne disease caused by the intracellular, Gram-negative bacterium, *Ehrlichia* with *E. chaffeensis* being the most common species infecting humans. HME can be difficult to distinguish from other tick-borne infections and causes of febrile illness. Traditional laboratory confirmation of HME requires serological testing performed on acute and convalescent plasma samples collected 2-4 weeks apart, which is infrequently achieved. These factors contribute to both under- and misdiagnosis of HME. Quantitative polymerase chain reaction (qPCR) offers a species-specific method of *Ehrlichia* identification. However, qPCR assays are expensive and not readily available outside of reference laboratories, which limits their utility in clinical management of acute disease. To address the current pitfalls in HME diagnostics, we developed a recombinase polymerase amplification (RPA) assay adapted to a lateral flow (LF) platform to isothermally detect *E. chaffeensis*. Five primer sets, targeting three gene segments, were tested using TwistAmp® Basic kit and kit manual from TwistDx™. The primer set with the best band intensity following gel electrophoresis was selected for adaptation to the RPA. A probe was designed according to the TwistAmp® nfo guidelines. The primer-probe set, targeting the groEL gene segment, which encodes a 60-kDa heat shock protein that is specific to *Ehrlichia chaffeensis*, was tested using the TwistAmp® nfo kits and visualized on lateral flow strips. The RPA-LF assay successfully detected genomic DNA specific to *E. chaffeensis* but did not detect DNA from *Anaplasma phagocytophilum, E. ewingii, Rickettsia rickettsii, R. amblyomatis, R. parkeri, R. africae, Brucella abortus*, or *B. suis*, which may cross-react with serologic assays for *Ehrlichia*. In conclusion, the RPA-LF assay targeting the groEL gene is specific for *E. chaffeensis*. Further testing to determine the limit of detection for the assay is underway.

0745

FIELD EVALUATION OF LOOP-MEDIATED ISOTHERMAL AMPLIFICATION FOR DETECTION OF *ONCHOCERCA* SPP. IN BLACKFLY POPULATIONS

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Onchocerciasis (river blindness) is a vector-borne neglected tropical disease caused by *Onchocerca volvulus*. Worldwide an estimated 20.9 million individuals live with infection and a further 205 million are at risk of disease, predominantly in sub-Saharan Africa. As a current target for disease elimination, monitoring of blackfly vector populations (*Simulium damnosum s.l.*) is necessary to determine whether transmission is ongoing in endemic areas. Presently, this requires centralised testing by PCR. In the current investigation, we evaluated the performance of a novel Loop-mediated Isothermal Amplification (LAMP) assay for detection of *O. volvulus* and/or the closely related cattle parasite *O. ochengi* in infected *Simulium damnosum s.l.* populations. First, *Simulium damnosum s.l.* were collected from a location with confirmed *O. ochengi* transmission. Pooled samples were tested by LAMP assay using a generic O-150 primer, with 90 pools of 100 flies per pool. Results were compared to infection status determined by dissection of flies collected over the same time period, and conventional PCR. Second, the sensitivity and specificity of the LAMP assay using an *O. volvulus*-specific *Ov*-GST-1α primer set was tested through analysis of pooled DNA samples extracted from heads of laboratory-bred, *O. volvulus*-infected *Simulium damnosum s.l.*, with 30 pools of 10 heads per pool; alongside pooled DNA samples with confirmed *O. ochengi* infection from the initial investigation. These investigations determined that the LAMP assay was: (a.) as effective as conventional methods at detecting *Onchocerca* spp. infection under field conditions using generic O-150 primers, (b.) capable of detecting *O. volvulus* infection with a high degree of sensitivity from 8 days post-infection in fly heads using species-specific primers, but (c.) current primers and/or methods may indicate presence of other *Onchocerca* spp. DNA in addition to *O. volvulus*. Pending further field study and evaluation, these findings show the potential of LAMP assays as a screening tool for *O. volvulus* transmission with a possible future role in ongoing disease elimination programmes.

0746

INVESTIGATION OF SEROPREVALENCE OF EHRLICHIOSIS AND ANAPLASMOSIS ALONG THE TEXAS-MEXICO BORDER

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Ehrlichia sp. and *Anaplasma* sp., both members of the family Anaplasmatacea, are tick-borne pathogens of public health importance that are endemic to the US. Symptoms for these diseases range in severity from asymptomatic infection (80% of cases) to a febrile illness that requires hospitalization. Since these pathogens were first described in the late 1980s and 1990s, the incidence of human infection of both *Ehrlichia* spp. and *Anaplasma* sp. have been increasing in the US. Additionally, cases likely still remain underreported due to lack of physician awareness, non-specific clinical presentation, and insufficient access to diagnostic tests. Our current understanding of the epidemiology of these diseases remains in its infancy and the US, and specifically in Texas. Our study aims to determine the seroprevalence of Ehrlichiosis and Anaplasmosis in a large cohort (n=610) of adults residing along the Texas-Mexico border. We screened the cohort using a dual spot immunofluorescent assay (IFA) to determine the IgG reactivity to *Ehrlichia* spp. and *Anaplasma phagocytophilium*. Seropositivity was defined as a titer of ≥1:64. We identified 24% of the cohort were seropositive for *Ehrlichia* spp. and 3% were seropositive for *A. phagocytophilium*. End-point titers were determined for seropositive samples and a risk-factor analysis was conducted using survey data. These findings indicate a high disease burden, especially along the Texas-Mexico border. While it is suspected that the majority of *A. phagocytophilium* is imported, there is growing evidence that transmission of Ehrlichiosis

is ongoing in the border region. There is a need to develop more robust screening tools and organize a public health response in the region that focusing on detection.

0747

THE EMERGENCE OF TICKS AND TICK-BORNE DISEASE IN SOUTH CAROLINA: ESTABLISHING A STATEWIDE INITIATIVE LEVERAGING ACADEMIC-PUBLIC PARTNERSHIPS

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Tick-borne diseases have tripled in the last two decades, with several novel pathogens and an invasive tick species recently discovered in the United States. Local vector control agencies have traditionally focused on mosquito abatement; however, the need to establish tick surveillance activities has grown as tick-borne disease incidence has concomitantly expanded. In response to this emergent public health threat, the state health department and flagship university in South Carolina established a productive tick surveillance program. This presentation will discuss the capacity building and partnership leveraging aspects of starting a large-scale public health program, and results from the past three years of surveillance. This program yields an average of 5,000 ticks annually from a variety of sources: state and county parks, state forests, animal shelters, and cattle ranches and auctions. Nine tick species have been collected in South Carolina as apart of the three-year surveillance program, including four non-native species: Asian longhorned tick, Gulf Coast tick, the Northern clade blacklegged deer tick, and the rabbit tick. Collected ticks tested positive for pathogens that cause spotted fever group rickettsioses, Lyme disease, anaplasmosis, and ehrlichiosis. Species and pathogen geographic distribution will be presented. Overall, this presentation will provide a solid understanding of the changing epidemiologic profile of tick-borne diseases in South Carolina.

0748

THE SEROPREVALENCE AND RISK FACTORS FOR SPOTTED FEVER GROUP AND TYPHUS GROUP RICKETTSIA ALONG THE TEXAS-MEXICO BORDER

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Rickettsial pathogens are gram-negative, obligate intracellular bacteria classically divided into two main groups: Spotted Fever Group Rickettsia (SFGR) and Typhus Group Rickettsia (TGR). Ticks are the predominant vectors for SFGR species, whereas fleas and lice are the primary vectors for TGR species. Both groups represent a significant and emergent source of disease in Texas and along the U.S.-Mexico border. Understanding risk factors associated with the transmission of these pathogens is necessary for developing prevention strategies and targeted interventions for high-risk groups in Texas. To better understand the prevalence and risk factors for SFGR and TGR, we conducted a cross-sectional study using plasma samples from participants of an ongoing cohort study (N=616) in south Texas. Samples were screened for SFGR and TGR using enzyme-linked immunosorbent assays (ELISAs). All ELISA positive samples were then confirmed using a dual spot indirect immunofluorescent assay (IFA). Seropositivity was determined as having an endpoint titer ≥1:64. Additionally, demographic and epidemiologic data were collected from participants for a risk factor analysis. Our preliminary analysis indicated a higher seroprevalence of TGR compared to SFGR, at 30% and 8% respectively. These findings demonstrate that SFGR and TGR are likely endemic to regions along the Texas-Mexico border and require further investigation to fully understand the disease burden.

0749

FIRST WHOLE GENOME ISOLATION OF CRIMEAN-CONGO HAEMORRHAGIC FEVER VIRUS (CCHFV) IN TICK SPECIES WITHIN GHANA AND THE RISK OF HUMAN EXPOSURE TO THE VIRUS

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Ticks are important blood-sucking arthropod vectors. They are known to spread a wide range of diseases that cause severe and life-threatening illnesses in animals and humans, including military personnel. In population-dense and trade-dominant areas such as the Greater Accra and Upper East Regions, the risk of zoonotic infections may be on the rise. This study, therefore, sought to identify the circulating tick species, determine the pathogens they carry, and assess the risk of exposure of primary animal handlers and impact it may have on force health protection. A total of 705 ticks were collected from cattle (n=188) and horses (n=11). Three tick genera (*Hyalomma, Amblyomma* and *Rhipicephalus*) were observed in the study with the predominant species being *Hyalomma rufipes* (n=290, 41.13%), followed by *Amblyomma variegatum* (n=157, 22.27%) and the least abundant, *Rhipicephalus sanguineus* (n=1, 0.14%). Out of the 705 tick samples, Crimean-Congo haemorrhagic fever virus (CCHFV) infection rates of 0.78% (95% CI, 0.02-3.96), 0.69% (95% CI, 0.08-2.4) and 0.64% (95% CI, 0.02-3.24) were recorded in *Hyalomma truncatum*, *H. rufipes* and *A. variegatum*, respectively. No infection was detected in the *Rhipicephalus* species. Further, a strain was successfully recovered using Next Generation Sequencing for PCR positive tick samples with analysis based on complete open reading frame of the S-segment of the CCHFV genome. The strain belonged to the third genotype (Africa 3) and shared 98.9% nucleotide identity with DQ211641_Mauritania_1984 and MF287636_Spain_2016. Preliminary analysis for antibodies to CCHFV was detected in 42.5% of the human serum (n=120) samples pending confirmatory Plaque Reduction Neutralization Test (PRNT). Findings from this study suggest the possible importation of the virus into the country through trade, which puts livestock and humans who may have primary contact with livestock at risk of infection.

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TICKS AND ZOONOTIC TICK-BORNE PATHOGENS OF LIVESTOCK IN KASSENA-NANKANA DISTRICT, GHANA

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Ticks play a significant role in the transmission of infectious pathogens that affect both animals and humans, including U.S. military personnel whose

medical readiness is affected due to increased morbidity. Even though tick-borne infections continue to increase globally, there are no effective measures to prevent infection spread. The Upper East Region of Ghana is a conducive environment for the proliferation and spread of disease-causing pathogens, especially those of zoonotic origin due to the high dependence on livestock production by inhabitants. With the trade of livestock across the borders, there is an increased risk of zoonotic infections. This study focused on identifying tick species within selected sites in the Kassena-Nankana District and sought to determine infectious zoonotic pathogens using livestock. A total of 1,550 ticks were collected from 448 livestock that included cattle, sheep, and goats, with tick infestations recorded as 78.60%, 25% and 5.88%, respectively. *Amblyomma variegatum* (62.98%) was identified as the most predominant tick species. Out of the 491 tick pools screened, initial PCR results indicated the presence of *Rickettsia* species (n=279, 56.82%), *Babesia/Theileria* species (n=40, 8.15%), Crimean Congo haemorrhagic fever virus (CCHFV) (n=2, 0.41%) and *Coxiella* species (n=18, 3.67%). Co-infections were found in 33 (6.72%) tick pools with pathogens *Rickettsia/Babesia/Theileria* (n=23, 4.68%), *Rickettsia/Coxiella* (n=5, 1.02%), *Rickettsia*/CCHFV (n=2, 0.41%), *Coxiella/Babesia/Theileria* (n=1, 0.20%), and *Rickettsia/Coxiella/Babesia/Theileria* (n=2, 0.41%). Furthermore, 276 livestock dry blood spots were examined using PCR from which *Rickettsia* (n=9, 3.26%) and *Babesia* (n=37, 13.41%) were identified with co-infection in one cattle sample (1%). The findings suggest multiple zoonotic pathogens circulating in the sampling sites with a high occurrence of *Rickettsia* spp. Thus, there is an increased risk of infections to inhabitants, U.S. military personnel, and the livestock populations with no present treatment or preventative strategies.

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RISK FACTORS FOR TICK INFESTATION AND DISTRIBUTION ON LIVESTOCK IN GHANA

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Ticks are important disease vectors affecting animal and human health and causing substantial economic loss, especially in the tropics and subtropics. In addition, vector-borne diseases directly and negatively impact the ability of U.S military personnel to conduct contingency operations due to morbidity. Ticks were collected from 400 animals including cattle (388), horses (11) and sheep (1) from five regions in Ghana. The animals were mostly female (51%), older than 3 years (66%), of Ghanaian breed (92%) and were unvaccinated (91%). Of the animals sampled, 2,204 ticks were collected with a mean tick burden of 4.9 ticks/livestock. Although more ticks were collected from the udder/scrotum (53%) of the animals, on average, the ticks preferred the abdomen (Mean=6.5, SE=1.2). Furthermore, there was a significant association between the tick burden on the udder/scrotum of the animals with age (χ^2=22.5, df=2, P<0.001) and vaccination status (χ^2=16.7, df=1, P<0.001). The tick species identified were predominantly *Amblyomma variegatum* (44.1%) and *Hyalomma rufipes* (28.4%). *A. variegatum* had a high preference for the udder/scrotum (62.9%, χ^2=74.27, p<0.001) while *H. rufipes* preferred the anal region (63.6%, χ^2=95.09, p<0.001). Using the Generalized Linear Mix Model (GLMM), tick burden on the udder/scrotum was significantly higher than on the anal region (P=0.01197), and tick abundance was found to be significantly higher in livestock older than 3 years. It was observed that there was a significantly higher tick burden among the indigenous Ghanaian animal breeds compared to livestock from Mali (GLMM, P=0.03165) and South Africa (GLMM, P=0.0025). In addition, the vaccination status of the livestock did not influence the tick abundance (GLMM, P=0.497). The abundance of tick species in Ghana suggests a need to formulate effective control measures to reduce the burden on livestock farming and the potential spread of tick-borne diseases to local and U.S. military populations.

0752

A RETROSPECTIVE ANALYSIS OF CUMULATIVE MALARIA INCIDENCE IN HEALTH ZONES APPLYING INDOOR RESIDUAL SPRAYING WITH AND WITHOUT SEASONAL MALARIA CHEMOPREVENTION IN NORTHERN BENIN FROM JANUARY TO DECEMBER 2019

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Malaria is endemic in Benin with seasonal and spatial variation in intensity. Some districts in northern Benin have the highest malaria incidence rates in the country. In 2019, indoor residual spraying (IRS) with Actellic and seasonal malaria chemoprevention (SMC), in children aged 3-59 months, with sulfadoxine-pyrimethamine (SP) and amodiaquine targeted several health zones (HZ) in northern Benin. This study provides a precursory retrospective analysis of routine health facility data collected for 12 months (January-December 2019) comparing the cumulative malaria incidence in sites that received IRS alone and IRS + SMC with control sites that did not receive IRS or SMC. Three HZ sites comprising 9 districts were used in the study analysis. In 2019, the HZ of Djougou-Copargo-Ouaké received IRS only, Kandi-Gogounou-Ségbana received SMC + IRS, and Natitingou-Toukountouna-Boukoumbé did not receive IRS nor SMC (control HZ). Routine monthly malaria cases from the HZ information system were analyzed for incidence trends. The cumulative incidence (new cases/HZ population at-risk/year) was calculated for the 3 HZ. An unadjusted incidence rate ratio (IRR: incidence of IRS+/- SMC HZ over control HZ) was calculated in R using rateratio.test package. The cumulative malaria incidence in the control HZ was 420 cases/1000. For the IRS only HZ, the incidence was 320 cases/1000 with an IRR of 0.76 (95% confidence interval [CI]: 0.66-0.88). For the SMC + IRS HZ, the incidence was 218 cases/1000 with an IRR of 0.52 (95% CI: 0.44-0.61). Incidence peaked from June to October in the 3 HZ, with the amplitude highest in control HZ (56 cases/1000) followed by IRS only HZ (39 cases/1000), and IRS + SMC HZ (35 cases/1000). While in this limited analysis, IRS +/- SMC HZ had lower malaria incidence than control HZ, more analysis is needed with a longer pre- and post-time series and an assessment of study confounders to assess impact. Thus, these results are preliminary pending a more robust analysis. Additional studies assessing different malaria control combinations may assist Benin's National Malaria Control Program plan strategies that combat malaria transmission.

0753

WHOLE TRANSCRIPTOMIC ANALYSIS OF *ANOPHELES ARABIENSIS* RESISTANT TO PYRETHROIDS AND ORGANOPHOSPHATES FROM WESTERN KENYA REVEALS OVEREXPRESSION OF SALIVARY GLAND AND CUTICULAR PROTEINS

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Effective vector control is key to malaria prevention. However, this is now compromised by increased insecticide resistance in malaria vectors due to continued reliance on insecticide-based control interventions, thus posing a global challenge. In Kenya, resistance to pyrethroids and organophosphates has been shown to occur at varying levels in *Anopheles arabiensis* which is one of the major malaria vectors. We investigated the gene expression profiles of insecticide resistant *An. arabiensis* populations from Migori and Siaya counties in Western Kenya using RNA-Seq. CDC bottle assays were conducted using deltamethrin (DELTA), alphacypermethrin (ACYP) and pirimiphos-methyl (PMM) to determine the resistance status in both sites. RNA-Seq analysis was done on pools of mosquitoes which were resistant or non-exposed, alongside the susceptible *An. arabiensis* Dongola strain. Gene expression profiles of mosquitoes from Migori resistant to DELTA (average mortality of 91%), ACYP (92%), and PMM (58%); and mosquitoes from Siaya resistant to DELTA (85%), ACYP (86%), and PMM (30%), showed overexpression of mainly salivary gland proteins belonging to both the short and long form D7 genes, and cuticular proteins (including CPR9, CPR10, CPR15, CPR16). Additionally, the overexpression of detoxification genes including cytochrome P450s (CYP9M1, CYP325H1, CYP4C27, CYP9L1 and CYP307A1), 2 carboxylesterases and a glutathione-s-transferase (GSTE4) were also found to be shared between DELTA, ACYP, and PMM survivors, reflecting their association with both pyrethroid and organophosphate resistance. This study provides preliminary results of the molecular basis of resistance in *An. arabiensis* in Western Kenya, further adding to the evidence base that suggests that salivary gland proteins and cuticular proteins may play an important role in conferring resistance across insecticide classes.

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ASSESSMENT OF BEHAVIOR AND SOCIOCULTURAL RISK FACTORS IMPACTING DURABILITY OF INSECTICIDE-TREATED NETS IN MALI

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Within the context of a net durability study, an assessment of household behavior and sociocultural risk factors that could affect the physical durability of insecticide-treated nets (ITNs) was caried out. Cohorts of 120 and 90 households from Kenieba and Kita districts respectively, were identified and monitored at 6, 12, 24, and 36 months after the regional net distribution in 2017. Household behaviors and sociocultural risk factors were assessed following WHO and PMI guidelines, considering type of sleeping place, leaving the nets hanging during the day, exposure to informational messaging about net care, washing and repairing nets. A chi-square analysis was applied to compare the proportion of households responding to each specific category at each sampling time. The most common risk factors related to net damage in both sites across all sampling periods were storing food in the sleeping room and presence of rodents. More than half of all nets in both sites were found hanging loose over the sleeping place during the day. Heterogeneity in behavior was detected between villages. The risk of net damage by drying them over bushes or fences varied from 1.0% to 78.0% in Kenieba and from 1.0% to 36.0% in Kita ($p<0.001$) at 6, 12, and 24 months. At the time of each survey, the net washing frequency within the last six months ranged from 1 to 3 times in both sites. The use of detergent/bleach for washing nets was the same in both sites (>45.0%) at 6, 12, and 24 months; however, at 36 months, it was significantly higher ($p=0.0258$) in Kenieba (71.8%) than in Kita (37.8%). The respondents' exposure to messages on net usage within the previous 6 months was ($p<0.001$) lower in Kenieba (8.9% to 27.4%) than in Kita (29.2 to 43.8%). The proportion of respondents with a positive attitude/capacity to keep nets in good condition and repair net damage ranged from 13.6% to 56.1% in Kenieba and from 4.4% to 50.0% in Kita. This assessment provided valuable data on sociocultural determinants that could be used to develop social behavior change messages to promote increased ITN lifespan.

0755

RESULTS OF EXPANDED INSECTICIDE RESISTANCE MONITORING TO SEVERAL ECOLOGICAL ZONES IN CAMEROON FOR APPROPRIATE VECTOR CONTROL DECISION MAKING DATA

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Cameroon deploys insecticide-treated nets (ITNs) as its primary malaria vector control intervention. Collecting entomological data across ecological zones is key to informing distribution strategies to optimize vector control interventions based on resistance profiles. In 2021, an annual insecticide resistance monitoring was conducted in 10 sites (Bertoua, Djohong, Garoua, Gazawa, Mada, Mogode, Ndelele, Ngaoundere, Njombe, Touboro) in four ecological zones (rainforest, wet and humid littoral forest, and dry savanna) to support data-driven decision making. Bioassays were conducted using World Health Organization (WHO) susceptibility test kits or Centers for Disease Control and Prevention bottles. *Anopheles gambiae* s.l. larvae collected in the field and reared to 2-5-day-old adult females were tested against alpha-cypermethrin (0.05%), deltamethrin (0.05%), permethrin (0.75%), pirimiphos-methyl (0.25%), bendiocarb (0.1%), clothianidin (2% and 4 µg/bottle), and chlorfenapyr (100 and 200 µg/bottle). Resistance status was assessed using WHO criteria. When pyrethroid resistance was found, resistance intensity (5x and 10x the diagnostic doses) and synergist assays using 4% piperonyl butoxide (PBO) were performed. About 40% of *An. gambiae* s.l. (dead and alive) were screened for molecular resistance markers [knock down resistance (*kdr*)-west, *kdr*-east, acetylcholinesterase (*Ace-1*) and N1575Y]. High pyrethroid resistance (< 98% mortality at 10x the diagnostic dose) was found in all sites. Pre-exposure to PBO fully restored susceptibility to deltamethrin in Bertoua and Mogode. Susceptibility to chlorfenapyr was recorded at seven sites at 100 µg/bottle and all sites except Ngaoundere at 200 µg/

bottle. All sites recorded susceptibility to clothianidin (2%) and six sites to clothianidin (4 µg/bottle). Genetic markers of resistance were detected in all sites, with high frequency (0.9-1) of *kdr*-west found in eight sites. These results will help guide Cameroon's National Malaria Control Program on its vector control strategy (indoor residual spraying vs. ITNs) and optimal tool selection (type of ITNs) in the country.

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HABITAT-SPECIFIC SIGNALS OF SELECTION ON CYTOCHROME P450 GENES SUGGEST EMERGING INSECTICIDE RESISTANCE IN SOUTH AMERICAN MALARIA-TRANSMITTING *NYSSORHYNCHUS* (*ANOPHELES*) *DARLINGI*

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Malaria in South America remains a serious public health problem. Cases of *Plasmodium* infection are on the rise in some localities, and observations of drug resistance threaten to undermine control efforts. *Nyssorhynchus* (*Anopheles*) *darlingi* is the most important vector of these parasites in the western hemisphere. Insecticides have not been heavily used for malaria control in the neotropics and insecticide resistance is believed to be relatively low for *An. darlingi*, though surveillance is limited. It will be critical to understand if and how mosquitoes are poised to adapt to pesticide-based control measures and other anthropogenic changes. To investigate evolution and variation in this species, we have sequenced whole genomes from hundreds of *An. darlingi* specimens, representing the first large population genomic dataset from a malaria vector in the Americas, and we have characterized patterns of population structure and genetic diversity. We have generated 139 high-coverage genomes from French Guiana alone, collected at three ecologically disparate locations. At one French Guianese village, we see striking differences in allele frequencies within clusters of cytochrome P450 genes, relative to nearby populations that are otherwise genetically similar. Population genetic statistics indicate that these differences reflect recent, ongoing selective sweeps. This gene family is known to underlie insecticide resistance in numerous arthropod species. Thus, we hypothesize that these mosquitoes are adapting to local agricultural runoff, indirectly narrowing future vector control options. Other classic insecticide resistance mutations (e.g. *kdr*, *Rdl*) are not observed, suggesting novel mechanisms. This pioneering population genomic dataset suggests putative signals of insecticide resistance that was previously unsuspected and could threaten future vector control options, while also pinpointing candidate causal polymorphisms that could facilitate strategies to monitor and counteract its spread. These observations warrant further study, and trials to associate phenotypes with these variants are currently underway.

0757

DURABILITY OF LONG LASTING INSECTICIDAL NETS WITH AND WITHOUT PIPERONYL BUTOXIDE

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Long Lasting Insecticidal Nets (LLINs) supplemented with the synergist piperonyl butoxide have been developed in response to growing pyrethroid resistance however their durability in the field remains poorly described. A pragmatic cluster-randomised trial was embedded into Uganda's 2017-2018 distribution to compare the durability of pyrethroid LLINs with PBO (Olyset Plus and PermaNet 3.0) and without PBO (Olyset Net and PermaNet 2.0). Nets were sampled at baseline, 12, and 25 months post-distribution to assess physical condition, chemical content, and bioefficacy. Bioefficacy was assessed with WHO Cone and Wireball assays using pyrethroid-resistant *An. gambiae*. Ambient Chamber Tests (ACTs) with free-flying pyrethroid-resistant *An. gambiae* were performed with Olyset Plus and Olyset Net to investigate bloodfeeding with holed nets. There was no difference in the risk of being 'Too torn' between LLIN products assessed ($p=0.644$). The pyrethroid content of all LLIN products remained stable across timepoints but PBO content declined by 55% ($p<0.001$) and 58% ($p<0.001$) for Olyset Plus and PermaNet 3.0 respectively. Both PBO-LLINs were highly effective against pyrethroid-resistant mosquitoes when new, knocking down all mosquitoes. However, bioefficacy declined over time with Olyset Plus knocking down 45.72% (95% CI: 22.84-68.62, $p=0.021$) and Permanet 3.0 knocking down 78.57% (95% CI: 63.57-93.58, $p<0.001$) after 25 months. In ACTs mosquitoes were observed to enter a hole in the top of nets at a higher rate than a hole in the size (Olyset Plus: OR=10.71, 95%CI=1.38- 20.03). Here we demonstrate that both Olyset Plus and PermaNet 3.0 are as durable as their pyrethroid-only equivalents and had superior bioefficacy against pyrethroid-resistant *An. gambiae*. However, the superiority of PBO-LLINs decreased with operational use, correlating with a reduction in total PBO content. This decline in bioefficacy after just two years is concerning and there is an urgent need to assess the durability of PBO LLINs in other settings.

0758

IVERMECTIN-TREATED BIRDFEED CONFERS DOSE-DEPENDENT TOXICITY TO *CULEX TARSALIS* MOSQUITOES WHILE REMAINING SAFE FOR AVIAN CONSUMPTION

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West Nile Virus transmission is sustained in an enzootic cycle between ornithophilic *Culex* species mosquitoes and birds, highlighting this relationship as a potential target for intervention. Specifically, we can expose ivermectin (IVM) to *Culex tarsalis* via bloodmeals from birds treated with IVM-treated feed. IVM binds to glutamate-gated chloride channels (GluClR), causing paralysis and death in invertebrates while maintaining a robust safety profile in vertebrates due to differences in GluClR localization between species. To investigate this method, we provided chickens with IVM-treated feed at doses of 200 mg IVM per kg of feed (mg/kg IVM) and 360 mg/kg IVM for up to 7 days. We collected sera via jugular venipuncture on days 3 and 7 of the diet, then reconstituted it with chicken red blood cells to provide bloodmeals to 3-6 day old female laboratory-raised *Cu. tarsalis* mosquitoes. Additionally, we observed the birds' behavior to determine whether IVM caused any adverse effects during or following treatment. Our results demonstrate dose-dependent toxicity in *Culex tarsalis* mosquitoes with Mantel-Haenszel Hazard Ratios of 3.150 at day 3 of a 200 mg/kg IVM diet (IVM n=65, control n=63, P value<0.0001) and 7.068 at day 7 of the same diet (IVM n=58, control n=42, P value<0.0001), compared to 26.41 at day 3 of a 360 mg/kg IVM diet (IVM n=50, control n=84, P value<0.0001) and 28.74 at day 7 of the same diet (IVM n=53, control n=69, P value<0.0001), showing a pattern of decreased probability of survival with increased dose and feed consumption. Additionally, treated birds experienced no adverse events and consumed similar amounts of feed compared to control birds (IVM n=11, control n=12, two-way ANOVA for mean weight gain statistics ranged from P value = 0.0698-0.1123). Analysis of 500 mg/kg IVM diet

results, IVM concentration in sera, and histopathology is ongoing, and experiments with wild-type *Culex* species mosquitoes and wild-caught birds are planned for the upcoming field season. Results from these experiments will inform future decisions regarding the safest and most efficacious dose and formulation of IVM-treated feed to proceed to field trials.

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TRANSCRIPTOMIC ANALYSIS OF *ANOPHELES GAMBIAE* FROM BENIN REVEALS OVEREXPRESSION OF SALIVARY AND CUTICULAR PROTEINS ASSOCIATED WITH CROSS-RESISTANCE TO PYRETHROIDS AND ORGANOPHOSPHATES

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Insecticide resistance (IR) is one of the major threats to malaria vector control programs in endemic countries. However, underlying insecticide resistance mechanisms are poorly understood. Thus, investigating gene expression patterns related to IR can offer greater insight into the molecular basis of IR in mosquitoes. In this study, RNA-Seq was performed to characterize gene expression following exposure to pyrethroids (deltamethrin, alphacypermethrin) and an organophosphate (pirimiphos-methyl). Larvae of *Anopheles gambiae* s.s. were collected from Bassila and Djougou in Benin and reared to adulthood. Four-to-five-day old female mosquitoes were phenotyped for IR using the modified CDC intensity bottle bioassay. The results showed that mosquitoes from Djougou were more resistant to pyrethroids (5x deltamethrin: 51.7% mortality, 2x alphacypermethrin: 47.4%) than Bassila (1x deltamethrin: 70.7%, 1x alphacypermethrin: 77.7%), while the latter was more resistant to 1.5x pirimiphos-methyl (48.3%; 1x pirimiphos-methyl Djougou:21.49%). RNA-Seq was conducted on resistant mosquitoes, non-exposed mosquitoes from the same locations, and the susceptible Kisumu laboratory strain. RNA-Seq analysis showed over-expression of detoxification genes, including cytochrome P450s (CYP12F2, CYP4C27, CYP6Z3, CYP9K1, CYP4H15) and glutathione S-transferases (GSTE2, GSTMS3) in all the three resistant mosquito groups analyzed. Genes encoding cuticular proteins (CPR130, CPR10, CPR15, CPR16, CPR127, CPAP3-C, CPAP3-B, and CPR76) were also overexpressed in all the resistant groups, indicating their potential role in cross resistance in *An. gambiae*. Salivary gland protein genes related to 'salivary secreted peptide' and 'kDa salivary' were also over-expressed and shared across all resistant groups. These genes need further investigation to validate their functional role in *An. gambiae* resistance. Our results suggest that in addition to metabolic enzymes, cuticular and salivary gland proteins could play an important role in cross-resistance to multiple classes of insecticides in Benin.

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TEMPORAL EVALUATION OF INSECTICIDE RESISTANCE IN POPULATIONS OF THE MAJOR ARBOVIRAL VECTOR*AEDES AEGYPTI*FROM NORTHERN NIGERIA

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AbstractContemporary information on the major arboviral vector Aedes aegypti is inexistent in the sub-Sahel of northern Nigeria, where this vector is becoming omnipresent. To support evidence-based control measures, two populations of this vector, from BUK (Kano state) and Pantami (Bauchi state) were characterised. Larval bioassay (across three years) using temephos and deltamethrin revealed a significant increase in deltamethrin resistance, with LC_{50} of 0.018mg/L (resistance ratio compared to New Orleans, RR = 2.250) in 2018 increasing ~6-fold, by 2019 (LC_{50} = 0.100mg/L, RR = 12.5), and ~11-fold in 2020 (LC_{50} = 0.198mg/L, RR = 24.750). For the median deltamethrin concentration (0.05mg/L), a gradual decrease in mortality was observed, from 50.6% in 2018, to 44.9% in 2019, and 34.2% in 2020. Extremely high DDT resistance was observed, with <3% mortalities and LT_{50}s of 352.87 min, 369.19 min and 406.94 min in 2018, 2019 and 2020, respectively. Significant temporal increase in resistance was observed towards ƛ-cyhalothrin (a type II pyrethroid) over three years. Synergist bioassays with diethylmaleate and piperonylbutoxide significantly recovered DDT and ƛ-cyhalothrin susceptibilities respectively, implicating glutathione S-transferases and cytochrome P450s. Cone bioassays revealed increased resistance to the PermaNet® 3.0, side panels (mortalities of 94% in 2018, 66.4% in 2019, and 73.6% in 2020), while full susceptibility was obtained with the roof panels of PermaNet® 3.0. The F1534C *kdr* mutation occurred in low frequency, with significant correlation between heterozygote genotypes and DDT resistance. This temporal increase in resistance is a major challenge for control of this vector of public health importance, especially at the face of increasing yellow fever and dengue infections reported across Nigeria.

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MOSQUITOCIDAL ACTIVITY OF IVERMECTIN METABOLITES IN *ANOPHELES STEPHENSI*

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Ivermectin (IVM) is an antiparasitic drug to treat neglected tropical diseases in humans. Ivermectin is also an endectocide, a drug capable of killing arthropods, such as mosquitoes, feeding on a treated person. Mass drug administration of IVM has been suggested as a vector control tool for malaria elimination by reducing *Plasmodium* transmission through mosquito bites. Mosquitoes feeding on treated volunteers show increased mortality even after the parent drug is no longer detectable in the blood, a phenomenon known as a "post-ivermectin effect". Therefore, we aimed to assess whether not only the parent drug, but also its metabolites could contribute to the mosquitocidal effect in *Anopheles stephensi*. Twelve healthy participants were given a single oral dose of 12 mg IVM, and peripheral venous samples were collected over three days in a pharmacokinetic (PK) study. The levels of IVM and its metabolites were measured by LC-MS/MS in human blood. For the mosquito feeding, IVM metabolites were produced by incubating IVM with recombinant cytochrome P450 3A4/5, that were purified using semi-preparative high-pressure liquid chromatography. Nine metabolites were isolated and spiked to human whole blood matching the maximal blood intensities previously observed in the human PK study samples. Mosquito mortality and activity were recorded daily over three days post blood feeding. The time to reach maximal concentrations in blood was delayed for IVM metabolites compared to IVM. The metabolites elimination half-life was also longer in general. Three days after ingesting the blood containing the treatment, the survival and activity of mosquitoes was reduced for those that received IVM, M1, M2 and M4, compared to the blank blood. All other IVM metabolites did not have an appreciable effect on mortality. As

the mosquitoes were not only susceptible to IVM, but also to three of its metabolites, we conclude it could serve as a possible explanation for the "post-ivermectin effect".

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IMPROVEMENT OF INSECTICIDAL ACTIVITY OF NEONICOTINOIDS WITH COMMON DETERGENTS

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The development and evaluation of new insecticides as well as a reduction of environmental pollution due to their usage is crucial to preserve the efficacy of vector control tools such as long-lasting insecticidal nets and indoor residual spraying. With their unique mode of action, neonicotinoid insecticides provide promising alternatives to control mosquito populations that are resistant to insecticides rolled out in large-scale malaria control efforts. The aim of this work was to evaluate the efficacy of black soap, a common detergent, as an adjuvant to enhance the insecticidal action of neonicotinoids in malaria vectors. Using CDC bottle tests, we assessed the susceptibility of laboratory and field populations of Anopheles gambiae and An. coluzzii to two neonicotinoids, clothianidin and acetamiprid, alone and in combination with the detergent (SN). To determine if SN enhances insecticide toxicity, we established log-dose response curves of four populations with varying levels of susceptibility to clothianidin adding 1% SN to insecticide preparations. We then conducted a broader evaluation of the synergistic effect of SN by testing the diagnostic doses of clothianidin, acetamiprid and the pyrethroid deltamethrin containing 1% SN against field populations. At a concentration of 1%, SN had no insecticidal effect on An. gambiae and An. coluzzii when tested alone. However, SN dramatically enhanced the toxicity of clothianidin as revealed by the drastic reduction of the diagnostic dose from 150 µg/mL its absence to 8µg/mL in presence of the adjuvant 24 hours post-exposure. Moreover, susceptibility to clothianidin and acetamiprid was fully restored (100% mortality) in resistant field populations when 1% SN was used. By contrast, mortality to deltamethrin was lower in presence of SN (from 46% to 18%) suggesting an antagonistic effect of SN. Black soap provides a cheap, available and environmentally friendly adjuvant that can be used in neonicotinoid formulations intended for mosquito control. The search of other vegetable oils with synergistic effects will expand the possibilities of using neonicotinoids in malaria vector control.

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DRUG REPURPOSING FOR OPTIMAL USE OF IVERMECTIN AGAINST MALARIA: LONG LASTING FORMULATIONS ALLOWING EFFICACY AGAINST WILD-DERIVED ANOPHELES FOR AT LEAST TWO MONTHS

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Endectocides, in particular Ivermectin, are being considered as potent complementary tools helping wiping out Malaria disease. Compelling evidences accumulate, where administration of Ivermectin to humans or animals renders their blood toxic to residual *Anopheles* vectors. The short duration of Ivermectin exposure after single oral administration is not significantly decreasing the vector populations to levels impacting malaria incidence. Increasing the dosage and/or the administration frequency could compensate this limitation, but at the expense of logistical issues linked to repeated mass administrations or toxicity. Long-lasting injectable formulations of Ivermectin were developed based on the BEPO® technology for subcutaneous use, allowing a controlled and sustained release of Ivermectin at physiological meaningful concentrations for at least 2 months. Three candidate formulations were tested on calves, in Burkina Faso, against 2 Anopheles colonies that differed for their species and insecticide resistance status: Kisumu (*An. gambiae s.s.*, susceptible reference colony) and VK5 (*An. coluzzii*, wild derived). A 5-arm design, with a non-treated control, was used to characterize the PK and efficacy on mosquitoes' mortality during 4 months following single subcutaneous injection. All formulations were increasing mosquitoes' mortality from both colonies with a Hazard Ratio range of 5-20 for at least 42 days. Lethal concentrations inducing 90% cumulative mortality at 5 days were between 11.1-15.1 ng/ml for VK5 and 6-9.1 ng/ml for Kisumu; LC50 values were, respectively, between 3.1-7.6 and 0.4-2.2 ng/ml. With the support of a transmission model using different vectors/hosts scenarii, this work allowed the selection of a lead formulation with a sustained mosquitocidal efficacy above LC50 for more than 2 months, that would reduce infectious vector populations by at least 50% for 4 months. Discrepancies between both colonies pointed possible cross-resistance mechanisms displayed by field Anopheles. Further modeling at the epidemiological level and safety studies are ongoing towards human application in the future.

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THE ENTOMOLOGICAL IMPACT OF INSECTICIDE-TREATED NETS (ITNS) AND INDOOR RESIDUAL SPRAYING (IRS), IN THE AMERICAS: FILLING THE KNOWLEDGE GAPS

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Malaria vector control in Colombia has traditionally relied on indoor residual spraying (IRS), with insecticide-treated nets (ITNs) introduced over the past 15 years. However, the effectiveness of these tools against malaria vectors in the Americas remains poorly characterized. A two-arm cluster-randomized trial was designed to determine the entomological impact of pyrethroid-only ITNs and IRS in Cauca Department on the Pacific coast of Colombia, with biting rates (measured by human landing catches) as the primary indicator. Clusters were randomly assigned to receive either ITNs (alpha-cypermethrin) or IRS (deltamethrin). Baseline data collection began in January 2021, interventions were deployed in March 2021 (2,500 ITNs were distributed and 835 houses were sprayed) and the trial will run through March 2023. At eleven months post-intervention, a total of 87,166 anophelines had been collected, 80% of *Anopheles* caught were *Anopheles neivai* and 20% were *An. albimanus*. No significant differences were detected between the indoor and outdoor abundances of the species. When tested for insecticide resistance, both species were susceptible to both deltamethrin and alpha-cypermethrin using CDC bottle bioassays. Net bio-efficacy and integrity was evaluated at six months after distribution in 40 ITNs randomly selected from across the 20 ITN clusters. Bio-efficacy was very low, with a mean knock-down and mortality of 3% and 5%, respectively. Although 67% of ITNs had at

least one hole, 80% remained in serviceable condition. Seven days post-spraying, WHO cone bioassays were carried out in 2 households in each of 20 IRS clusters, showing a mean knockdown of 80% and mortality of 40%. Ovary dissections of mosquitoes collected in both intervention arms only detected a reduction in the proportion of parous females at 1-month post-intervention, with 49% of females being parous; at 2-months post-intervention, parous rates were > 90%. These preliminary data raise concerns over the entomological efficacy of the ITNs and IRS used in the study area, and ongoing research will enable a deeper understanding of how this may impact malaria elimination strategies.

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DETERMINING A DIAGNOSTIC DOSE OF PIRIMIPHOS METHYL FOR *AEDES AEGYPTI* USING TREATED BOTTLES

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There is a pressing need to develop innovative strategies for the control of diseases transmitted by *Aedes aegypti*. The modification of indoor residual spraying to target *Ae. aegypti* is one such strategy. A clinical trial quantifying the epidemiological impact of targeted indoor residual spraying (TIRS) for *Ae. aegypti* control is using a product with pirimiphos-methyl as the active ingredient in the city of Mérida, Mexico. In order to monitor the susceptibility of the local *Ae. aegypti* populations over the course of the trial, we determined a diagnostic dose for pirimiphos-methyl using the Centers for Disease Control and Prevention (CDC) bottle assay method. Two independent laboratories tested a series of 8 concentrations of pirimiphos-methyl eliciting a range of mortality between 0% and 100% in an insecticide-susceptible reference strain of *Ae. aegypti* (Rockefeller). The results suggested a diagnostic dose of 25 µg/ml with a diagnostic time of 30 minutes. This diagnostic dose was used to screen 16 field populations of *Ae. aegypti* (≈ 2000 mosquitoes) prior to the implementation of TIRS, with susceptibility reported in all populations at baseline. This diagnostic dose of pirimiphos-methyl will be used to monitor pirimphos-methyl susceptibility in *Ae. aegypti* throughout the course of the trial.

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MODELING THE SPREAD OF INSECTICIDE RESISTANCE AND ITS IMPACT ON ATSB DEPLOYMENT IN SUB-SAHARAN AFRICA

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ATSBs are a potentially valuable tool to control programs worldwide in their fight against malaria transmission but insecticide resistance threatens to undermine the efficacy of this intervention. Understanding the evolution and propagation of resistance is imperative to mitigating loss of ATSB effectiveness. Based on simulations of the ATSB trials currently being held in Kenya and Zambia, we leverage a multi-locus model of vector genetics that accounts for many-to-many mapping of genotypes to phenotypes to model insecticide resistance in all the major Anopheline species in the region. Combining this insecticide resistance model with an agent-based mathematical model of malaria transmission that simulates the interactions between human hosts and mosquitoes, we investigate deployment strategies and the choice of insecticides that are most likely to lead to the development of resistance in vector populations in near elimination to high transmission settings in sub-Saharan Africa. We predict the impact of resistance in Anophelines on malaria transmission and investigate various spatiotemporal deployment strategies of ATSBs alongside traditional vector control tools such as ITNs and IRS to best manage resistance and ensure continued efficacy of ongoing control and elimination efforts.

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VPRAM (VOLATILE PYRETHROIDS AGAINST MOSQUITOES): A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE ASSOCIATION BETWEEN THE USE OF VOLATILE PYRETHROID-BASED SPATIAL REPELLENTS AND MOSQUITO BITE PREVENTION

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Mosquitoes are the largest contributors to the global burden of vector-borne diseases, responsible for the spread of malaria, dengue, and more. The largest share of the burden is due to malaria, with 241 million cases reported in 2020. Outdoor transmission of malaria is growing in prominence, revealing an urgent need for interventions targeting this mode of transmission. Passive spatial repellents that use volatile pyrethroid-class insecticides are promising products for this indication; however, there is a lack of clarity on their efficacy, longevity, and range of effect due to heterogeneity between studies. We aimed to fill this gap by conducting a systematic review on entomological studies of volatile pyrethroid-based spatial repellents (PROSPERO #CRD42021268852). We included semi-field and field studies that compared volatile pyrethroid-based spatial repellents to no treatment or placebo, investigating their effects on *Anopheles*, *Aedes*, and *Culex* mosquitoes. Our primary outcomes are the number of mosquito landings using human landing catch or measurement of mosquito density using traps. Secondary outcomes examine entomological effects, including mosquito knock-down, delayed mortality, blood feeding inhibition, fecundity, deterrence, and non-contact irritancy. To date, we identified 1,145 abstracts of which 42 full text articles met our inclusion criteria. Next, we will extract individual-level mosquito data for analysis. Data will be synthesized through forest plots summarizing primary outcomes at the study level, as well as efficacy estimates for each product format derived from aggregate data, stratified by study design, active ingredient, mosquito species, capture method, and use case indoors vs outdoors. We will also incorporate weather data, conducting a sensitivity analysis to establish its effects on spatial repellent efficacy and duration thereof. This study intends to consolidate, clarify, and advance the evidence base on spatial repellents, informing researchers and vector control policymakers on their prospective use to reduce vector-borne diseases including the outdoor transmission of malaria.

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TEMPERATURE ALTERS THE TOXICITY OF MALATHION AND DELTAMETHRIN ON THE WEST NILE VIRUS VECTOR, *CULEX TARSALIS*, PHOENIX, AZ

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West Nile Virus (WNV), vectored by *Culex tarsalis*, is the leading mosquito-borne disease in the United States and according to the CDC, Arizona accounted for over half of the total reported WNV cases in the country in 2021. Concerningly, there are no prophylactics or drug treatments which exist for WNV and as such, public health programs rely heavily on vector

control efforts to lessen the incidence of disease. Insecticides can be highly valuable in reducing vector numbers if implemented strategically but can diminish in effectiveness and/or promote insecticide resistance otherwise. Vector control programs which employ mass-fogging applications of insecticides, often conduct these methods during the late-night hours, when diel temperatures are coldest. This study's aim was to quantify the effect of temperature on the toxicity of the conventional insecticides: malathion and deltamethrin, to *Cx. tarsalis*. An additional aim of this study was to underline the importance of understanding temperature-toxicity coefficients, in a contextual manner (i.e., local climate, vectors, and employed insecticides), to inform vector control programs of efficacious practices. Immature *Cx. tarsalis* were collected from the Salt River Pima-Maricopa Reservation and were reared to adults, where non-blood-fed females (aged 2-5 days old) were used to carry out experimentation during April - June 2021. Under three experimental temperature regimes (15, 25, and 35°C; 80% RH), a modified WHO tube bioassay - conventionally used for insecticide resistance monitoring - was used to evaluate the toxicity of the aforementioned insecticides on *Cx. tarsalis*. Insecticide doses ranged from low, medium, and high to reflect the decrease in atmospheric droplet density over relatively short distances. The data show that malathion and deltamethrin became less toxic to local *Cx. tarsalis* at colder temperatures. Our results suggest that programs employing large-scale applications of insecticides should consider temperature-toxicity relationships to maximize their efficacy to reduce mosquito-borne disease burden.

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INSECTICIDE RESISTANCE OF *AEDES AEGYPTI* AND *AE. ALBOPICTUS* IN PAPUA NEW GUINEA

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Information about insecticide resistance is crucial to vector control programs in public health. This study provides an update from 2017-2022 on the insecticide resistance status against *Aedes albopictus* and *Ae. aegypti* vectors across nine provinces of Papua New Guinea (PNG). Mosquito larvae were collected from *Aedes* larval habitats in each province, reared to adults and tested against 8 insecticides in WHO susceptibility tube bioassays. The mosquitoes were morphologically identified, labelled and stored in ethanol for genetic analyses of resistance markers. The total number of aedine mosquitoes tested was 8294. We detected pyrethroid resistance in all *Ae. aegypti* populations. Specifically, deltamethrin and lambda-cyhalothrin showed average 24h mortality rates ranging from 20%-32% indicating high levels of resistance. High levels of DDT resistance was also detected with 24h mortality rates ranging from 0% to 71%. Our studies also indicated possible bendiocarb and malathion resistance in some locations. Genetic analyses resulted in detection of 6 composite resistance genotypes identified in *Aedes aegypti* with no wild type identified. *Ae. albopictus* was susceptible to the pyrethroids (ranging from 98-100% mortality) and bendiocarb (99-100% mortality). However, possible resistance to deltamethrin was indicated in one province with 92%, (95% CI: 79%-98%) 24h mortality. DDT resistance was indicated in most provinces with 24h mortality rates ranging from 60%-79%. Known mutations conferring resistance to pyrethroids were identified in a few samples of *Aedes albopictus.* In summary, *Ae. aegypti* exhibited high levels of phenotypic resistance and a complex genetic resistance profile in PNG. We also identified *Ae. albopictus* resistant to DDT and with low rates of resistance mutations which may be an indication for emerging pyrethroid resistance. Further research is needed to elucidate whether the resistance phenotypes and genotypes observed in this study are imported or have arisen locally in PNG.

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PACMOSSI: THE PACIFIC MOSQUITO SURVEILLANCE STRENGTHENING FOR IMPACT PROGRAM

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The Pacific has experienced unprecedented outbreaks of dengue, chikungunya and Zika virus alongside ongoing malaria and lymphatic filariasis transmission. In response, The Pacific Mosquito Surveillance Strengthening for Impact Program, or PacMOSSI, was created with the goal to support Pacific Island Countries and Territories (PICs) to strengthen vector surveillance and control to prevent, contain and control mosquito-borne diseases and improve the health and wellbeing of Pacific communities. PacMOSSI is a partnership between 21 PICs and 13 international institutions with a focus on building south-to-south networks. Leading the consortium is James Cook University, the World Health Organization (WHO) and the Pacific Community (SPC). PacMOSSI activities focus on essential components to support vector control, including building capacity for improved vector surveillance, data management, communication and community engagement. A vector control needs assessment (VCNA) defined the existing capacity of PICs to prevent mosquito-borne diseases and thereby identified focus areas for training, operational research and capacity building. Shortly after inception, the COVID pandemic struck. PacMOSSI responded by pivoting to an online interactive course that is more sustainable than traditional training formats. The interactive online format enabled the course to be available to all vector control staff and supporting disciplines at both national and subnational levels. This more cost effective approach also facilitating out reach to all PICs, and a great number of students. The initial course attracted over 150 participants from not only the PICS, but also Asia and Africa. This presentation will present an analysis of the capacity and activities of the region and link the results with the capacity building activities of PacMOSSI. More information is available here: https://pacmossi.org/

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IMPACT OF INDOOR RESIDUAL SPRAYING VECTOR CONTROL TOOL ON MALARIA VECTOR POPULATION IN PAPUA NEW GUINEA

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Despite high coverage of long-lasting insecticidal nets (LLIN) in Papua New Guinea (PNG) malaria transmission remains high. Currently, LLIN are the only vector control tool used in PNG. There is a great need to evaluate other vector control tools such as Indoor Residual Spraying (IRS) as potential complementary tool. In this study, we are assessing the impact of IRS on the malaria vector population, *Anopheles punctulatus* complex, in four malaria endemic villages in Madang Province of PNG. The four study villages are located on the north coast of PNG. Two villages are 5-6km inland from the coastline and two villages are immediately on the coast. Our study adopted a controlled interrupted time series study design with 12 months pre-intervention and 12 months post-intervention vector monitoring. One inland and one coastal village was selected for the IRS intervention while the others served as controls. Vector monitoring included human landing catches, barrier screen collections, indoor resting collections and larval surveillance. Baseline data indicated strikingly different vector composition between inland and coastal villages. High anopheline biting rates were observed in all study sites with most vectors exhibiting preference for outdoor biting. Preliminary phenotypic vector data will be presented comparing control to intervention villages. Pre- and post IRS intervention on *Anopheles* spp biting rates; feeding and resting behaviors will also be compared between villages. The results of this study will contribute to a better understanding of IRS, a complementary vector control tool in PNG. By conducting two-monthly mosquito surveys in our study villages located in different geographical settings, we hope to quantify the impact of IRS on its mosquito populations. Our pilot study is also geared towards building in-country IRS capacity in PNG to strengthen the National Malaria control program.

0772

MODELLING THE IMPACT OF VECTOR CONTROL INTERVENTIONS ON MALARIA TRANSMISSION BASED ON SEMI-FIELD AND FIELD DATA

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Vector control is an effective intervention for reducing transmission of many vector-borne diseases. We present a novel mathematical framework for estimating the impact of vector control interventions on the reduction of biting, repellency, pre-prandial killing, post-prandial killing and disarming (preventing host-seeking) from entomological semi-field and field study data. Semi-field studies were conducted in Thailand to estimate the impact of transfluthrin spatial repellents and etofenprox insecticide-treated clothing on mosquito landing, feeding and survival. Here time-stratified human landing catch (HLC), feeding rate (HLC and alive uncaught mosquitoes subsequently offered a blood meal) and 24-hour survival rate data was collected. Combining a mathematical model for mosquito host-seeking with a multinomial stochastic hierarchical model we used Bayesian inference to fit this data and estimate relative impact on mosquito host-encountering, biting, repellency, mortality and disarming. To better estimate the impact of interventions in real-world conditions we fit a random-effects negative-binomial model, accounting for variability in time and space, to a subsequent entomological field study measuring HLCs in Cambodia. This was used to modulate the intervention impact on biting, repellency, mortality and disarming by the observed efficacy in the field. We used these estimates to simulate the impact of these interventions on *P. falciparum* malaria transmission and disease using the individual-based transmission model, OpenMalaria. Results suggest that spatial repellents and insecticide-treated clothes not only provide personal protection but are likely to have a community benefit comparable to insecticide-treated nets, especially if coverage is high. The vectorial capacity was reduced even at low intervention coverage in the population, with the interventions having a stronger reduction in clinical incidence in lower baseline transmission settings. We predicted the spatial repellents to have a stronger impact than the treated clothing, which also saw a larger decay in effectiveness over time due to washing.

0773

EXPERIMENTAL HUT TRIALS REVEAL THAT *CYP6P9A* AND *B* P450 ALLELES ARE REDUCING THE EFFICACY OF PYRETHROID-ONLY OLYSET NET AGAINST THE MALARIA VECTOR *ANOPHELES FUNESTUS* BUT PBO BASED OLYSET PLUS NET REMAINS EFFECTIVE

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Malaria remains a major public health concern in Africa. Metabolic resistance in major malaria vectors such as *An. funestus* is jeopardizing the effectiveness of Long-lasting insecticidal nets (LLINs) to control malaria. Here, we used experimental hut trials (EHT) to investigate the impact of cytochrome P450-based resistance on the efficacy of permethrin-only net (Olyset) compared to a PBO-based net (Olyset Plus) revealing a greater loss of efficacy for the latter. EHT performed with progenies of F5 crossing between *An. funestus* pyrethroid-resistant strain FUMOZ and pyrethroid susceptible strain FANG revealed that PBO-based nets (Olyset Plus) induced a significantly higher mortality rate (99.1%) than pyrethroid-only nets (Olyset) (56.7%)(P<0.0001). The blood-feeding rate was higher in Olyset compared to Olyset Plus (11.6% v 5.6%; P=0.013). Genotyping the *CYP6P9a/b* and the intergenic *6.5kb* structural variant (SV) resistance alleles showed that, for both nets, homozygote resistant mosquitoes have a greater ability to blood feed than susceptible. Homozygote-resistant genotypes significantly survived more with Olyset after cone assays (e.g. *CYP6P9a* OR=34.6; P<0.0001) than homozygote susceptible. A similar, but lower correlation was seen with Olyset Plus (OR= 6.4; P<0.001). Genotyping of experimental hut trial samples confirmed that *CYP6P9a/b* and *6.5kb_SV* homozygote resistant mosquitoes survive and blood-fed significantly more than homozygote susceptible when exposed to Olyset. Our findings highlight the negative impact of `p450-based resistance on pyrethroid-only nets further supporting that PBO nets such as Olyset Plus are a better solution in areas of P450-mediated resistance to pyrethroids.

0774

LONGITUDINAL SURVEILLANCE OF MALARIA VECTORS FROM VILLAGE AND FOREST AREAS OF STUNG TRENG AND MONDULKIRI PROVINCES, CAMBODIA USING FOUR DIFFERENT MOSQUITO COLLECTION METHODS

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Cambodia has experienced a significant reduction in malaria cases in the last decade, yet 58% of the population remain at risk, with highest

transmission in forested areas in the northeast. To assess heterogeneity in malaria transmission, we conducted longitudinal entomological surveillance in village and forest sentinel sites in two northeast provinces, Stung Treng and Mondulkiri from October 2020 through November 2021. Adult *Anopheles* were collected hourly from 18:00 to 06:00 in village sites using cow-baited and human-baited double-net traps (CDNs and HDNs) and Furvela tent traps (FTTs) outdoors, and CDC light traps (not hourly) indoors (LT). FTTs and HDNs were conducted in forest sites. Pyrethroid resistance of wild caught adults was determined using diagnostic doses of alphacypermethrin, permethrin, and deltamethrin. A total of 24,291 *Anopheles* comprising 32 species were caught. The largest proportion and highest species richness were from CDNs (75.1%, 30 species) and HDNs (20.3%, 29 species). Among primary vectors, *An. dirus* s.l. was caught at highest densities by HDNs in forest sites (mean 14.4/person/night in Stung Treng, 20.5/person/night in Mondulkiri). *An. maculatus* s.l. and *An. minimus* s.l. were caught in higher densities from CDNs. LT and FTT caught few primary vectors. *An. dirus* s.l. highest human biting rates from HDNs were observed in September at all sites (43-64 bites/person/night), and peak human biting activity was observed outdoors from 19:00 to 22:00. In contrast, *An. minimus* s.l. densities peaked in February, and human biting activity for this species and *An. maculatus* s.l. was low. No pyrethroid resistance was detected in these three species, and determination of sporozoite infection rates is ongoing. Results indicate that HDNs and CDNs may be best suited for future surveillance activities. The pyrethroid susceptibility of primary vectors indicates that pyrethroid-only LLINs remain appropriate for vector control, but the higher forest densities and outdoor and early biting behavior may require additional interventions. Studies of LLINs use and human behavior could identify gaps in protection.

0775

INVESTIGATIONS ON THE EFFECT OF TEMPERATURE ON THE VERTICAL AND TRANSSTADIAL TRANSMISSION RATES OF RIFT VALLEY FEVER VIRUS IN *CULEX TARSALIS* AND *AEDES AEGYPTI* MOSQUITOES

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Rift valley fever virus (RVFV) is an emerging zoonotic, mosquito-borne virus that can cause encephalitic, neurological and/or hemorrhagic disease in sheep, cattle and humans. RVFV (*Phlebovirus*) is transmissible vertically within mosquito populations, through mosquito bites or by aerosolization of viral particles. RVFV is classified as a Select Agent due to its pathogenicity and because it poses a significant risk to human and animal health, which can be detrimental to society, industry, and the economy. Though endemic to East Africa, RVFV is well-poised for introduction to the United States due to human travel, and vector competence has been demonstrated for many mosquito species native to North America. The factors that govern how efficiently mosquito species transmit RVFV transovarially (parent to offspring) is a gap in our current understanding of interepidemic viral maintenance. In particular, understanding how environmental conditions such as temperature may modulate transovarial transmission of RVFV is not yet understood. Transovarial transmission is one mechanism through which viruses persist in the environment across seasons. To elucidate how larval rearing temperature can affect transovarial transmission of RVFV from *Culex tarsalis* and *Aedes aegypti* mosquitoes to their progeny, mosquitoes were given an infectious blood meal of RVFV strain KEN128B-15. Seven days after oviposition, they were subsequently fed an uninfected blood meal, and progeny from this second gonotrophic cycle were reared to examine viral load and infection prevalence at each developmental stage. This experiment will be repeated at 28C, 18C and 32C rearing temperatures. The results of these ongoing experiments will be presented, specifically infection rates and viral loads of RVFV in mosquitoes reared from infected females. We hypothesize that larval habitat temperature influences the efficiency of transstadial transmission. Through this study, we hope gain crucial insight for vector competence that can be applied to other mosquito-borne disease systems.

0776

CAN TRANSGENIC MALARIA-REFRACTORY MOSQUITOES ALSO SUPPRESS GENETICALLY DIVERSE *PLASMODIUM FALCIPARUM* FIELD ISOLATES?

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Malaria, a disease caused by *Anopheles*-transmitted protozoans of the *Plasmodium* genus, remains a major global public health challenge. Despite continuous efforts to eradicate or significantly reduce malaria transmission, the lack of effective vaccines and the rapid emergence of drug-resistant parasites and insecticide-resistant mosquitoes highlight an urgent need for the development of alternative disease control strategies. Multiple genetically modified *Plasmodium*-refractory mosquito strains have been shown to achieve suppression of the NF54 laboratory isolate of *Plasmodium*. However, the efficacy of transgenic blocking mechanisms has yet not been validated with genetically diverse field-derived malaria parasites. The application of *Plasmodium*-resistant transgenic mosquitoes to combat malaria *in natura* will require assessment of the effectiveness of engineered blocking barriers against diverse *P. falciparum* field isolates. We have initiated a study on the infectivity of *P. falciparum* isolates from various geographical locations in both wild-type (wt) and transgenic mosquitoes using Standard Membrane Feeding Assay (SMFA) to determine the competence of selected transgenic mosquito strains to suppress *P. falciparum* infection. We are also exploring the use of a humanized mouse malaria infection model to perform more realistic human malaria transmission studies, and to enable the restoration of *P. falciparum* gametocyte infectivity that is known to subside during extensive laboratory culturing. Our studies will evaluate transgenic blocking mechanisms for use in *Anopheles* population modification -based malaria control, and provide a wider repertoire of diverse *P. falciparum* strains for transmission-blocking studies.

0777

DEEP ANALYSIS OF HOST SEEKING ACTIVITIES IN MALARIA VECTORS ACCOUNTS FOR HIGH LEVEL OF RESIDUAL TRANSMISSION DESPITE EXTENSIVE LLIN COVERAGE IN BURKINA FASO

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Burkina Faso is among the 10 high sub-Saharan countries where a stalling in the fight against malaria has been registered and the incidence remains still very high despite the countrywide LLIN distribution campaigns recommended by WHO every three years since 2010. Our overarching goal is to understand how vector behaviours in response to LLINs (i.e. increased zoophagy, outdoor biting and/or altered biting rhythms) and their interactions with human activities and net usage can contribute to this epidemiological scenario. In previous studies, conducted within 5 years after LLIN introduction in Goden village in Burkina Faso, we defined a scenario of marked zoophily in the dominant vector species (*A. coluzzii* and *A. arabiensis*) despite sporozoite (SR=6.1%) and entomological inoculation (EIR=1.4 infective bites/person/hour, ibph) rates in the range observed in pre-intervention settings. We here present results of Human Landing Catches (HLC) conducted in 2020 in Goden during the whole mosquito biting period (4pm-8am) alongside a survey on human habits and net usage. GAM results show: 1) SR=1.1%; 2) a roughly

homogeneous plateau of intense biting activity from 10pm to 5am (mean 37.4 mosq/person/hour) and a non-negligible biting pressure before and after this time window (6.6), with no difference indoors and outdoors. Under an unrealistic scenario of full human exposure, the mean EIR during the 16h-HLC is 4 ibp. However, adjusting human exposure according to LLIN usage as estimated based on questionnaires, the mean EIR drops to 0.6 ibp. Interestingly, 0.14 ibp occurs before 8pm and after 6am when 100% of inhabitants are awake and thus fully exposed to bites. This shows how interaction between human activities and vector host-seeking pressure contributes to a non-negligible gap in LLIN protection. We expect that this interplay between human and vector behaviours may represent one of the main factor accounting for residual malaria transmission in other epidemiologically similar settings characterized by high vector density and insecticide resistance.

0778

TOWARDS THE LABORATORY MAINTENANCE OF *HAEMAGOGUS JANTHINOMYS*, THE MAJOR NEOTROPICAL VECTOR OF SYLVATIC YELLOW FEVER

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Haemagogus janthinomys (Dyar, 1921) is the main vector of yellow fever virus (genus *Flavivirus*) and a prominent vector of Mayaro virus (genus *Alphavirus*) in neotropical forests. It is notoriously difficult to maintain in the laboratory, and almost no vector competence studies have been performed with this species since the 1940s. Zika, dengue (both genus *Flavivirus*), and chikungunya (genus *Alphavirus*) viruses have emerged or resurged in the Americas in recent decades, creating risk for spillback into sylvatic cycles, potentially involving *Hg. janthinomys*. Vector competence studies are, therefore, needed, and would be facilitated by the existence of a stable laboratory colony of this species. To develop techniques to rear and maintain *Hg. janthinomys*, we collected 413 adult female mosquitoes from rainforest bordering Manaus, Brazil, in the first three months of 2022. Feeding rates of 63.9% (242/379) were achieved by exposing caged, field-derived mosquitoes to a human-blood-soaked cotton pad, affixed to the base of a plastic cup containing 40 - 45 °C water. This resulted in the production of 2,763 F1 generation eggs (mean 11.4 per mosquito) obtained mainly by placing gravid females in filter paper lined petri dishes at 5 days post feeding. Preliminary data show eclosion rates >60% can be obtained through ≤10 four-day cycles of egg immersion in a bamboo leaf infusion (2 days) and partial drying (2 days), starting within 3 days of oviposition. We are attempting to produce F2 generation eggs by forced copulation; these results are pending. We do not yet know whether these methods can be used to establish a stable *Hg. janthinomys* colony, nonetheless our established techniques to artificially blood feed adult females will permit future vector competence studies.

0779

THE PROMISE AND PITFALLS OF MOSQUITO REPRODUCTIVE CONTROL: LESSONS FROM THE DENGUE VECTOR, *AEDES AEGYPTI*

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Mosquito mating is a critical life history moment and a major target for future vector control strategies. Once considered a brief random encounter, we now understand mosquito mating and reproduction to be complex. Our research, and those of others, shows that mosquito sex involves a complex orchestration and interplay of events involving male and female behaviors, transfer of molecules and induced female responses. Here, I review our current understanding of mating dynamics in the dengue vector mosquito, *Aedes aegypti*. I share our latest results from mating behavior and acoustic research, ejaculatomics and female transcriptomics studies and post mating response phenotypes that influence female vector potential. I conclude with a discussion of what we have learned in the context of emerging vector control strategies that rely on modified male releases as well as important outstanding questions.

0780

PERSISTENT FINE-SCALE GEOGRAPHIC CLUSTERING OF LA CROSSE VIRUS DISEASE IN SOUTHERN APPALACHIA (UNITED STATES)

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La Crosse virus (LACV) is a mosquito-borne pathogen that causes more neuroinvasive pediatric disease than any other arbovirus in the United States. From 2003-2021, approximately 40% of all neuroinvasive LACV disease occurred in east Tennessee and western North Carolina. Recent research in North Carolina found multiple cases of LACV disease occurring at individual households in different years, demonstrating the persistent fine-scale risk of this disease. As an extension of that research, our objective is to investigate the spatial-temporal distribution of LACV disease in east Tennessee and western North Carolina. We hypothesize that the geographic distribution of high-risk disease clusters is persistent, such that the same areas have consistently maintained high disease risks. We received case-specific data for reported cases of neuroinvasive LACV disease in Tennessee and North Carolina from 1997-2020 from the state health departments. We used spatial scan statistics to investigate the geographic clustering of the disease at the county and census tract levels in 5-year increments throughout the study period. We confirm that in counties where LACV disease is endemic, cases are not randomly distributed but instead are clustered within specific census tracts. Consequently, county-level measurements of incidence risk consistently underestimate the risk of LACV disease in the specific neighborhood where most cases are clustered. These findings demonstrate the potential for the prevention of LACV disease through targeted interventions that focus on the specific fine-scale geographic areas with persistently high disease risks.

0781

EMPLOYING STATE-OF-THE-ART MOSQUITO CONTROL STRATEGIES, REMOTE SENSING AND MACHINE LEARNING, *TO* PRIORITIZE *AEDES SPP.* ABUNDANCE AND MOSQUITO BREEDING HABITAT RISK

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Mosquito-borne diseases are a continuing public health concern in the United States and globally. Current technologies often used by the local mosquito and vector control divisions are costly, cumbersome, and outdated. This has resulted in little or no data driven proactive mosquito control efforts. This study demonstrates the utility of remote sensing and machine learning to effectively predict *Aedes* mosquito egg abundance in Miami, Florida. Mosquito collection data from May 2019 to Dec 2021 was obtained from routine collection. Using multiple Sentinel-2 imageries, a U-Net convolutional neural-network machine learning algorithm was employed to generate the land-use land-cover classification map. Additionally, indices for vegetation (NDVI) and water content (NDWI) were derived from the same images. The mosquito data was analyzed from a spatiotemporal perspective. A predictive model of mosquito abundance by these micro-environmental factors was developed using a suite of 5 different machine learning statistical techniques. The highest overall

accuracy model was used to derive a predicated mosquito risk map for Miami, FL. With data available, the deep learning approach developed in this study could be easily applied to a large-scale vector control daily surveillance decision making. We believe integrating this technology into routine vector control activities could release the burden of mosquito-borne disease management and limit insecticide residence through targeted abatement.

0782

TRACING THE SPREAD OF *ANOPHELES STEPHENSI* IN DIFFERENT STATES IN SUDAN

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In the year 2019, the presence of the invasive *Anopheles Stephensi* was reported in Sudan (Abubakr et al. 2021). This increases the risk of malaria, particularly in urban and suburban areas in the country. *Anopheles Stephensi* has been reported in the capital city of Sudan, Khartoum, among many other cities in different states e.g., the Red Sea and Gedaref states. Hence, there is an urgent need to launch a national entomological survey to determine the distribution of this vector throughout the country. This survey will result in the collection of essential information on *Anopheles Stephensi* bionomics and susceptibility to the available malaria vector control methods in several states. One of the main outcomes of this research is to find the most suitable intervention methods to both control and limit the spread of this vector, especially during the rainy seasons and consequently reduce the burden of malaria incidence in Sudan. In this talk, I will present the early results of our survey conducted in the Northern state describing the geographical presence and distribution of *Anopheles Stephensi* as well as provide evidence on the feeding and resting behaviours of *Anopheles Stephensi*. The results of our survey will be essential in shaping the current Ministry of Health and Vector control division policies on possible vector control measures that can effectively reduce the burden of Malaria resulting from this invasive mosquito vector.

0783

BUILDING VECTOR CONTROL CAPACITY TO REDUCE MALARIA TRANSMISSION IN PAPUA NEW GUINEA

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Papua New Guinea (PNG) has the highest prevalence of malaria in the Western Pacific region, and despite renewed focus on bed nets and malaria case management over the past decade, malaria transmission is increasing. Key underlying causes include insufficiently resourced public health infrastructure compounded by geographic remoteness. As significantly, malaria vector bionomics in PNG is complex with a heterogenous distribution of vector species across the county, high plasticity in host preference, diverse larval habitats and a considerable amount of outside and early evening biting occurring when bed nets are not protecting people. Vector-control is crucial to the prevention of malaria and multiple, complementary vector control tools are needed reduce transmission. To address this situation the NATNAT program, Newly Adapted Tools Network Against mosquito borne disease **T**ransmission is testing and optimising new and existing vector control tools in PNG. A new vector control testing facility is being established in Madang province that will enable product evaluation under laboratory and semi-field conditions. In addition, we are conducting several small-scale pilot studies to assess the efficacy and acceptability of vector-control strategies such as residual spraying, larval source management and spatial repellents. The program will investigate the acceptability of vector control tools at community and health system levels, and aims to strengthen policy and implementation networks with the PNG National Department of Health and other stakeholders. This presentation will provide a mid-project overview of the NATNAT program and introduce preliminary findings and experiences of the indoor residual spraying pilot study conducted on the north coast of PNG for accompanying NATNAT project presentations.

0784

A FOLLOW-UP ON THE RECENTLY ESTABLISHED *AEDES ALBOPICTUS* PRESENCE IN JORDAN

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Aedes albopictus is a main concern of the public health sector and the World Health Organization since its introduction to Jordan in 2016 and vector-borne diseases (VBD) have had dramatic impact on U.S. Forces stationed and deployed in CENTCOM. Jordan hosts the second highest share of Syrian refugees pro capita in the world. The presence of Syrian refugees and foreign workers is providing an open platform for the emergence and re-emergence of different VBD, which would critically impact public health including US force health protection in Jordan. Lack of up to date *Ae. albopictus* distributional data since its introduction in 2016 and potential distributional modelling hampers effective vector surveillance and control. Monthly mosquito surveillance was carried out in 3 Governorates representing the 4 biogeographical zones of Jordan and different land use. Residences in the urbanized/peri-urbanized areas in the 3 Governorates were checked for the presence of *Ae. albopictus* throughout the year. In general, there was an obvious decline in the numbers collected starting summer 2019 through winter 2021. The vector population peaks were shown in the summer and fall of 2018 demonstrating together over 65% from the total collected numbers. At-risk areas were found in populated areas in 2 Governorates: Al Zarqaa and Al Shona Al Janoubeya in north Amman and upper coast of the Dead Sea (Mediterranean and Sudanian penetration, respectively). A prediction map was developed based on the negative and positive records and at-risk areas are currently undergoing analysis for validity. Continuing efforts are ongoing to expand surveillance to cover additional areas and districts to elucidate the relative health risks associated with the existence and spread of the invasive *Ae. albopictus* vector in the Kingdom of Jordan.

0785

USE OF UNMANNED AERIAL VEHICLES (UAVS) TO IDENTIFY LANDSCAPE FEATURES RELATED TO ARBOVIRAL TRANSMISSION IN NORTHERN, COASTAL ECUADOR

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Vector-borne diseases such as dengue are a prevalent public health concern in the Americas. Different environmental and behavioral variables, such as factors related to land use and water storage, can impact the density of vector populations, resulting in dengue transmission in both urban and rural communities. Unmanned aerial vehicles (UAVs, e.g., drones) may be a useful tool to collect detailed spatial information, with

exciting applications to public health and vector-borne disease research. The objective of this analysis was to determine whether UAV-identifiable features are associated with *Aedes Aegypti* mosquito densities in Esmeraldas province, Ecuador. We used UAVs to cross-sectionally map five communities located along an urban-rural gradient and conducted contemporaneous household entomological surveys, with aspiration of adult mosquitoes by Prokopack aspirator. Within each UAV image, 40-meter buffers generated from each house in qGIS. Within each buffer, the mean normalized difference vegetation index (NDVI), number of standing water containers, distance to the nearest river were calculated and related to adult mosquito densities using regression models. Our results support prior evidence that local vegetation is associated with increased *Aedes Aegypti* mosquito densities. These results inform our understanding of dengue risk in the study communities and may contribute to future spatially targeted interventions to reduce arboviral disease risk.

0786

DIFFERENTIAL DENSITIES OF KEY VECTORS OF RVFV IN SPACE IN THE KENYAN EPIZOOTIC NORTHEASTERN REGION

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Rift Valley fever epizootics have previously occurred in Kenya, most recently, 2006-2007, in Ijara sub-county, Garissa county, northeastern region. We investigated intra-regional distribution, diversity and densities of key RVFV vectors. We sampled mosquitoes for two years in four areas, seven sites: Sangailu (Marey & Wakabharey), Ijara (Bulagolol & Jalish), Kotile (Abalatiro & Kotile Central) & Boni forest, using CDC light traps. We collected n=109,923 mosquitoes belonging to four species, all primary vectors, albeit in varying densities (*P<0.0001*) across the four areas: Sangailu (43.3%), Ijara (15.8%), Kotile (33.3%) & Boni forest (7.6%); & seven sites: Marey (9%), Wakabharey (34.3%), Bulagolol (8.7%), Jalish (7.1%), Abalatiro (7.6%) & Kotile Central (25.7%). Overall, *Aedes tricholabis* was most abundant species (n=67,031), mostly in Sangailu (n=40,773); followed by *Ae. ochraceus* (n=23,141) mostly in Kotile (n=11,822) & *Ae. mcintoshi* (n=17,935) mostly in Kotile (n=14,811). *Ae. sudanensis* was least sampled (n=3,433), mostly in Kotile (n=2,439). Densities were also compared between sites covering short distances within each area. In Sangailu, all species were significantly sampled in Wakabharey, where *Ae. tricholabis* was most sampled (n=32,123, 78.8%), Mare (n=8,650, 21.2%); followed by *Ae. ochraceus*, Wakabharey (n=3,876, 82.5%), Marey (n=823, 17.5%) and *Ae. mcintoshi*, Wakabharey (n=1,309, 78.6%), Marey (n=356, 21.4%). In Ijara, the species were mostly sampled in Bulagolol compared to Jalish, though not statistically significant (*P>0.05*). In Kotile, all species were significantly sampled in Kotile Central compared to Abalatiro: *Ae. mcintoshi* (n=12,225, 83.9% and n=2,476, 16.1%), *Ae. ochraceus* (n=8,347, 70.6% & n=3,475, 29.4%), *Ae. tricholabis* (n=6,126, 81% and n=1,439, 19%) and *Ae. sudanensis* (n=1,467, 60.1% and n=972, 39.9%) respectively. This study underscored potential of localized transmission of RVFV based on differential densities of primary vectors between sites which are separated by short distances. Therefore, mapping these areas is critical for focused vector control to prevent risk of epizootics.

0787

POTENT HYDROXYETHYLAMINE BASED DRUG CANDIDATES AGAINST ZIKA VIRUS INFECTION: BIOACTIVITY AND PHARMACOLOGICAL EVALUATION

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Zika virus (ZIKV) is a vector-borne disease and primarily transmitted by a bite of daytime-active Aedes mosquitoes, mainly Aedes aegypti, also responsible for the transmission of dengue, chikungunya, and yellow fever. ZIKV associated fatal microcephaly in Brazil and other parts of the world was appalling and resulted in numerous deaths and lifelong disabilities. Inadequacy of vaccines and lack of effective drugs against ZIKV disease created alarming situations for public health and therefore warrants the discovery of therapeutics. As such, hydroxyethylamine (HEA) analogs have entered the clinical trials for their antiviral properties, and thus presents a validated pharmacophore option for the design of potent antiviral treatments against ZIKV. We thus synthesized a library of novel HEA-based compounds and tested them against ZIKV using in-vitro viral cultures that led us to advance two hits. One of the compound showed 72-fold higher efficacy to block the infectivity of ZIKV infection over the positive control, 6-methylmercaptopurine riboside (6MMpr). The compound displayed 50% inhibitory concentration (IC_{50}) and the selectivity index (SI) of 0.34 µM and 22.47, respectively. The computational studies predicted the target for the potent analog to be the main protease, unfortunately, the compound did not show any inhibition at 200 µM in an enzymatic assay. To study the toxic effect of the compound as per the observed accumulation, acute and subacute cytotoxicity of compound was evaluated in mice at different oral doses, and the biochemical/histopathological results indicated a negligible sign of toxicity. In nutshell, the study supports this compound as a prime antiviral contender for the preclinical evaluation against ZIKV disease.

0788

NEW INSIGHTS IN DENGUE EPIDEMIOLOGY AND IMMUNE RESPONSES USING A NOVEL MULTIPLEX LUMINEX ASSAY

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Dengue viruses 1 to 4 (DENV1-4) are a major cause of mosquito-borne disease. While primary (1°) infections result mostly in inapparent or non-severe dengue, severe disease is more common in secondary (2°) infections, which can be enhanced by prior DENV immunity. Thus, knowing the infection history of individuals and communities is important for assessing risk of disease severity. We developed a 5-plex Luminex assay composed of the envelope protein domain III of DENV1-4 and Zika virus (ZIKV) to study serotype-specific prevalence of DENV in Nicaragua and document DENV immune history and serotype-specific transmission in urban and rural communities of northwestern Ecuador. In Nicaragua, we analyzed >160 1° inapparent DENV infections spanning 2004-2019 from a long-standing pediatric dengue cohort study in Managua. Although the distribution of serotypes causing 1° inapparent and symptomatic (RT-PCR-confirmed) infections was similar in some years, in others, the analysis revealed silent transmission of DENV1 in inapparent infections that was not captured in dengue cases. This serotyping study also enabled detection of homotypic DENV2 repeat infections in 22 participants. In Ecuador, we determined remote infection history and reconstructed past DENV epidemics in a region with historically little or no arbovirus surveillance by analyzing 120 participants living in either remote villages or more urban areas from serum samples collected in 2020. While a significantly lower proportion of 2° infections was observed in remote populations, rural areas had high prevalence of more recently introduced DENV1. We also detected 1° DENV4 and ZIKV infections in individuals likely infected 5-10 years ago, as well as more recent 2° DENV1 and DENV2 infections. Expanding to a 10-plex system that incorporates NS1 from DENV1-4 and ZIKV improved the ability to discriminate DENV from ZIKV infections in endemic adult populations and identify DENV serotype in hospital-based

studies. Overall, we demonstrate the benefits of a multiplex Luminex assay for identifying DENV serotype and flavivirus infection history in multiple epidemiological and clinical contexts.

0789

EXPLORING THE SPATIOTEMPORAL RELATIONSHIPS BETWEEN CLIMATE AND ZIKA, CHIKUNGUNYA AND DENGUE VIRUS TRANSMISSION ACROSS BRAZIL

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In recent years, Brazil has experienced large-scale outbreaks caused by dengue virus (DENV), chikungunya virus (CHIKV) and zika virus (ZIKV). Transmission of each of the arboviruses may influence the others, for example, reduced DENV incidence was observed in 2017-2018 after the 2016 ZIKV outbreak. However, the extent of cross-protection on co-circulation is not well elucidated, nor is the interconnected relationships between arbovirus transmission and climate. In this study, we use a Bayesian modelling approach to estimate the time-varying reproduction number (Rt) of CHIKV (between 2015-2020), ZIKV (2016-2020) and DENV (2012-2020) using state-level case notification timeseries for Brazil. Daily temperature, humidity, and rainfall factors, as well as population metrics, are assessed as predictors of Rt in spatiotemporal models. In addition, we perform wavelet analyses to explore the temporal relationships between CHIKV, ZIKV and four DENV serotypes, and the synchronisation between their transmission and climate timeseries. Preliminary findings show significant spatial heterogeneity in the temporal patterns of transmission of the three arboviruses, with states in the centre-west region of Brazil experiencing peaks earlier in the annual transmission season than those in the north-east. Furthermore, there is a strong and continuous annual periodicity in the timeseries for CHIKV, ZIKV and DENV at the national level, with greater variability observed at the state level, particularly for CHIKV. Ongoing work is investigating these spatiotemporal patterns further, and will provide greater insight into the relationships between transmission intensity of the three arboviruses and climate across space and time in Brazil.

0790

ASSESSING THE ROLE OF NON-NEUTRALIZING ANTIBODIES IN ANTIBODY-DEPENDENT CELLULAR PHAGOCYTOSIS OF DENGUE VIRUS INFECTED CELLS

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Dengue virus (DENV) is endemic in over 100 countries causing widespread morbidity and mortality. 400 million people are thought to be infected by DENV each year, with 100 million suffering symptomatic illness and 22,000 dying. It has been previously described that antibodies against DENV E protein can cause antibody dependent enhancement during secondary DENV infection, increasing infection. However, there are other potential antigen targets created during DENV infection. Non-structural protein 1 (NS1) is a non-structural protein that is both secreted from and expressed on the surface of DENV infected cells. IgM, IgG, and IgA isotype antibodies against NS1 can be readily detected after DENV infection. Our study aims to determine if NS1 expressing cells opsonized by αNS1 antibodies can cleared via antibody-dependent cellular phagocytosis (ADCP) by monocytes, what receptors are used in both IgG and IgA isotype mediated phagocytosis of NS1 expressing cells, and if secreted NS1 functions to protect DENV-infected cells from ADCP. To this end, we analyzed ADCP using a flow cytometry based ADCP assay. We observed IgG- and IgA-mediated phagocytosis based on the presence of target cell membrane in CD14+ effector cells. Using an αCD89 antibody known to block FcαR binding to IgA, we observed reduced phagocytosis of opsonized NS1-expressing cells with an IgA monoclonal antibody, but no change in phagocytosis using an IgG monoclonal antibody. Future studies aim to: asses the ability of FcγR to mediate phagocytosis of NS1-expressing cells, assess potential synergistic effects of IgG and IgA in mediating phagocytosis of NS1-expressing cells by monocytes, and study the effects of secreted NS1 protein in monocyte phagocytosis by sequestering αNS1 antibodies.

0791

MONITORING LEVELS OF DENGUE VIRUS 1-4 NS1 IN ACUTE PRIMARY AND SECONDARY SAMPLES USING A NEW QUANTITATIVE NS1 CAPTURE ELISA

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Dengue virus (DENV) infection by any of the four serotypes (DENV1-4) can lead to severe disease that is characterized by potentially fatal vascular leak and shock. These adverse events are believed to be driven by a "cytokine storm" resulting from sequential DENV infections with distinct serotypes, leading to uncontrolled viral replication and misdirected immune cell activation. We and others have shown that DENV nonstructural protein 1 (NS1) is a contributing factor to vascular leak through its interaction with endothelial and immune cells, and clinical samples have correlated DENV NS1 levels with severe disease. However, questions remain regarding the importance of NS1 in disease pathogenesis and the magnitude and kinetics of NS1 across different patient characteristics, such as the infecting serotype, immune status, and stage of infection. Here we developed a new quantitative DENV NS1 capture ELISA that uses a highly sensitive DENV mouse monoclonal antibody to capture DENV NS1 in serum/plasma of infected patients, together with a different biotinylated mouse antibody monoclonal to detect and quantify levels of captured NS1. The estimated limit of detection of this assay using purified recombinant NS1 is 1 ng/ml. We implemented the NS1 capture ELISA across diverse hospital and community surveillance sites in Vietnam, Nicaragua, and Ecuador to quantify and evaluate NS1 levels in patient samples in the early and late acute phases. Our results reveal that higher NS1 levels correlate with increased severity and plasma leakage score. We observed differences in NS1 levels by serotype and location. Further, NS1 levels vary depending on DENV immune status, with significantly higher levels in primary infections and more rapid decrease in secondary infections. In sum, this study details the methods and functionality of this quantitative DENV NS1 capture ELISA with high analytical sensitivity across multiple sites to elucidate the role of DENV NS1 in disease pathogenesis.

0792

RECONSTRUCTING DENGUE TRANSMISSION IN A MULTIGENERATIONAL COHORT IN KAMPHAENG PHET, THAILAND

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The mean age of dengue virus (DENV) infection continues to rise in many endemic areas and therefore understanding risk factors for DENV infection and disease across wide age groups is increasingly important. However, quantifying infection risk at the individual and population level remains challenging because of the large proportion of infections that are subclinical and therefore not captured by surveillance systems. In this study, we used data from an ongoing longitudinal study of 2849 individuals from 470 multigenerational households in Kamphaeng Phet, Thailand, to reconstruct DENV transmission between 2015 and 2019 and to examine immune and demographic mediators of risk for DENV infection. This study collects yearly serum samples from enrolled participants, and performs household investigations triggered by PCR positive DENV infections. We used data on changes in hemagglutination inhibition (HI) titers measured in paired annual serum samples to identify subclinical infections, by applying a gradient boosted regression model trained on the serological data from 71 immunoassay confirmed acute DENV infections. This approach is able to accurately classify these laboratory confirmed cases and identifies ~75% more subclinical cases than commonly used methods relying on fourfold changes in titers. We identified a total of 636 infections, which implies that, on average, ~9% of the cohort was infected each year and that approximately 90% of DENV infections were subclinical in this cohort. This ranged from 85% to 95% in seronegative and seropositive individuals at enrollment, respectively. We then performed regression to determine which individual and household-level factors were associated with increased risk of DENV infection and disease. Younger age and lower antibody titers increased the likelihood of experiencing an infection. Our results provide a framework for understanding how household structure and individual characteristics drive dengue epidemiology.

0793

DENGUE SEVERITY AND DIAGNOSTIC TEST PERFORMANCE DURING THE LARGEST DENGUE OUTBREAK IN PARAGUAY

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Paraguay experiences among the highest annual rates of dengue in South America. DENV-4 was first detected in Paraguay in 2012, causing a minority of cases throughout most subsequent years. However, in 2019, it became the predominant type, and in 2020, the country suffered its largest recorded dengue outbreak. As part of an ongoing study to characterize arbovirus infections in metropolitan Asunción, we enrolled participants from January 2019-March 2020 who presented to a tertiary care hospital and an outpatient clinical site with a suspected arboviral illness lasting ≤7 days. Of 799 participants, 250 dengue cases (31%) were confirmed by real-time RT-PCR (rRT-PCR). DENV types included 236 DENV-4 (94%), 13 DENV-2 (5%), and 1 DENV-1 (<1%). A subset of 502 individuals was tested with a rapid test for DENV non-structural protein 1 (NS1), which, compared to rRT-PCR, had a sensitivity and specificity of 53% and 96%, respectively. Among dengue cases, 158 were women (63%) and mean age was 30.5 years-old (SD 19.9). Individuals presented a mean of 3.4 days post-symptom onset (SD 1.5), most commonly with fever, myalgias, headache and/or arthralgias. Severe dengue occurred in 11 cases (4%), all were caused by DENV-4 and characterized primarily by shock. In severe dengue cases, the average age was 62.7 years-old (SD 13.0); 10/11 had comorbidities such as diabetes mellitus, hypertension and cardiac disease; and 9/11 died during the hospitalization. An additional 103 cases (41%) had dengue with warning signs, with an average age of 34.8 years-old (SD 19.0), and 28/103 (27%) had comorbidities. Mean viral load among all cases at presentation was 6.7 $\log_{10}$ copies/mL serum (SD 1.5) and did not significantly differ by disease severity or DENV type. Notably, we observed a negative correlation between DENV viral load and NS1 sensitivity. The 2019-2020 DENV-4 outbreak in Paraguay followed years of DENV-1 predominance in the country. This may have contributed to the size and severity of the outbreak, particularly among adults and those with comorbidities. DENV detection was hampered by poor rapid diagnostic test performance, even among individuals with high viral loads.

0794

ASSOCIATION BETWEEN MAGNITUDE OF ANTI-DENGUE VIRUS ANTIBODY AVIDITY AND PROTECTION AGAINST SYMPTOMATIC DENGUE VIRUS INFECTION

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Dengue is a mosquito-borne disease caused by four dengue virus serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) with an estimated 390 million infections annually, of which approximately 96 million are symptomatic. Neutralizing antibody titers are a common measure of protective immunity to flaviviruses. However, there is increasing evidence that additional aspects of antiviral immune responses may also be involved. The degree of antibody affinity maturation is one aspect, which measures the evolution of polyclonal antibody repertoire in response to vaccination or natural infection. Previously, we reported the affinity maturation of antibodies against all four DENV serotypes from recipients of Takeda's tetravalent dengue vaccine candidate (TAK-003) using a novel avidity assay employing bio-layer interferometry and dengue virus-like particles. Here we assessed the association between the avidity index and protection from symptomatic natural secondary DENV infections in the Nicaraguan Pediatric Dengue Cohort Study. Healthy annual blood samples are collected from all participants each year (2004 to present) in Managua, Nicaragua, with an average active cohort of ~4,000 children aged 2-17 years old. Symptomatic DENV infections are confirmed by molecular, virological, and serological assays. Plasma was selected from 121 study participants prior to a secondary DENV-1, -2, or -3 infection (58 symptomatic and 63 inapparent infections), and we analyzed the antibody avidity and DENV inhibition enzyme-linked immunosorbent assay (iELISA) titer. The avidity index was significantly higher in samples collected prior to inapparent infection, compared to samples from participants prior to developing a symptomatic DENV infection. Study participants with high avidity index were more likely to have experienced a subsequent inapparent infection, regardless of iELISA titer. These results suggest an association between degree of affinity maturation and protection from symptomatic secondary DENV infection and highlight the importance of assessing a wide range of attributes when characterizing protective immune responses against dengue.

0795

MIDGUT MICROBIAL COMMUNITY SIGNIFICANTLY INTERFERES ARBOVIRAL INFECTION IN MOSQUITOES: AN AXENIC MOSQUITO STUDY

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Vector competency is a dynamic trait influenced by numerous factors such as host genetics, phenotype x phenotype interactions, and the environment. In recent years, evidence has emerged that the gut microbiota can also influence a mosquito's competency for viruses and parasites by modulating gut immunity. However, these studies relied upon oral antibiotics to clear the resident bacteria. This can be problematic as antibiotic clearance does not eliminate all bacteria in the gut, but rather causes a dysbiosis. Further, it is known that extended antibiotic exposure can cause immunologic and metabolic changes in the host and mitochondrial dysfunction. Consequently, it is difficult to distinguish the impact of the microbiome on pathogen/virus transmission from the impact of sustained antibiotic exposure on mosquito phenotype. To answer this question, we compared the vector competence of axenic mosquitoes (microbe-free), antibiotic-treated mosquitoes and colony mosquitoes for dengue virus 2 (DENV2) and chikungunya virus (CHIKV). After extended exposure to antibiotics we observed a significant increase in DENV2 midgut infection rates compared to the axenic and colony control groups. Interestingly, we observed CHIKV midgut infection rates were significantly increased in the control group compared to either the antibiotic treated or axenic. However, there were no significant differences in dissemination rates or viral titers between the three groups for both DENV and CHIKV. To interrogate this discrepancy, we performed transcriptomics on the midguts of colony and axenic mosquitoes with and without prolonged antibiotic exposure. Surprisingly, the transcriptomic analysis indicated that antibiotic exposure did not affect gene expression in those receiving antibiotics. Together, these data suggest that the composition of the gut microbiota is more important in mediating virus infection than the mere presence or absence of bacteria.

0796

IMPACT OF DENGUE FEVER ON MENTAL HEALTH IN ESMERALDAS PROVINCE, ECUADOR: A PROSPECTIVE CASE-CONTROL STUDY WITH 6-MONTHS FOLLOW-UP

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Physical symptoms of dengue have been documented extensively, but knowledge gaps on mental health hazards associated with this arbovirus infection remain. We aimed to study the frequency of psychiatric symptoms, as well as neurocognitive performance in domains relevant to mood disorder, during the first year after a dengue episode in patients, compared to controls. We enrolled 102 febrile, anti-dengue IgM positive adults and 78 age, sex, and socio-demographically matched healthy controls in a prospective cohort during the 2021 dengue outbreak in Esmeraldas province, Ecuador. We assessed the mental health status by administering the 'depression, anxiety and stress scale' (DASS21), with scores ≤4 designated normal; scores 5-7, 8-10 and ≥11 indicating mild, moderate and severe depression, respectively. We assessed 'delayed matching to sample' (DMS) and 'spatial working memory' (SWM), using the Cambridge Neuropsychological Test Automated Battery (CANTAB), at 3 and 6 months after acute dengue. Cases had experienced COVID-19 more frequently than controls (34 vs. 22%, p=0.09). At 3 months, 40/90 cases available for follow-up, and 12/70 controls had DASS21 scores ≥5 (RR 2.7, 95%-confidence interval [1.5-4.7]). After controlling for age, sex, and COVID-19, dengue remained an independent risk factor for increased depression scores at 3 months post-infection. At 6 months, the risk for increased DASS21 scores between groups had normalized. Neurocognitive assessments of DMS, SWM did not differ between groups at 3 and 6 months. However, among cases we identified a significant decline of SWM at month 6, compared to month 3. Our observations of higher DASS21 scores in dengue patients compared to controls at 3 months, should alert care providers to increased depression, anxiety and stress after acute dengue, and should facilitate timely referral to mental health services. Future studies with adequate follow-up are warranted to validate our observations regarding the impact of dengue on mental health and quality of life in affected patients and communities.

0797

IN VITRO DETECTION OF DENGUE 1 VIRUS IN HUMAN WHOLE BLOOD, PLASMA, AND SERUM WITH NEAR-INFRARED SPECTROSCOPY

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Dengue (DENV) is the world's most common arboviral infection with an estimated 390 million people at risk of the infection, 100 million symptomatic cases and 10,000 deaths per year. Current diagnostic tools for DENV include molecular and serological methods such as RT-PCR and ELISA which can be labour intensive and costly. The Near-infrared spectroscopy (NIRS) which involves shining a beam of infrared light on a biological sample, collecting a reflectance spectrum and using machine learning algorithms to develop predictive models for pathogens, is a rapid and inexpensive technique that could potentially be used as a diagnostic tool for arboviruses. In this study, we assessed the ability of NIRS to detect DENV1 at different concentrations ranging from 1.58×10^7 - 3.16×10^3 infectious units/mL by spiking the virus directly into whole blood, plasma, and serum collected from 48 human donors and 20 pooled serum donors. Machine learning algorithms were developed using artificial neural networks using samples from 57 donors and the resultant models were used to predict remaining samples from 11 donors (independent samples). Our results show that regardless of the virus concentration, NIR models developed to predict DENV1 were 92.3% sensitive and 96.2% specific when plasma was analysed. The sensitivity for detecting DENV1 in serum and whole blood samples was 53.5% and 75% and the specificity was 66.7% and 33.3%, respectfully. NIRS spectral peaks representing methyl (1137 nm and 1142 nm), C-H stretch (812 nm and 819 nm), and saturated fatty acids (2127 nm) were observed as distinct features for DENV1. This is the first study to report the ability of NIRS as a potential diagnostic tool for DENV and represents a big step forward in the field. However, further studies should investigate the robustness of the models developed to detect DENV under real world conditions and determine its capacity to detect and differentiate DENV serotypes and other arboviruses particularly in an area where co-infection has been reported.

0798

REAL-TIME GENOMIC SURVEILLANCE OF DENV-1 AND DENV-2 IN BRAZIL: IMPROVING PUBLIC HEALTH OUTBREAKS RESPONSE

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Brazil accounted for a total number of 3,418,796 notified cases of Dengue fever between 2017 and 2022. Additionally, between 2018 and 2019, Brazil has observed a significant 5-fold increase in warning signs cases and a 4-fold increase in the incidence of severe cases and deaths, in which Midwest and Northeast regions appear to show the worst epidemiological scenario. Due to the alarming epidemiological situation, promoting the surveillance of circulating strains appears to be pivotal for outbreak response. Thus, in this study, we used nanopore sequencing to generate 185 near-complete genomes sampled between March 2019 to January 2022 from infected patients residing in different localities in Northeast and Midwest Brazilian regions during two rounds of sequencing training at the Public Health Laboratories and provide a retrospective reconstruction of its transmission dynamics in these states. Phylogenetic analysis for DENV-1 revealed a complex pattern of transmission within and among the Midwest, Northeast, and Southeast regions. Our phylogeny showed new DENV isolates clustered to form many distinct clades throughout the tree, with most of the instructions occurring in 2019. A preliminary epidemiological analysis seems to show a difference in the seasonality pattern between the Midwest and Northeast regions, in which we observe two and a single peak of cases, respectively. Bayesian analysis for DENV-2 and further epidemiological assemblies remain in progress. In conclusion, our partial results highlight the importance of genomic surveillance outputs allied with training initiatives for rapid response and decision-making assistance to control and monitor emerging viruses.

0799

PHYLOGENETICALLY DISTINCT DENGUE VIRUS IS ANTIGENICALLY RELATED TO ALL FOUR DENGUE VIRUS SEROTYPES

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Among the arthropod-borne viruses, the existing four serotypes of DENV (DENV-1-4) represents the largest threat to public health, with nearly half of the world population at risk of the infection, mostly in tropical and sub-tropical areas. Recent reports have identified highly divergent DENV strains in humans (DENV-1 Brun2014; DENV-2 QML-22; DENV-4 DKE-121) that are genetically distinct from endemic and sylvatic strains of the same serotype. Here, we characterized the genetic and antigenic features of the DENV-2 strain QML-22 isolated from an Australian traveler who visited the island of Borneo in 2015 and developed dengue-like symptoms. When we compared the envelope (E) protein sequence of QML-22 to 30 genetically diverse DENV-2 strains, we observed a total of 32 amino acid changes in QML-22 that were 100% different from all other DENV-2 strains. Applying genetic and antigenic cartography, we demonstrated that even though QML-22 clusters genetically with DENV-2, it is antigenically similar to all DENV serotypes, clustering in the central zone of the antigenic map. To try to understand the cross-neutralization among DENV-1-4, we performed assays to measure virion breathing using monoclonal antibodies targeting the fusion loop or E dimer epitopes. Overall, we did not see a clear pattern between QML-22 and others DENV-2 that could explain the broad cross-neutralization. We also evaluated the effect of the maturation state of the virus, testing sera from our cartography panel against QML-22 and representative strains of DENV-1-4 amplified on C6/36 insect cells (standard virus) and on Vero cells that over-expresses furin (mature virus). Although there was a large drop in neutralization when using mature as opposed to standard viruses, the sera lost both cross-reactive and serotype-specific neutralization capability, especially the QML-22 strain. Experiments are underway to evaluate the antigenic effects of QML-22 specific amino acid changes in the E protein. In conclusion, we demonstrated that while QML-22 clusters genetically with DENV-2, it is unusually well recognized by a global panel of DENV-1-4 antisera.

0800

A SINGLE NUCLEOTIDE U59C SUBSTITUTION IN THE DENGUE VIRUS 5′ UNTRANSLATED REGION DESTABILIZED AN ATTENUATING MUTATION IN MOSQUITOES

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Dengue vaccine development has largely opted for a live attenuated vaccine approach. However, live attenuated vaccine strains hold the danger of reverting to their wildtype pathogenic phenotypes.

Understanding the factors that influence genome stability is therefore critical for vaccine safety. Here, we hypothesize that other sites in the dengue genome could impact the stability of attenuating mutations. To explore the stability of attenuating mutations we used a dengue 2 wild type strain 16681, and its live attenuated vaccine derivative strains, PDK53. Attenuation of PDK53 is predominantly mediated by a glycine substitution to aspartic acid at residue 53 (G53D) of the non-structural protein 1. The G53D attenuated substitution was introduced into the dengue 2 16681 backbone and genomes stability was measured using next generation sequencing. We unearthed a naturally occurring U to C variant at position 59 of the 5'untranslated region of our dengue 2 16681 population that when present at a consensus level, enabled reversion of the attenuating G53D mutation to the wildtype residue in C6/36 insect cells as well as mosquitoes. Remarkably, this U59C mutation elicited a general increase in the number of single nucleotide variants present throughout the genome, increasing the overall genome diversity of the chimeric dengue 2 16681 G53D virus. In particular, the U59C mutation created a single nucleotide variant at the attenuating G53D site which enabled reversion to the wildtype residue. Moreover, when the G53D mutation and the 5'UTR of dengue 16681 were introduced into another dengue 2 strain, no viable virus could be produced, indicating that long range interactions may further impact viral fitness. Our findings suggest that the sequence of the 5' untranslated region can, at least in part, influence the stability of attenuating mutations and have critical implications on the stability of dengue virus genomes.

0801

PERSISTENT NEUROLOGICAL SYMPTOMS AND COGNITIVE IMPAIRMENT COMPLICATE CONVALESCENCE FROM DENGUE AND ACUTE VIRAL RESPIRATORY ILLNESS

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Long Covid has raised awareness of the long-term neurological and cognitive sequelae after acute viral infection. Indeed, flaviviral infections such as dengue have also been reported to result in chronic sequelae, but due to a lack of prospective studies, the prevalence and functional impact of such sequelae are poorly defined. We prospectively enrolled 209 patients with acute dengue (n=48; one with severe dengue) and other acute viral respiratory infections (ARI) (n=161), and followed them up for long-term sequelae and health outcomes up to one year post-infection, prior to the onset of the Covid-19 pandemic. 86% of patients completed the study. Baseline demographics and co-morbidities were balanced between both groups except for gender, with more males in the dengue cohort (63% vs 29%, p<0.001). Except for the first visit, data on symptoms were collected remotely using a purpose-built mobile phone application. Health outcomes were evaluated using the validated SF-12v2 Health Survey. Almost all patients (95.8% of dengue and 94.4% of ARI patients) experienced at least one neurological or cognitive symptom - headache, lethargy, lack of concentration, poor memory or drowsiness, within the first week. Kaplan Meier analysis indicated that time to symptom resolution was longer in dengue compared to ARI patients; 19.3% and 6.9% of dengue and ARI patients remained symptomatic at one year (p=0.01). SF-12v2 mental component scores at 3 months after acute illness onset were significantly lower in patients who remained symptomatic at 3 months and beyond, compared to those whose symptoms fully resolved (53.2 vs. 46.9, p<0.001). This finding indicates that cognitive symptoms were not merely subjective but resulted in functional impairment. No statistically significant difference in age or gender distribution was observed between those with and without chronic sequelae. Our findings reveal an under-appreciated burden of post-infection cognitive sequelae in dengue and ARI patients. They call for studies to define the pathophysiology of this condition, and determine the efficacy of both vaccines as well as antiviral drugs, in preventing such sequelae.

0802

A LIVE-ATTENUATED TETRAVALENT DENGUE VACCINE INDUCES ANTIBODY EFFECTOR FUNCTION AGAINST ALL FOUR DENGUE VIRUS SEROTYPES IN DIFFERENT POPULATIONS IRRESPECTIVE OF BASELINE SEROSTATUS

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The complement system (CS) is an arm of innate immunity which plays a role as an effector mechanism of the humoral immune response. Antibodies that can activate CS interact avidly with the component of the classical pathway C1q and are called complement-fixing antibodies (CFAs). CFAs contributes to the protection against flaviviruses, including dengue virus (DENV), by potentializing virus neutralization while inhibiting the antibody-dependent enhancement (ADE) of infection involved in severe dengue disease manifestation. Takeda's tetravalent live-attenuated dengue vaccine candidate TAK-003 has been shown to induce neutralizing antibodies against all four DENV serotypes and is efficacious against virologically confirmed dengue infection and hospitalization. In this study, we measured the levels of CFA against all four DENV serotypes in serum samples from baseline seropositive and seronegative TAK-003 recipients of two phase III clinical trials conducted in different geographic regions among children and adolescents from dengue endemic regions in Asia Pacific and Latin America countries (DEN-301; NCT02747927), and adults from non-endemic areas in the United States (DEN-304; NCT03423173). The data obtained showed that CFAs are produced in response to TAK-003 vaccination against all four DENV serotypes in individuals from both trials. The investigated antibody effector function was detected for at least 1 year post-vaccination and the responses were highly correlated with neutralizing antibody titers. Taken together, TAK-003 induced lasting antibody effector function that is generally associated with protective responses against DENV in different age groups and baseline serostatus of vaccine recipients. The role of CFAs for TAK-003 efficacy is under investigation.

0803

MAGNITUDE AND AVIDITY OF VIRUS-BINDING IGG ELICITED BY A LIVE-ATTENUATED TETRAVALENT DENGUE VACCINE ARE CORRELATED WITH NEUTRALIZING AND COMPLEMENT-FIXING ANTIBODY EFFECTOR FUNCTIONS

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Virus neutralization and complement fixation are effector mechanisms of the humoral immune response associated with antibody Fab and Fc functions, respectively, that contribute to protection against dengue virus (DENV) infection and pathogenesis. Affinity maturation of the virus-binding IgG response, a process that leads to antibodies with higher affinities in response to repeated antigen exposure, is a critical attribute of functional antiviral immunity. Takeda's live attenuated tetravalent dengue vaccine, TAK-003, is safe and well-tolerated, and has been shown to induce production of affinity matured virus-binding IgG, and tetravalent neutralizing and complement fixing antibodies. Here we characterize the relationship between level of affinity maturation of vaccine-driven binding IgG response, and magnitude of neutralizing and complement-fixing antibodies elicited by the vaccine in vaccine recipients from two phase III clinical trials conducted adults in the United States (DEN-304 - NCT03423173), or children and adolescents in Asia and Latin American (DEN-301 - NCT02747927) countries, who received two doses of TAK-003 at days 1 and 90. The results indicated that irrespective of age or DENV exposure history prior to vaccination, the avidity and magnitude of virus-binding IgG produced after TAK-003 vaccination were correlated and in agreement with both neutralizing and complement-fixing antibody functions, across all DENV serotypes. These results suggest that TAK-

003-mediated antibody effector functions involved in virus neutralization and complement fixation are a subset of affinity matured binding IgG responses elicited by the vaccine.

0804

LAB EVALUATION AND DEPLOYMENT OF DENGUE NS1 AND IGM/IGG RAPID DIAGNOSTIC TESTS IN AN EPIDEMIC CONTEXT IN SENEGAL

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Recently, there is an increasing need for Rapid diagnostic tests (RDTs) in low and middle income countries as they have the potential to improve the management of infectious diseases and have revolutionized diagnostic methods in recent years. In Senegal the burden of dengue is constantly increasing and expanding into new areas, as case management and traditional diagnostic methods can be difficult to implement, using RDTs as point of care (POC) could be ideal for active outbreak investigations. The aim of this study is to evaluate the diagnostic performance of Dengue NS1 RDT and Dengue IgG/IgM on positive dengue serum/plasma samples in a laboratory setting and in the field. During laboratory evaluation, diagnostic performance of the NS1 RDT was assessed using RT-PCR as gold standard. The over-all sensitivity was 88% [75-95] and specificity 100% [97-100]. The IgG/IgM RDT lab evaluation was done using MAC ELISA, indirect IgG and PRNT as gold standards, the IgM test line displayed a sensitivity of 94% [83-99] and specificity of 91% [84-95]. The IgG test line displayed a sensitivity of 70% [59-79] and a specificity of 91% [79-98%]. On the field, the Dengue NS1 RDT displayed a sensitivity of 82% [60-95] and a specificity of 75% [53-90], the IgM test line displayed a sensitivity of 86% [42-100] and specificity of 85% [76-92]. The IgG test line displayed a sensitivity of 78% [64-88] and a specificity of 55% [36-73%]. These results show that the RDTs are ideal for use in a context of high prevalence or outbreak setting and can be implemented in the absence of confirmatory test for acute and convalescent patients.

0805

RELATIONSHIP BETWEEN MATERNAL ANTIBODY TITERS AND SEVERE DENGUE DISEASE IN INFANTS

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Dengue virus remains hyper-endemic in the tropics and sub-tropics, causing a significant burden to healthcare systems. Mothers who have been infected by dengue virus at some point in their lives will pass maternal dengue antibodies to their infants which can protect from infection in the early months of life. However, as the maternal antibodies decay in young infants, there is known to be a window of risk where the presence of sub-neutralizing antibodies places infants at risk of severe disease through the mechanism of antibody-dependent enhancement. However, it remains unclear if there are specific titer levels linked to the risk of severe disease. Here, we analyze data from two longitudinal cohort studies in Thailand where blood was sampled from 473 infants, with 2-5 blood draws each in the first year of life and tested for dengue serotype-specific haemagglutination inhibition (HI) titers. Serotype-specific PRNT titers were additionally available for a subset of 140 infants. We use a mathematical model to reconstruct the dynamics of maternal dengue antibody titers in the first year of life and correlate these with the age distribution of hospitalized infant dengue cases in local hospitals. We find that mean HI antibody titers fall from 124.6 (109.8-145.5) at 3 months to 1.3 (1.1-1.5) at one year. Hospitalized infant dengue cases peak at 8 months of age with a relative risk of 2.1 (2.0-2.2), compared to the risk at 12 months of age, when mean antibody titers are estimated to be 9.8 (8.6-11.4). This titer risk window we identify is consistent with previously identified antibody titer correlates of severe disease in children and adults experiencing secondary dengue virus infections, suggesting a common mechanism of risk for severe dengue disease from pre-existing antibodies in both infants and older individuals. Further, we explore how the age at which infants experience the highest risk of severe dengue disease may be influenced by the quantity of maternal antibodies received by the infant and how factors such as mothers age and changes in dengue virus transmission intensity might modulate the age of increased infant disease risk.

0806

PREDICTORS OF SEVERITY BASED ON CLINICAL, DEMOGRAPHIC AND SEROLOGICAL ASPECTS IN PEDIATRIC PATIENTS WITH SUSPECTED DENGUE DURING THE 2019 DENGUE EPIDEMIC IN BRAZIL

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Dengue is the main arbovirosis, in terms of morbidity and mortality. The clinical presentation ranges from mild/asymptomatic to a severe disease with vascular leakage, bleeding, shock, and death. The difficult of dengue diagnose in children leads to late appropriate clinical treatment. In this context, the interaction between clinical, epidemiological, and virological characteristics in dengue-confirmed patients, during 2019 epidemic was analyzed based on risk of severe forms of disease. For that, 341 patients were analyzed retrospectively, based on medical records and serum samples, confirmed to DENV by NS1, RT-PCR and serological test (anti-dengue IgM detection). All of them, 54.84% patients were included, being 30.48% dengue with warning signs (DWS) or severe dengue (SD) leading to hospitalization. The most frequent dengue signs and symptoms were fever 88.24%, leukopenia 51.91% and exanthema 42.25%. Abdominal pain 81.67%, fluid accumulation 46.67% and bleeding 38.33% were the predominant warning signs. And SD cases showed more frequently shock 57.14%, respiratory distress and neurological involvement 42.86%. No death was identified on confirmed patients. Different age ranges or sex did not associate with risk of severe forms of dengue (DWS/SD), while the presence of comorbidities OR 4.2 (CI 95% 1.65-10.694; p<0.003), immunosuppression OR 11.167 (CI 95% 1.218-102.40; p<0.33) and anti-Zika IgG presence OR 8.75 (CI 95% 3.115-24.578; p<0.001) were associated with risk of severity forms of Dengue (DWS/SD). Interestingly, the detection of anti-dengue IgG did not influence the development of DWS/SD (OR 1.226, CI 95% 0.369-0.887, p=0.622). The study was developed in an endemic region, with a high seroprevalence of IgG antibodies to dengue in the adult population, asking the question of whether the pediatric population also might not have been exposed to multiple dengue infections. In addition, other risk factors were observed for severe forms. Thus, highlighting the need for further studies to better evaluate the virological status of this population to understand and mitigate the serious evolution of the disease.

0807

IMPACT OF PRIOR EXPOSURE TO ZIKA VIRUS ON ACUTE DENGUE INFECTION

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Recent studies, after the emergence of Zika, have suggested that previous immunity triggered by an infection by another flavivirus could promote such a physiopathogenic mechanism with exacerbation of immune response and, consequently, more severe evolution to dengue. This study aimed to evaluate whether the presence of anti-Zika IgG antibodies resulting from a previous infection represents a risk predictor for severe forms of dengue (dengue with signs of alarm (DWS) and severe dengue (SD)) and hospitalization for the disease. Between December 2018 and November 2019, 1,043 confirmed dengue cases were enrolled up to 7 days of symptoms and evaluated for a history of dengue (DV) or Zika (ZV) infection through IgG antibody detection. Three groups were compared i) control (DV-/ZV-; 19.4%), DV-/ZV+ (4.6%) and DV+/ZV- (60.1%). 78.6% of cases were classified as dengue without alarm signals (DwWS), 20.3% DWS and 1.1% DS. 30.2% of patients required hospitalization and the lethality rate was 0.2 deaths per 100 confirmed individuals. There was a higher occurrence of severe forms (DWS + SD) in the DV-/ZV+ group ($p<0.001$), as well as a higher hospitalization rate (68.4%) in DV-/ZV+ ($p<0.001$). Patients DV-ZV+ had a 2.34 higher risk (CI 95% 1,239-4,429) for DWS+SD and 3.39 higher (95% CI 1,594-7,209) for hospitalization compared to control. The quantification of viral load revealed that there was no greater viral load of DENV in DV-/ZV+ patients when compared to the control ($p=0.37$ for Ct mean and $p=0.69$ for Quantify mean). DV-/ZV+ was associated with higher levels of IL-10 ($P<0.001$) and reduced EGF ($p<0.05$) compared to control, in addition to a lower relationship between IFNy/IL-10 ($P<0.05$) and higher between IL-1ra/IL-1B ($p<0.05$), demonstrating a different inflammatory response to the expected in antibody-dependent enhancement (ADE) by DENV, but still being skewed to Th1. The findings show that previous ZIKV infection is associated with the risk of more severe forms of dengue and hospitalization, however this risk does not seem to be associated with previous reported and known mechanism.

0808

EMERGENCE OF A NEW DENGUE VIRUS 2 LINEAGE DURING A SEVERE 2018-2019 DENGUE OUTBREAK IN NICARAGUA

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Dengue is a mosquito-borne viral disease whose ongoing global expansion poses a significant threat to public health. Dengue virus evolution is often characterized by lineage turnover in which a new lineage of viruses replaces a former one. Such clade replacement, along with other ecological and immunological factors, has been linked to changes in dengue phenotype affecting epidemic dynamics. Utilizing epidemiologic, clinical and virologic data from two long-term population-based studies (the Nicaraguan Pediatric Dengue Cohort Study and Nicaraguan Dengue Hospital-based Study), we describe a lineage turnover of DENV serotype 2 (DENV-2) and the emergence of a distinct lineage during a severe 2018/19 dengue outbreak in Managua, and a smaller outbreak in León. Prior to this outbreak, Nicaragua had experienced relatively mild levels of DENV transmission since the 2013/14 season, followed by a severe Zika virus (ZIKV) outbreak in 2016/17. Our phylogenetic analyses confirmed that all Nicaraguan DENV-2 isolates from 2018/2019 formed its own clade within the Nicaraguan lineage of the Asian/American genotype. León samples all shared, non-exclusively, a weakly supported cluster within this lineage. The emergence of the new lineage reflects a DENV-2 lineage turnover event in which the formerly dominant clade presiding from 2005 to 2009 was replaced. To elucidate evolutionary drivers of lineage turnover, we performed selection pressure analysis, and reconstructed the demographic history of DENV-2. We found evidence of adaptive evolution by natural selection at the codon level as well as in branch formation. The timing of its emergence, along with a statistical signal of adaptive evolution and a distinctive mutation in the NS5 gene for this lineage lead us to propose that this lineage may have increased fitness relative to prior strains, and contributed to the increase in size and severity observed during 2018/19 DENV-2 outbreak, in addition to the previously identified immunological factors associated with pre-existing Zika virus immunity. Further laboratory experiments are needed to confirm this hypothesis.

0809

FIRST DETECTION OF THE DENV-2 COSMOPOLITAN GENOTYPE IN SOUTH AMERICA

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The replacement of the American genotype of DENV-2 after the introduction of the Southeast Asian-American genotype in 1981 caused numerous epidemics in the Americas and a substantial increase in the incidence of severe disease. Since then, the Southeast Asian-American genotype has been the only DENV-2 genotype circulating in the Americas during periods of endemic and epidemic transmission. A dengue outbreak investigation conducted in collaboration with the Instituto Nacional de Salud de Peru, reported transmission of DENV-2 with 4,893 total cases. Genomic sequencing detected the emergence of the Cosmopolitan genotype concomitant with active transmission of the Southeast Asian-American genotype in other regions of the country. Two years later, the Cosmopolitan genotype was detected in a male patient in the state of Goiás, Midwest Brazil in 2021 using mobile genomic sequencing technology. To infer the origin of the Cosmopolitan viruses detected in Peru and Brazil, we constructed phylogenetic trees using the genomic sequences obtained in this study and a wide selection of genomes obtained from GenBank to provide a global context. Time-resolved maximum likelihood phylogenetic trees showed that the South American Cosmopolitan viruses cluster together and are closely related to viruses

sampled in Bangladesh between 2017-2019. Our analysis suggests a complex cross-border transmission scenario initiated by virus introduction events likely mediated by air travel from Asian countries. The emergence of the DENV-2 Cosmopolitan genotype in the Americas merits active outbreak risk assessment and surveillance across the region to prevent further spread and reduce epidemic potential.

0810

COMPREHENSIVE MUTAGENESIS OF DENGUE VIRUS ENVELOPE PROTEINS TO MAP ANTIBODY EPITOPES AND IDENTIFY RESIDES ESSENTIAL FOR FUNCTION

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To characterize the immune response to dengue virus (DENV) infection, we have epitope mapped over 200 anti-DENV monoclonal antibodies (MAbs), using high-throughput, rapid screens of MAb binding to DENV prM/E comprehensive mutation libraries for all four DENV serotypes, 3,380 mutations in total. Each library of individual mutant expression plasmids was transfected into human cells to achieve native protein expression and folding, and immunoreactivity of MAbs to each individual prM/E variant was quantified by high-throughput flow cytometry. The epitopes obtained were both conformational (including quaternary) and non-conformational, were spread across prM and E domains I-III, and many have been correlated with their abilities to protect against DENV infection. A number of anti-DENV MAbs cross-reacted with ZIKV prM/E, predominantly within the fusion loop but also within Domain II of the E protein, identifying critical immunogenic residues shared by DENV and ZIKV. We have also produced DENV virions from all four DENV mutation libraries using a previously developed DENV reporter virus particle (RVP) system, allowing us to screen each individual DENV Env variant protein for DENV particle budding and infectivity. For DENV3, we identified residues whose mutation eliminated virus infectivity but did not impact E protein expression, antigenicity, virion assembly, or particle budding. We identified variants that showed increased DENV virion budding, up to 5-fold above wild-type, indicating the ability to engineer highly expressed, non-infectious DENV variants for use in vaccine design. To identify uncharacterized DENV cellular receptors we assayed wild-type DENV RVP infectivity in non-permissive cells expressing our membrane proteome array (MPA) of 6,000 unique human membrane proteins. This has identified candidate membrane proteins that enable DENV infectivity. We have identified neutralizing epitopes in DENV prM/E and specific sites that are critical for DENV infectivity, providing new targets and opportunities for vaccine development.

0811

A PHARMACOMETRIC APPROACH TO EVALUATE DRUGS FOR POTENTIAL REPURPOSING AS COVID-19 THERAPEUTICS

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Developing and evaluating novel compounds for treatment or prophylaxis of the SARS-CoV-2 virus is costly and time consuming. Repurposing of already available marketed compounds is an appealing option as they already have an established safety profile. This approach could substantially reduce cost and time required to make effective treatments available to fight the COVID-19 pandemic. However, this approach is challenging since many drug candidates show efficacy in *in-vitro* experiments, but fail to deliver effective treatment when evaluated in clinical trials (e.g. chloroquine/hydroxychloroquine). Better approaches to evaluate *in-vitro* data are needed, in order to prioritize drugs for repurposing. This project evaluated potential drugs that might be of interest for repurposing in the treatment of patients with COVID-19 disease (i.e. chloroquine, mefloquine, amodiaquine, daclatasvir, sofosbuvir, favipiravir, nitazoxanide, ivermectin, atazanavir/ritonavir, and colchicine). A pharmacometric simulation-based approach was used to evaluate *in-vitro* activity data in combination to expected clinical drug exposure, in order to evaluate the likelihood of achieving effective clinical concentrations. The pharmacokinetic properties of the different drugs were reviewed and a suitable pharmacometric model used for population-based simulations. Standard daily dosing was extended for an assumed total duration of 10 days of treatment, and population-based pharmacokinetic simulations were compared to corrected target values reported in the *in-vitro* system. Half of the evaluated drugs showed simulated total plasma concentrations associated with effective inhibition of SARS-COV-2 in *in-vitro* systems. This provides a relatively unbiased and simple framework for prioritizing and de-risking the selection process of drugs to evaluate further in prospective randomized controlled clinical trials.

0812

INFERENCE OF THE REPRODUCTION NUMBER IN HETEROGENEOUS EPIDEMICS

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Real-time estimation of the reproduction number has become the focus ofmodelling groups around the world as the SARS-CoV-2 pandemic unfolds. One of the most widely adopted means of inference of the reproduction number is via the renewal equation, which uses the incidence of infection and the generation time distribution. In this paper, we derive a multi-type equivalent to the renewal equation to estimate a reproduction number which accounts for heterogeneity in transmissibility including througha symptomatic transmission, symptomatic isolation and vaccination. We demonstrate how use of the renewal equation that misses these heterogeneities can result in biased estimates of the reproduction number. While the bias is small with symptomatic isolation, it can be much larger with asymptomatic transmission or transmission from vaccinated individuals if these groups exhibit substantially different generation time distributions to unvaccinated symptomatic transmitters, whose generation time distribution is often well defined. The bias in estimate becomes larger with greater population size or transmissibility of the poorly characterized group. We apply our methodology to Ebola in West Africa in 2014 and the SARS-CoV-2 inthe UK in 2020-2021.

0813

GEOSPATIAL ANALYSIS OF SARS-COV2 INFECTIONS IN WESTERN ETHIOPIA 2020-2021

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Lack of testing and accompanying laboratory services have limited our understanding of the trueSARS-CoV2 infection prevalence in rural areas of Ethiopia. Integrating SARS-CoV2 antigen targets into established serologic assays used for ongoing malaria surveillance studies can offer a unique perspective on community and household transmission dynamics of SARS-CoV2. We measured IgG antibodies to SARS-CoV2 receptor binding domain (RBD) and Spike (S) proteins before widespread implementation of COVID-19 vaccination to determine the seroprevalence in existing malaria cohorts in the Arjo-Didessa sugar cane plantation in the Oromia region and the Saudi Star rice plantation in the Gambela region of Ethiopia. Plasma samples were considered seropositive if MagPix mean fluorescence intensity values of IgG antibodies for both RBD and S proteins were greater than 2 SD above the mean of plasma from North American control plasma collected before the COVID-19 pandemic. SARS-CoV2 seropositivity was nil for plasma samples collected from the Ethiopia study cohorts before 2019. SARS-CoV2 seropositivity in the Arjo-Didessa study site increased from 14.3% (90/629) in 2020 to 23.0% (113/492) in

2021 (p-value 0.0002). SARS-CoV2 seropositivity did not change over the same time interval in the Gambela cohort (11.1% (44/398) and 14.2% (45/316), respectively; p > 0.05). Clustering of SARS-CoV2 seropositive individuals was apparent in some households. Ongoing analyses include in-depth geospatial and demographic analyses of variables associated with seropositivity and addition of assays that allow for distinction of natural SARS-CoV-2 infection from COVID-19 vaccine responses (IgG antibody to the viral nucleocapsid protein).

0814

UTILIZATION OF BEST-FIT ANIMAL MODELS AND BIOASSAY METHODS TO INVESTIGATE CURRENT AND EMERGING SARS-COV-2 VARIANTS

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Since its initial emergence in 2019, the severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) has killed over six million people and infected almost 500 million people in over 210 countries worldwide. As a preclinical CRO, Bioqual Inc. has supported a multitude of SARS-CoV-2 research studies including the evaluation of potential vaccines, vaccine therapeutics and drug therapies, both *in vitro* and *in vivo*. *In vitro* services are available for evaluation of immunological, viral, and molecular parameters of SARS-CoV-2 variants, such as Delta, Omicron, and Alpha (WA strain) within BSL-2 and BSL-3 containment laboratories. These services include sample processing, virus stock generation, quantitation of infectious virus, virus neutralization assays, quantitative PCR, ELISA, multiplex serological testing, and ELISpot assays, flow cytometry, and other cell-based assays which directly support Bioqual's use of a wide variety of animal models. Bioqual's established animal models for COVID-19 include Golden Syrian hamsters, BALB/c mice, hACE2 tg mice, ferrets, rhesus and cynomolgus macaques. The utilization of various animal models enables us to investigate specific questions using the best-fit animal model for that purpose. Recent data from finalized study projects demonstrate that the animal models and corresponding immunogenic bioassays provides an advantage to investigate emerging research questions involving known and unknown SARS-CoV-2 variants.

0815

HIGH SEROPOSITIVITY OF SARS-COV-2 DURING THE OMICRON WAVE IN AN URBAN CITY IN GHANA

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A significant proportion of SARS-CoV-2 infections on the African continent were identified as asymptomatic, facilitating the silent spread of the virus especially in populated urban cities. With the surge of the highly transmissible Omicron variant, the inclusion of the asymptomatic in epidemiological surveys is key in estimating true infections and seroprevalence in the population. The aim of the study was to determine seroprevalence, active infection and circulating variants in Accra, the capital city of Ghana during the Omicron wave. The study was a cross-sectional survey conducted in 22 communities in December 2021. Naso-oropharyngeal swabs and serum samples were collected from 1027 consenting individuals aged 5 years and above, for detection of infection by RT-PCR and estimation of total antibodies using the WANTAI ELISA kit. Our results show 10% (105/1027) SARS-CoV-2 prevalence, with the Omicron and Delta variants accounting for 44.1% and 8.8% of infections, respectively. Omicron was most prevalent (48.9%) among the 20-39-year strata. However, 77.24% of the SARS-CoV-2 infected participants showed no symptoms. There was 86.8% (891/1027) seropositivity within the population, with the 60+ year group having a significantly higher likelihood of exposure (OR 10.22: 95% CI: 3.51-29.73; *p*<0.001). This seemed to have been because of increased vaccination among this group (OR 2.7: 95% CI 1.78-4.09, *p*<0.001). The high seropositivity of SARS-CoV-2 in the capital could be a good indication of herd immunity among the population. Ongoing vaccination efforts remain central to reducing viral transmission.

0816

SURVIVAL ANALYSIS OF OMICRON VARIAN OF COVID19 PATIENTS WITH COMPLETE AND INCOMPLETE VACCINATION STATUS AT SAMARINDA CITY

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Samarinda city is the capitol of east Borneo province of Indonesia. in the early 2022, since January until late March 2022, Samarinda has an increase of Omicron Variant of COVID19 curve. 29.515 confirmed cases since the pandemic begins, with the proportion of 3584 cases per 100.000 person in Samarinda city only. with 2.45% death percentage among confirmed cases, Samarinda is categorized as high risk city. 67 death cases from January to March 2022, were recorded with 6 death cases of complete vaccine received, 38 death cases of incomplete vaccine received. Using survival analysis of Stata 13 documentation, 52 subject were monitored, with 0 entry time and 5.07 mean of exit time. subjects with gap is 0 and time at risk is 264 with 29 failures. The results are 2 subjects with 25% survival time, 7 subject with 50%, 13 subjects with 75% survival time. the odd ratio between complete vaccination and incomplete vaccination is 0.03. 26 subject of death for complete vaccination status, with 4,8 mean of exit time, subject with gap is 0 and time at risk is 126 with 3 failures. the result is the death cases of omicron variant with complete vaccination status is less compared to incomplete vaccination status. Mean of Exit time per subject for complete vaccination is 4,8 while incomplete vaccination is 5,3. this indicate that incomplete vaccination has longer days of treatment with death results compared to complete vaccination.

0817

WHOLE GENOME CHARACTERIZATION AND COMPARATIVE GENOME ANALYSIS OF GENOGROUP-1 AND GENOGROUP-2 ROTAVIRUS STRAINS CIRCULATING IN VELLORE INDIA 2002 TO 2017

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Rotaviruses (RVs) are the most common etiological agent of acute gastroenteritis (AGE) in pediatric age group. A whole-genome nomenclature of GxP[x]IxRxCxMxAxNxTxExHx, representing the 11 genes, VP7-VP4-VP6-VP1-VP2-VP3-NSP1-NSP2-NSP3-NSP4-NSP5 was introduced. The common infecting strains carry the classical Wa constellation- G1P[8]I1R1C1M1A1N1T1E1H1 and DS-1 constellation-G2P[4]I2R2C2M2A2N2T2E2H2. This study was performed to characterize the whole genome of predominant circulating strains over 15 years prior to vaccine introduction in Vellore, India. Whole genome characterization of 90 G1P[8], 67 G2P[4], 32 G12 strains and few other strains was done. 91% of G1P[8] had classical Wa constellation and 9% were reassortants. One strain had DS-1 like backbone with rare E6 NSP4 gene (G1P[8]I2R2C2MxA2N2T2*E6*H2). Most of G2P4 strains (95%) had DS-1 backbone while 5% were reassortants, carrying upto 4 reassortant genes. G12P[8]/P[4] strains had Wa backbone. 81% of G12P[6] samples had Wa backbone while 19% were single gene reassortants. Reassortant G9P[4] strains with rare E6 NSP4 and G9P[8] strain with 6 DS-1 like genes were observed**.** Phylogenetic analysis revealed that most of the study strains clustered into previously defined sub genotypic alleles.VP4 gene tree of P[8] clustered into 4 distinct clades, where 6 strains belonged to the OP-354 like genetically distinct subtype of P[8]. The common RV G1P[8], G2P[4], G9P[8], G9P[4], and G12 strains mostly carry stable genotype constellations over years . However, reassortment does occur, and unusual constellations may be found indicating the need for continuing to track

virus evolution. We identified the E6 NSP4 in combination with DS-1 like G1P[8] for the first time in India, as well as emergence of the OP-354 subtype of P[8]. Few reassortant gene sequences were similar to sequences of bovine origin, indicating bovine-human interspecies transmission. While RV have stable genetic backbones, reassortment and inter-species transmission do occur. In the context of vaccine use in India from 2016, maintaining phylogenetic surveillance is essential to track virus evolution.

0818

SARS-COV-2-SPECIFIC IGG MEASURED IN SALIVA REFLECTS IMMUNE STATUS ARISING FROM SARS-COV-2 INFECTION AND COVID-19 VACCINATION

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Respiratory viruses, including emerging viruses with pandemic potential, represent a major global health threat. Robust systems for detecting virus-specific antibody responses, to support vaccine development and implementation, are critical in combatting such infectious diseases. Moreover, improved approaches to enable population-scale testing, particularly in resource-limited settings, are urgently needed. This study asked whether prior SARS-CoV-2 infection affected antibody immunity elicited by COVID-19 mRNA vaccines. We employed saliva-based antibody testing on a Luminex platform to test the hypothesis that prior infection will increase the peak magnitude and duration of IgG against the SARS-CoV-2 spike (S). The utility of this method in improving sampling inclusivity and biosafety for field workers was also explored. We found that IgG serostatus to the SARS-CoV-2 nucleocapsid (N) antigen successfully identifies seroprevalent and seroincident infections in a longitudinal cohort of healthcare personnel followed prior to vaccine availability. SARS-CoV-2 infection prior to vaccination leads to an increased level of IgG binding to S and the receptor-binding domain (RBD) of S. Differences between groups are most pronounced 7-14 days after the first of two mRNA vaccine doses but maintained through 6 months post-vaccination. We assessed the correlation of salivary IgG levels with serum-based neutralization titers, given the potential to develop a non-invasive measure of protective immunity. In summary, our data, relying primarily on measuring SARS-CoV-2-specific IgG in saliva, are consistent with accumulating literature on hybrid immunity to SARS-CoV-2. This study also demonstrates the vast potential of our approach in providing a key tool for supporting many public health priorities, including tracking immunity to variants and multiple respiratory viruses with known morbidity and mortality in the young and elderly.

0819

SARS-COV-2 BREAKTHROUGH INFECTIONS AND ITS IMPLICATIONS ON BOOSTER VACCINATION STRATEGIES

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COVID-19 vaccines are critical for controlling the SARS-CoV-2 pandemic. Despite their ability to prevent symptomatic and severe COVID-19, vaccines are less effective at preventing asymptomatic infection. We observed 5 waves of SARS-CoV-2 in the Philippines with the 1st wave attributed to the original Wuhan strain, followed by various lineages with the D614G mutation. The 3rd wave was brought about by the Alpha and Beta VOCs , the 4th wave was caused by the Delta variant, and the most recent wave caused by the Omicron variant (BA.2) which occurred from end of Dec 2021 to February 2022. Vaccination started in March 2021 with CoronaVac as the predominant vaccine administered by the government. From April-September 2021, there were 1,594 breakthrough infections from fully vaccinated personnel with breakdown as follows: 1,404 CoronaVac (Sinovac), 118 ChAdOx1-S (AstraZeneca), 47 Sputnik V (Gamaleya), 20 BNT162b2 (Pfizer-BioNTech), and 5 mRNA-1273 (Moderna). Sub-analysis of rRT-PCR Ct values among breakthrough infections showed that healthcare workers (HCWs) had significantly lower Ct values (higher viral loads) compared to non-HCWs. The higher viral loads may be due to the continuous and sustained exposure of HCWs to COVID-19 infected patients. Some COVID-19 vaccines produce neutralizing antibody titers that are short-lived and declined below the seropositive cut-off after just a few months. Vaccine efficacy against some VOCs have invariably declined but the degree of decline in protection is variable and is brand/platform dependent. Higher breakthrough infections are expected if COVID-19 vaccines with lower efficacy are given and if circulating variants have enhanced immune escape abilities. Booster vaccination strategies should consider the best combination of vaccine brand/platform and approach (homologous vs heterologous) which will provide the highest protection for those with higher exposure or higher risk for severe morbidity/mortality.

0820

CROSS-SECTIONAL SURVEY OF PAST SARS-COV-2 INFECTIONS AND EVALUATION OF THE NEUTRALIZING ANTIBODY RESPONSE AMONGST COVID-19 VACCINATED ACTIVE DUTY U.S. MILITARY MEMBERS IN THE ASIA-PACIFIC REGION

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Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) virus infections remain a threat to the operational readiness of U.S. military forces in INDOPACOM and around the world, especially with the recent emergence of variants of concern (VOC). The U.S. Naval Medical Research Unit TWO (NAMRU-2), along with regional and U.S. partners, designed and executed a combination cross-sectional and cohort survey with operational Navy and Marine Corps units in the Asia-Pacific region to evaluate the underlying distribution of previous SARS-CoV-2 infections and the overall neutralizing antibody (Ab) response of vaccinated service members. We used ELISA to N protein to estimate seroprevalence, and S IgG and Ab neutralization to study serology to the ancestral strain (Wuhan-D614G) and to VOCs in service members who received the Moderna SARS-CoV-2 vaccine. A total of 1,036 serum samples were collected from early February to September 2021, from service members assigned to four different vessels operating to INDOPACOM. Approximately 20-30% of the participants were IgG/IgM positive to N, suggesting prior SARS-CoV-2 infection. Serology data from 717 fully vaccinated service members indicated a strong correlation between S IgG and Ab neutralization (correlation: 0.7014, $p<0.05$), as well as a negative trend in S IgG and Ab neutralization over 270 days post-vaccination (S IgG $R^2=0.513$, $p<0.001$; neut $R^2=0.279$, $p<0.001$). Service members who had a previous infection showed a significantly higher Ab neutralization following vaccination as compared to those who were naïve following vaccination (N+ vs N-: $p=0.0049$, $Chi^2=12.89$). Ab neutralization showed a significant reduction against Omicron variants BA.1 and BA.2. Using pesudoviruses displaying mutations on individual domains of RBD, NTD, SD (subdomain aa528-625) and S2 of Omicron, the domain responsible for Ab escape was mapped largely to RBD, much less to NTD, and no to SD and S2. This study suggested a significant reduction of Ab neutralization to VOCs including Omicron, and the requirement of effective vaccination to protect against SARS-CoV-2 variants among our operational forces worldwide.

0821

SARS-COV-2 AND MALARIA INTERACTIONS IN PREGNANCY AND THEIR IMPACT ON BIRTH OUTCOMES IN UGANDA

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The impact of SARS-CoV-2 infection in malaria endemic settings remains poorly understood. Rates of COVID-19 morbidity and mortality appear lower in parts of sub-Saharan Africa than in resource-rich settings; high prevalence of malaria parasitemia, and resulting immune-modulating effects, may drive these lower rates. Further, though both SARS-CoV-2 infection and malaria during pregnancy are known to adversely impact birth outcomes, it is unknown whether gestational exposure to both pathogens leads to synergistic inflammatory responses and placental effects. To gain insights, we leveraged an ongoing randomized controlled trial of antimalarial chemoprevention regimens among pregnant women living in Eastern Uganda. In this trial, 2757 pregnant women are being enrolled during the second trimester and followed through delivery. Between December 2020-January 2022, 831 women were enrolled and 377 delivered. SARS-CoV-2 vaccination was not routinely available in the study cohort until February 2022. Malaria parasite prevalence by microscopy at enrollment was 29.6% (246/831), the incidence of malaria during pregnancy was 0.46 episodes per person year, and 27.6% (104/377) of participants experienced adverse birth outcomes including spontaneous abortion, stillbirth, low birth weight, preterm birth, small-for-gestational-age, and neonatal death within the first 28 days. At delivery, 116/168 (67.7%) participants were seropositive for SARS-CoV-2 spike protein as measured by Luminex/Magpix assay, increasing from 61.8% in samples collected before December 2021 (pre-Omicron variant surge) to 76.9% from December 2021 onwards (p=0.03). Despite this high seropositivity, only 5 symptomatic participants were referred for SARS-CoV-2 rapid antigen testing, and 2/5 were positive. Thus, the majority of SARS-CoV-2 infections were undetected. We are currently testing additional samples to identify seroconversion events during pregnancy, to determine if seroconversion is affected by malaria parasitemia, and to determine if SARS-CoV-2 infection with or without malaria during pregnancy is associated with adverse birth outcomes.

0822

DETERMINATION OF CLINICAL PARAMETERS IN PREDICTING LONG-TERM SARS-COV-2 ANTIBODY RESPONSES AMONG COVID-19 PATIENTS IN BANGLADESH

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Information on antibody responses following SARS-CoV-2 infection, including the magnitude and duration of responses and the correlates of protective immunity, is limited. This study aims to identify the clinical parameters during acute infection which can predict the long-term IgG antibody response against SARS-CoV-2 following natural infection. We conducted a prospective longitudinal study in Dhaka, Bangladesh. COVID-19 diagnosed patients (n=100) were enrolled from November 2020 to February 2021 and prospectively followed up to day 90. Association of some clinical parameters on enrollment, including lactate dehydrogenase (LDH), neutrophil-lymphocyte ratio (NLR), ESR, C-reactive protein (CRP), ferritin, procalcitonin (PCT), and D-dimer, with SARS-CoV-2 IgG antibody concentration on day 90 was assessed using linear regression. IgG antibody concentration and several biomarkers were log-transformed for normal distribution. A total of 68 patients were included in this analysis after excluding death, dropout, receipt of COVID-19 vaccine, and re-infection. The mean age of the patients was 45.0 ±14.3 years on enrollment, and 58.8% of the patients were male. The median duration between disease onset and enrolment was 10 days (IQR: 8-12). LDH (β=0.63, 95% CI: 0.14, 1.12; p<0.05), NLR (β=0.51, 95% CI: 0.25, 0.76; p<0.05), ESR (β=0.01, 95% CI: 0.003, 0.02; p=0.01), CRP (β=0.32, 95% CI: 0.20, 0.45; p<0.05), ferritin (β=0.24, 95% CI: 0.10, 0.39; p<0.05), PCT (β=0.24, 95% CI: 0.10, 0.39; p<0.05) and D-dimer (β=0.54, 95% CI: 0.00, 0.04; p=0.01) were found to be associated with IgG concentration on day 90. Compared to O blood group patients, the B blood group patients had 0.55 units higher IgG concentration on Day 90, although the association is marginally significant (95% CI: -0.05, 1.15, p=0.070). Several clinical biomarkers (LDH, D-Dimer, NLR, and CRP) in the acute phase of SARS-CoV-2 infection are associated with enhanced IgG antibody response even after three months of disease onset. Further analyses are required to see whether these biochemical parameters can predict SARS-CoV-2 specific antibody response even at later time points.

0823

SHIFTING LINEAGE DOMINANCE OF SARS-COV-2 IN BANGLADESH; DRIVEN BY POPULATION MOBILITY IN THE FIRST WAVE AND THE IMPACT OF GENOMIC SURVEILLANCE TO INFORM COUNTRY-LEVEL HEALTH POLICIES

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Genomics, combined with population mobility data, has been used to map importation and spatial spread of SARS-CoV-2 in high-income countries and has enabled implementation of local control measures. As a part of the nationwide SARS-CoV-2 genomics surveillance and to monitor the SARS-CoV-2 evolution in Bangladesh, we analysed the outbreak trajectory and variant emergence using genomics in Bangladesh. We integrated population mobility data with the genomics data to determine the possible introduction of SARS-CoV-2 in Bangladesh in 2020. Since the first reported case of SARS-CoV-2 on March 8, 2020, we sequenced complete genomes of 917 SARS-CoV-2 samples collected between March 2020 and March 2022. The sample collection represented the six administrative areas (divisions) of Bangladesh, and we used oxford nanopore minion platform to sequence all the genomes. Sequence analysis revealed that at the start of the COVID-19 pandemic in Bangladesh, early repeated international introductions of the virus were replaced by endemic spread of three dominant SARS-CoV-2 lineages that dispersed the country in late March 2020. Bayesian time-scaled phylogenetic analysis predicted that SARS-CoV-2 first emerged in Bangladesh in mid-February 2020, and sustained community transmission was observed at the end of March 2020 consistent with a mass exodus from urban areas to rural areas. Phylogenetic analysis further indicated the importation of several SARS-CoV-2 variant of concern (VOCs) into Bangladesh over the years such as Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.351), and Omicron (B.1.351) and very quickly became dominant in the country. As an integral part of the nationwide SARS-CoV-2 genomic surveillance, the study provides real time SARS-CoV-2 genomic data to the Government of Bangladesh to devise effective and necessary control measures.

0824

EVALUATION OF SALIVADIRECT RNA EXTRACTION PROTOCOL FOR MOLECULAR DETECTION OF SARS-COV-2 USING SALIVA SPECIMEN

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COVID-19 first emerged in Wuhan, China in December 2019. Globally, as of 3rd April 2022, the diseases affected 494 million people with 6.17 million fatalities. In Bangladesh, the first confirmed COVID-19 case was detected on 8th March 2020. Since then, there have been 1.9 million confirmed cases and 29,123 reported deaths. Saliva specimen has proved to be an alternative to nasopharyngeal swab (NPS) specimen for COVID-19 detection. To reduce the cost, time, and effort of currently approved RT-qPCR assays for COVID-19 detection from saliva specimens, Yale School of Public Health designed a dualplex PCR approach named SalivaDirect. It is simple, extraction free, accessible, fast, non-invasive, and economical ($1.29-$4.37/specimen). In this study, we evaluated the utility of SalivaDirect protocol with the gold standard RNA extraction protocol using NPS specimens collected from the ambulatory patients presented at the dedicated COVID-19 Screening Unit of Dhaka Hospital of icddr,b. Viral RNA was extracted from saliva using SalivaDirect protocol which is based on protein lysis, skipping other steps to reduce the time and cost. On the other hand, viral RNA was extracted from NPS using the QIAamp viral RNA mini kit (Qiagen, Germany). RT-qPCR was performed using primers and probes targeting the RdRp and N genes. The positivity rates for COVID-19 using standard protocol for NPS and SalivaDirect were 36.5% (73/200) and 35.0% (70/200) respectively. In comparison with RT-qPCR from NPS, the sensitivity of SalivaDirect was 89.04% (95% CI:79.54% to 95.15%), the specificity was 96.06% (95% CI: 91.05% to 98.71%), the positive and negative predictive values were 92.86% (95% CI: 84.58% to 96.86%) and 93.85% (95% CI: 88.79% to 96.71%) respectively. We also found increased sensitivity (100% and 88.5%) during the early Ct values (<20 & 20-30) and decreased sensitivity (50%) at the late Ct stage (>30) for SalivaDirect when compared to the standard protocol for NPS. In conclusion, the extraction-free and simplified approach SalivaDirect can be used in lower complexity laboratory settings for COVID-19 detection during the pandemic.

0825

EFFECTIVENESS OF COVID-19 VACCINES IN BANGLADESH, A TEST-NEGATIVE DESIGN EVALUATION

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There has been roll out of several different Covid-19 vaccines in large campaigns in Bangladesh from February 2021. This offered the opportunity to evaluate vaccine effectiveness of the vaccines and more specifically against the Delta variant of SARS-CoV-2 which surged in Bangladesh from May to December 2021. For this purpose, a prospective, test-negative case-control study was conducted in five large hospitals in Dhaka between September and December, 2021. Study subjects were patients at least 18 years of age who presented with COVID-19 like symptoms for care. Cases had PCR-confirmed infections by SARS-CoV-2, and up to 4 PCR test-negative controls were matched to each case by hospital, date of presentation, and age. Vaccine protection was assessed as the association between receipt of a complete course of vaccine and the occurrence of SARS-CoV-2 disease with symptoms beginning at least 14 days after the final vaccine dose. Genotyping of case isolates revealed over 99% to be the Delta variant. Receipt of any vaccine was associated with 9% protection against all episodes of SARS-CoV-2. Among the three vaccines for which protection was evaluable (Moderna (mRNA-1273); Sinopharm (Vero Cell-inactivated); Serum Institute of India (ChAdOx1 nCoV-19), only the Moderna vaccine was associated with significant protection (64%). Protection by receipt of any vaccine against severe disease was 85%, with protection estimates of 75% to 100% for the three vaccines. Vaccine protection against COVID-19 disease of any severity caused by the Delta variant was modest in magnitude and significant for only one of the three evaluable vaccines. In contrast, protection against severe disease was high in magnitude and consistent for all three vaccines.

0826

DIAGNOSTIC ACCURACY OF RT-PCR SALIVA VERSUS NASOPHARYNGEAL SWAB FOR COVID-19 DIAGNOSIS

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The nasopharyngeal (NP) Real-Time Polymerase Chain Reaction (RT-PCR) swab, which is considered the current reference standard for Covid-19 diagnosis, provokes discomfort to the patient, requires well-trained professionals, and likely causes nasal bleeding in patients with certain conditions. This method also triggers coughs or sneezes from patients, generating aerosols and increasing the risk of transmission to operators. Alternative biological samples for RT-PCR assays with low risk yet high accuracy, such as saliva, can be obtained easily and comfortably. Here, we report our findings on the diagnostic accuracy of saliva specimens compared to NP swabs for Covid-19 diagnosis. From April to June 2021, we enrolled 120 adult patients resembling pneumonia Covid-19 signs and symptoms in Siloam Lippo Village Hospital Emergency ward. All enlisted patients aged 18-81 years old underwent anamnesis, physical examination, NP RT-PCR swab, and saliva Covid-19 RT-PCR test. Saliva was collected with the drooling method, using the VereRTCoV™ ZeroStep Saliva Collection Kit with a prohibition to eat, drink, smoke, or use oral hygiene products within 30 minutes. Our data show that the sensitivity of salivary samples compared to NP swabs reached 86.67% (95%CI 76.84-93.42), specificity 91.11% (78.78-97.52), Positive Predictive Value 94.20% (86.39-97.65), Negative Predictive Value 80.39% (69.57-88.03), and

88.33% (81.20-93.47) accuracy. Furthermore, the results of our subgroup analysis show that the performance of saliva samples as an RT-PCR test material for detecting Covid-19 is quite reliable in all demographic groups. We also found that the mean CT value RT-PCR of saliva samples tended to be significantly higher than NP samples both on the N gene (mean saliva 26.22±5.14 vs. mean NP 22.18±6.23; p= 0.01) and on the ORF1AB gene (mean saliva 26.39±5.36 vs. mean NP 23.24±6.11; p<0.01). Nonetheless, considering the good positivity rate, sensitivity, and specificity of the diagnostic ability of saliva samples compared to NP swabs, this examination can certainly be recommended for use. This value will help improve Covid-19 diagnostic in Indonesia.

0827

CHALLENGES FACED IN PURSUING MILWAUKEE PROTOCOL IN A RESOURCE POOR SETTING - A CASE STUDY

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Rabies, a preventable virus disease caused by RNA virus Rabies lyssavirus, is signature of death. It was hypothesized that by decreasing neuronal activity, replication of virus can be suppressed, giving time to immune system to eliminate virus. Hence a novel procedure, Milwaukee protocol is introduced and is being tried to save a rabies patient. A 47-years-old woman with history of street dog bite 3-months back on left middle and ring fingers not received rabies vaccines, presented with complains of paraesthesia in left upper arm of 5-days duration, hydrophobia and aerophobia of 2-days duration. She went to local hospital and then immediately referred to tertiary care centre (here). She received in the facility and shifted to ICU immediately. After explaining about disease prognosis to caretakers, she was electively intubated and treated with antiviral mocktail according to modified Milwaukee protocol with ketamine, insulin, fludrocortisone, ribavirin, and amantadine. Her initial CSF analysis was acellular and rabies RT-PCR and rabies virus neutralizing antibodies was negative at first instance. MRI Brain showed no significant abnormality. She developed high grade continuous hyperthermia (central origin) of since the day of admission that was not relieved with paracetamol, still managed with various external and internal cooling. She developed neurogenic shock on day 6 of intubation. Repeated culture reports were negative including serum procalcitonin. Her condition improved in next 3-days and weaning was planned. However, at day 12 of intubation, her shock worsened and patient died on day 13 of intubation. We couldn't do repeat CSF examination and MRI brain timely as per protocol. A lack of understanding among general population regarding rabies is still prevalent leading to lack of timely vaccination. Rabies can present as hyperthermia and neurogenic shock. Current Milwaukee protocol makes an uncomfortable panic like situation among caretakers due to induced coma state and it is highly difficult to follow the protocol strictly in resource poor settings.

0828

EVALUATION OF PANBIO RDTS FOR THE DIAGNOSIS OF SARS-COV-2 INFECTION

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On March 2022, there have been 470839745 confirmed cases of COVID-19, including 6092933 deaths, reported to WHO. This infection is a public health emergency. The WHO African Region remains one of the least affected by this pandemic, accounting for 1.8% of all reported cases (8 524 056) with 170837 deaths. In Gabon, we recorded 47584 cases with 303 deaths was reported in March 2022. The diagnosis of COVID-19 involves the use of RT-PCR, the gold standard but access to this technique is limited in some areas due to its cost and technicals requirements. The WHO recommends the use of tests with a sensitivity greater than 80% and a specificity greater than 97%. These data indicate that the RTDs can be used as an alternative for the diagnosis of SARS-Cov 2 infection in regions where the use of NAATs would be impossible. We processed patient samples at the Centre Hospitalier Universitaire d'Owendo in Gabon between April and September 2021 using Panbio Covid-19 rapid diagnostic tests in comparison to the results obtained by RT-PCR of patients between 6 and 70 years old who went to the CHUO for screening for SARS-Co 2 infection. After obtaining consent to participate in the study, socio-demographic data, medical history and the reason for the examination were collected. Symptoms such as cough and flu syndrome were frequently found while high blood pressure and diabetes were the most common comorbidities. For each patient, two nasopharyngeal samples were taken. After analysis, the prevalence of SARS-Cov-2 infection was higher in adults regardless of technique used. This prevalence was 30% with PCR and 29% with RDTs. We found 100 samples positive by PCR against 99 found positive by TDR. The sensitivity and specificity of the TDR Panbio were therefore 99%. False positives were found in two patients while one patient ended up with a negative TDR result while his PCR result was positive. The positive predictive value is 98% and the negative predictive value is 99%. these results are consistent with the characteristics required by the WHO. Thus, our data can be used to demonstrate that Panbio RDTs could be used as an alternative to PCR in symptomatic or non-symptomatic patients.

0829

THE FATAL CLINICAL OUTCOME OF SEVERE COVID-19 IN HOSPITALIZED PATIENTS: FINDINGS FROM A PROSPECTIVE LONGITUDINAL COHORT STUDY IN BANGLADESH

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The morbidity and mortality associated with COVID-19 burdened worldwide healthcare systems beyond available capacities, forcing them to promptly investigate the virus characteristics and its associated outcomes to plan preventive measures. This clinical analysis aimed to explore the key factors related to the fatal outcome of severe COVID-19 cases in Bangladesh. Thirty-five adult severe COVID-19 patients were enrolled in two COVID-19 dedicated hospitals in Dhaka, Bangladesh. Clinical manifestation, comorbid conditions, medications, SARS-CoV-2 RT-PCR cycle threshold (Ct) value, hematology, biochemical parameters with SARS-CoV-2 specific IgG and IgM responses at enrollment were compared between the survivors and deceased participants. A total of 27 COVID-19 severe patients survived and 8 patients died within 3 months of disease onset. Deceased patients suffered longer from shortness of breath than those who survived (p<0.05). The majority of the deceased patients (n=5) had multiple comorbidities compared to 48% of survivors. The anti-viral medication was initiated earlier among the deceased patients [median day of 1 (IQR:0-1.5) versus 6.5 (IQR:6.25-6.75)] and 55% of survivors received a combination of anticoagulants (p=0.034). Liver enzymes, creatinine kinase, and procalcitonin were higher among the deceased patients at the time of enrollment. The median Ct value among the deceased was significantly lower in specimens from the survivors (p=0.025). A significant difference for initial IgG (p=0.013) and IgM (p=0.030) responses was found between the survivor and the deceased groups, respectively. The factors including older age, male gender, early onset of respiratory distress, multiple comorbidities, low Ct value, and poor antibody response may contribute to the fatal outcome in severe COVID-19 patients. Early initiation of anti-viral and a combination of anticoagulant treatment may prevent or lower the fatality among severe COVID-19 cases.

0830

ISOLATION AND GENETIC CHARACTERIZATION OF NOVEL VIRUSES WITH POTENTIAL PATHOGENIC CONCERN FROM SANDFLIES IN KENYA

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Until recently, arbovirus surveillance has mainly focused on mosquito and tick vectors resulting in the discovery of multiple mosquito-borne and tick-borne arboviruses. Surveillance studies done in parts of Kenya have shown the presence of novel arboviruses circulating among Phlebotomine sand-fly populations. This study sought to isolate and characterize arboviruses from the Phlebotomine sandflies sampled from selected regions in North Rift Kenya. Arbovirus surveillance conducted between 2015 and 2017 led to the collection of approximately 28,226 sandflies translating to 824 sand-fly pools from three selected regions of North-rift Kenya namely Turkana, Baringo and West Pokot Counties. Virus isolation was performed on Vero cells and positive pools were tested by RT-PCR targeting Alphaviruses, Flaviviruses and Bunyaviruses. The isolates were also subjected to High-Throughput Sequencing. A total of 10 isolates were obtained in this study. Four of the isolates were identified as Chandipura Virus, with approximately 80% identity to other Chandipura viruses from India and West-Africa. Chandipura virus was recently associated with explosive outbreaks in rural areas of India between 2003 and 2007. One isolate was identified as Koutango lineage of the West-Nile virus. Other viruses identified in the study include Phleboviruses which were recently discovered; Ntepes and Bogoria Viruses. Additionally, three Sindbis isolates were also obtained. This is the first isolation of Sindbis Virus from sandfly vectors. In conclusion, this study has successfully isolated and characterized a number of viruses. The findings highlight the need to consider Phlebotomine sandflies in arbovirus transmission dynamics. Some of the viruses isolated have very low percent identity thresholds, suggesting that Phlebotomine sandflies are hosts to many potentially pathogenic viruses that remain unidentified. Therefore, there is need for more studies to be carried out to determine the public health importance and the level of exposure of these viruses.

0831

DEVELOPMENT OF VIRAL RNA REFERENCE MATERIALS FOR DIAGNOSIS OF SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME (SFTS)

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Severe Fever with Thrombocytopenia Syndrome (SFTS) is a tick borne hemorrhagic fever which is caused by *Dabie bandavirus*. Since its first description in 2009, SFTS has spread rapidly among East Asian countries. Clinical mortality rate ranges from 6% to 30%, and accurate early diagnosis is important to reduce the mortality rate since approved vaccines or drugs are not available. Nucleic acid amplification techniques (NAT) such as PCR, quantitative PCR and digital PCR are considered a golden standard in the diagnosis of infectious diseases including SFTS. Here, we describe the development of *Dabie bandavirus* RNA reference materials for identification of virus that causes SFTS. Using lentiviral system, *Dabie bandavirus* RNA is packaged into a lentiviral particle which is designed to be safe, non-infectious and non-replicative. Therefore, this viral RNA reference material allows researchers and clinicians to perform NAT based diagnostic assays for SFTS without biological safety concerns raised by handling live or inactivated viruses.

0832

SINGLE-DOSE AND DOSE-RANGING EFFICACY AND IMMUNOGENICITY OF THE EBS-LASV VACCINE CANDIDATE IN NONHUMAN PRIMATES

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Lassa fever is an acute viral illness caused by Lassa virus (LASV) and is associated with severe morbidity in 20% of cases and a case fatality ratio over 1%, with substantial economic and health security consequences. There are no approved therapeutic or prophylactic vaccines for the prevention of Lassa virus infection or Lassa fever. Vaccines based on recombinant, live-attenuated vesicular stomatitis virus (rVSV) vector technologies are in various stages of development for diverse indications. A rVSV vaccine (EBS-LASV) is being developed to protect against disease associated with LASV infection. The EBS-LASV vaccine candidate was constructed by insertion of the full-length LASV glycoprotein precursor complex gene (Josiah strain) at position 1 of the VSV genome. The attenuation strategy included translocation of the VSV N gene to the 4th position (N4) and deletion of the VSV G gene. EBS-LASV has been shown to be safe, immunogenic, and efficacious in nonclinical studies. To further evaluate the immunogenicity and efficacy of the vaccine candidate, a dose-ranging study was completed in cynomolgus macaques. EBS-LASV was administered intramuscularly (IM) as a two-dose regimen ($1x10^1$, $1x10^3$, $1x10^5$, and $1x10^7$ $TCID_{50}$) four weeks apart, or as a single dose regimen ($1x10^7$ $TCID_{50}$), and animals were challenged IM with a target dose of 1000 plaque forming units of LASV (Nigeria) 4 weeks after the last vaccination. Post-vaccination samples were collected for immunogenicity testing and post-challenge samples were collected for hematology, clinical chemistry, and viremia testing at designated time points. All animals receiving two doses of 10^3 - 10^7 $TCID_{50}$ EBS-LASV survived infection. Three out of four animals vaccinated with two doses of 10^1 $TCID_{50}$ or a single dose of 10^7 $TCID_{50}$ survived infection (75% survival), with a delay to death (Day 16-24) observed compared to control animals (Day 12) who did not survive infection. These data may support the use of a lower clinical dose for EBS-LASV than has typically been used for other rVSV-vectored vaccines and the potential for EBS-LASV to provide a protective benefit when administered as a single dose in humans.

0833

VARIANT PCR GUIDED MINION SEQUENCING FOR EARLY TRACKING OF CIRCULATING SARS-COV-2 VARIANTS IN BANGLADESH

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Since the first reported case of SARS-CoV-2 in Bangladesh on March 08, 2020, there were 1,951,831 confirmed cases of COVID-19 with 29,123 deaths until April 2022. In consistent with the global pandemic, Bangladesh has also experienced the COVID-19 waves due to the SARS CoV-2 variant of concerns (VOCs) such as the alpha variant (B.1.1.7) (201/501Y.VI), beta variant (B.1.351) (20H/501Y.V2), delta variant (B.1.617.2), and Omicron (B.1.1.529.1 & B.1.1.529.2). Therefore, continuous regional monitoring of the evolution of SARS-CoV-2 is

necessary to take the required actions to provide treatment to the infected individuals. The variant PCR surveillance was designed to investigate the SARS-CoV-2 variants currently circulating in Bangladesh and their associated clinical features. The variant PCR method which targeted a set of five S-gene specific point mutations- N501Y, P681R, L452R, E,484K, and E484Q, was performed to detect the specific SARS-CoV-2 variants. A total of 190 SARS CoV-2 positive specimens were collected and analyzed between 6 June, 2021 and 10 March, 2022. A subsample was selected for whole-genome sequencing using MinION platform to confirm the variants assignment. We found 81 samples having N501Y mutation (probable Omicron or Alpha), 105 samples having both P681R and L452R mutations (probable Delta), and 4 samples with P681R, L452R, and E484Q mutations (probable Kappa). Whole-genome sequencing was conducted to confirm the variant PCR result with N501Y mutation and detected as omicron variant for the first time in Bangladesh. Our study indicates that the variant PCR method can be used as a rapid screening approach to identify the SARS-CoV-2 circulating variants. Compared to direct sequencing, this method is rapid and less expensive. Moreover, initial variant PCR based diagnosis can also be used as complementary to guide the direct sequencing method for the early detection of new emerging SARS-CoV-2 variants and provide information to the health policy makers to take necessary actions.

0834

PARENTS/CAREGIVERS AND HEALTH CARE PROVIDERS PERCEPTIONS AND BARRIERS RELATED TO CHILDHOOD ROUTINE IMMUNIZATION AND COVID-19 VACCINE HESITANCY DURING PANDEMIC IN PAKISTAN

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The COVID-19 pandemic had a detrimental impact on the provision of all basic healthcare services in LMICs. The aim of this study was to explore the impact of COVID-19 on routine childhood and adult immunizations and understanding the reasons for potential barriers to EPI programs. Further, we investigated the possible challenges of incorporating child COVID-19 vaccination in the Pakistan EPI system. Using semi-structured interviews and a purposive sampling approach, an exploratory qualitative research design was used in three different sites across the province Sindh. Zoom was used for seven FGDs with health care providers(n=51), while phone calls were used for sixty IDIs with caregivers/parents (n=60). We used thematic and content analysis to understand participants perceptions. Majority of the parents/caregivers believed timely routine immunizations; nonetheless, lack of understanding about immunization programs, vaccine efficacy and pandemic itself were found as major barriers. Our findings revealed fear of getting COVID infection was as a major obstacle in downward surge of routine immunization. Healthcare providers shared that by compliance of COVID-19 SOPs, EPI programs remained instrumental and believed in the implementation of routine immunization outreach services for defaulters during pandemic, further HCPs from the urban site were in favor of including child COVID vaccine in EPI program as compared to HCPs from the rural site. Despite the hurdles posed by the pandemic in childhood regular vaccination and COVID-19 vaccine programs, both caregivers and healthcare providers were motivated to vaccinate the children. We concluded that by improving caregivers' awareness of vaccinations, their side effects, and their management is critical to increase routine immunization and COVID vaccine coverage during the current COVID-19 outbreak and future pandemics. We recommend strengthening the healthcare provider's capabilities and training to increase confidence related to vaccine efficacy and promote it through community participation strategies.

0835

VALIDATING A LOW-REQUIREMENT METHOD FOR SARS-COV-2 DETECTION: EQUIPPING POOR RESOURCED SETTINGS FOR DIAGNOSIS OF COVID-19

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The rapid spread of COVID-19 warranted the need for early detection of infected people to control community spread. The gold-standard RT-qPCR diagnostics, although sensitive, is costly and unavailable to many under-resourced healthcare facilities especially in rural settings in low-and-middle income countries. This resulted in the inability of such populations to diagnose and manage the disease. This study aimed to evaluate the performance of a lyophilized loop mediated isothermal amplification (LAMP) bead using crude viral isolation methods that would allow relatively cheaper, and easy sample processing for detection of SARS-CoV-2 infection. SARS-CoV-2 positive (N=20) and negative (N=10) naso/oropharyngeal swab samples in 0.9% saline were retrieved from storage. We first explored different sample treatment methods including heat-shock and addition of proteinase K to isolate the virus and, addition of bovine serum albumin (BSA) to reduce potential inhibitors. The expected colour change was dark orange (negative) to green (positive). Preliminary data indicates that proteinase K treatment inhibited amplification as colour change were not distinguishable between positive and negative samples. The results from heat- and BSA-treated were comparable with a pink (negative) to orange/green (positive) colour change. Sensitivity from these methods was estimated to be 65% compared to 80% for extracted RNA from the same test samples. Saline as a collection media may be impacting the colours seen after incubation. Improvements to this assay will explore using swab collection into nuclease-free water, colour quantification using colorimeter and generation of colour chart for standardization.

0836

GENETIC DIVERSITY OF ROTAVIRUS INFECTION AMONG YOUNG CHILDREN IN THE KASENA-NANKANA DISTRICTS OF GHANA

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Diarrhoeal disease is a global health concern, persisting as one of the top five causes of mortality and morbidity in children. Those in developing countries are the most affected. Viral diarrhoea is associated with about 70% of all childhood diarrhoeas with rotavirus and norovirus being the most common pathogens involved. The main aim of this study was to characterize rotavirus genotypes associated with diarrhoea in the Kasena-Nankana Districts (KND) of Ghana despite the introduction of effective vaccines. Stool samples were collected from four health centres and two hospitals in KND. Ribonucleic Acid (RNA) was extracted from frozen samples and analyzed through the first and second amplification of Semi-Nested Polymerase Chain Reaction (PCR). PCR products were run on a gel. Wet mounts were prepared for fresh stool to determine the presence of intestinal parasites. A questionnaire was also administered to obtain background social, demographic and clinical data from the participants. A total of 263 stool samples were collected, showing a prevalence of 14.8% for rotavirus. The total household size (p=0.035), location of participant (p=0.018), the outcome of treatment (p=0.007), vomiting (p=0.039), season (p=0.017) and month of sample collection (p=0.000) were found to be significantly associated with rotavirus infection. The genotypes identified were G1P8, G3P6, G4P9, G10P6 and G12P8 with the G10P6 being the most predominant genotype detected. All the different genotypes were detected in the Kasena-Nankana East Municipal while only G10P6, G12P8 and G4P9 were detected in the Kasena-Nankana West District. The vaccine-type G1P8 was not found in Kasena-Nankana West District. *Plasmodium* parasite was the predominant parasite with other parasites being *Giardia lamblia, Trichomonas hominis,* and *Ascaris lumbricoides*. The prevalence rate was low compared to the pre-

vaccination era probably due to the effectiveness of the vaccine and other interventions. The role of parasites and other microbial agents in causing diarrhea, need to be further investigated.

0837

COVID-19 INDUCED AXONOPATHY- A RARE COMPLICATION

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The novel SARS-CoV-2 virus causes a Covid-19 disease, known to lead the long-term complicated sequelae. Among them, neurological manifestation occurred in about 36.4 % of patients. However, foot drop was not commonly associated with SARS-CoV-2. A 27-years-old man presented with a 1-week history of dry cough followed by low grade, intermittent fever, and shortness of breath to the tertiary care center (here). He was tested positive for SARS-CoV-2. During the hospital stay, his condition was worsened and he was intubated and given steroids for the management of the Covid-19 disease. He was gradually weaned off from ventilator. After four weeks he developed bilateral symmetrical, ascending lower limb weakness with normal symmetrical reflexes. Later on, he developed a left lower limb tingling sensation followed by a foot drop. He had a normal MRI brain and spine, CSF analysis, serum electrolytes, serum creatine kinase, hs-CRP, vitamin B12, and folic acid levels. A nerve conduction velocity (NCV) study revealed bilateral pure motor axonal neuropathy. A diagnosis of Covid-19 induced axonopathy was considered. He was managed conservatively and given a splint for foot drop. After two weeks his weakness gradually improved and was closer to baseline with some residual mild bilateral lower limb weakness and tingling sensation. Recent literature reports cases of Guillain-Barre Syndrome (GBS) as a complication of Covid-19 disease. GBS is a polyneuropathy characterized by ascending paralysis with loss of deep tendon reflexes. Immune attack of nerve cells causes the typical tingling sensation in the extremities. In this case, preserved reflexes with normal CSF study rule out the possibility of GBS. However, infection-induced axonopathy is not being reported. So, every SARS-CoV-2 patient should be followed up for the neurological deficit and if it is there, can be confirmed with NCV, and awareness of the same among physicians and patients is the need of the hour.

0838

GENOMIC EPIDEMIOLOGY OF SARS-COV-2 IN MALI

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Genomic epidemiology of SARS-CoV-2 has been important in the control of COVID-19 pandemic. SARS-CoV-2 genome sequencing has made it possible to detect new variants and inform the COVID-19 control strategies. However, local sequencing capabilities of SARS-CoV-2 are limited in Mali as well as genomic data on SARS-CoV-2. Therefore, we conducted a genomic epidemiology study of SARS-CoV-2 in Mali with the aim of monitoring the evolution, tracking geographical origins of SARS-CoV-2 variants circulating in Mali. A retro-prospective study was conducted in three laboratories of Bamako and in Timbuktu from March 2020 to April 2021. Samples were collected by nasopharyngeal swab and oropharyngeal. Collected samples were from the first three waves of the outbreak in Mali. RNA extraction was performed using the Qiagen kit. Libraries were prepared using the Illumina TruSeq stranded RNA protocol. Libraries were sequenced on the Illumina MiSeq at the MRTC. Sequence data was analyzed on a local server. We successfully sequenced twenty-nine (29) viral genomes. In addition to the newly sequenced samples, we downloaded 21 Malian sequences from the GISAID repository. We observed a total of seven hundred and forty-five (745) polymorphisms with six hundred and twenty-four (624) polymorphisms in the samples sequenced locally in Mali. We detected eight (8) variants: A, A.1, A.21, A.27, B, B.1, B.1.525, B.39. Except the A.21 variant, which might have emerged locally, the other variants detected were all cases introduced into our country. Our results highlight the importance of sequencing SARS-CoV-2 locally and provide information on variants that were circulating in Mali during the first three waves of the COVID-19. Keys words: SARS-CoV-2, COVID-19, variants, sequencing, Mali

0839

SEROPREVALENCE OF ANTIBODIES AGAINST SARS-COV-2 IN THE MORE THAN TEN YEARS OLD POPULATION DURING THE PRE VACCINATION PERIOD (SEPTEMBER TO OCTOBER 2021) IN OUAGADOUGOU, THE CAPITAL CITY OF BURKINA FASO

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The Covid19 pandemic has lead to unprecedent crisis faced by humanity. Despite the huge dramatic burden expected from Subsaharan Africa, a limited number of death was reported across the continent compare to America, Asia and Europe. In Burkina Faso, by April 2022, 20,858 confirmed cases and 382 deaths have been registered. These numbers may under estimate the really burden of the disease. To give the real picture we used rapid serology test to estimate the burden of SarsCoV2 infection in Ouagadougou where above 80% of Burkina Faso cases are reported. A cross-sectional survey was conducted in Ouagadougou, between September and October 2021. The study areas/sites included markets and lorry stations for the public screening, while the targeted screening was focused on the staff of institutions Covid19 testing facilities and hospitals. The serological test was performed on site using capillary bleeding on 2019-nCoV IgG/IgM device. These were antigenic tests using the principle of immunochromatography In total 1,009 participants were enrolled in the study; the mean age was 36.4±14.92 years. 56.89% were female. Only 3.96% were less than 18 years. The proportion of positive participants for IgG was 16.17% (CI95%: [13.94028-18.59582]) and 1.80% (CI95% :[01.06805-02.82429]) for IgM. In this cross sectional survey, the distribution of positive recipients according to the study site location was waning from 11.26% (CI95%:[09.38501-13.4007]) to 33.17% (CI95% :[30.22257-36.14438]).The higher value recorded (33.17%) was drawn from COVID19 testing facilities and the lower value was reported in motors/lorry parks. The antigen testing detected 19 antigen positive subjects in 411 participants (4,62%) (CI95%: [02.80588-07.125]). The positive serology participants in this study attest that the residents of Ouagadougou have been exposed to Covid19 infection. Although low, these data highlighted the spatial distribution of exposed participants. Further large investigations in each district of Ouagadougou should be undertaken to have the real picture of the Covid19 seroprevalence.

0840

EVALUATION OF THE INDIRECT EFFECTS OF ROTAVIRUS VACCINATION PROGRAMS IN WORLD HEALTH ORGANIZATION MEMBER STATES

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Rotavirus is a leading cause of diarrhea-related deaths in children under 5 years old, most of which occur in low-to-middle income countries (LMICs). Licensed rotavirus vaccines provide high levels of direct protection, but their indirect effect – the protection provided to unvaccinated individuals within a partially-vaccinated population – is not fully understood. We aimed to quantify the population-level effects of rotavirus vaccination and identify factors that drive indirect protection. We used a transmission

model to estimate the indirect effects of vaccination on rotavirus deaths in 112 LMICs. Indirect effects were estimated by quantifying the difference between predicted impacts if vaccination did (overall effects) or did not (direct effects) change the force of infection, and both scenarios were compared with a no vaccine scenario. We performed a linear regression analysis to identify predictors of indirect effect magnitude. We also used logistic regression to understand predictors of negative indirect effects. Regional indirect effect sizes 8-years post-vaccine introduction ranged from 16.9% in the WHO European region to 0.97% in the Western Pacific region. Under-5 mortality rate and vaccine coverage were positively associated with indirect effect magnitude. Birth rate was negatively correlated. Of the 112 countries analyzed, 18 (16%) had at least one year with a predicted negative indirect effect. Negative indirect effects were more common in countries with higher birth rate and were less common in countries with higher under-5 mortality and higher vaccine coverage. These results suggest that the rotavirus vaccine provides indirect benefits to unvaccinated individuals within a partially-vaccinated population. The strength of this effect varies by country and depends on country-specific birth rate, under-5 mortality rate, and vaccine coverage. Rotavirus vaccination may have a larger impact than would be expected from individual analysis alone.

0841

NOVEL MURINE AND IN UTERO TRANSMISSION MODELS FOR STUDYING CACHE VALLEY VIRUS; AN EMERGING ORTHOBUNYAVIRUS IN THE AMERICAS

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Cache Valley Virus (CVV) is an emerging *orthobunyavirus* with significant importance to public health and the agricultural sector in North and Central America. CVV is associated with substantial agroeconomic losses due to high embryonic lethality and developmental malformations in ruminants. CVV is also known to cause disease in humans, including fever, headaches, nausea, fatigue, encephalitis, meningitis, spontaneous abortions, and macrocephaly in infants. Although CVV pathogenesis has been well described in ruminants, small animal models are unavailable, which limits the ability to study its pathogenesis and perform preclinical evaluations of vaccines and therapeutics. Here, we explored various models, including an immune -competent and -compromised murine models, to study CVV pathogenesis, tissue tropism, and disease progression in mice. Our results indicate that CVV disease in mice is dependent on innate immune responses and the type-I interferon signaling cascade to prevent infection. IFN-$\alpha\beta^{-/-}$ mice infected with CVV developed lethal infections with insignificant differences in age-dependent pathogenesis, which suggests this is an appropriate model for studying CVV, both long and short term, for in-depth pathogenesis studies and therapeutic efforts. Additionally, we developed a novel CVV *in utero* transmission model which demonstrated high levels of transmission, spontaneous abortions, and congenital malformations in fetuses. CVV infections presented with the highest tissue tropism in organs like the liver, spleen, and placenta. Our data show, that immune competent mice are generally unaffected by infection with CVV and only develop disease in an age-dependent manner. Given CVVs broad dispersal throughout the Americas, high seropositivity rates among ruminants and humans; and the associated geographic expansion of competent mosquito vectors, make the risk of emergence and exposure to CVV incredibly high. Interventions are urgently needed to reduce the risk of emergence or diminish disease burden for this important pathogen.

0842

MODELLING THE HETEROGENEITY AND HISTORICAL CHANGES IN DENGUE TRANSMISSION INTENSITY IN SRI LANKA USING ROUTINEAGE-SPECIFIC CASE SURVEILLANCE DATA

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The first dengue case in Sri Lanka was reported in Colombo, the capital, in 1962. Since then, dengue has become endemic and has expanded and become established in other districts. Colombo has the highest burden of reported incidence of dengue compared to other districts to date. However, it remains unclear the extent to which different levels of reporting, driven by unequal healthcare seeking and underlying differences in surveillance could mask the true patterns of infection across the country. It is also important to examine how correlated dengue incidence is across the country. In order to fill this knowledge gap, we fitted a catalytic model to age-specific case data from the routine national surveillance system. The data were from a seventeen year period (2000-2016) from three ecologically distinct districts in the country (Colombo, Batticaloa district in the East and Kurunegala district in the Northwest). We used catalytic models in a Bayesian inference framework to fit single year age-stratified case incidence data in these three districts. We estimated the time-varying annual force of infection, an age-specific reporting parameter (comparing above and below 15 years), and the probability of case detection for primary versus secondary infections within each location. We also estimated the proportion expected to be seropositive at a given age, which we compare to cross-sectional seroprevalence studies in the country. Our approach is robust to different reporting levels across locations. We found that our models were able to recover the observed age distribution of cases in each year. Understanding the spatial heterogeneity in dengue transmission intensity can help inform which populations and areas to target in a future dengue vaccination strategy.

0843

FACTORS ASSOCIATED WITH SARS-COV-2 TESTING THROUGH AN ACUTE ILLNESS SURVEILLANCE SYSTEM AMONG A COMMUNITY-BASED COHORT IN PONCE, PUERTO RICO

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As of March 2022, >267,000 SARS-CoV-2 confirmed cases have been reported in Puerto Rico (PR). Testing is a key tool to prevent additional transmission. The Communities Organized to Prevent Arboviruses (COPA) cohort study was established in 2018 to measure arboviral infections in 38 communities in Ponce, PR. An acute illness surveillance (AIS) was implemented in COPA to identify participating households where ≥1 member reported fever or COVID-like symptoms in ≤7 days via a weekly text message and during study visits. Participants reporting symptoms were offered free testing for dengue and respiratory viruses, including SARS-CoV-2, by polymerase chain reaction (PCR). To describe SARS-CoV-2 testing practices in a community setting, a multivariate logistic regression adjusted for age and sex was used to calculate risk ratios to identify factors associated with SARS-CoV-2 testing in AIS. During May 2020-January 2022, among 995 participants (498 households) reporting symptoms at least once, 582 (58%) were females and 613 (62%) provided a nasal swab, of which 137 (22%) tested positive for SARS-CoV-2.

Participants ≤17 and 18-49 years old were 1.42 (95%CI:1.19,1.68) and 1.21 (95%CI:1.02,1.43) times as likely to get tested compared with ≥50 years old, respectively. Testing in AIS was also more likely among those retired and caretakers (aRR:1.19; 95%CI:1.02,1.40), those with ≥1 chronic condition (aRR:1.34; 95%CI:1.19,1.50), and an annual household income of ≤$10,000 (aRR:1.22; 95%CI:1.08,1.38) and $10,000-$19,999 (aRR:1.18; 95%CI:1.04,1.34) compared to those employed, without a diagnosis, and income of ≥$30,000. Among 382 participants not tested, 35% reported a reason for declining testing; having been tested for SARS-CoV-2 elsewhere (67%) and symptom resolution (15%) were the most common. Study limitations include self-report bias. Increased risk perception among those with chronic conditions and testing access disparities by age and income could explain these findings. Information related to factors associated to SARS-CoV-2 testing can be used to assess the representativeness of surveillance data and to improve testing access.

0844

DEVELOPMENT OF LATERAL FLOW IMMUNOASSAY (LFIA) FOR THE DETECTION OF RIFT VALLEY FEVER VIRUS

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Rift Valley fever virus (RVFV) is a prototype bunyavirus that is classified as a Category B pathogen and an emerging viral pathogen of potential pandemic concern. RVFV causes natural infections in many parts of Africa and the Arabian Peninsula and is transmitted by infected mosquitoes. RVFV poses a critical threat to livestock and causes massive abortion storms and newborn mortality. There are currently no FDA approved therapeutics or vaccines available for RVFV, which places the onus of disease management on early detection. Our research focuses on developing prototype lateral flow immunoassays (LFIAs) to detect RVFV in several biological specimens including clinical samples. We have completed preliminary development of two prototype LFIAs targeting RVFV Nucleocapsid protein (N-protein) and Glycoprotein-N (Gn). The N-protein LFIA was developed by screening well-characterized monoclonal antibodies generated in-house using N-protein antigen (BEI Resources: NR-12121). Antibody epitope screening enabled selection and identification of optimal antibody pairs with the greatest sensitivity and specificity. Two superior antibody combinations (RVFV mAb-01 and RVFV mAb-02) were chosen as capture and detector pairs for N-protein detection. To determine the assay's lower limit of detection (LOD) and optimal range for testing, we tested serial dilutions of the N-protein antigen (BEI Resources: NR-12121) in addition to the inactivated RVFV spiked into human serum with inactivated CCHFV as a control. The LFIA detected recombinant N-protein as low as 62.5ng and the N-protein in inactivated RVFV at 1:480 dilutions with no cross-reactivity observed at 1:60 dilutions of Crimean-Congo Hemorrhagic Fever virus (CCHFV) and Vero E6 cell lysate. The limit of live RVFV N-protein detection in serum was significant with at the 1:40 dilution. Using a similar approach, we also developed the RVFV-Glycoprotein-N (Gn) detection assay prototype by screening monoclonal antibodies targeting known epitopes accessible on the surface of intact RVFV. These results provide a framework for further clinical diagnostic application studies.

0845

SARS-COV-2 INFECTION AMONG EVACUEES FROM CHENNAI, TAMILNADU IN NAGALAND, INDIA, AUGUST 2020

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Government of India relaxed the nationwide lockdown on April 14, 2020 in regions where COVID-19 spread was minimal or none. A special train carrying the first batch of evacuees from Chennai arrived Dimapur, Nagaland on May 22, 2020. We investigated to estimate the COVID-19 burden among evacuees who arrived from Chennai, Tamilnadu, an area with more than 10000 confirmed cases then. We reviewed list of Chennai evacuees available at State Surveillance Unit (SSU)**.** We defined a case as COVID-19 (RT-PCR positive for SARS-CoV-2) in a special train carrying Chennai evacuees on May 22, 2020. We reviewed reports received from Bio Safety Lab-3 at SSU. We analyzed data using Epi Info 7.1. Among 1288 Chennai evacuees in May 2020, 344 (27%) were SARS-CoV-2 positive. Median age of COVID-19 cases was 22 years (range:1-40 years). Among the 344 cases, 75% (259/344) were males and 47% (161/344) were employed in hospitality sector. Majority of the cases (83%) were educated till standard ten. First three index cases were identified on May 25, 2020. Cases peaked on June 22, 2020 and declined on July 22, 2020. A total of 28 (8%) cases were hospitalized. There were no deaths. Most positive cases (67%, 231/334) were from Peren district, Nagaland. Of the 344 cases, 8% (28) were symptomatic. Major presenting symptoms were fever (93%, 26/28), headache (29%, 8/28) and cough (21%, 6/28). One among the 344 (0.3%) had tuberculosis. From list of Chennai evacuees at SSU, we found that cases shared same train compartments. We found over one third of the Chennai evacuees were SARS-CoV-2 cases who travelled together in the same train compartments. We recommended Information, Education and Communication activities regarding correct use of mask, physical distancing and frequent hand washing.

0846

VICTIM BLAMING, DEHUMANIZATION, AND OTHERING DURING THE COVID-19 PANDEMIC

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Severe social challenges have arisen in the wake of the COVID-19 pandemic in manifestations of victim-blaming, dehumanisation, othering, and stigmatisation. During both past and present pandemics, people have equally scapegoated 'the other' for causing and spreading diseases such as smallpox, the third bubonic plague, the 1918 influenza, and, more recently, HIV, SARS, and Ebola. Once more, COVID-19 triggers such pervasive social mechanisms in human societies across the globe. An exploratory phenomenological study on COVID-19-related stigma was undertaken by the Child Health and Mortality Prevention Surveillance Network (CHAMPS) utilizing qualitative methods in seven sites in Bangladesh, Ethiopia, Kenya, Mali, Mozambique, Pakistan, and South Africa. Informants were found to harbour strong sentiments towards those blamed for the virus. Meanwhile, being associated with COVID-19 was stigmatised and those working with infected patients discriminated against. Foreigners and outsiders were blamed directly for the disease and healthcare workers and researchers dehumanised as 'COVID-19 people'. In instances of othering, culpability and blame for the Coronavirus were widely ascribed to travellers, white people, 'the rich', or ill-intended, shadowy entities among flurries of counterfactual claims and conspiratorial speculations circulating in an ambit of fear and confusion. In summary, the stigmatisation and dehumanisation brought on by pandemics necessitates research providing insights into how people make sense of unknown threats of which they know little in uncertain times of blame.

0847

THE DEVELOPMENT OF MACHINE LEARNING ALGORITHMS FOR PREDICTING ANTI-EBOLA VIRUS INHIBITORS: IMPLICATIONS FOR DRUG DISCOVERY

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Ebola virus disease (EVD) is a deadly and highly virulent disease caused by Ebola virus from the filovaridae family. Apart from zoonotic transmissions, EVD is spread amongst individuals through direct contact or contact with body fluids of infected persons. So far available therapeutic interventions have challenges including limited efficacy. The identification of small molecule inhibitors with the potential to be optimized as therapeutic agents is a plausible route for searching for a cure. The proteases of the virus play vital roles in viral invasion of the host cells. Since inhibitors disrupt the mechanisms of viral entry of the host cells, they are considered as forming the basis for the identification of novel drug candidates. The study developed machine-learning algorithms for predicting anti-Ebola virus small molecules, which could serve as basis for the design of novel drug candidates. Datasets obtained from viral cell entry inhibition assays were used to develop five machine-learning algorithms comprising random forest (RF), support vector machine (SVM), naïve Bayes (NB), k-nearest neighbor (kNN) and logistic regression (LR). The models were evaluated using 10-fold cross-validation technique with RF model emerging on top with an accuracy of 89% and an area under the curve (AUC) score of 0.95. The LR and SVM models attained overall accuracy values of 0.84 and 0.86, respectively.

0848

ACUTE RESPIRATORY INFECTIONS SURVEILLANCE AT A SENTINEL SITE IN CARTAGENA, COLOMBIA: PRELIMINARY RESULTS FROM NOVEMBER 2021 TO MARCH 2022

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Annual epidemics of influenza (flu) A/B viruses have a seasonal pattern. The epidemiology and circulation patterns of flu, however, have been disrupted by the implementation of COVID-19 control strategies. Worldwide, the opportunity to detect flu was limited by the need to expand the diagnostic capacity to COVID-19, and also by the challenge of distinguishing diseases that share multiple signs and symptoms. Cartagena is the fifth-largest and one of the most important city in Colombia, and also one of the most affected cities by the COVID-19 pandemic in the Colombian Caribbean region, accounting over 157K laboratory-confirmed cases, and over 2K COVID-19-associated deaths. The disruption of routine surveillance systems, and the lack of information regarding the burden and trends of non-SARS-CoV-2 viruses limit the prompt adoption of specific control measures in Cartagena. Herein, we describe preliminary results of an ongoing passive surveillance study conducted in Cartagena from November 2021 to March 2022 among health seekers presenting with and without respiratory signs or symptoms. Subjects provided written informed consent, and nasopharyngeal swabs were collected for flu A/B and SARS-CoV-2 testing by lateral flow assay, RT-PCR, or both. Demographic and clinical information were collected, and influenza-like illness (ILI) and COVID-19-like illness (CLI) definitions were used to classify subjects based on their clinical profile. Among 111 subjects, the median age was 37 years (IRQ: 15), 69.4% were male, and 39.6% were symptomatic. All symptomatic cases were non-ILI/CLI, and tested negative for flu and SARS-CoV-2. Among 44 symptomatic cases, 15.9% and 27.3% tested positive for flu and SARS-CoV-2, respectively. No co-infections were detected, and CLI definition was the most sensitive for the detection of flu, SARS-CoV-2, or both. Interestingly, all flu cases were detected in December 2021 when the incidence of COVID-19 plateaued. Overall, our results highlight the need to expand systematic surveillance to flu, and also inform the circulation of flu during a low-incidence COVID-19 period.

0849

TRENDS OF ARTEMETHER LUMEFANTRINE TREATMENT FAILURE DURING ROUTINE CONSULTATION IN DANGASSA COMMUNITY HEALTH CENTER A MALIAN VILLAGE WITH LONG SEASONAL MALARIA TRANSMISSION

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Malian National malaria control program recommended Artemisinin-based combination therapy (ACT) with Artemisinin plus Lumefantrine (or Amodiaquine, Sulfadoxine-Pyriméthamine) for the treatment of uncomplicated malaria since 2006. Emergence of *Plasmodium* resistance to artemisinin derivates in Southeast Asia call for monitoring of its spread to other areas, particularly in Mali. The aim of this study was to monitor the therapeutic efficacy of artemether-lumefantrine used for uncomplicated malaria treatment during routine consultations in Dangassa, Mali. During the transmission season from 2018 to 2021, 154 patients with uncomplicated malaria were enrolled and treated with artemisinin + lumefantrine over three days and follow up over 28 days. Malaria symptom and parasitemia were assessed on day 1 (D1), D2, D3, D7, D14, D21, and D28. The treatment failure criteria of treatment failure were (i) occurrence of parasitemia after D3, (ii) symptoms of severe malaria according to WHO, and (iii) increase of parasitemia during the first three days of treatment. Overall treatment failure rate was 14.3% (22/154). This rate fluctuates from 0% (0/39) in 2018, 21.7% (5/23) in 2019, 13% (7/54) in 2020, and 26.3% (10/38) in 2021. Most of the treatment failure was observed in D28 (7.1%). In conclusion, ACT drugs remains efficacious to treat uncomplicated malaria treatment in Dangassa village. Our results suggest the necessity to continuous monitoring *P. falciparum* resistance antimalarial drugs in this area.

0850

USING DICRE-LOXPINT TO FUNCTIONALLY VALIDATE GENOMIC DISCOVERIES FROM *P. FALCIPARUM PIGGY BAC* MUTANTS

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Plasmodium falciparum is responsible for most of the morbidity and mortality associated with malaria, causing 627,000 deaths and 241 million cases worldwide in 2020. Forward genetic screens of this major human pathogen using random *piggyBac* mutagenesis has defined essential genes and provided critical functional data for drug targets. To functionally validate genomic discoveries from *P. falciparum piggyBac* mutants, we used a modified Cre-loxP method in which loxP site was placed into a short synthetic intron of *P. falciparum sera2* gene to produce a module loxPint so that it combines loxP and intron functions when it is placed in open reading frame. We are using this targeted mutagenesis approach to create epitope tagged and KO mutants to characterize genes of interest identified as essential for heat shock survival and sensitivity to artemisinin and other stress conditions (*fikk9.3, dxs, caf1, dhc, lrr5*). LoxPint plasmid-integrated and target gene knockout parasites were able to be used for localization, quantitative and pulldown analysis by IFA-HA signal, evaluating GFP expression and nano-luciferase assay. Initial phenotypic screens of loxPint and paired *piggyBac* mutants performed to characterize drug response to selected MMV compounds, artemisinin (QHS), dihydroartemisinin (DHA) and bortezomib (BTZ). Preliminary results

have showed that validating genomic discoveries from *P. falciparum piggyBac*mutants by DiCre-loxPint method can be achieved in blood stages.

0851

EFFICACY OF ARTEMETHER-LUMEFANTRINE FOR THE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN NIGER, 2020

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In Niger, malaria is the leading cause of childhood morbidity and mortality. Malaria case management is based on the principle of early diagnosis and treatment with effective medicine. Artemether-lumefantrine (AL) is one of the first-line artemisinin-based combination therapies recommended to treat uncomplicated Plasmodium falciparum malaria in Niger. To assess whether AL remains efficacious, a therapeutic efficacy study was conducted using the 2009 World Health Organization (WHO) protocol for monitoring antimalarial efficacy. Patients between 6 months and 15 years old with uncomplicated malaria (≥ 1,000 - < 200,000 parasites/µl) were assessed from September to October 2020 in a 28-day in vivo efficacy trial in sites from regions representing the three epidemiological zones in Niger: Agadez in the north (hypoendemic), Tessaoua in the center (mesoendemic), and Gaya in the south (hyperendemic). Polymerase chain reaction (PCR) using *msp1*, *msp2*, and *glurp* loci was used to distinguish recrudescence from reinfection, which allows determination of the PCR-corrected day 28 efficacy. Assays for molecular markers of resistance, including K13, *pfdhfr*, *pfdhps*, *pfcrt* and *pfmdr1* were carried out. A total of 255 patients were enrolled in the study, of whom 3.5% (9/255) were lost to follow-up. There were 30 clinical/parasitological failures. The day 28 uncorrected AL efficacy per site was 94.3% (95% CI 88.8-99.7) in Agadez, 71.1% (95% CI 60.5-81.7) in Tessaoua, and 97.8% (95% CI 94.3-100) in Gaya. PCR-corrected AL efficacy was 97.1% (95% CI 93.1-100) in Agadez, 92.2% (95% CI 85.9-98.5) in Tessaoua, and 98.9% (95% CI 96.4-100) in Gaya. The study of K13 resistance markers in 269 samples showed an emergence of the R255K mutation (4 samples) found in Southeast Asia and new mutations (N594K in 1 sample and V714S in 1 sample) that will require continued close monitoring. This study indicates that the current first line treatment for malaria, AL, has a therapeutic efficacy above the 90% WHO acceptable cut-off. Monitoring of therapeutic efficacy every two years should continue to ensure malaria treatments in Niger remain efficacious.

0852

A PREDICTIVE MODEL OF SEASONAL MALARIA CHEMOPREVENTION PROTECTIVE EFFICACY WITH CHANGING *DHFR/DHPS* PREVALENCE

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Seasonal malaria chemoprevention (SMC) is a core malaria intervention in the Sahel region of Africa. SMC involves the monthly administration of a full course of sulfadoxine-pyrimethamine and amodiaquine (SP-AQ), to children in areas of high endemicity during the peak transmission season. However, resistance in the *dhfr* and *dhps* genes, conferring resistance to pyrimethamine and sulfadoxine, respectively, could threaten the efficacy of SMC. Additionally, trials are currently underway to determine the potential benefit of implementing SMC with SP-AQ in new geographies. These regions have established high-grade SP resistance, dating from the historic use of SP for case-management. There is a need to understand how pre-existing resistance affects the efficacy of SMC and to develop a framework for estimating potential efficacy in new settings. We use existing pharmacokinetic models for SP, alongside chemoprevention trial data to statistically fit the relationship between concentration and efficacy in different settings. We create a drug interaction framework to estimate the protective efficacy of SP-AQ in combination. From initial analysis we estimate a protective efficacy of SP alone of ~87% at low SP resistance, based on a trial in the Sahel. Additionally, we estimate there will be a 'boosting' protective effect of adding AQ to SP as part of SMC in this area, halving the hazard of malaria relative to SP alone. This is consistent with clinical trial data from Senegal during early SMC trials. However, at high levels of SP resistance, we estimate that AQ contributes substantially more to the expected protective efficacy. Using data from trials implementing intermittent preventive treatment in infants using SP in Mozambique, our preliminary analysis estimates that SP-AQ still has the potential to provide a protective efficacy of up to 87% by day 30, compared with an expected protective efficacy of 54% from SP alone. This analysis is being extended to estimate the expected protective efficacy of SMC according to local frequency of resistance-conferring mutations.

0853

EVALUATION OF THE SAFETY AND EFFICACY OF DIHYDROARTEMISININ-PIPERAQUINE FOR INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN HIV-INFECTED PREGNANT WOMEN: PRELIMINARY RESULTS OF A MULTI-CENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SUPERIORITY CLINICAL TRIAL (MAMAH PROJECT)

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Malaria infection during pregnancy is an important driver of maternal and neonatal health especially among HIV-infected women. In Africa, at least one million pregnant women are annually co-infected with malaria and HIV. The interaction between the two infections is particularly deleterious during pregnancy, leading to an increased risk of malaria and HIV viral load, which may increase the frequency of mother to child transmission of HIV (MTCT-HIV). Intermittent preventive treatment in pregnancy (IPTp) with sulphadoxine-pyrimethamine is recommended for malaria prevention in HIV-uninfected women but it is contraindicated in those HIV-infected women on cotrimoxazole prophylaxis (CTXp) due to potential adverse effects. A randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of dihydroartemisinin-piperaquine (DHA-PPQ) for IPTp in HIV-infected pregnant women receiving CTXp and antiretroviral drugs and using long-lasting insecticide-treated nets was conducted in Mozambique and Gabon where malaria and HIV infection are moderate to highly prevalent. The primary study endpoint was the prevalence of maternal peripheral parasitemia at delivery. A total of 667 HIV-infected pregnant women were enrolled in the trial between September 2019 and November 2021. Despite the COVID-19 pandemic and related disruptions in antenatal care services in the study countries, planned project milestones were achieved. Preliminary results will be available in July 2022. The MAMAH project addresses important unmet needs and

health inequities by providing scientifically sound evidence aiming at improving malaria prevention in part of the most vulnerable and currently underserved African populations.

0854

MONITORING THERAPEUTIC EFFECTIVENESS OF ANTIMALARIAL DRUGS TREATMENT OF UNCOMPLICATED MALARIA IN A SMC CONTEXT

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Artemisinin-based combination therapies (ACTs), specially artemether-lumefantrine (AL) and artesunate-amodiaquine (ASAQ) are the current first-line treatments for uncomplicated malaria recommended by the National Malaria Control Programme in Mali. This study assessed the therapeutic effectiveness of artemether plus lumefantrine in areas where the dihydroartemisinin-piperaquine (DHA-PQ) being tested as alternative drug to sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) for seasonal malaria chemoprevention (SMC). From July to December 2021, children between 6 months and 10 years of age with uncomplicated *P. falciparum* malaria were enrolled in three rural communities in the health district of Koulikoro, Mali following World Health Organization drug resistance monitoring protocol. Each patient was monitored for 28 days, with a fixed schedule of follow-up visits and clinical and laboratory examinations. Monitored indicators included early therapeutic failure, late clinical failure, late parasitological failure, and parasitemia density dynamics. A total of 190 children were screened, and 81 children met the inclusion criteria, and 58 (71%) of these children completed the study. The early treatment failure rate was 22.4% (n=13 patients), and three patients carried parasitemia on day 3 and had an axillary temperature of at least 37.5 °C, 31/45 (68.88%) patients had late clinical failure, and 10/14 (71.42%) patients have presented a late parasitological failure . MANOVA analysis showed a significant decrease from 20865 to 590 parasites/ µl in the mean parasite load after drug administration during follow-up ($p < .0001$). This study indicates that ACTs are still effective in the treatment of symptomatic malaria, but not sufficient for parasitological cure. Therefore, it is necessary to monitor these molecules to prevent the possible spread of resistance.

0855

SINGLE-CELL TRANSCRIPTOMICS REVEALS SIGNALS OF INCREASED PROTEIN EXPORT RESPONSE AND ELEVATED GARP AFTER DIHYDROARTEMISININ EXPOSURE IN ISOGENIC WILD-TYPE AND K13C580Y MUTANT *PLASMODIUM FALCIPARUM*

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The use of artemisinin and its derivatives in antimalarial combination therapy has been a cornerstone of global malaria control. However, emerging resistance in *Plasmodium falciparum (Pf)*, primarily driven by mutations in the Kelch 13 gene, threaten these advances. *Pf's* response to artemisinin has been previously investigated, revealing a significant and dynamic transcriptional response to treatment. However, the molecular details on how wild-type and K13 mutant *P. falciparum* respond and how this contributes to resistance remains to be fully unraveled. To better investigate the transcriptional responses due to dihydroartemisinin (DHA) treatment, we applied single cell RNAseq to the unsynchronized isogenic parasite lines MRA1250^{WT} and MRA1251^{C580Y} over 6hrs after a pulse exposure to 700nM of DHA. We present the transcriptomic profile of *P. falciparum* parasites across all erythrocytic stages of development and show the expression changes initiated upon DHA treatment at a single cell level. We observed the greatest transcriptional changes in response to DHA at the early trophozoite and mid ring stage of the K13^{C580Y} mutant and K13^{WT} respectively. The transcriptional response to DHA treatment in both the mutant and WT parasite involved the arrest of metabolic processes (such as protein synthesis and glycolysis), and the enhancement of protein trafficking and the unfolded protein response. However, this transcriptional response is more enhanced in the K13^{C580Y} mutant parasite. These deregulated metabolic processes could lead up to the dormancy phenomenon of the parasite upon treatment. We also observed an increased expression of surface proteins, highlighted by the increased expression of GARP, a key vaccine and antimalarial target, in the K13^{C580Y} mutant at baseline and upon drug exposure, suggesting this as a potential target for drug development in combination with artemisinins. Our work provides more comprehensive insight of gene transcription in the K13^{C580Y} mutant and K13^{WT} *Pf.* parasite across all life cycle stages and reveals the enhanced drug response patterns in the mutant that would minimize drug sensitivity.

0856

THERAPEUTIC EFFICACY OF PYRONARIDINE-ARTESUNATE (PYRAMAX®) FOR THE TREATMENT OF *PLASMODIUM VIVAX* AND MOLECULAR CHARACTERIZATION OF VIVAX ISOLATES IN DAK NONG PROVINCE IN THE CENTRAL HIGHLANDS OF VIETNAM

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Chloroquine-resistant *Plasmodium vivax* malaria has been reported in at least two provinces in Vietnam. However, the extent of chloroquine-resistant vivax malaria in Vietnam is still unknown. Pyronaridine-artesunate (Pyramax®) is recommended for the treatment of both uncomplicated *P. falciparum* and *P. vivax* malaria. We evaluated the therapeutic efficacy of Pyramax® in treating malaria infections in Cu Jut and Dak Mil districts, Dak Nong province, Vietnam, in 2018-2019. By malaria blood film microscopy diagnosis, 59 patients were identified with a monoinfection of *P. vivax* and were treated with a 3-day course of Pyramax® plus primaquine (0.25 mg/kg daily for 14 days). Before treatment, patients' blood samples were tested by polymerase chain reaction (PCR) for *Plasmodium* species confirmation and characterization of potential molecular markers of drug resistance in *P. vivax* parasites. The geometric mean parasitemia before Pyramax® treatment was 6,489 parasites/µL for children (n=6) and 6,406 parasites/µL for adults (n=53), with 86.4% (51/59) having an axial body temperature >37.5°C prior to treatment. Pyramax® rapidly cleared vivax malaria with a median parasite clearance time of 24 h (range: 12-60) and a median fever clearance time of 24 h (range: 12-84). Based on the per-protocol population of 50 evaluable patients, two patients had a recurrence of vivax malaria within the 42-day follow-up period. The adequate clinical and parasitological response at day 42 was 96.0% (48/50; 95% CI 90-100). Data are presented on polymorphisms in the four putative drug resistance loci K12 (a *P. vivax* homolog of the *PfKelch13* gene), *Pvmdr1*, *Pvcrt-o* and plasmepsin 4, as these genes may have an association with reduced susceptibility in *P. vivax* to artemisinin, mefloquine, chloroquine and piperaquine, respectively. The work presented herein will guide treatment of *P. vivax* infections in Vietnam.

0857

HOW TO INCREASE THE AVAILABILITY AND USE OF INJECTABLE QUININE TO TREAT SEVERE MALARIA

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In Madagascar, with 100% of the population at high risk of malaria, preventive, diagnostic, and treatment commodities are essential for controlling cases and preventing deaths. The national treatment guidelines (Jan-2021) recommend two drugs (injectable artesunate [first-line] and injectable quinine [second-line]) to treat severe malaria. The National Malaria Control Program (NMCP) and Improving Market Partnerships and Access to Commodities Together (IMPACT), a USAID-funded project, conducted a malaria market assessment to understand product availability and the market, and to make recommendations. A cross-sectional survey was conducted in 2019 within the primary outlets serving the population in 10 USAID-supported regions to assess availability and prices of antimalarial products. All 3,123 outlets were visited in 44/753 (22 urban and 22 rural) sub-districts randomly selected using probability proportionate to size. Outlets included public hospitals, public primary health care units, community health volunteers, NGOs, faith-based organizations, pharmacies, drug shops, and private doctors. Routine data for 2018 from the public, commercial, and nonprofit sectors were collected and analyzed to determine commodity sales and distribution volume. STATA 13.0 was used for data analysis. The volume of quinine distributed was higher than that of artesunate in the commercial sector (165,163 versus 2,045 vials). Injectable quinine was more often always available than artesunate in both sectors at 83.7% [95%CI= 53.7-95.8%] in public hospitals and 88.1% [95%CI= 77.0-94.2%] in private pharmacies, while artesunate was available at 54.4% [95%CI=14.5-89.4%] in public hospitals and 22.0% [95%CI= 12.2-37.3%] in private pharmacies. This difference is thought to be due to the lower price of quinine (median retail price US$0.38) compared to artesunate (US$3.03). These findings could inform the NMCP strategy for the quinine transition with injectable artesunate for malaria severe case management.

0858

KEEPING EYE ON NON-FALCIPARUM SPECIES *PLASMODIUM OVALE* AND *P. MALARIAE* INFECTIONS TO ACHIEVE DISEASE CONTROL AND ELIMINATION GOALS

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One of the key obstacles to control and eliminate malaria is attributed to non-falciparum malaria parasites such as *Plasmodium ovale* and *P. malariae* that are not specifically targeted by current malaria intervention tools such as dug treatments. These parasites can respectively cause relapsing malaria and chronic infections and therefore sustain malaria transmission without new infectious mosquito's bite. Despite availability of artemisinin combination therapies effective on *P. falciparum*; *P. malariae* and *P. ovale* are being increasingly detected in malaria endemic countries.Here, we optimized and adapted ex-vivo conditions under which *P. malariae* can be cultured and used for screening antimalarial drugs. Subsequently, this enabled us to test compounds such as artemether, chloroquine, lumefantrine, and quinine for ex vivo antimalarial activity against *P. malariae* and *P. ovale*. Our study also revealed high frequency of *P. malariae* (15%) and P. ovale (7%) infections with a significant reduction in ex-vivo susceptibility to chloroquine, lumefantrine and artemether against *P. malariae* infections. Unlike these compounds, potent inhibition of *P. malariae* and *P. falciparum* was observed with piperaquine exposure. All compounds potently inhibited both *P. ovale* and *P. falciparum*.Furthermore, we evaluated advanced lead antimalarial compounds. In this regard, we identified strong inhibition of *P. malariae* and *P. ovale* using GNF179, a close analogue of KAF156 imidazolopiperazines, which is a novel class of antimalarial drug currently in clinical Phase IIb testing. Finally, in addition to GNF179, we demonstrated that the Plasmodium PI4K-specific inhibitor KDU691 is highly inhibitory against *P. malariae*, *P. ovale* and *P. falciparum*.

0859

DYNAMICS OF CHLOROQUINO-RESISTANCE MARKERS *PFCRT* K76T AND *PFMDR*-1 N86Y FROM 2001 TO 2015 IN KOLLE SITE AND MALI

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Chloroquine was discontinued due to the very high resistance rate of *Plasmodium falciparum*. The drugs recommended for the treatment of uncomplicated malaria today are artemisinin-based combination therapy (ACT). Recent studies have shown that parasites are becoming increasingly resistant to these ACTs in Asia and in some parts of Africa. There are very few antimalarial drugs under development. The goal of this study was to evaluate the prevalence of molecular marker of chloroquinoresistance in Kolle. Samples collected in Kollé from 2001 to 2015 were analyzed. Parasite DNA was extracted by Qiagen kit and PCR was performed using RFLP method. Single Nucleotide polymorphism for the *Pfcrt* K76T genes (the change of lysine to threonine at position 76) and *Pfmdr-1* N86Y (the change of asparagine to tyrosine at position 86) were evaluated. In total, the averages of the prevalences of mutant alleles of the *Pfcrt* K76T and *Pfmdr-1* N86Y genes, were respectively of 72.7% and 19.8% of the samples analyzed. The prevalence of mutant alleles of the two genes remained constant and comparable throughout the study period ($p > 0.05$). The *in vivo* chloroquine resistance deduced by the GRI model was 35.1%. In conclusion, the prevalence of molecular markers of chloroquine resistance remains high in this setting despite the wide use of ACTs. No decrease of the prevalence of these mutations was observed over 15 years.

0860

DEVELOPMENT OF AN OPTIONS ASSESSMENT TOOLKIT FOR NATIONAL MALARIA PROGRAMS TO DETERMINE BEST COMBINATIONS OF VIVAX RADICAL CURE FOR THEIR GIVEN CONTEXTS

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Recent advances in tackling *Plasmodium vivax* infections, including shorter treatment regimens with Primaquine, single-dose Tafenoquine, and novel quantitative point-of-care G6PD tests, are changing the landscape of tools becoming available to national malaria programs (NMPs). Global policy recommendations addressing new tools are expected from the WHO's Global Malaria Program, but these will need to be adapted to country contexts. Furthermore, having multiple options for decision-makers to

choose among can delay decision-making. Therefore, this project aims to develop and implement an options assessment toolkit (OAT) that enables NMPs to determine the optimal set of radical cure tools for their settings and potentially reduce policy process delays. The OAT will be co-developed along with 2-3 NMPs from the Asia Pacific countries using participatory research methods. In addition, at least 12 regional experts will be purposively selected to advise on key factors underpinning decision-making processes. In-depth interviews and participatory group discussions will be conducted with NMPs, and experts will be consulted using an adapted Delphi process. The toolkit will contain guidance on using the OAT, including; baseline assessment of vivax and the health system, evidence briefs on efficacy and effectiveness of current tools and latest information on new tools, 4-5 epidemiological and contextual scenarios representative of the Asia Pacific region, combinations of test and treatment options for each scenario, weighting for different variables, and policy evaluation criteria. The OAT will be piloted among all Asia Pacific NMPs to catalyze discussions around policy change. The primary benefit of OAT will be in facilitating policymakers assess key parameters, both technical (i.e., epidemiological and health system factors) and non-technical (i.e., political and economic) factors, that impact radical cure policy for their country settings. Secondarily, the OAT can be instrumental in reducing decision-making delays and accelerating the availability of new tools, thus reducing vivax-related morbidity and mortality.

0861

SEASONAL MALARIA CHEMOPREVENTION AND THE SPREAD OF *PLASMODIUM FALCIPARUM* PARASITES RESISTANT TO SULFADOXINE-PYRIMETHAMINE: A MATHEMATICAL MODELLING STUDY

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Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) prevents millions of clinical malaria cases in the Sahel. However, a genotype with five mutations causing partial resistance to SP has emerged. It is unknown at which rate this quintuple mutant will spread in the Sahel due to SMC implementation, nor how its spread will reduce SMC effectiveness. Using an individual-based model of malaria transmission dynamics incorporating pharmacokinetic-pharmacodynamics, we estimated the time required for the quintuple mutant to spread from 1% to 50% frequency of inoculations for several SMC deployment strategies and settings. We further quantified the influence of multiple factors on the spread of the mutant through global sensitivity analysis and estimated the reduction in SMC effectiveness expected due to the mutant spread. We found that high coverage, transmission intensity, and access to treatment promote spread of SP resistance. We predict that under current SMC implementation (four rounds to children under five years with 95% initial coverage declining each round), the mutant needs 53·1 years (95% CI 50·5-56·0) to spread from *1%* to *50%* of inoculations in a typical setting of the Sahel (moderate transmission intensity mostly occurring over four months, with low access to treatment). This time was reduced by 13 and 10 years when an additional round of SMC was deployed at the beginning and the end of the transmission season, respectively, and was halved when SMC targeted children under ten years. For the same setting and under current SMC implementation, the mean percentage of clinical malaria averted during SMC implementation was 79·0% (95% CI 77·8-80·8) when the mutant was absent in the population and 60·4% (95% CI 58·6-62·3) when the mutant was fixated. Overall, our study shows that SMC with SP+AQ leads to a relatively slow spread of SP-resistant quintuple mutants and is likely to remain effective in preventing child clinical malaria despite the mutants spread. Furthermore, our study supports calls to consider SMC with SP-AQ in seasonal settings where the quintuple mutant already has a high prevalence.

0862

ANTIMALARIAL SUSCEPTIBILITY OF *PLASMODIUM FALCIPARUM* FIELD ISOLATES FROM BUSIA COUNTY IN KENYA

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Busia county borders Kenya and Uganda and hence there is a possibility of importation of malaria between the two nations. Studies have reported artemisinin resistance in South East Asia which may eventually spread to Africa. Busia county being both an entry and exit point between Kenya and Uganda warrants prompt antimalarials surveillance to detect any emergence of antimalarials resistance. This study sought to find out the response of malaria field isolates to a panel of antimalarials. A total of 30 clinical samples from Busia county of an ongoing approved surveillance study in Kenya have been screened against chloroquine (CQ), quinine (QN), atovaquone (AV), Primaquine (PQ) and Artemisinin (ART), Dihydroartemisinin (DHA), Artemether (AR) and Amodiaquine (AMQ) Inhibition curves in, *in vitro* assays, were obtained using Graph Pad Prism (San Diego, CA, USA). During the study period, chloroquine median drug concentration that inhibits parasite growth by 50% (IC50) was 18.68 ng/ml (95% CI, 12.31 to 28.57) while Quinine IC50 was 19.43 ng/ml (95% CI, 12.3 8 to 33.42). Atovaquone median (IC50) was 7.170ng/ml (95% CI, 3.071 to 12.04) as Primaquine median (IC50) was 893.0 ng/ml (95%CI,619.5 to 1210). Doxycycline had a median (IC50) of 2418 ng/ml (95% CI, 723.0 to 5662) as, Artemether posted a median (IC50) of 2.926 ng/ml (95% CI,1.957 to 3.942), Tafenoquine a median (IC50) of 933.3 ng/ml (95% CI,577.9 to 1213), Dihydroartemisinin a median (IC50) of 0.4047 ng/ml (95%CI,0.3192 to 0.6633) and piperaquine median (IC50) of 38.86 ng/ml (95%CI,26.32 to 81.48). Artemisinin, Artesunic acid and Amodiaquine posted a median (IC50) of 2.384 ng/ml (95%CI,1.385 to 4.072), 4.169 ng/ml (95%CI,1.748 to 5.912) and 0.8535 ng/ml (95%CI,0.4478 to 1.597) respectively. Malaria field isolates from Busia County were susceptible to the antimalarials hence it calls for continued surveillance to detect any emerging drug resistance.

0863

WEEKLY PRIMAQUINE IN G6PD DEFICIENT PATIENTS WITH ACUTE *PLASMODIUM VIVAX*.

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The WHO recommends 0.75 mg/kg primaquine weekly for 8 doses (PQ8W) for the radical cure of *Plasmodium vivax* in patients with glucose-6-phosphate dehydrogenase deficiency (G6PDd) but data on its antirelapse efficacy and safety are limited. Within the IMPROV study, we enrolled patients with uncomplicated *P. vivax* malaria and G6PDd into a 12 month observational study. Patients were treated with PQ8W combined with dihydroartemisinin piperaquine (Indonesia) or chloroquine (Afghanistan, Ethiopia, Vietnam). G6PD status was diagnosed at enrolment using the fluorescent spot test (FST) and subsequently confirmed by genotyping for locally prevalent G6PD variants. In total, 50 G6PDd patients were recruited (42 male, 8 female): 6 in Afghanistan, 5 in Ethiopia, 19 in Indonesia and 20 in Vietnam. The median age was 23 years (range 4–41). G6PDd variants were confirmed in 32 patients: Viangchan (14), Mediterranean (4), 357A-G (3), Canton (2), Kaiping (2), and one each for A^-, A^+, Chatham, Gaohe, Ludhiana, Orissa, and Viangchan-Vanua Lava. By the end of follow up, only two patients from Vietnam had recurrent *P. vivax* parasitaemia (Days 68 & 207) for a cumulative efficacy of 94.9% (95%CI 81.1–98.7). Overall, the median (range) absolute and fractional falls in haemoglobin (Hb) from baseline to nadir Hb was -1.8 (-5.6–0) g/dL and -13.0% (-33.0–0) and occurred on median day 7 (IQR 3-7). No patients vomited any of their primaquine doses within 24 hours. A 16y old hemizygous male with G6PD Kaiping had a 33.3% fall in Hb (from 13.5 to 9 g/dL) on

day 5; his 2nd primaquine dose was withheld but he was recommenced on primaquine at his third visit and he completed his 8 week course. This comparatively large multicentre cohort of G6PDd vivax patients demonstrated that PQ8W provides high antirelapse efficacy and is well tolerated across a range of G6PD variants.

0864

EVALUATING THE EFFECTS OF SYNCHRONIZATION AND PARASITES CULTURE ADAPTATION ON THE SUSCEPTIBILITY OF *PLASMODIUM FALCIPARUM* PARASITES TO ANTIMALARIALS

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Plasmodium falciparum parasites can dynamically shift from synchronous to asynchronous in *in vitro* cultures, leading to a corresponding shift in the patterns of response to antimalarials. Furthermore, asynchronous clinical isolates are known to harbour more diverse parasite genotypes than synchronous ones. Therefore, this study evaluated the effects of sorbitol and Percoll synchronization of *P. falciparum* parasites on their susceptibility to antimalarials. Using *in vitro* growth inhibitory assays, this study evaluated the response of asynchronous clinical *P. falciparum* parasites to antimalarials and compared it to those synchronized with sorbitol and Percoll. From the data, the sorbitol synchronized parasites were more susceptible to the antimalarials compared to the Percoll synchronized parasites. We also observed that the response of the asynchronous and synchronous parasites to the antimalarials varied with respect to the antimalarial compound, the life cycle stage of the parasites, the synchronization method and between the clinical isolates and laboratory strains. Furthermore, the clinical isolates had increased sensitivity to the antimalarials during long-term culturing activities. Therefore, during compound screening activities, it is important to consider the effect of synchronization and long term culturing of clinical isolates on their response to antimalarials. Achieving this will provide a broader analysis of the potency of antimalarial compounds before they are further developed for clinical use.

0865

LONGITUDINAL IMPACT OF HIV-1 AND ARTS ON *PLASMODIUM FALCIPARUM* GAMETOCYTE PREVALENCE IN ASYMPTOMATIC MALARIA INFECTIONS AND CORRESPONDING TRANSMISSION TO *ANOPHELES* MOSQUITOES

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We examined over 780 samples collected from a longitudinal cohort of 300 volunteers in the endemic region of Kisumu, Kenya, in order to understand the epidemiological impact that HIV-1 and ARTs have on *Plasmodium falciparum* gametocyte transcript prevalence and *Anopheles* oocyst development. We analyzed these samples using our highly sensitive digital droplet PCR (ddPCR) assay of three gametocyte specific transcript markers and observed an overall gametocyte prevalence of 51.1% across all HIV-1 groups and time points. After correcting for multiple comparisons, HIV-1 status, time, CD4+ T-cell levels and RBC did not significantly predict gametocyte prevalence or transmission. For a specific study group that was newly tested and diagnosed for HIV-1, the initiation of ARTs (including TS) and prescription of Coartem at Month 0 resulted in a significant impact on the reduction of gametocyte transcript prevalence in the subsequent month when compared to our control group (HIV-1 negative). Using a standard membrane feeding assay and mosquito midgut dissections, we found that 50% of the samples that tested positive for oocysts in the mosquito midgut failed to test positive for parasites by *18S* qPCR and 35% failed to test positive for any gametocyte specific transcript marker by ddPCR. These finding suggest that transmission can occur even at such low densities that they are undetectable through highly sensitive molecular assays. The results also highlight the complexity surrounding HIV-1 malaria coinfection and the need to further understand asymptomatic infections and their unpredictable role in transmission to mosquitoes.

0866

TRANSCRIPTOMICS OF HEAT SHOCK PROTEINS IN ADULT MOSQUITOES IN RESPONSE TO HEAT SHOCK

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Odisha state in India is known for extremes of temperature and *An. culicifacies* is known to transmit malaria in that region. Multiple heat shock protein's (HSP's) are known to be expressed in mosquitoes in response to thermo-tolerance, which can alter their gene expression. In order to determine the expression of HSPs in mosquitoes, we subjected mosquitoes to heat shock treatment for various durations and temperatures. Molecular pathways of HSP70 in *An. culicifacies* mosquitoes were also explored through transcriptomics to study their pathogenesis. Insectary reared female *An. culicifacies* were exposed at 38 °C, 39 °C, 40 °C, 42 °C and 44 °C for 0.5, 1, 2, and 4 hours each. Live mosquitoes from heat shock treatment were further isolated and allowed to revive under control conditions. Insectary reared mosquitoes served as control. After RNA extraction and cDNA synthesis revived mosquitoes were further quantified by quantitative real-time polymerase chain reaction. The expression of *Hsp70*, was examined by comparing relative transcript expression levels with insectary reared controls using $2^{-\Delta\Delta Ct.}$ Method. Data revealed that adults at 39 °C and 40 °C were more sensitive to heat shock treatment than at any other temperatures. The mean level of expression for *HSP70* genes was 3.75 ± 3.60 folds when compared to the reference gene (actin). Relative *Hsp70* expression levels were 10-folds higher than *the control.* Statistical analysis indicated that *Hsp70* genes were significantly upregulated at 40 °C for 1 hour and 42 °C for 0.5-hour exposure. *HSP70* was significantly up-regulated, which suggest that *their* expression can be a sensitive indicator of thermo-tolerance in *An. culicifacies*. HSP'S can be used as important markers and may function as critical proteins to protect and enhance survival of *An. culicifacies* in extreme temperature conditions in Odisha. These findings provide a host protein biomarkers for diagnosis of malaria and its pathogenesis. Transcriptomics study revealed that heat resistant mosquitoes characterized by polymorphic variation in heat shock protein (Hsp) 70 with decreased gene expression.

0867

IS GESTATIONAL AGE AT ONSET OF ANEMIA IN PREGNANCY ASSOCIATED WITH ADVERSE PERINATAL OUTCOMES IN A MALARIA ENDEMIC SETTING?

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More than one-third of pregnant women present with anemia in pregnancy, and this burden is significantly higher among women in malaria endemic zones. While it is known that malaria in pregnancy is associated with poor perinatal outcomes, it is unknown if gestational age at onset of anemia shows similar correlation. The objective of this study was to determine if perinatal outcomes vary by gestational age at onset of anemia in pregnancies in a malaria endemic setting. This was a retrospective study that utilized data from two double-blinded randomized controlled trials of intermittent preventative malaria regimens during pregnancy in

Uganda. Maternal hemoglobin was measured for all eligible patients at enrollment (<20wks), at 24, 28, 32, 36 weeks and at time of delivery. Anemia was defined as hemoglobin <11gm/dl for all gestational ages. Associations between gestational age at onset of anemia and outcomes of interest (preterm birth and small-for-gestational-age) were assessed using logistic regression models controlled for gravidity and age. A total of 1082 mothers enrolled in the study with a mean age of 23.2 years (SD 5.3). A total of 656 (60%) had anemia in pregnancy, among which 288 (26.6%) had onset of anemia at <24 weeks. A total of 396 (42%) of patients had placental malaria of which 71% presented with anemia in pregnancy and 37% with anemia <24 weeks. Compared to women without anemia, women with anemia onset at <24 weeks had higher odds of delivering small-for-gestational age (OR=1.53 [95% CI: 1.0-2.3]; p<0.05) and preterm babies (OR=1.18 [95% CI: 0.68-2.05, p=0.55), though findings for preterm birth were weak and did not reach statistical significance. Patients with placental malaria and onset of anemia less than 24 weeks were two times more likely to have small-for-gestational-age at birth (OR 2.11; CI 1.14-3.15, p<0.01). Onset of anemia <24 weeks of gestation was associated with higher rates of small-for-gestational age at birth among all pregnancies in malaria endemic areas. Prevention and treatment of malaria and anemia at earlier gestational age could help decrease incidence of small-for-gestational-age at birth in malaria endemic areas.

0868

DIFFERENTIAL EXPRESSION OF BASIGIN/OKA ANTIGEN IN THE GHANAIAN POPULATION

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A number of erythrocyte-associated polymorphisms with high frequencies have been associated with malaria in endemic regions for which some of these polymorphisms have provided the best-known host malaria resistance mechanisms. Recently, a blood group antigen known as the Oka antigen identified to play a crucial role in the pathogenesis of *Plasmodium falciparum* malaria has received much attention, however it is poorly understood for its possible role in host resistance within endemic regions. The *BSG* gene carries the Oka blood antigen. Circulating *BSG* polymorphisms in malaria endemic populations have not been described. Previous work done in a non-endemic population showed an association of Oka blood antigen expression levels and *Pf*RH5 binding in vitro. Data from other literature show that polymorphisms in the *BSG* gene could provide a more potent *P. falciparum* protection compared with antimalarial strategies involving the parasite's cognate ligand *Pf*RH5, which is the leading blood-stage malaria vaccine candidate currently. In this study, preliminary investigation was carried out in a Ghanaian population to assess native RNA expression levels of the Oka blood antigen in both malaria and non-malaria individuals. Over 200 blood samples have been profiled so far of their Oka blood antigen RNA expression. Preliminary results show a 12-fold difference between low expression and high expression individuals at the RNA level with a 3-fold difference at the protein level as determined by RT-PCR and western blotting respectively. In vitro ELISA-based erythrocyte binding assay demonstrated a correlation between RBC surface Oka expression and the binding of recombinant PfRH5 ligand, suggesting that the expression levels might be the mechanism influencing *P. falciparum* resistance. Comparing the expression profiles of other RBC blood group antigens such as glycophorins and complement receptor 1, known to be involved in *Plasmodium* merozoite invasion could highlight some significant associations or patterns that explains individual resistance to *P. falciparum* malaria.

0869

CELL DEATH OF *PLASMODIUM VIVAX*-BLOOD STAGES OCCURS IN ABSENCE OF CLASSICAL APOPTOTIC EVENTS

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Elucidation of pathways regulating parasitic cell death is believed to contribute to identification of novel therapeutic targets for protozoan diseases and, in this context, apoptosis-like cell death has been reported in different groups of protozoa, in which a family of cysteine-dependent proteases, called metacaspases, seems to be involved. In *Plasmodium*, apoptotic markers have been detected in *P. falciparum*, *P. yoelii* and *P. berghei*, with no study focusing on *P. vivax* cell death. Thus, in the present study, we investigated the susceptibility of *P. vivax* to undergo apoptotic cell death. Trophozoites were enriched from blood samples of malaria vivax patients and, then, incubated in the presence of chloroquine or classical inducers of apoptosis (staurosporine and camptothecin). Parasite growth and viability as well as apoptotic events were detected by flow cytometry assays, and cell morphology was examined using transmission electron microscopy. Additionally, real-time quantitative PCR was used to estimate the expression of *P. vivax* metacaspase 1 (*Pv*MCA1) gene. It was observed that all stimuli inhibited the intraerythrocytic development, which was accompanied by a decrease in parasitic viability, as evidenced by analysis of the DNA content and plasmodial mitochondrial activity, respectively. However, typical signs of apoptosis, such as DNA fragmentation, chromatin condensation and nuclear segregation, as well as augmented expression of metacaspase gene, were not detected in cell death-induced parasites. On the other hand, a relation between the parasite development and *Pv*MCA1 expression was observed in non-treated parasites. In conclusion, the results indicate that *P. vivax* blood forms are not susceptible to apoptosis-like cell death, while suggest that metacaspase can be involved in progression of parasite development. Further studies are still required to better describe cell death phenomena in *P. vivax*.

0870

UNDERSTANDING THE NOVEL ENDOSPLENIC LIFECYCLE OF *PLASMODIUM VIVAX*: MECHANISMS OF INTRASPLENIC RETICULOCYTE RETENTION AND ACCUMULATION

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Global malaria elimination is complicated by the existence of hidden infectious reservoirs. Our recent splenectomy studies in Indonesian Papua revealed the human spleen as a major extravascular niche accounting for more than 98% of *Plasmodium vivax* biomass in chronic infections, transforming the vision of malaria as an infection replicating predominantly in the spleen rather than exclusively in the blood. Significant concentration and colocalization of immature $CD71^+$ reticulocytes and asexual stages in specific splenic compartments sustain a novel endosplenic *P. vivax* lifecycle. We hypothesize that *P. vivax*-specific adaptations, splenic remodeling and extramedullary hematopoiesis contribute to splenic reticulocyte enrichment. In a prospective study of 48 spleens from Papua, ex-vivo deformability assays indicate greater rigidity of splenic reticulocytes than those in matched peripheral blood

and, together with their localization to the splenic red-pulp, suggest a biomechanical retention process. Splenomegaly-related architectural changes characterized by red-pulp expansion and congestion with red blood cells, paralleled by relative loss of white-pulp, revealed remodeling of larger spleens with evidence of increased splenic filtration stringency, likely exacerbating trapping of both rigid and non-rigid reticulocytes and normocytes. A greater number of $CD71^+$ reticulocytes were apparently adherent to endothelial cells lining the sinus lumen walls in *P. vivax* than in *P. falciparum*-infected spleens, supporting ligand-based erythrocyte interactions with the splenic matrix and an increased affinity in *P. vivax*. Fine depositions of $CD71^+$ nucleated cells and cell clusters are currently being analyzed in more detail. Collectively, biomechanical trapping and cytoadherence contribute to immature reticulocyte retention that is likely exacerbated by length and intensity of *P. vivax* exposure. Intrasplenic production cannot be excluded as an additional source of target cells for *P. vivax* invasion in the spleen. Further human splenic malaria studies may reveal novel targets for detection and targeted intervention.

0871

VARIABILITY IN GLUCOSE-6-PHOSPHATE DEHYDROGENASE ENZYME ACTIVITY WITH GENETIC VARIANT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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8-aminoquinoline drugs are essential for the radical cure of *Plasmodium vivax*, however they can cause severe haemolytic anaemia in individuals with G6PD deficiency. G6PD deficiency exhibits vast genotypic and phenotypic variability, confounding diagnosis. This study investigated the degree to which quantitative G6PD activity varies within and between different genetic variants and the implications of this for diagnosis. A systematic review was conducted to identify studies reporting G6PD spectrophotometry and G6PD genotyping (PROSPERO CRD42020207448). Individual-level data were pooled, excluding those with malaria and infants <1yr age. G6PD activity was converted to % normal activity using study-specific definitions of 100%. For each variant, the median, IQR, total range, and potential outliers were derived for hemi-/homozygous and heterozygous individuals separately. Distributions of G6PD activity were compared against clinical thresholds for G6PD activity. In total, 3590 individuals were included from 17 studies across 9 countries of whom 1495 (41.6%) had one of 22 G6PD mutations. G6PD activity varied considerably for both hemi-/homozygous individuals and heterozygous individuals, even among individuals with the same genetic variant. The median G6PD activity of hemi-/homozygotes was 31.5% (range: 1.7% to 154.1%) for A- (202A) (n=77), 10.2% (range: 0-32.5%) for Mahidol (n=201), 16.9% (range 3.3-20.7%) for Mediterranean (n=44), 9% (2.9-23.2%) for Vanua lava (n=36), and 7.5% (0-17.5% for Viangchan (n=112). Among hemi/homozygous individuals, 99.5% with the Mahidol mutation and 100% with the Mediterranean, Vanua lava and Viangchan mutations had <30% enzyme activity. Among hemi/homozygous participants with A- (202A) 45.8% had <30% activity. Our results highlight marked variability in enzyme activity among individuals with the same G6PD variant. G6PD activity distributions spanned previous classification thresholds used to demarcate severity classes, supporting calls to update this schema. Additional data correlating G6PD enzyme activity and genetic variant with risk of haemolysis are required.

0872

PHAGOCYTOSIS OF *PLASMODIUM FALCIPARUM* HEMOZOIN ALTERS PRO-INFLAMMATORY MEDIATOR PRODUCTION THROUGH THE CD40-TRAF6 PATHWAY

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Severe *Plasmodium falciparum* malarial anemia (SMA, Hb<5.0g/dL and any density parasitemia) remains one of the most common causes of pediatric mortality. Deciphering the molecular mechanisms of SMA is a prerequisite for developing effective therapeutics. It has been demonstrated that phagocytosis of malarial pigment (*Pf*Hz) is a potent modulator of pediatric SMA pathogenesis. Although the molecular pathway(s) through which *Pf*Hz influences enhanced disease is only partially understood, *Pf*Hz alters the expression of pro-inflammatory mediators (e.g., IL-1β, IL-6 and TNF-α). As such, the relationship between the CD40 pathway and cytokine expression was explored in malaria-naïve study participants using a CD40-TRAF6 pathway activator (i.e., anti-CD40 antibody) and a small molecule CD40-TRAF6 pathway inhibitor (i.e., 6877002). Temporal kinetics were examined at 4, 12, 24 and 48 hours in cultured PBMCs. Gene expression and protein levels of IL-1β, IL-6 and TNF-α were determined by RT-qPCR assays and ELISA, respectively. Phagocytosis of *Pf*Hz caused a significant ($P<0.001$) increase IL-1β (5.7-fold), TNF-α (4.6-fold) and IL-6 (6.5-fold) expression. Transcripts levels for each of the cytokines increased until peak expression at 24 hours and were back to baseline levels by 48 hours. Anti-CD40 antibody in combination with *Pf*Hz treatment further augmented mRNA expression levels: IL-1β (14.1-fold), TNF-α (12.6-fold) and IL-6 (11.0-fold, $P<0.001$ for all measures). Conversely, inhibition of the CD40-TRAF6 pathway by 6877002 blocked the effect of *Pf*Hz on cytokine expression ($P<0.05$, for all measures). IL-1β, IL-6, and TNF-α protein levels in the treatment groups showed a similar pattern. Results presented here demonstrate that *Pf*Hz exerts its effects on pro-inflammatory mediators (i.e., IL-1β, IL-6, and TNF-α) through the CD40-TRAF6 pathway. Future studies aimed at exploring compounds that alter CD40 signaling may offer important insight into novel immunotherapeutic approaches for the treatment of SMA.

0873

A HIGH BASELINE HEMOLYTIC INDEX IS ASSOCIATED WITH ACUTE KIDNEY INJURY AND MORTALITY AMONG CHILDREN WITH SEVERE MALARIA

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Hemolysis is an obligate part of the malaria lifecycle and is implicated in the pathophysiology of severe anemia and acute kidney injury (AKI) in severe malaria. The aim of this study was to characterize hemolysis in children with severe malaria and evaluate the relationship between hemolysis, disease severity, and post-discharge morbidity and mortality. Using ELISA, we evaluated markers of hemolysis (hemin, lactate dehydrogenase (LDH)), the heme/hemoglobin detoxification system

(haptoglobin, hemopexin), sCD163 a scavenger receptor for hemoglobin-haptoglobin, and ferritin, which is upregulated in response to circulating heme-proteins. We enrolled 600 children with SM aged 6 months to 4 years at two hospitals in Uganda and followed children for one year to assess survival. Among children with SM, 21.4% had severe AKI and 7.3% died in-hospital. Using factor analysis, we computed composite indices of hemolysis based on correlated biomarkers with similar biological functions. Two latent constructs emerged: i) a hemolytic index (HI) (LDH, 0.43; hemin, 0.16; sCD163, 0.21; ferritin, 0.28); ii) heme-detoxification index (HDI) (haptoglobin, 0.31; hemopexin, 0.19; sCD163, 0.22; hemin, –0.24). To validate these indices, we compared levels across three clinical complications representing the "hemolytic triad"— blackwater fever, jaundice, and severe anemia. There was an increase in the HI and decrease in the HDI across all three complications in the hemolytic triad ($p<0.0001$ for all). Further, there was a 2.5 and 8-fold mean increase in the HI in children with AKI and severe AKI respectively ($p<0.0001$ for both) and the HI, but not the HDI, was associated with mortality with a 1.59-fold increase in the odds of in-hospital mortality (95%CI 1.24, 2.04) adjusting for age, sex, and site. Among survivors, the HI was associated with persistent kidney disease following AKI at 1-month follow-up and increased post discharge mortality adjusting for age, sex, and site. These data provide strong evidence that hemolysis is associated with kidney disease and post discharge mortality in SM.

0874

THE EFFECT OF MALARIA IN PREGNANCY ON ANAEMIA AT DIFFERENT LEVELS OF MALARIA TRANSMISSION IN AFRICA; AN ECOLOGICAL META-ANALYSIS

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Malaria in pregnancy is an important cause of maternal anaemia. We conducted an aggregated data meta-analysis to explore the relationship between maternal anaemia and malaria transmission intensity in Africa. We used an existing dataset from the Malaria in Pregnancy Library for studies with data on anaemia and haemoglobin from January 1950 to September 2016. Data on malaria transmission intensity ($Pf PR_{2-10}$) was obtained from the Malaria Atlas Project. Random effects meta-regression was used to assess the relationship between malaria transmission (as continuous variable) and maternal anaemia (haemoglobin [Hb] <11 g/dl), severe anaemia (Hb<8 g/dl) and mean Hb. Mean Hb was negatively associated with increasing malaria transmission ($p=0.001$ for trend, 66 studies) in pregnancy, but not at delivery ($p=0.495$, 55 studies). Similarly, the risk of anaemia increased with increasing malaria transmission intensity during pregnancy ($p<0.0001$, 108 studies), but not at delivery. No trends were seen for severe anaemia. A positive malaria smear was associated with an increased risk of anaemia (pooled RR=1.33, 95% CI 1.26-1.41, 50 studies, I^2 90.9%, $p=0.019$) and severe anaemia (pooled RR=1.95, 95% CI 1.62-2.35, 26 studies, $p=0.023$); level of transmission modified the association between malaria and anaemia, with a trend towards a lower association with increasing malaria transmission intensity (meta-regression $p=0.019$ for anaemia and $p=0.046$ for severe anaemia). The median population attributable fraction of malaria to anaemia was 6% (range 0-21%) in areas of low transmission ($Pf PR_{2-10}$<10%, 7 studies) and 9% (range 0-39%) in areas of high transmission ($Pf PR_{2-10}$>35%, 19 studies); for severe anaemia this was 35% (range 19-54% 3 studies), and 18% (range 3-73%, 11 studies), respectively. Populations of pregnant women residing in areas with higher malaria transmission in Africa are more likely to have lower Hb levels and more anaemia than populations in low transmission areas. However, the impact of malaria in pregnancy on Hb<8 g/dl seems greater in populations in low transmission areas.

0875

SPATIAL HETEROGENEITY OF *PLASMODIUM KNOWLESI* MALARIA INFECTION IN THE PIG-TAILED MACAQUE LIVER

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Non-human primates (NHPs) are valuable models for pre-clinical evaluation for malaria vaccines. The most commonly used NHP model for malaria vaccination and challenge studies is the rhesus macaque/*Plasmodium knowlesi* model, which has enabled impactful vaccine research over many decades. However, it is increasingly recognized that this model has certain limitations, which mainly arise because rhesus macaques are not natural hosts for *P. knowlesi* but rather susceptible experimental hosts. Driven by the recent rhesus macaque shortage, we have initiated multiple studies to explore whether pig-tailed macaques, a natural forest host for *P. knowlesi*, can be used for pre-clinical malaria vaccination and challenge studies. Here we present data from a pilot study where a single pig-tailed macaque was infected intravenously with 50,000 purified, cryopreserved, wild-type *P. knowlesi* sporozoites (PkSPZ) and necropsied five days later to analyze the magnitude and spatial heterogeneity of infection in the macaque liver. We sampled tissue from 40 discrete sites across the liver and analyzed parasite burden by 18S rRNA reverse transcription PCR. Additional tissue from adjacent sites was sampled for histology and other spatial analyses. We detected parasite 18S rRNA in 39/40 sites, confirming that the high dose of PkSPZ led to robust infection in this host. Quantification of parasite 18S rRNA revealed remarkable heterogeneity of infection, with copy numbers ranging from 2-9 $\log_{10}$ copy numbers/mL, equivalent to a >10 million-fold difference between sites. To our knowledge, this is the first time the spatial heterogeneity of infection has been quantified to this level of detail in a macaque malaria model. This data will inform our ongoing studies of PkSPZ-based vaccines in pig-tailed macaques and lay the foundation for future research to explore liver stage parasite-host interactions in this natural NHP model.

0876

PATIENT ADHERENCE TO REFERRALS FROM THE PRIVATE TO PUBLIC SECTOR: A FEASIBILITY STUDY FROM LAO PDR

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Lao PDR aims to eliminate malaria by 2030 and establishing a strong private sector engagement program that is linked to the national malaria program is crucial to achieving this goal. National treatment guidelines in Lao PDR require patients with P. vivax or severe malaria be referred to a public health facility. However, there is currently no system in place to track patient referral and completion rates from private to public facilities. From February to October 2021, PSI Laos conducted a mixed methods study to explore the feasibility of a referral system. We assessed referral completion rates and explored the facilitators of completed referrals through in-depth interviews with patients. A referral record was established to track positive malaria cases that presented in 11 private health facilities in Lamam district, Sekong province. Positive cases were issued a referral voucher and instructed to present at a public facility within 1 day. In total, all 55 positive malaria cases identified in the facilities participating in the research were referred and all presented at a public facility within 1 day of referral. Key informant interviews revealed, that the robust patient counselling and the proactive follow up of providers to complete referral were key reasons for completion. Although all patients completed their referral, when asked about barriers they faced, the patients revealed a reluctance to go to public health facilitates due to the fear of infections like COVID19, as well as cultural beliefs associated with the worship of ancestors. For all

patients, travel time to the public facility ranged from less than 1 to over 2 hours. The results of this study show a high rate of referral completion, influenced by provider counselling and patient trust. It confirms other studies that show that patients first seek treatment in the private sector because of convenience and that trust in their provider is a facilitator for adhering to medical advice including referral completion This study demonstrates that managing the continuum of malaria case management across the private and the public sector is feasible but dependent on well engaged private providers.

0877

DELETIONS OF *PLASMODIUM FALCIPARUM PFHRP2* AND *PFHRP3* GENES IN SPECIMENS COLLECTED FROM PARTICIPANTS IN AN ANTIMALARIAL EFFICACY TRIAL IN MADAGASCAR IN 2020

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The emergence of *pfhrp2* and *pfhrp3* (*pfhrp2/3*) gene deletions allows parasites to evade detection by HRP2-based RDTs and contributes to false-negative test results. In 2019, the WHO recommended switching from HRP2-only tests when the local prevalence of *pfhrp2* deletions in the parasite population reaches ≥ 5%. In this current study, dried blood spots (DBS) were collected from 710 RDT-positive children ≤15 years of age enrolled in an antimalarial therapeutic efficacy study (TES) conducted at four sites in Madagascar in 2020. Enrollment required participants to have microscopically-confirmed *P. falciparum* mono-infection with parasitemia between 1000-100,000 p/µl and a positive HRP2-RDT. A multiplex bead-based antigen detection assay screened DBS to identify samples with low levels of HRP2/3 antigen expression relative to pan-*Plasmodium* lactate dehydrogenase and aldolase. Samples with low or absent HRP2/3 expression were selected for *pfhrp2/3* genotyping. To ensure DNA quantity and quality, selected samples were first screened by a *Plasmodium* PCR speciation assay and *pfmsp1* and *pfmsp2* nested PCRs. Genotyping samples with a low HRP2/3 antigen profile (n=31) revealed two infections with *pfhrp2*-single deletions (0.3%), seven *pfhrp3*-single deletions (1.0%), and no *pfhrp2/3*-double deletions. No evidence of clustering of deleted samples among study sites was observed. Since the enrollment criteria required positivity HRP2-based RDT, patients with double-deleted parasites would likely have been excluded from enrollment, and these data should be interpreted in that context. Overall, DBS collected from TES participants provides a convenience sampling method for serological and molecular analysis. While not able to provide valid or precise prevalence estimates for the entire country, this current report, combined with the report of *pfhrp2* deletions in Madagascar in 2018, provides consistent evidence for the existence of these gene deletions in the *P. falciparum* parasite population in Madagascar.

0878

SPATIOTEMPORAL DYNAMICS OF *PLASMODIUM FALCIPARUM* HISTIDINE-RICH PROTEIN 2 AND 3 DELETIONS IN PERU

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Plasmodium falciparum isolates lacking *pfhrp2/pfhrp3* were first reported in Peru despite the limited use of rapid diagnostics tests (RDT) in the country. This scenario provides a unique opportunity to study the dynamics of *pfhrp2* and *pfhrp3* gene deletions without RDT selection pressure.We assessed the presence of *pfhrp2* and *pfhrp3* genes on 324 *P. falciparum* samples collected in Iquitos and surrounding communities between 2011 and 2018. Gene deletions were determined by *pfhrp2* and *pfhrp3* specific PCRs and absence of HRP2 expression in gene deleted parasites was assessed by HRP2 and pLDH ELISA. Population structure and genetic relatedness were explored on a subset of 254 samples using a panel of seven neutral microsatellite markers. Overall, 67% (217/324) samples were determined to have dual *pfhrp2* and *pfhrp3* deletions. Prevalence of *pfhrp2* and *pfhrp3* deletions was geographically heterogeneous (adjusted p<0.005) but with an increasing trend of dual *pfhrp2/3*-deletions through time from 14.3% in 2011 to 65% in 2018. A total of 16 unique haplotypes were obtained from 203 successfully genotyped samples on seven microsatellite markers. Two of these haplotypes named H8 and H13 accounted for 70.9% (144/203) and 11.8% (24/203) of all the samples, respectively. The overall increase of dual deletion prevalence was associated with the increasing prevalence of H8 consisting of 83.3% of dual pfhrp2/pfhrp3-deleted parasites in all study sites.In conclusion, our study showed an increasing trend of *pfhrp2/3* dual deleted parasites from 2011 until 2018 in Iquitos that is associated with the spread of a new parasite line (H8). This increase does not appear to be driven by RDT use but likely to previous malaria eradication efforts conducted in Peru. These results suggest that other factors linked to the *pfhrp2/3* deletion provide a selective advantage over non-deleted strains and highlight the need for additional studies and continuing surveillance.

0879

IMPROVING LABORATORY PERFORMANCE IN MADAGASCAR THROUGH OUTREACH TRAINING AND SUPPORTIVE SUPERVISION, 2019-2021

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Madagascar's malaria treatment policies require all suspected severe cases to be confirmed with malaria microscopy (MM) and all uncomplicated cases to be confirmed with malaria rapid diagnostic tests (mRDT). Maintaining high quality diagnostic services is a challenge in Madagascar due to factors such as limited availability of equipment and reagents, and lack of training. To evaluate and improve laboratory and technician performance in malaria diagnostics, the National Malaria Control Program, supported by U.S. President's Malaria Initiative (PMI) Impact Malaria, conducts quarterly lab Outreach Training and Supportive Supervision (OTSS+). Performance is assessed through five indicators calculated using OTSS+ checklist data: health facility readiness (including availability

of commodities and trained staff), proficiency testing, microscopy observation, external quality assurance (EQA), and mRDT observation. Between 2019 and 2021, 46 public and private labs across five regions each received five OTSS+ visits, which included on-the-job training based on supervision findings and feedback sessions to relay results and recommendations and sign an action plan. Between rounds, OTSS+ supervisors made coaching calls to labs to follow up on the action plan. After each round, labs were classified into class A (90-100%), B (80-89%), or C (<80%) based on the average score of all indicators. Results showed an improvement in lab performance from the first round of OTSS+ (R1) to the fifth round (R5): scores increased from 57 to 85% for health facility readiness, 50 to 73% for proficiency testing, 87 to 93% for microscopy observation, 62 to 88% for EQA, and 60 to 95% for mRDT observation. After R1, only 2% of labs were in classes A or B; this increased to 72% in R5 (11% class A, 61% class B). On-the-job training, coaching calls, and formal training likely contributed to the increase in scores. To continue to strengthen performance of malaria diagnosis through OTSS+, a consistent supply of reagents and consumables, continued on-site training during supervision, formal training of lab technicians in panel testing, and microscopy observation are needed.

0880

HIGH SENSITIVITY OF THE RAPIGEN BIOCREDIT RDT FOR THE DIAGNOSIS OF CLINICAL AND SUBCLINICAL *PLASMODIUM FALCIPARUM* INFECTIONS IN A HIGH TRANSMISSION SETTING IN BURUNDI

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Rapid diagnostic tests (RDTs) have become a mainstay for the diagnosis of malaria infections among febrile patients and subclinical individuals. Low-density infections, and deletions of the *P. falciparum hrp2/3* genes (encoding for the HRP2 and HRP3 proteins detected by many RDTs) present challenges for RDT-based diagnosis. We have evaluated a novel RDT, the Rapigen Biocredit three-band HRP2/LDH RDT, for diagnosis of *P. falciparum* among 444 febrile patients and 468 subclinical individuals in a high transmission setting in Burundi. Results were compared to the AccessBio CareStart HRP2 RDT, an established product routinely used in multiple countries, and qPCR with a sensitivity of <0.1 parasites/µL blood. The limit of detection (LOD) was calculated as parasite density where 95% of infections are RDT positive. 73.7% (327/444) of febrile patients were positive by qPCR for *P. falciparum*. Sensitivity of the Biocredit RDT was 77.4% (253/327, counting either band (HRP2 or LDH) positive), compared to 70.0% (229/327) for the CareStart RDT. Prevalence of subclinical infections by qPCR was 50.8% (238/468). Sensitivity of the Biocredit RDT was 68.9% (164/238) and reached 85.2% (52/61) in children below 15 years. Sensitivity of the CareStart RDT was 55.5% (132/238). The Biocredit HRP2 band was more sensitive than the LDH band, in particular among subclinical infections (clinical infections: HRP2 75.2% vs. LDH 68.8%; subclinical infections, HRP2 67.2% vs. LDH 47.0%). Specificity was 83.7% for the Biocredit and 94.2% for the CareStart RDT. The LODs were 27 parasites/µL for the Biocredit (any band), 30 parasites/µL for Biocredit HRP2, 190 parasites/µL for Biocredit LDH, and 85 parasites/µL for CareStart HRP2. No (0/372) *hrp2* and 2/376 *hrp3* deletions were observed. In conclusion, the novel RDT showed improved sensitivity for the diagnosis of *P. falciparum*. In children, which are at greatest risk of severe malaria, it detected 85% of subclinical infections, opening up new avenues to target the asymptomatic reservoir. Where no deletions are present, HRP2-based RDTs remain the most sensitive tool for field diagnosis.

0881

A LONGITUDINAL ANALYSIS OF HRP2 AND PLDH ANTIGEN DYNAMICS IN A COHORT OF MALARIA INFECTED INDIVIDUALS FROM NAMIBIA

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Rapid Diagnostic Tests (RDTs) for malaria detect the presence of the Histidine Rich Protein 2 (HRP2) or Lactate Dehydrogenase (LDH) antigens expressed by Plasmodium falciparum and all Plasmodium spp. parasites respectively. The post-treatment time to negativity (TTN) of an RDT is based on the decay of the antigen on which the test is based and the limit of detection (LOD) of the test. These factors have significant implications for diagnostic sensitivity and specificity and need to be considered when assessing the performance of more sensitive next-generation RDTs. This analysis utilized data from a longitudinal cohort study of 162 malaria-infected participants in the Zambezi Region of Namibia conducted in 2018. Individuals were treated and followed up for a maximum of 132 days. Approximately every 7 days concentrations of HRP2 and LDH were measured and standard and next-generation RDTs were conducted. We fitted linear fixed effect models to the data to estimate post-treatment biphasic decay rates of both antigens. Kaplan-Meier Survival Analyses were used to generate survival curves and median TTN estimates for when participants became RDT negative by the Abbot NxTek Eliminate-RDT. Utilizing data generated in a separate benchmarking analysis, the time to negativity of several additional next-generation RDTs were estimated by relating antigen concentrations in the study population to LODs determined during the benchmarking. We estimated that HRP2 would decay to half its initial concentration 3 days after treatment, whereas LDH decayed more rapidly, with a half-life of 1 day. The median TTN for the Abbot NxTek Eliminate-RDT was estimated at 68 days post-treatment compared to 42 days for a standard RDT, 49 days for the Abbot FK90 RDT, 56 days for the Rapigen pf RDT, and 10 days for the Rapigen pf/pv RDT. This analysis highlights how HRP2 decays more slowly than LDH post-treatment leading to longer TTN in HRP2-based tests, which could potentially increase with new RDTs that have lower LODs. LDH tests may typically be less sensitive, but more rapid TTN could be beneficial for discriminating between active and treated infections.

0882

A SINGLE TIME POINT IS NOT SUFFICIENT: THE DAILY DYNAMICS OF ASYMPTOMATIC LOW-DENSITY *PLASMODIUM* INFECTIONS FROM SELF-COLLECTED DBS IN KATAKWI DISTRICT, UGANDA

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Many *Plasmodium* infections are below the limit of detection of standard diagnostic tools, but little is known about the natural history of such infections. In this study, asymptomatic, rapid diagnostic test (RDT)-negative participants in Katakwi District, Uganda, were trained in dried blood spot (DBS) collection and asked to collect DBS daily between weekly clinic visits for 28 days. Self-collected daily DBS were thus obtained from enrolled adults and children along with venous blood and clinic-collected DBS taken at enrollment and four weekly clinic visits. Samples were analyzed by *Plasmodium* 18S rRNA quantitative reverse transcription PCR (qRT-PCR). The feasibility of this approach and infection patterns of qRT-PCR-positive individuals was analyzed. A total of 3579 unique DBS were received from 100 adults and 28 children (2955 at-home DBS; 624 clinic DBS). Overall, 40% of participants had no *Plasmodium* detected during the

28-day period. Adult females were more likely to be negative than adult males (52% vs. 33%). Among those who were positive (n=77), 36% of infections were *P. falciparum* (*Pf*) only, 36% were non-*Pf*, and 27% were mixed infections or multiple infections over the study period. Three-fourths (n=56) of those infected were qRT-PCR-positive at baseline. Eleven infections cleared during the study period, and six led to symptomatic, RDT-positive cases. A distinct saw-tooth pattern in parasite density was visualized in almost all series. On average, individuals who tested positive at least once during the 28-day period were negative on 5.7 days of sampling [IQR: 0 to 9.0 days]. Some individuals showed steadily increasing parasite densities and others showed decreasing densities. The results demonstrate that *Plasmodium* infections are highly dynamic. Sampling individuals on a single day will miss the full complexity and burden of infection, which could skew our understanding of vaccine and therapeutic study outcomes. Self-collected DBS are a feasible and reliable way to sample individuals across multiple days and should be added to epidemiological and clinical studies.

0883

PRESENCE OF PFHRP2-MRDT FALSE NEGATIVE RESULT IN PATIENTS WITH *PLASMODIUM FALCIPARUM* IN WESTERN KENYA WARRANTS MOLECULAR SURVEILLANCE

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Malaria is a life-threatening disease caused by *Plasmodium* species. The Kenya National Malaria Control Program (NMCP) follows World Health Organization's (WHO's) guidelines on the use of antigen-based malaria rapid diagnostic tests (mRDT). The most sensitive and commonly used mRDT targets *P. falciparum* histidine-rich proteins 2, encoded by *pfHRP2*. In recent years, the spread of *P. falciparum* with deletions in the *HRP2* genes and non-*falciparum* species has led to false-negative Pfhrp2-mRDT results, posing significant public health threats for malaria treatment and elimination. For instance, substantial numbers of patients with malaria can escape detection by the pfhrp2-mRDT and remain untreated, thereby, increasing transmission, and malaria-related morbidity and mortality. To better understand the performance of Pfhrp2-mRDT in clinicals setting, we are conducting a study at Siaya County Referral Hospital in western Kenya, a *P. falciparum* holoendemic area. A pediatric cohort (n=248) presenting at the hospital with *P. falciparum* infection (diagnosed by microscopy) were evaluated during acute infection (pretreatment, day 0, n=187) and at a well-visit (posttreatment, day 14, n=61). There were 20 (10.7%, smear positive) patients in the acute infection group who tested negative using the Pfhrp2-mRDT (CareSmart™). The remaining 167 patients (83.9%, smear positive) with acute infections tested positive with the Pfhrp2-mRDT while all day 14 visit patients (n=61; 100%, smear negative) tested positive with the Pfhrp2-mRDT (*P*=0.003). Parasitemia was higher in mRDT (+) samples relative to mRDT (-) samples (*P*=0.001). These results indicate the presence of *P. falciparum* parasites with *PfHRP2* deletions and/or existence of non-*falciparum* species circulating in the community. As such, we are currently conducting molecular surveillance using multiplex qPCR and sequencing to detect the *PfHRP2/3* deletions and *non-falciparum* species in a longitudinal cohort in the Siaya community and other regions of Kenya. Success in the ongoing project is expected to facilitate efforts for the Kenya NMCP to better mitigate malaria transmission.

0884

PERFORMANCE OF THE GAZELLE™ PLATFORM AS POINT-OF-CARE DIAGNOSIS OF CLINICAL *PLASMODIUM KNOWLESI* MALARIA

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Development of rapid and sensitive point-of-care (POC) diagnosis is essential for effective clinical management of *Plasmodium knowlesi* malaria. In Malaysia, microscopy remains first line POC malaria detection method, however misidentification with other endemic species occur. There is no commercial rapid test for *P. knowlesi* currently available. Validated sensitive molecular methods require extensive laboratory infrastructure. The novel Gazelle™ device (Hemex Health, USA) utilizes magneto-optical technology to detect hemozoin in blood and was evaluated as a POC knowlesi malaria detection method. Blood was collected from microscopy-diagnosed knowlesi malaria patients and malaria-negative controls, with confirmation via real-time PCR. Diagnostic accuracy of the Gazelle™ was evaluated and compared to both microscopy and PCR. The Gazelle™ was also evaluated on patient samples taken after administration of anti-malarial treatment. A limit of detection (LoD) analysis was conducted on a subset of clinical samples via two-folds dilution with parasite-free whole blood. From 241 study participants, the median age was 36 years (range 4 - 87). Patients identified as positive for *P. knowlesi* had a geometric mean parasitaemia of 799/µL (range: 18 - 331727). When compared to reference microscopy, the Gazelle™ recorded a sensitivity of 97.2% (n=148, 95% CI 92.9 - 99.2) and differentiated non-malaria samples with specificity of 100% (n=33, 95% CI 92.9 - 100). In comparison to reference PCR, the Gazelle™ detected *P. knowlesi* at a sensitivity of 93.2% (95% CI 87.9 - 96.7) and specificity of 100% 95% CI 89.4 - 100). For post-treatment samples (n=60), the median time between treatment to test conducted was 2.7 hours (IQR 1.6 - 5.1 h). For this post-treatment group, a sensitivity of 90% (95% CI 79.2 - 95.5) was observed but not statistically significant compared to pre-treatment group. The average calculated LoD from a subset of 20 samples is 32 parasites/µL (95% CI 16 - 65). The Gazelle™ shows promise as a potential point of care tool for rapid and sensitive detection of *P. knowlesi* by healthcare workers in remote endemic areas.

0885

MALARIA DIAGNOSTIC COMPETENCY ASSESSMENT IN NON-ENGLISH SPEAKING COUNTRIES OF AFRICA

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Accurate malaria diagnosis is important for rational use of antimalarials and preventing drug resistance. Hence, a need to implement a comprehensive and regular malaria microscopy training and competency assessment program. Since 2016, Cheikh Anta Diop University (UCAD) has been conducting External Competency Assessment in malaria microscopy (ECAMM) courses for non-English speaking countries in Africa. Here, we assess the outcomes of the first three years of this program. The audience was limited to 12 individuals per course. Each course was conducted over five consecutive days during which pre-assessment, learning units and assessment modules for malaria microscopy, including parasite detection, species identification, and parasite quantitation were done. The slides sets were from the WHO Slide Bank. Only Level 1 and Level 2 microscopists were certified as WHO experts. Since 2016, sixteen ECAMM courses have been conducted with 138 participants from 22 countries. Out of the 138,

96 (69.6%) were certified as experts either as level 1 or level 2. Eighteen countries had at least one microscopist certified. Out of the 138, 116 (84.1%) participants had both their sensitivity and specificity higher than 90%. The assessment results showed that accuracy in parasite detection ranged from 68% to 100%, with 60 out of 138 participants achieving 100%. Accurate results for species identification were variable, ranging from only 39% to 100%, with 55 out of 138 achieving more than 90%. The results for parasite counting were also variable, ranging from 14% to 100%, with 81 out of 138 achieving 50% or more of their counts within 25% of the true count. Significant improvements were reported in malaria microscopists after attending the program. Although all participants gained knowledge and awareness about the benefits of ECAMM courses at UCAD, its implementation should be extended to more participants. We recommend that all higher officials and policymakers in the field of malaria diagnosis give attention to it and allocate adequate budgets on a continuous basis.

0886

A MIXED METHOD FIELD SURVEY TO ELUCIDATE HIGH AND VARIABLE MALARIA RAPID DIAGNOSTIC TEST (MRDT) POSITIVITY RATES OBSERVED IN THE DEMOCRATIC REPUBLIC OF THE CONGO (DRC) - NOT A MALARIA ISSUE

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A project was initiated in 2020 with the primary objective to understand the reasons of the high and variable mRDT positivity rates observed in the DRC. In its course a literature search, a data quality review of routine malaria incidence indicators and a field survey on underlying factors were carried out.The field survey used a mixed methods approach consisting of data collection, technical assessments, focus group discussions and structured interviews. Of two provinces (Haut-Uélé, Sud Kivu), two health zones and of each two health areas were randomly chosen. Malaria indicator data were collected in health facilities of all levels and at Provincial and National levels. Four different sets of data collection tools were used to allow comprehensive data collection and triangulation of findings. The desk review of existing National Malaria Control Program data from 2015 to 2019 revealed an increase and significant variation in the mRDT positivity rate in several provinces of the DRC. Interviews were conducted with staff of 12 health facilities, 10 managers at Provincial or National level (public and supporting partners) and 84 adult patients (or caregivers). No major errors in the execution and interpretation mRDTs could be identified and there were no acceptance concerns among health workers. All major issues detected were health systems rather than malaria related: Lack of a reliable denominator (population served), inconsistencies in the attribution of data from non-registered private facilities, shortages in reporting templates, absences of the responsible for data transmission with no trained deputy, and the incoherent reporting of stockouts.
In conclusion, there was no single factor explaining the increase and fluctuations in mRDT positivity levels was detected. However, there were significant deficiencies in the collection, handling, and transmission of data which impact the data quality of the SNIS (Système National d'Information Sanitaire = DHIS2) and the functionality of the health care system. A series of recommendations for improvement of Health Care System and Quality of Care were developed.

0887

DEVELOPMENT OF DNA-BASED ELECTROCHEMICAL BIOSENSORS FOR ULTRASENSITIVE DETECTION OF *PLASMODIUM MALARIAE* AND *P. OVALE* IN CLINICAL SAMPLES

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In recent years, non-falciparum malaria is increasingly gaining public health attention. However, the absence of a reliable species-specific detection tool for non-falciparum malaria at the point of care (POC) has hampered effective disease diagnosis and management. This study describes the first label-free DNA-based electrochemical biosensors for species-specific detection of *Plasmodium malariae* and *P. ovale*. The detection mechanism was based on a change in charge transfer resistance following an interaction between the immobilised detection probe and the target DNA. The limits of detection for the *P. malariae* and *P. ovale* biosensors were 61.7 ± 1.2 aM and 20.7 ± 1.1 aM, respectively. More importantly, the diagnostic performance of the biosensors were compared to qPCR assays using purified genomic DNA and whole blood lysates. Remarkably, all the qPCR-positive purified genomic DNA samples were correctly identified by the biosensors indicating a sensitivity of 100% for each of the species-specific biosensors. However, the sensitivities using whole blood lysates were 66.7% and 75.0% for *P. malariae* and *P. ovale* biosensors, respectively. The specificities of the biosensors under different conditions ranged from 66.7% to 100.0%. The turnaround time was within 30 minutes which is comparable to the readout time for current POC malaria diagnostic tools. This work demonstrates a significant step towards the development of accurate and rapid species-specific toolkits for POC diagnosis of malaria.

0888

EVALUATION OF AN ULTRASENSITIVE HRP2-BASED RAPID DIAGNOSTIC TEST FOR DETECTION OF ASYMPTOMATIC *PLASMODIUM FALCIPARUM* PARASITEMIA AMONG CHILDREN IN WESTERN KENYA

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Accurate detection of asymptomatic malaria parasitemia in children living in high transmission areas is important for malaria control and reduction programs that employ screen-and-treat surveillance strategies. Ultrasensitive rapid diagnostic tests (us-RDTs) have demonstrated low limits of detection in laboratory settings and increased detection of parasitemia in symptomatic individuals. In this study the performance of the NxTek™ Eliminate Malaria P.f test was compared with traditional microscopy and quantitative nucleic acid sequence-based amplification (NASBA) methods of detection for *Plasmodium falciparum* (*Pf*) parasitemia among asymptomatic children aged 7-14 years living in an area of high malaria transmission intensity in western Kenya. In October 2020, 240 healthy children were screened for the presence of *Pf* parasitemia, with 120 children randomly selected to participate in a follow-up visit at 6-10 weeks. Sensitivity, specificity, and predictive values were calculated for microscopy and the us-RDT using NASBA as the gold standard. Parasite density distributions were compared to determine the effectiveness of the us-RDT at low parasite densities. The us-RDT detected significantly more *Pf* infections than microscopy (42.5% vs. 32.2%, P=0.002). The positive predictive value was higher for microscopy (92.2%) than for us-RDT (82.4%). False-negative rates were high for both microscopy and us-RDT, with negative predictive values of 53.7% and 54.6%, respectively. While us-RDT detected significantly more overall asymptomatic infections than microscopy, the density distribution of detectable infections did not differ

(P=0.21), and NASBA detected significantly more low-density infections than either field methods (P<0.001, for both comparisons). Even if the detectable parasite density distributions in our study did not significantly differ from microscopy, the additional sensitivity of the us-RDT resulted in more identified asymptomatic infections in this important group of the population and makes the use of the us-RDT advisable compared to other currently available malaria field detection methods.

0889

DETECTION OF *PLASMODIUM FALCIPARUM* FROM MIXED INFECTION SAMPLES COLLECTED FROM PREGNANT WOMEN FROM GHANA VIA LOOPAMP MALARIA PAN/PF

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In sub-Saharan Africa, a substantial percentage of the population is exposed to parasitic diseases such as malaria caused by *Plasmodium falciparum* and soil-transmitted helminth (STH) infection. Women who are pregnant in malaria-endemic regions are more likely to become infected with *Plasmodium falciparum* during pregnancy. Significantly women with STH infection are five times more likely to have malaria infection. Some consequences off such co-infection include intrauterine growth retardation, poor birth weight, preterm delivery, neonatal mortality, and infant death. However, few studies have examined the rate of co-infection of malaria with specific species, and STH during pregnancy, and none are conducted in Ghana. We have addressed this issue by detecting *Plasmodium* genus (all the species causing human malaria) and *P. falciparum* species from a single co-infected filtered urine sample collected from 100 pregnant women from two districts of Ghana using a highly sensitive and specific test called Loopamp malaria PAN/Pf. The purpose of the Loopamp Malaria PAN kit was to detect the *Plasmodium* genus and then to detect *P. falciparum* from positives by using LoopAmp Malaria Pf kit. 50 samples each were tested from Adidome and Battor district of Ghana. In Adidome district 47 (94%) individuals were tested positive for *Plasmodium* genus with only 39 (83%) tested positive for *P. falciparum*. Whereas, in Battor district 31 individuals (62%) were tested positive for *Plasmodium* genus with only 19 (61%) individuals tested positive for *P. falciparum.* Adidome district had a predominant *P. falciparum* infection and both districts likely had other *Plasmodium* spp. infections. This study highlights the successful detection of malaria genus- and species-specific DNA from a single mixed infection urine sample using Loopamp Malaria PAN and Pf kit. The results will be utilized as a starting point for future research aiming at gathering nationally representative data in Ghana on the prevalence of coinfection for the vulnerable pregnant women population.

0890

FALSE-POSITIVE AND FALSE-NEGATIVE HRP2-BASED MALARIA RAPID DIAGNOSTIC TEST RESULTS AMONG ASYMPTOMATIC CHILDREN AND ADULTS IN COASTAL TANZANIA

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Rapid diagnostic tests (RDTs) that detect histidine-rich protein 2 (HRP2) remain the mainstay of falciparum malaria diagnosis in Sub-Saharan Africa and are used widely for surveillance, but false- positive and negative results do occur. From 2018-2021, as part of a study of the asymptomatic malaria reservoir in rural Bagamoyo district, Tanzania, we screened 5704 children and adults >5 years of age for malaria using an HRP2-mRDT (SD Bioline), microscopy, and 18S real-time PCR (limit of detection 1 parasite/ul). Screening took place at schools and among those visiting clinic for purposes other than malaria. Among those screened, 30% (1,727) were positive for *P. falciparum* by any diagnostic (RDT, microscopy, PCR), and 37% (637) of these were RDT-positive. 13% of RDT-positive (82/637) were negative by both microscopy and PCR, suggesting false positivity due to HRP2 persistence. Children were overrepresented among those with suspected false-positive RDTs (56% vs 43%, p =0.02). Among those who tested RDT-negative but PCR-positive (RDT-/PCR+), the majority were attributable to low density infection (92% had <100p/µL by PCR). We further evaluated RDT-/PCR+ samples with >100p/µL by PCR or microscopy (n=72 samples out of 92 identified) for evidence of *hrp2* deletion using a 1) multiplex real-time PCR assay targeting *pfldh*, *hrp2*, *hrp3*, and human beta tubulin genes and a 2) multiplex bead-based immunoassay targeting parasite LDH, aldolase, and HRP2. Up to half of samples did not have sufficient parasite material for reliable deletion assessment (a non-HRP2 parasite gene (*pfldh*) or antigen (*pLDH or aldolase)* was not detected). Among samples with sufficient parasite material, 13/34 (38%) had evidence of *hrp2/3*-deletion by PCR (5 *hrp2-/3+*, 3 *hrp2-/3-*, and 5 with mixed infections by *hrp2-* and *hrp2+* strains) and 16/48 (33%) had evidence of deletion by immunoassay, while only 3/23 (13%) were identified as candidate deletions by both assays. In this area of low to moderate malaria transmission, false-positive RDTs among asymptomatic persons are common (13%), but false-negative RDTs due to *hrp2* deletion (rather than low density infection) remain rare (<1%).

0891

REASONS FOR LOW LEVELS OF MALARIA DIAGNOSTIC TESTING AMONG PRIVATE SECTOR HEALTH PROVIDERS IN MYANMAR: RESULTS FROM QUALITATIVE INTERVIEWS WITH SUN QUALITY HEALTH(SQH) GENERAL PRACTITIONERS

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Myanmar has made significant progress in reducing malaria morbidity and mortality over the past decade and aims for elimination by 2030. TheGreater Mekong Sub-Region Elimination of Malaria Surveillance project has supported 397 private SUN Quality Health(SQH) general practitionerdoctors to test, treat and report malaria cases since 2015. Their levels of diagnostic testing became low and 82% and 70% did not meet thetesting target of 5 per month in 2020 and 2021 respectively. We conducted a qualitative study to understand the reasons for low levels of testingand awareness of Myanmar's malaria elimination progress. Twenty in-depth interviews were conducted with SQH providers in December 2021,selected by criterion sampling. Interviews took place by phone, were recorded and transcribed verbatim, and coded using Atlas. ti 7.0. We useddeductive content analysis to define themes and group findings. SQH providers were aware of malaria elimination goals. They perceivedthemselves to key players, offering detection, timely treatment and surveillance for patients seeking treatment outside the public sector. Providers used their clinical experience and patients' history to differentiate malaria cases from other diseases. Most commonly reported criteriafor conducting diagnostic testing for cases were having high or intermittent fever, multiple malaria symptoms, travel history from malaria area,and less common ones were no response to antibiotics and for forest related workers. Declining malaria cases, the COVID-19 pandemic andrecent political crisis were also frequently cited as barriers to consistent testing. A few reported prescription of anti-malarials without any testingif the symptoms were resembled malaria and initial treatment failed. SQH providers with low levels of malaria testing were aware of Myanmar'selimination goal but universal testing of all fever cases seemed a challenge. A provider behavior change package with stronger technical supportand feedback for assisting providers in diagnostic decision making together with guidance on trusting test-driven results for treatment is neededin this particular setting.

0892

ACTIVE CASE DETECTION AND TREATMENT OF MALARIA IN PREGNANCY USING LAMP TECHNOLOGY (LAMPREG): A PRAGMATIC RANDOMIZED DIAGNOSTIC OUTCOMES TRIAL - AN INTERIM ANALYSIS

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Thirty-three million pregnant women are at risk of Malaria in Pregnancy (MiP) each year. MiP resulted in 822,000 low-birthweight (LBW) newborns in 2019. Diagnosis of MiP is challenging due to low parasitemia and asymptomatic status. This study aims to evaluate the clinical impact of active MiP diagnosis using a molecular method for the detection of Plasmodium DNA by loop-mediated isothermal amplification (LAMP) compared to microscopy and antigenic rapid diagnostic tests (RDT) during antenatal care (ANC) in Ethiopia where no chemoprophylaxis is used. A pragmatic randomized diagnostic outcomes trial is being conducted at three rural hospitals and five health centres in moderate to high transmission areas. Women (target n= 2583) are randomized to either the standard of care (SOC-arm, 1/3) or the enhanced cased detection arm (LAMP-arm, 2/3) at their first ANC visit. Malaria diagnosis is performed by microscopy in symptomatic patients (SOC) or using Malaria-LAMP (LoopampTM, Human Diagnostics, Wiesbaden, Germany), microscopy, and RDT. Treatment of women positive for malaria was according to the Ethiopian national guidelines. In the interim analysis, 1,388 women were enrolled, 550 in the SOC-arm and 788 in the LAMP-arm. At inclusion, there were no significant differences in terms of maternal age (p=0.052), gestational age (p=0.218), or hemoglobin level (p=0.155). Malaria detection during ANC was superior using active LAMP detection with 56 positive (7.3%, n=37 Pf, n=13 Pv and n=5 mixed infections), compared to 13 (1.7%) with RDTs. Eighty-eight women were followed until delivery to date. The average newborn weight was 47g higher in the LAMP-arm (3,011g vs. 3,058g, p=0.673). The proportion of LBW newborns was 11.5% (SOC-arm) and 9.7% (LAMP-arm) (p=0.792). Prematurity was 15.4% in SOC versus 9.6% LAMP (p=0.473), while newborn anemia was 7.7% in SOC versus 4.8% in LAMP (p=0.598).

0893

DISCOVERY AND STRUCTURAL OPTIMIZATION OF TAMBJAMINES AS NOVEL MULTIPLE-STAGE ANTIMALARIALS

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Malaria is a global infectious disease caused by *Plasmodium* parasites, among which *Plasmodium falciparum* is the most dangerous one, with the highest rate of complications and mortality. The impact of malaria is staggering. Each year, malaria causes about 200 million clinical cases and claims nearly half a million lives, mostly children under the age of five and pregnant women. With increasing multi-drug resistance, absence of a clinically effective vaccine, and the spread of insecticide-resistant vectors, there is an urgent and continuous need for novel, affordable, effective, and safe drugs for prevention and treatment of malaria infection. Over the past few years, our research has focused on the discovery and development of novel antimalarials from the natural sources and we have developed tambjamine natural products as novel antimalarials that are effective against multiple life-cycle stages of the malaria parasite. We present the structural optimization and structure-activity relationships of the multiple-stage active novel tambjamine chemotype.

0894

SECOND-GENERATION NOVEL LIVER STAGE ACTIVE ANTIMALARIALS

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Malaria remains one of the deadliest diseases in the world today, as it has been so for thousands of years. The demoralizing impact of the disease extends beyond the annual body count to effects on family and social structure, on sustained poverty in endemic areas, and on creating untold suffering for nearly half of the world's population. The situation is worsening due to the emergence and spread of strains of Plasmodium parasites that harbor resistance to multiple drugs, including the front-line antimalarial artemisinin-based combination therapy. If the global effort to eradicate malaria is to be successful and sustainable, both prevention and treatment must address the gaps and weaknesses in the armamentarium of available therapies. Ongoing needs include affordability, safety in the most vulnerable patients, single-dose treatment, aptitude to kill liver stage parasites with relapses prevention, low susceptibility to drug resistance, and ability to block transmission. We have developed a novel antimalarial acridone chemotype with dual stage efficacy against both liver stage and blood stage malaria, as well as single-dose cure ability and potential to prevent relapsing infection. Our novel acridone chemotype represents a broad-spectrum approach with potential to vanquish the aforementioned challenges.

0895

SAFETY AND TOLERABILITY OF ARTEMETHER-LUMEFANTRINE + ATOVAQUONE-PROGUANIL TRI-THERAPY FOR TREATMENT OF UNCOMPLICATED MALARIA IN ADULTS AND ADOLESCENT IN GABON- ASAAP PROJECT - PILOT STUDY

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Malaria is a lethal parasitic disease with an estimated 241 million cases occurring in 2020, resulting in 627000 deaths. Current first-line treatment for malaria - Artemisinin-based Combination Therapies (ACTs)- has demonstrated reduced efficacy in South East Asia, with evidence now showing spread to Sub-Saharan Africa. A strategy to increase the lifespan of existing ACTs in Africa is to add a second partner drug, making a triple-ACT (T-ACT) that further limits susceptibility to resistance. The ASAAP project consists of two clinical trials aiming at evaluating

the efficacy, safety tolerability, and pharmacokinetics of Artemether-lumefantrine (AL) joint with Atovaquone-Proguanil (AP) as T-ACT. Here, we present the preliminary results of the first clinical trial. It was a Phase IIb, double-blind, randomized, placebo-controlled study in a semi-immune population in Lambaréné, Gabon. Adults and adolescents aged ≥15 years with uncomplicated *Plasmodium falciparum* malaria were enrolled. 60 Participants were randomly assigned 2:1; the intervention group (40) received AL twice daily + AP once daily over three consecutive days and the control group (20) received AL twice daily + placebo once daily over three days. Subjects had follow-up visits until day 42. 85 patients with an overall median age of 21 years (IQR:15-18) were screened for eligibility and 60 were randomized. The majority of the screening failures were due to low parasite density and hyperbilirubinemia. Five of the randomized participants vomited after drug administration. 59 subjects completed study visits, with one subject lost to follow-up on day 21. 47 (78%) participants experienced at least one adverse event, all were considered mild to moderate. One subject experienced a serious adverse event unrelated to the study medication. Preliminary findings suggest good safety and tolerability in both arms. This is favorable for the continuation of investigation in younger children (≤5yrs) to evaluate efficacy and safety in the target group which is most vulnerable to malaria.

0896

ARITHMETIC AND GEOMETRIC MEANS FOR *PLASMODIUM FALCIPARUM* QPCR AT LOWER PARASITE DENSITIES

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In controlled human malaria infection (CHMI) studies convention dictates that each quantitative polymerase chain reaction (qPCR) samples undergo a single DNA extraction followed by triplicate testing from which a representative value, typically a geometric mean, is calculated to estimate the true parasite count. CHMI studies assessing pre-erythrocytic vaccines and prophylactic drugs often employ sub-microscopic qPCR cut offs to determine effects on liver stage parasites (parasite count at first positivity) and as triggers for anti-malarial rescue therapy. At low qPCR values variation is likely to have a disproportionate effect. In CHMI qPCR repeats often contain undetectable values alongside low-level positive qPCR counts, raising the question of how best to calculate a final representative value; representative value: a geometric mean (which excludes zero counts from the denominator) or an arithmetic mean. Two healthy adult, malaria-naïve volunteers were inoculated with 3,200 cryopreserved *Plasmodium falciparum* sporozoites on Day 1 and were subject to daily monitoring from Day 7 onwards using 18S-qPCR. Volunteers were rescued upon reaching 18S-qPCR threshold ≥250 parasites/mL. Volunteers continued daily testing until two consecutive negative 18S-qPCRs. Blood samples underwent two DNA extractions followed by four technical repeats. Volunteer 1 and 2 reached the threshold for treatment on Days 13 and 14 respectively. Volunteer 1 exited the study on Day 17 and volunteer 2 on Day 24. Altering the method of mean qPCR calculation altered the parasite count at first positivity and the parasite growth and decay curves, but not the time to first qPCR positivity, treatment threshold or exit from study. There was no significant difference in qPCR results between the two DNA extraction groups. A comparison of analysis methods, using the actual data, will be presented to assess the impact of reducing the number of replicates and to assess the different summary statistics used to track parasite dynamics during follow-up.

0897

PREVENTION OF MALARIA IN PREGNANT WOMEN WITH HIV (PREMISE): A RANDOMIZED, DOUBLE-MASKED, PLACEBO-CONTROLLED TRIAL OF TRIMETHOPRIM-SULFAMETHOXAZOLE AND AZITHROMYCIN

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This phase IIB randomized clinical trial was designed to test the efficacy of a novel regimen to prevent malaria in pregnant women living with HIV in Cameroon, where Plasmodium falciparum is holoendemic and the HIV prevalence among pregnant women is 5.7%. Pregnant women in prenatal care with confirmed HIV, gestational age < 28 weeks and singleton pregnancies were randomized in a placebo-controlled manner to a novel regimen of monthly azithromycin (AZ) 1 gram daily for 3 days and daily trimethoprim-sulfamethoxazole (TMPS) or the standard regimen of daily TMPS alone through delivery. The main outcome of interest was the proportion of women with P falciparum parasitemia by microscopy or PCR at the time of delivery. Composite adverse birth outcomes included preterm delivery, low birthweight, fetal demise, congenital anomaly, and neonatal death within 28 days. A total of 308 women were enrolled at three hospital facilities in Cameroon between March 2018 and August 2020 with follow up completed in January 2021. A total of 155 women were randomized to the intervention arm and 153 women were randomized to the standard of care arm. A total of 260 women (84%) had delivery samples collected. Both groups had similar characteristics at baseline with median age 32 years, maternal education (71% secondary school or university), median HIV diagnosis 3 years prior and 94% reported excellent adherence to antiretroviral therapy. Median CD4 count was 473 cells/mm3 (IQR 326-663). At baseline, 3.2% had malaria infection according to microscopy and 73.4% had an insecticide treated bednet at home. There was no difference in the proportion of women with malaria at delivery in the active or standard arm (PCR positive 6.4% vs 4.4% [p=0.47] or microscopy 5.7% vs 5.1% [p=0.84]. Adverse birth outcomes were lower in the active AZ arm, but the difference was not significant (preterm delivery 5% vs 10.3% [p=0.1], low birthweight 2.8% vs 5.1% [p=0.34], composite adverse outcome 8.4% vs 13.1% [p=0.19]. In conclusion, the addition of monthly azithromycin to standard daily TMPS prophylaxis for malaria in pregnant women living with HIV in Cameroon did not reduce the rate of parasitemia at delivery.

0898

MULTI-DRUG COMBINATION-THERAPIES TO PREVENT THE DEVELOPMENT OF DRUG RESISTANCE. PHASE II CONTROLLED CLINICAL TRIAL ASSESSING CANDIDATE REGIMENS OF MULTIPLE-ANTIMALARIAL COMBINATIONS FOR THE TREATMENT OF UNCOMPLICATED MALARIA IN AFRICA. THE MULTIMAL-STUDY

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Artemisinin combination therapy (ACT) is the combination of an artemisinin derivative with a partner drug and constitutes to date the most successful treatment of malaria. To combat development of artemisinin

resistance and partner drug resistance an increasing number of studies investigate triple or quadruple antimalarial combinations to reduce the emergence and spread of drug resistance. The MultiMal study assessed the safety and efficacy of the two antimalarial combination treatments of artesunate-pyronaridine-atovaquone/proguanil (APAP) and artesunate-fosmidomycin-clindamycin (AFC) in comparison to standard treatment with artesunate- pyronaridine (AP). Open-label randomised controlled trial conducted in Lambaréné, Gabon and Kumasi, Ghana. Recruitment of malaria patients in three age groups was performed in a step-down procedure: First, 20 semi-immune patients aged 18-65 years, then 40 patients aged 11-17 years and finally 40 patients aged 6 months to 10 years. Weight-adjusted oral doses were administered under direct supervision over three days once daily for AP and APAP regimens and twice daily for AFC regimen. Participants were followed up over a 42-day period. Adverse events were ascertained over the whole observation period and adequate clinical and parasitological response (ACPR) was ascertained on day 28 and day 42 of follow-up as efficacy measure. A total of 100 participants were recruited and followed-up. Treatment combinations were well tolerated and safe. Efficacy results were analyzed according to per-protocol and intention to treat populations with genotyping for correction of reinfection. During the congress detailed efficacy and safety data, as well as, pharmacokinetic data will be presented.

0899

ASSESSMENT OF THE TRANSMISSION BLOCKING ACTIVITY OF ANTIMALARIAL COMPOUNDS BY MEMBRANE FEEDING ASSAYS USING WEST AFRICAN PATIENT DERIVED *PLASMODIUM FALCIPARUM* GAMETOCYTES

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Antimalarial drugs that can block the transmission of *Plasmodium* gametocytes to mosquito vectors would be highly beneficial for malaria elimination efforts. Unfortunately, there are few known transmission-blocking antimalarial drugs available. Identifying transmission blocking drugs currently relies on evaluation with laboratory parasite strains but would benefit from a testing pipeline with field isolates. The aim of this study was to establish novel assays and evaluate the transmission blocking activity of a set of marketed and experimental compounds against *P. falciparum* gametocyte field isolates. The study was conducted in Burkina Faso in an area of intense, seasonal malaria transmission zone of Saponé. Venous blood samples from naturally infected *Plasmodium falciparum* gametocytes carriers were exposed for 24 hours to eleven different compounds with varying mechanisms of action before being offered to *Anopheles gambiae* lab strain by direct membrane feeding assays (DMFA). Then, mosquito midguts were dissected at 7-8 days post feeding for oocyst quantification. Overnight incubation at 37°C of gametocytes in RPMI was shown to retain parasite viability, demonstrated by successful mosquito infections with mosquito infection rate ranging from 10 to 75%. For the compounds tested, the transmission-blocking effects were well in line with results from a laboratory strain NF54, with the exception of dihydroartemisinin, that was not active against field isolates. In conclusion, this study allowed the establishment of a protocol for the use of field *P. falciparum gametocyte* isolates to test new antimalarial compounds. With this limited set of compounds, we see that field isolates and lab strains could respond differently to the antimalarial products making it necessary to include field isolates in the pipeline for evaluation of new antimalarial drugs.

0900

EVALUATING ANTIMALARIALS OPTIONS FOR RADICAL CURE PRE-VACCINATION DURING FUTURE MALARIA VACCINE FIELD EFFICACY TRIALS IN CHILDREN AGED 1.5 - 12 YEARS LIVING IN HIGH AND SEASONAL MALARIA TRANSMISSION AREA OF BANFORA, BURKINA FASO

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In malaria vaccine clinical trials, immune responses post vaccination could be impaired due to the immunosuppression caused by concurrent *Plamodium falciparum* infection. This has direct impact on the vaccine protective efficacy being evaluated. Therefore, clearance of parasites prior to vaccination is being considered. There is a general consensus that drugs with good safety and efficacy profile, and short-lasting post treatment prophylaxis period should be used. We have evaluated Artesunate (AS) as monotherapy and Dihydro-artemisinin-Piperaquine (DHAPQ) in children, in preparation for use in planned field efficacy trial of malaria vaccine candidates.A cohort of children aged 1.5 to 12 years living in the Banfora Health District area, was recruited. They were randomly assigned to receive supervised curative doses of AS monotherapy for 7 days, or DHAPQ for 3 days. A PCR was performed 21 days later post treatment, to confirm clearance of infections, and enroll only those with negative PCR in the study cohort for a 6 months longitudinal follow-up period. The cohort children were actively visited fortnightly to collect blood samples for *P. falciparum* detection by microscopy and by PCR. A passive surveillance was also in place at the local health facility to record incident malaria episodes occurring between 2 active visits.A total of 513 children received the treatment. Among them, 458 (89.3%) were free of *Plasmodium falciparum* malaria infection at day 21; 87.3% (226/259) in the AS group vs 91.3% (232/254) in the DHAPQ group (P=0.053).The mean time to the first malaria infection by microscopy was 20.3 weeks in the DHAPQ arm and 16.3 weeks in the AS arm (P<0.0001). Incidence rates of clinical malaria episodes were 6.0 episodes/1000 person-time at risk (95%CI 4.2-8.7) and 3.3 episodes/1000 person-time at risk (95% CI 2.0-5.3) during the follow- up period respectively in the AS and DHAPQ arm.Our findings suggest that although both drugs are effective in clearing *P. falciparum* infections, AS is likely to yield no greater than minimal interference with vaccine efficacy endpoints evaluation and could therefore be considered for use.

0901

OVERALL AND GENDER-SPECIFIC EFFECTS OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA WITH ARTEMISININ-BASED COMBINATION THERAPIES AMONG SCHOOLCHILDREN IN MALI: A THREE-GROUP OPEN LABEL RANDOMIZED CONTROLLED TRIAL

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Intermittent preventive treatment of malaria among schoolchildren (IPTsc) reduces clinical malaria, asymptomatic parasitemia, and anemia. IPTsc effects by gender have not been studied longitudinally. We investigated overall IPTsc efficacy and conducted a secondary analysis to explore gender-specific differences We enrolled schoolchildren aged 6-13 years in an open-label, rolling-cohort randomized controlled trial between September 2007 and February 2013 in Kolle, Mali. Annually, schoolchildren received two full-treatment courses of sulfadoxine-pyrimethamine (SP) plus artesunate, or amodiaquine (AQ) plus artesunate, or no malaria treatment as control. We used mixed-effects generalized linear models to estimate differences in treatment outcomes across groups with interaction terms to explore gender-specific differences associated with *Plasmodium falciparum* infection, hemoglobin, and grade-point averages (GPA) based on standardized testing. Overall, 305 students contributed 4,564 observations. Compared to the control, SP plus artesunate and AQ plus artesunate reduced the odds of *P. falciparum* infection (OR 0.33, 95% CI 0.26–0.43; OR 0.46, 95% CI 0.36–0.59). We found strong evidence of increased mean hemoglobin concentrations (g/dL) in the SP plus artesunate group versus control (difference +0.37, 95% CI 0.13–0.58). Collectively, schoolchildren given AQ plus artesunate had higher mean GPA (difference +0.36, 95% CI 0.02–0.69) relative to control. Schoolgirls, compared to schoolboys, given SP plus artesunate had greater improvement in GPA (+0.50, 95% CI -0.02–1.02 versus -0.27 95% CI -0.71–0.16); interaction p=0.048, respectively. IPTsc decreases *P. falciparum* infections in schoolchildren. Treatment regimens that include longer-acting drugs may be more effective at decreasing malaria-related anemia and improving educational outcomes as observed among girls in this setting.

0902

QUANTIFICATION OF TAFENOQUINE AND 5,6-ORTHOQUINONE TAFENOQUINE METABOLITE BY UHPLC-MS/MS IN BLOOD, PLASMA AND URINE, AND ITS APPLICATION TO A PHARMACOKINETIC STUDY

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We have developed and validated an ultra-high-performance liquid chromatography mass spectrometry (UHPLC-MS/MS) method for the quantification of the new 8-aminoquinoline antimalarial tafenoquine (TQ) and the 5,6-orthoquinone tafenoquine metabolite (5,6-TQ) in human blood, plasma and urine. Biological samples were precipitated with acetonitrile, and chromatography was performed using a Waters Atlantis T3 column with a gradient of 0.1% formic acid and acetonitrile at a flow rate of 0.5 mL per minute for blood and plasma, and with methanol containing 0.1% formic acid replacing acetonitrile for urine analysis. The calibration range for TQ and 5,6-TQ in plasma was 1 to 1200 ng/mL, and in urine was 10 to 1000 ng/mL. Whole blood calibration range for TQ was 1 to 1200 ng/mL. Whole blood could not be validated for 5,6-TQ. The inter-assay precision (coefficient of variation %) was 6.5 % for TQ in blood, and was 4.4 % for TQ and 4.0 % for 5,6-TQ at 1 ng/mL in plasma (n=8). For urine, the inter-assay precision (CV %) was 2.3 % for TQ and 4.5 % for 5,6-TQ at 10 ng/mL (n=7). Blood, plasma and urine concentration data of TQ and 5,6-TQ obtained from participants in a human malaria challenge study who received a single oral dose of 200 mg TQ will be presented together with pharmacokinetic and stability data for all 3 matrices. The accurate low-level quantification of TQ and 5,6-TQ allows for further investigations into TQ metabolism as well as optimising TQ's application for radical cure, prophylaxis and malaria elimination.

0903

THE IMPORTANCE OF CONTEXT: UNDERSTANDING THE INFLUENCE OF COVID-19 ON COMMUNITY ENGAGEMENT FOR A CLINICAL TRIAL ASSESSING THE IMPACT OF IVERMECTIN MASS DRUG ADMINISTRATION ON THE PREVALENCE OF MALARIA IN MOPEIA, MOZAMBIQUE

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COVID-19 has had an enormous global impact on routine daily activities and on research. This presentation will describe local understandings and responses to COVID-19 and to effects on local engagement with research in Mopeia district, Mozambique. The focus is on the effects of the pandemic on community engagement activities for the BOHEMIA (Broad One Health Endoctecide-based Malaria Intervention in Africa) consortium's project evaluating the impact of mass drug administration (MDA) with ivermectin to humans and livestock at the start of the malaria transmission season. Formative social science research is essential to inform appropriate and effective community engagement strategies for clinical trials. This is particularly true in trials of mass drug administration (MDA) for malaria control which require high uptake among the target populations. Recent trials of malaria MDA have found that engagement and drug delivery strategies based on understanding the local social, political, and cultural context, are key to ensuring high uptake. The formative social science research for the BOHEMIA trial was undertaken in Mopeia from July to October 2021 The qualitative, exploratory study used an ethnographic approach with social science researchers living in 10 of the trial communities prior to the start of the trial, collecting data through non-participant observations, in-depth interviews, and focus group discussions. The approach allowed for rich descriptions of the context and identification of local social structures and resources for engagement. The original focus of data collection was on perceptions and practices on malaria and health maintenance. However, it became clear that COVID-19 had created an environment in which social norms were being challenged and trust in health institutions was contested. International and local rumors were fueling debates around the purpose of research and had the potential to create barriers to participation. Key community concerns and the broader implications for community engagement in research, particularly during the pandemic, will be presented.

0904

CONTRIBUTING TO MALARIA ELIMINATION: LESSONS LEARNED FROM DELIVERING *PLASMODIUM VIVAX* RADICAL CURE TO HARD-TO-REACH COMMUNITIES IN FORESTED BORDER AREAS IN NORTHERN CAMBODIA

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Remaining malaria in Cambodia is concentrated in forested border areas and in hard-to-reach mobile and migrant populations. Since 2018, mobile malaria workers (MMWs) have been working at mobile malaria posts within and around forests and conducting outreach activities to even more remote areas to detect cases among these populations in northern Cambodia. While there was a steady, nation-wide decrease in *falciparum* malaria, *vivax* malaria has become more prominent. Primaquine radical cure prevents periodic *vivax* malaria relapses but requires prior testing for glucose-6-phosphate dehydrogenase (G6PD)-deficiency to ensure safe drug administration. National guidelines in Cambodia have been recommending primaquine radical cure since March 2021. This poses unique challenges as G6PD tests and primaquine are only delivered at

health facility (HF) level and not by MMWs. From March to December 2021, MMWs in six provinces along the Thailand, Laos and Vietnam borders tested 61,595 people for malaria, detecting 1 *mixed* and 219 *vivax* cases. 53% of eligible cases could not be referred to HFs for radical cure due to lack of transport or refusal. 3,944 health education sessions were held at target destinations, helping to raise awareness for radical cure and identify community-led solutions to low referral rates. This case study will outline the lessons learned from rolling out radical cure and community-led solutions to be implemented in the coming months: 1) Making the community centre of the solution: community dialogues at *vivax* hotspots will be increased to maintain high awareness of radical cure, and 2) Reaching people where they cannot reach you: new approaches to tackle low referral rates will include financial support to patients for transport to HFs; nurses from HFs will visit *vivax* hotspots to test and treat patients on site. Results from the implementation period will be included in this session. Lessons learned from rolling out *vivax* radical cure to hard-to-reach communities are relevant to many programmes in the Greater Mekong Subregion and other settings as elimination efforts need to start addressing the remaining *vivax* malaria burden.

0905

ACCEPTABILITY OF MASS DRUG ADMINISTRATION WITH DIHYDROARTEMISININ-PIPERAQUINE AND SINGLE LOW-DOSE PRIMAQUINE TO REDUCE MALARIA IN MODERATE-LOW TRANSMISSION SETTING IN SENEGAL

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Time-limited mass drug administration (MDA) is a promising strategy to accelerate moderate-to-low malaria transmission settings to elimination. A pilot MDA trial has been implemented in the Tambacounda Health District where, despite several malaria control strategies deployed by the Senegalese National Malaria Control Program, malaria incidence remains moderate-to-low (50–200 cases per 1000). A qualitative survey was carried out to determine the acceptability, desirability, adherence, and perceived risks and benefits of MDA. A total of 190 in-depth interviews and 10 focus groups were conducted, targeting health workers, drug distributors, and community members who received the MDA intervention and those who refused to participate. To understand the facilitating factors and operational challenges of MDA, 50 observational sessions were held during the staff training sessions, informed consent form administration, and drug delivery as well as workshops with key stakeholders including nurses, doctors, and community health workers. Four major themes emerged that potentially facilitated the success of the MDA campaign: (1) active communication and community engagement activities of the MDA campaign, (2) frequent refresher trainings and building motivation among health workers, and (3) utilizing experiences and lessons learned from previous mass campaigns, and (4) at the community level, the importance of understanding how socio-economic and cultural factors (weekly markets, traditional and religious ceremonies) influence coverage and community engagement activities. During the campaign, frequent absences (13-20%) and overreporting of illnesses (5-7%) were noted as possible drug refusal strategies that need to be considered in future MDA implementation. Some refusals (1-2%) may have been motivated by the fear of COVID-19, made worse by rumors circulating in the community through social media during the pandemic. Thus, rolling out a campaign amid a pandemic necessitates rigorous training and active community engagement to address the growing influence of social media in informing the public.

0906

OPERATIONAL CHALLENGES AND LESSONS LEARNT DURING MASS DRUG ADMINISTRATION WITH DIHYDROARTEMISININ-PIPERAQUINE AND PRIMAQUINE TO REDUCE MALARIA BURDEN IN RURAL SENEGAL

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Senegal is piloting mass drug administration (MDA) as a tool to accelerate toward malaria elimination in areas with low-to-moderate transmission. In 2021, a cluster randomized controlled trial was conducted in 60 villages of Tambacounda District where three rounds of MDA with dihydroartemisinin-piperaquine and single low-dose primaquine were administered to eligible individuals 3 months of age and compared to three rounds of seasonal malaria chemoprevention (SMC, sulfadoxine-pyrimethamine+amodiaquine administered to children 3 months–10 years of age). MDA and SMC were delivered through community distributors and coverage data were collected during implementation. Data on operational challenges and success factors were collected through focus group discussions. During MDA implementation, several operational challenges were noted. First, prioritization of other public health interventions (e.g., Covid-19 response, yellow fever immunizations) caused delays in MDA implementation. Frequent population movement was another challenge; 13%–20% of the target population were absent during MDA rounds. Third, logistical challenges in accessing remote villages during the rainy season hampered efficient delivery of MDA. Despite these challenges, MDA coverage was high; distributional coverage ranged from 78%–91% across the 3 rounds. Several factors led to this success, including commitment of local administrative and health authorities, strong community engagement through effective communication, and training and supervision activities throughout MDA rounds. Successful MDA campaigns during health crises and concurrent public health interventions requires careful planning and preparation of activities from all stakeholders, effective communication and buy-in from local leaders and the community, and more rigorous follow-ups to address the impact of population migration.

0907

IMPACT OF THE INNOVATIVE 1,7 - MALARIA REACTIVE COMMUNITY-BASED TESTING AND RESPONSE [1,7 MRCTR] ON MALARIA MORTALITY: AN INTERRUPTED TIME SERIES ANALYSIS

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Several control measures have been made to control Malaria by reducing the disease transmission in Tanzania, however, the country is still burdened by 5% deaths in African countries. As the World Health Organization emphasizes the importance of transforming the malaria surveillance response strategy as a core intervention, through its T3 Test-Treat-Track initiative a 1,7 malaria reactive community-based testing and response strategy is adopted in Tanzania to further reduce the malaria burden to as low as the community level. The 1,7 mRCTR approach was adapted from the '1-3-7' China's model strategy to fit the Tanzania transmission setting. This study implements the application of real-time surveillance data collected in southern-eastern Tanzania to assess the trends and describe changes in mortality and the impact of the community-based test and response during 2016-2021. Individual-level data from patient visits collected from health facilities in Kilwa and Kibiti districts from January 2016 to December 2021 were analyzed. Pre-intervention trends from January 2016 to August 2018 were used to predict the expected trend in the absence of 1,7 mRCTR. Interrupted time series models assessed the mortality before and after this community-based test and response intervention implementation. A total of 735,218 individuals underwent malaria diagnostic testing, and 32% tested positive for malaria. The community-based test and response strategy showed a reduction in mortality by 21% and 17% in Kilwa and Kibiti respectively. The strategy was statistically significant in Kilwa RR=0.16, 95%CI[0.14,018], P=0.00302 and Kibiti RR=0.14, 95%CI[0.12,0.16], P = 0.00504. A rapid decline in the mortality rate is seen during the implementation of the 1,7 mRCTR approach compared to the pre-intervention period through health facility routinely collected data. Scaling up this approach would accelerate malaria elimination efforts.

0908

THE USE OF DATA FOR DECISION MAKING FOR MALARIA CONTROL IN RWANDA

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The use of data to inform decision-making is paramount in the prevention and control of malaria as it can be utilized to optimize combinations of interventions, assess the impact of and gaps in interventions, and respond to outbreaks promptly. Rwanda's health systems reforms have created an enabling environment for an effective malaria control program. However, the fragility of gains against malaria were evident when in 2012, an upsurge of malaria, with a peak in 2016, was observed shortly after the country recorded malaria incidence below 50 per 1000. The country has been an early adopter of novel tools and strategies against malaria, including using routine health facility malaria data to inform the malaria control program's decisions. Various data sources are utilized, such as data from the routine health management information system, entomology sentinel sites, and data from the community health workers (CHWs). For example, insecticide resistance data from entomology sentinel sites as well as malaria incidence data per district guided the deployment of novel vector control interventions: 21 of 30 Rwanda districts, contributing to 89% of the national malaria burden in 2016, had documented mosquito resistance to pyrethroids and were therefore prioritized for indoor residual spraying using a different class of insecticide (12 districts) or new types of long-lasting insecticide-treated nets using a synergist (PBO nets) or dual-active ingredient (IG2 nets) in 9 districts. Malaria data were used to expand community-based case management by CHWs, who now manage around 60% of all malaria cases nationally. The same data were used to secure resources from the Government of Rwanda, the Global Fund, and PMI. With sustained evidence-based interventions, malaria incidence in Rwanda dropped from 409 per 1000 in 2017 to 86 per 1000 in 2021, while malaria cases dropped from 4.8 million to 1.1 million in the same period. Therefore, despite the challenges of obtaining malaria data in a complete, accurate, and timely manner, available data in Rwanda can be used to inform the program's planning and decision-making.

0909

THE EFFECTIVENESS OF MALARIA CAMPS AS PART OF THE DURGAMA ANCHALARE MALARIA NIRAKARAN (DAMAN) PROGRAM IN ODISHA, INDIA: FINDINGS FROM A CLUSTER-ASSIGNED QUASI-EXPERIMENTAL STUDY

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Durgama Anchalare Malaria Nirakaran (DAMaN) is a multi-component malaria control program for hard-to-reach villages in the eastern Indian state, Odisha. The main intervention, Malaria Camps (MCs), includes cycles of mass screening or fever screening, treatment, and intensified vector control measures including long-lasting insecticide-treated net distribution and indoor residual spraying, besides strengthening community awareness by village-level social health activists. We evaluated MC effectiveness using a quasi-experimental cluster-assigned stepped-wedge study with a pretest-posttest control group design in 15 villages (six immediate [Arm A], six delayed [Arm B], and three previous interventions [Arm C]). The primary outcome was *Plasmodium* infection identified by PCR. Participants completed brief surveys and provided a finger-pricked blood for malaria parasite detection by rapid diagnostic test and PCR at baseline (August-November 2019), and three follow-up (FU) visits (January-March 2020; June-September 2020; October-December 2020). Implementation cost data were also collected. There were almost five-fold higher odds for PCR+ infections at baseline in Arm A (adjusted OR [AOR]=5.96, 95% CI=1.04,23.59) but not Arm C vs. Arm B. Across all three arms, the odds of PCR+ infections were 54% lower at FU compared to baseline (95%CI=0.23,0.63). A time x study arm interaction term revealed significantly lower odds of PCR+ *Plasmodium* in Arm A (AOR=0.36, 95%CI=0.17,0.73) but not Arm C vs. Arm B at FU. Costs per MC round ranged between US$3-8 per person, US$4-7 per tested, and US$82-1,614 per treated. These results suggest that the DAMaN MC intervention was associated with reductions in malaria in the study villages and thus is a promising, financially feasible approach for malaria control in rural settings.

0910

PRIORITIES FOR ACHIEVING VIVAX ELIMINATION - A ROADMAP

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The WHO Global Technical Strategy (GTS) aims to achieve malaria elimination in at least 35 countries by 2030. Many countries close to that target are now considering their vivax burden as it becomes the dominant species in their settings. With limited emphasis on elimination of vivax malaria in the GTS, there is a significant gap in our understanding of stakeholders' current priorities to achieve vivax elimination. A Theory of Change framework was used to systematically identify key research and implementation questions that, if left unaddressed, could prevent countries from achieving their 2030 elimination goals. Through online workshops - National Malaria Programs (NMPs) and other stakeholders ranked questions most important for achieving vivax elimination. Once priorities were identified, ongoing activities to address those priorities were mapped to identify remaining key areas of focus required for research and implementation. At the time of submission, 78 participants from 12 Asia Pacific countries in different stages of control, elimination, or prevention of re-establishment of malaria had completed the ranking. Consultations are ongoing, with plans to do similar work in Latin America. Results are categorised into, Research & Development, Implementation Research, Evidence & Policy, Implementation and Financing. To date, key priorities emerging are; safety of short-course primaquine (54% ranked highest), deployment of higher-sensitivity Rapid Diagnostic Tests (54%), assessment of healthworkers capacity to adhere to treatment protocols with current or new vivax radical cure tools (57%), the need for technical support to ensure high quality training and supervision on the use of radical cure tools (68%), the need for better quality stock data (62%) and effective interventions to increase patient adherence (61%). These priorities will form the basis for regional vivax roadmaps. Outlining these gaps for stakeholders to address in the coming 12-24 months is essential to enable NMPs to get to the last kilometre of malaria elimination.

0911

FACTORS EXPLAINING PRONOUNCED VARIATION IN *PLASMODIUM FALCIPARUM* INFECTION PREVALENCE AMONG VILLAGES IN BUSIA COUNTY WESTERN KENYA

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Malaria infection prevalence often varies across small scales. Understanding the causes of this heterogeneity is required to develop better malaria control strategies. In Busia County in western Kenya, we collected finger-prick blood in a cross-sectional survey from 153 individuals each in 20 villages spanning an altitude range of about 300 m. Data on household structure were collected, i.e., roof material, use of window screens, eave gaps open/closed, and kitchen located indoors/outdoors were collected. Eight types of larval habitats (swamp, march, drainage ditch, pond, dam, shallow well, sand pit, river, forest) were mapped within a 100-meter radius around households. Blood samples were screened for *Plasmodium falciparum* by microscopy and *var*ATS qPCR. Overall prevalence was 19.5% by microscopy and 49.8% by qPCR. 2906/3061 (94.9%) of the individuals did not report malaria related clinical symptom at the time of blood collection. Pronounced heterogeneity among villages was observed. By microscopy, prevalence ranged from 7.8-32.7%, and by qPCR from 26.1-70.1%. 61.9% (943/1524) of infections were submicroscopic. Malaria prevalence was substantially higher among individuals living in households located at lower altitude compared with those at higher altitude (59.5% vs. 46.8%, $P < 0.001$). Household structure risk factors included grass-thatched roofing, open eaves and kitchen located indoors. A weak correlation between the number of larval habitats and infection prevalence was observed. Proximity to sugarcane plantations resulted in higher prevalence. In conclusions, pronounced heterogeneity in prevalence among villages (3-fold difference by qPCR) needs to be considered when implementing malaria control interventions. Improved household structures, and better vector control around sugarcane plantations, may help reduce transmission in the region.

0912

THE PUBLIC-PRIVATE SHARE OF USAGE OF EFFECTIVE ANTIMALARIALS IN CHILDREN WITH FEVER, THE GLOBAL ANALYSIS

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An effective health delivery system requires both public and private health sectors responsible for providing patient care adhering to recommended treatment guidelines. Ineffective antimalarials may penetrate the unregulated private sector resulting into poor clinical outcomes and, importantly, slowing down the progress in malaria control. This study assessed the public-private share of artemisinin-based combination therapy (ACT) and non-ACT antimalarial options for treating uncomplicated *plasmodium falciparum* infection in children under 5 years between 2001 - 2022. Utilizing data from 41 (2001-2019) demographic health surveys and malaria indicator surveys, a multinomial-hierarchical model taking four levels: public-ACT, public-nonACT, private-ACT, and private-nonACT was developed to estimate the country-year distribution of the usage. The model was adjusted for treatment-seeking rates, health systems and demographic variables while clustering the countries in the WHO subregions and regions. The country-year covariates for 2020-2022 were used to predict post-survey patterns. Overall, the public sector›s share in malaria services has increased by 24.4% from 2001 (46.7%) to 2022 (61.8%). ACT use has significantly improved within both sectors over time. In 2001, 28.3% of children were administered with ACT within the public sector, while among those who attended the private sector, only 16.4% received this option. In 2022, 79.8% of children treated in the public sector received ACT, and two-thirds (67.2%) in the private sector treated with ACT. The increase is higher in the private (75.6%) than in the public sector (64.5%). There are country and regional variations, with the public sector dominating in the sub-Saharan Africa. In recent years, Nigeria, which carries the highest malaria burden, has been dominated by the private sector, with most children treated with ACT. In contrast, in Democratic Republic of Congo public sector treats most cases but almost a third receive non-ACT despite being not the first-line. These findings are essential for targeted interventions to improve the health system's performance.

0913

THE CHALLENGES IN MALARIA ELIMINATION

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The scaling up of core malaria interventions to prevent onward transmission has led to large reductions in the global malaria burden since 2000. However, malaria cases are on the rise again and progress appears to have stalled. Though significant attention is given to the challenges of resistance (i.e.: drug resistance has emerged and spread in Greater Mekong Sub-region and insecticide resistance has spread rapidly across sub-Saharan Africa), 'residual' malaria is often associated with transmission resulting from outdoor-biting vectors, or by zoophilic/opportunistic mosquitoes (i.e. those mosquitoes feeding primarily on animals). But mosquito behaviors may only be part of the problem, as residual transmission may be driven by (a combination of) sub-optimal intervention coverage, acceptance, and/or usage, drug and insecticide resistance, refractory, resistant and changing vector and human behaviors, lack of, limited access or willingness to use healthcare, as well as governmental policy. Using an interactive poster, we invite you to discuss and rank the challenges that lie ahead.

0914

IMPROVED UNDERSTANDING OF SPATIO-TEMPORAL CHANGES IN MALARIA PREVALENCE AMONG URBAN COMMUNITIES IN FREETOWN SIERRA LEONE: A BASELINE FOR STRATIFIED URBAN MALARIA PROGRAMMING

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Malaria in Sierra Leone is hyperendemic and the third leading cause of childhood mortality. While there is seasonal variation in malaria prevalence, transmission occurs year-round in both urban and rural areas. Sierra Leone has also seen mass urbanization in the past decade where now close to 18% of the population lives within the Western Area Urban district where the capital Freetown is located. This urbanization has caused strain on the urban health care system and systemic poverty among residents of 'informal communities' limits access to effective malaria care and prevention commodities. To help devise stratified strategies to improve access to malaria care in urban areas a baseline 2-stage cluster survey was conducted in four communities, two informal communities (limited land tenure) and two formal communities (higher rate of land tenure) to determine rates of anemia and malaria prevalence in children under 5. Among the four communities, 4212 households were enrolled and questionnaire assessment housing design, construction, land tenure, wealth index as well as access and use ITNs were evaluated. 1125 children U5 were also tested for anemia and malaria prevalence by rapid diagnostic testing for point of care treatment and microscopy was conducted. Malaria RDT positivity was 11.1% informal communities and 10.0% informal communities. There was no statistical significance between community types (p=0.391). The highest prevalence is seen in the age group 36 to 47 months old. Likewise, the prevalence of anemia in the formal settlement (2%) is statistically the same as the one in the informal settlement (1.3%). Prevalence of anemia in children with age and it is highest in the age group 9 to 11 months of age. Additional data collection will continue, increasing the age range of sampled children and taking into account temporal variation. While strategies for improving urban malaria need to be introduced the evidence indicates that those approaches do not need to be further stratified among formal and informal communities.

0915

EPIDEMIOLOGY OF MALARIA IN MEGHALAYA: IMPLICATIONS FOR TRANSMISSION INTERRUPTION IN ENDEMIC SETTINGS

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India has made rapid progress in controlling malaria, and reduced annual incidence by 73% from 2000 to 2019, a decline from ~20 million to ~6 million cases per year. Although comprising 4% of India's population, the northeast region (NER) contributes ~8% of the country's malaria cases. Meghalaya is a hilly, forested state in NER with climate conditions conducive for perennial malaria transmission. Incidence of malaria has precipitously declined in Meghalaya since 2016, potentially due to the introduction of long-lasting insecticidal nets by the National Vector Borne Disease Control Program. To investigate recent malaria patterns, we conducted active case surveillance through community-based, cross-sectional surveys in 31 villages from three districts of Meghalaya (West Jaintia Hills [JH], West Khasi Hills [KH] and South Garo Hills [GH]), selected on the basis of a relatively elevated 2016 annual parasite index. Facility-based passive surveillance was also conducted in four primary health centers (PHC) in the same districts from 2018-2021. A total of 3729 participants were enrolled in the cross-sectional surveys, of whom 3599 (96.5%) provided blood samples for testing; 55 (1.5%) had *Plasmodium* infection detected by RDT or PCR. Infection prevalence was highest in GH (22/902, 2.4%) followed by KH (17/1234, 1.4%) and JH (16/1463, 1.1%); village-level infection prevalence ranged from 0-12.8%. Most infections (34/55, 61.8%) were submicroscopic (RDT negative but PCR positive), and all were *Plasmodium falciparum*. Of the 1062 participants with malaria-like symptoms enrolled in the PHC-based surveillance, 1054 (99.2%) provided blood samples. Of these participants, 46 (4.4%) had *Plasmodium* infection, including 18 (39.2%) with *P. vivax*, 27 (58.7%) with *P. falciparum* and 1 (2.2%) with mixed (*P. vivax* + *P. falciparum*) infection; almost all *P. vivax* infections (18/19, 94.7%) were from JH. The results depict a heterogeneous distribution of *Plasmodium* infection in Meghalaya with a high proportion of asymptomatic carriage. These findings highlight the need for continued surveillance to prevent malaria resurgence in low-transmission settings.

0916

ASSESSING THE UTILITY OF ANTENATAL CARE SURVEILLANCE IN TANZANIA FOR MONITORING COVERAGE OF MALARIA CONTROL INTERVENTIONS

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Estimates of malaria burden and intervention uptake in sub-Saharan Africa are primarily based upon nationally representative household (HH) surveys. However, their expense and infrequency limit their utility for operational action by malaria programs. We assessed whether surveillance of women attending first antenatal care (ANC1), consisting of collecting data on malaria prevalence using rapid diagnostic tests (routine) and coverage of malaria control interventions among women and their HH (March 2020-May 2021), could provide relevant data to guide decision-makers. Malaria prevalence from routine ANC-based surveillance in 39 health facilities (HF) in Geita Region were compared with those in children under 5 (U5) from cross-sectional HH surveys conducted in the same HF catchment areas in November-December 2019 (baseline) and June-July 2021 (end line). To examine the relationship between prevalence among ANC1 and HH prevalence we fitted a generalized additive model (GAM) with a random effect for each HF catchment. Among women <20 years old, prevalence (mean = 32.5%) approximates a linear relationship with prevalence among U5 (mean = 23.2%) (GAM fixed effect estimate = 4.5, 95% CI 0.5 - 10.9), whereas the relationship between women >20 years old (mean = 16.3%) and U5 is non-linear (GAM smooth effective degrees of freedom = 3.8, 95% CI 1.6 - 7.7). Insecticide-treated net (ITN) ownership among ANC attendees (mean = 0.38 nets/person, standard deviation, SD, = 0.22) was equivalent to ITN ownership among households surveyed at baseline (mean = 0.34, SD = 0.21, equivalence test $p < 0.001$) and at end line (mean = 0.34, SD = 0.19, $p = 0.03$) when considering all ANC dates. Our study revealed high prevalence among pregnant women <20 years old and relatively low ITN coverage across the study region and suggests that

in high prevalence areas, where older women have acquired immunity, prevalence among U5 exceeds that of older pregnant women. Malaria prevalence estimates and measurements of interventions derived from younger women at ANC1 surveillance correlate with estimates derived from HH surveys and may be useful in informing prevention efforts.

0917

THE ASSESSMENT OF DATA QUALITY OF INTERMITTENT PREVENTIVE TREATMENT IN PREGNANCY 3+ UPTAKE AT HEALTHCARE FACILITIES IN SIERRA LEONE

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Malaria is endemic in Sierra Leone and is a leading cause of mortality for children and adults, which, according to the health management information system, accounts for 40.3% of outpatient morbidity for all ages and 37.6% of hospitalizations in the country. Malaria poses a unique risk to pregnant women (PW), leading to maternal anaemia, abortion, low birth weight, and preterm birth. WHO recommends a minimum of three doses of intermittent preventive treatment using sulphadoxine-pyrimethamine (IPTp-SP) beginning in the 2nd trimester and at every scheduled antenatal visit thereafter, provided the doses are given at least one month apart. Sierra Leone's facility-level HMIS summary form does not allow providers to record separate subsequent IPTp doses after the 3rd dose, leading to misclassification and inhibiting calculation of IPTp3+ coverage. We assessed 183 randomly selected health facilities across 10 districts in Sierra Leone to calculate IPTp3+ coverage. IPTp data from the MNR were compared for completeness and accuracy, against HMIS data from January-December 2021. Preliminary findings highlight several gaps in the MNR, the Summary Form, and HMIS data. Tallying and transcription errors by data entry personnel when combining written IPTp3+ data into a single register column were noted. Accordingly, HMIS data overstated the IPTp3 uptake as IPTp3, 4, 5, and 6 data are aggregated and captured in a single IPTp3+ malaria indicator. Reconfiguring the facility level summary form and HMIS to enable separate inputting of subsequent doses of IPTp would improve data quality and accuracy. Further analysis is forthcoming.

0918

ASSESSING CLIMATE AND ENVIRONMENTAL FACTORS OF MALARIA ELIMINATION IN THAILAND

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Thailand is making consistent progress toward its malaria elimination target of 2024. In fiscal year 2021 (FY21), the surveillance system recorded 2,893 cases and 468 active foci. As malaria cases continue to cluster along international borders, the country has drafted guidance on prevention of re-establishment (POR) that incorporates vulnerability to parasite importation and receptivity for transmission at the province level. This analysis collated both routine case- and foci-level surveillance data with remote sensing data to investigate if climate and environmental factors could increase malaria risk. A spatial analysis highlighted that active foci are highly concentrated along Thailand's western border, where there is significant forest cover, and along the eastern and southern borders that are dense with various plantations, including rubber trees. Rainfall exhibited a nearly uniform pattern across foci classification from FY15 to FY20. A logistic regression model investigated associations of environmental factors; demographic factors (sex, age, travel history, and residential status); and historical foci classification with the probability of having reported an indigenous case within the previous year. The environmental factors with the highest predictive power based on a model selection approach were (1) distance from international borders, (2) percentage of tropical forest, and (3) percentage of tree plantations. These results confirm that Thailand's emphasis on border areas and forest-going populations is well placed. The results also indicate that demographic factors, such as percentage of males and non-resident cases, increase the probability of a focus to report a local case. The results suggest that environmental factors alone are not driving malaria transmission in Thailand; rather, other factors, including people's activities, may be contributors. However, these factors are syndemic, so human activities in areas covered by tropical forests and tree plantations may result in malaria importation that could ignite local transmission.

0919

INTENSIFIED SURVEILLANCE FOR MALARIA ELIMINATION IN NEPAL: AN ASSESSMENT OF NATIONAL DATA

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Nepal's Malaria National Strategic Plan 2014-2025 endorsed surveillance as the core intervention to achieve the vision of "Malaria Free Nepal by 2025". However, Nepal's surveillance system faces challenges, including delayed case notification, poor data quality, untimely and incomplete case and foci investigation and response. This study assessed national case notification and reactive case detection (RACD) from 2018 to 2020 in order to evaluate its effectiveness and continued feasibility. We reviewed surveillance data from the National Malaria Disease Information System (MDIS) (for case notification) and the Malaria Case Tracker (for RACD), and calculated notification rates and timeliness of notification between 2018-2021, comparing annual changes using the chi-square test for trend. Cost per case found through RACD was also determined. Total case notification rates from the public and private sector were 62%, 96%, 97% and 98% in 2018, 2019, 2020 and 2021, respectively; however, notification rates within 24 hours of case detection were lower: 43%, 79%, 77% and 81% in 2018, 2019, 2020 and 2021 respectively. Total case investigation rates were 85%, 96%, 96% and 95 % in 2018, 2019, 2020 and 2021, respectively. However, case investigation rates within 72 hours of case detection were also lower: 73%, 85%, 82% and 84% in 2018, 2019, 2020 and 2021 respectively. Over the study period, 1066, 695, 429 and 370 cases triggered RACD, which identified a further 18, 9, 6 and 4 cases in 2018, 2019, 2020 and 2021, respectively. The cost for finding one case using RACD was $2,057 in 2018, rising to $3212 in 2021. As Nepal progresses toward elimination, fewer cases are identified through RACD, making RACD less cost effective. Despite the COVID-19 pandemic, in 2019 case notification within 24 hours of detection was high and maintained in 2021. However, this study found that RACD identified very few secondary infections. The results suggest RACD is currently not appropriate where exposure to malaria occurs away from the community (e.g. forested areas or border regions). In addition, case notification should be required from public and private health facilities.

0920

NATURAL HISTORY OF SUBMICROSCOPIC MALARIA IN COASTAL TANZANIA

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The presence of asymptomatic submicroscopic malaria reservoirs presents a challenge to malaria elimination efforts. However, the natural history of submicroscopic malaria and the proportion that persist in low transmission settings is relatively unknown. In 2018-2021, we screened 6512 children and adults in rural Bagamoyo district, Tanzania for malaria using an HRP2-based mRDT, microscopy (parasites counted per 1,000 WBCs), and real-time 18s PCR (limit of detection 1 parasite/ul). 17% of these were *P. falciparum* positive by PCR but were microscopy and RDT negative, meeting our definition for submicroscopic malaria. Older age, female gender, and having screened instead of open windows were associated with carriage of submicroscopic compared to RDT or microscopy-positive infection. Among those with submicroscopic malaria, 322 were enrolled and followed to 2 and 4 weeks. At week 2, 33% (91) had persistent submicroscopic malaria, while 15% (42) became RDT/microscopy-positive. A slight majority (144, 52%) seemingly resolved their parasitemia, but 21% of these (30) likely had ultralow density infection as they were parasite-positive at week 4. By week 4, among those not lost to follow-up (269), one quarter (69, 26%) had become RDT or microscopy-positive with 51% (34) developing malaria symptoms; another quarter (63, 24%) had submicroscopic malaria and roughly half (128, 49%) had seemingly resolved their infection. Those who became RDT or microscopy-positive were younger (median 19 vs. 24 years, p=0.08) and had higher parasite density at screening (median 3.1 vs. 2.6 p/ul, p=0.02). Otherwise parasitological outcomes at week 4 were not associated with gender, BMI, season (wet vs. dry), or reported number of malaria episodes in the past year. Overall, submicroscopic malaria in a minority of younger persons rose to densities manifesting RDT positivity, while roughly half appeared to spontaneously resolve or control parasite densities to very low levels. Findings will be supplemented by amplicon deep sequencing data to better describe the dynamic flux of different parasite strains within those with asymptomatic submicroscopic malaria.

0921

IDENTIFICATION OF SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) IN SIX *PLASMODIUM FALCIPARUM* DRUG RESISTANT LOCI AND BARCODING USING A TAQMAN ARRAY CARD (TAC) IN IQUITOS, PERU

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New technologies are needed to quickly detect the emergence of polymorphisms associated with *Plasmodium falciparum* drug resistance and measure frequency changes in those polymorphisms. A 384-well TaqMan array card (TAC) has previously been evaluated in high-endemicity settings testing its multiplexed capacity for species identification, SNP-based genotyping and detection of *P. falciparum* polymorphisms associated with chloroquine (*Pfcrt*), atovaquone (*Pfcytb*), sulfadoxine/pyrimethamine (*Pfdhfr/dhps*), mefloquine (*Pfmdr1*) and artemisinin (*PfK13*) drug resistance. Here, we evaluate the performance of the malaria TAC in a low-endemicity area.Forty whole blood-EDTA samples collected in Iquitos, Peru in 2018 with confirmed *P falciparum* infection by microscopy were assessed using the malaria TAC. The 87 assays included probes specific for 5 *Plasmodium* species, drug resistance genotyping of *Pfcrt, Pfdhfr, Pfdhps, Pfcytb*, *Pfmdr1, PfK13* genes, and SNP-barcoding. The malaria TAC amplified samples with parasitemia between 24 to 64,593 par/µL, confirming all as single *P. falciparum* infections. All samples harbored one drug resistance genotype: i) wild type alleles in *Pfcytb (codons* 258, 268 and 272) and *PfK13 (codons* 446, 458, 493, 539, 543, 561, 574, 578 and 580); ii) mutant alleles in *Pfcrt* 72S(tct), 76T, 326D and 356L, iii) double mutants of *Pfdhfr* at 51I/108N, iii) triple mutants of *Pfdhps* at 437G/540E/581G and iv) mutant alleles in *Pfmdr1* 184F, 1034C, 1042D and 1246Y. Finally, SNP-barcoding detected 3 different populations with one identified in 78% of the samples. The turnaround time from DNA extraction to data analysis was 40 hrs. The malaria TAC provides comprehensive genotyping for high-throughput drug resistance surveillance efforts in the low-endemicity setting of the Peruvian Amazon Basin allowing early detection of ACTs resistance. Our findings were consistent with previous publications from the same study area using NGS both in mutant haplotypes detection and number of parasites population. Malaria TAC data collection is a versatile RT-PCR format, adaptable to laboratory settings that do not have sequencing capability.

0922

PREVALENCE OF ASYMPTOMATIC AND SUB-MICROSCOPIC MALARIA IN INDIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Malaria is one of the important public health problems in all low- and middle-income countries accounting for many other morbidity and mortality. India has planned for elimination of malaria by 2030. Asymptomatic malaria and sub microscopic malaria is one of the important roadblocks for the same. Thus, the study was planned to find the prevalence of asymptomatic and sub microscopic malaria in India. Method: All relevant search engines (PubMed, Embase, Google Scholar) and major journals dealing with malaria, public health and tropical diseases were searched. All studies conducted till 2021 December, reporting the prevalence of malaria were included in the study. The detailed search strategy is provided in the annexure. All the data were extracted in the Microsoft excel and analysis was done using Stata-12. Random effects model was used for finding the proportion of asymptomatic and sub microscopic malaria. A total of eleven studies were included in the study. Almost all studies were conducted in the decade of 2011 to 2020. The overall prevalence of the asymptomatic and sub microscopic malaria was found to be five percent. Prevalence ranges from as high as eleven percent to as low as three percent. The overall heterogeneity in the included studies were found to be 87.3%. The funnel plot shows publication presence of publication bias in the current metanalysis.The overall prevalence was found to be varying throughout the country. The presence of asymptomatic and sub-microscopic malaria may be helpful in transmitting the malaria in the country thus continuing the transmission.

0923

TOWARDS A GENEPICALIBRATION OF MALARIA TRANSMISSION IN SENEGAL USING EPIDEMIOLOGICAL AND GENETIC DATA

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Population genetics is a versatile tool for understanding malaria transmission and diversity at the population level. As countries approach elimination, it becomes increasingly important to gain insights from sparser data, and as malaria control programs adapt new sequencing technologies, genetic models with flexible internal representations can be valuable for relating complex genomic features to epidemiological and programmatic data. Here, we present preliminary analyses of genomic data from Makacolibantang, Senegal, using GenEpi, a layered and modular framework for interfacing simulations of parasite genetics with transmission records from epidemiological models. We describe updates to GenEpi designed to improve the mechanistic accuracy of the model for evaluating parasite genetic diversity and interpreting multiplicities of infections. Recombination of gametocytes in vectors are simulated in detail at the oocyst level, providing a means for interpreting signals of superinfection and cotransmission among individual hosts. We also investigate genetic drift and explore the impact of importation on a population's diversity. We outline strategies for a sequential calibration to epidemiological and genomic data from Makacolibantang. A key requirement for calibration is characterizing model sensitivities to the parameters of interest over realistic ranges of values. The model itself has been developed as a Python package and is intended to be a tool that can be adopted by collaborators. We conclude with a demonstration of early calibration efforts using regional cross-sectional surveys, and we discuss some preliminary insights from the model.

0924

100 YEARS OF MALARIA IN ZANZIBAR

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We present 100 years of malaria data from the island of Zanzibar (Unguja), showing changes in prevalence levels, primary vector, and parasite species from 1920-2020. Documenting Zanzibar's malaria situation over a 100 year period shows a clear pattern of instability and allows us to present three new findings. Results are based on thousands of pages of archival data collected from nine different archives on three continents. A newly created panel dataset brings together contemporary and historic malaria data including community prevalence rates, entomological surveys, and parasite data. Epidemiological and entomological information has been carefully overlaid with histories of control and elimination activities on the island, including efforts by the Omani Sultanate, British colonial activities, the WHO elimination attempt, the USAID spraying program, and international efforts since 2000. First, we show dramatic changes in community prevalence levels, including a significant epidemic of rebound malaria that began in 1969, peaked in 1983, and didn't return to pre-intervention levels until 1985. Second, there have also been shifts in the primary mosquito vector on the island from Anopheles costalis to Anopheles funestus to Anopheles gambiae. Third, we document shifts in the primary parasite species. Until 1925, p. vivax was the primary species; only after 1934 did p. falciparum become responsible for a majority of malaria cases on the island. These findings raise important questions about the changing nature of malaria on the island. While the disease has remained present, it has looked quite different, challenging impressions of endemic malaria as being stable or static. This research paper is the result of an interdisciplinary collaboration involving a medical historian, malaria experts, global health practitioners in Zanzibar, and undergraduate students. We focus on Zanzibar as there are few, if any, other spaces on the African continent that have been the site of so many international malaria interventions over the last century.

0925

USING GRAVITY MODELS TO ESTIMATE FACILITY-LEVEL CATCHMENT POPULATIONS AND MALARIA INCIDENCE RATES FROM HEALTH SURVEILLANCE SYSTEMS

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Strengthening routine digital health surveillance systems across sub-Saharan Africa is vitally important for supporting subnational intervention targeting. There is a need for standardized tools that allow stakeholders to connect information from health surveillance systems to inform evidence-based subnational policies. Presently, decision-makers lack tools for converting aggregated count data from facilities into more informative rate-based metrics. Facility-level population denominators required for estimating incidence rates are difficult to maintain within surveillance systems. Reported headcount data are infrequently updated and may not respond to changes within a specific facility or neighboring facilities (e.g., commodity stock-outs, opening/closing of nearby facilities). Simple geospatial methods, such as the nearest facility by distance or travel time, may not be representative of treatment-seeking behavior and may result in skewed rate estimates. Gravity models offer a natural method for estimating spatial accessibility patterns and incidence rates from aggregate facility data. Benefits of this method include accounting for differences between individual facilities, incorporating information on health system organization and referral structures, and creating geographically overlapping catchment areas. While gravity models have been used in some specific facility-level research studies, there is a lack of tools and resources for standardized implementation. Here we present an open-source R package for implementing gravity models with a contextual focus on health facility access and reporting. We demonstrate the functionality of this tool, including catchment population estimation and incidence mapping, using routine malaria surveillance data from DHIS2.

0926

EFFECT OF DEFORESTATION ON THE OCCURRENCE OF MALARIA IN COLOMBIA

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Background: About 80% of rural Colombia has climatic, geographic, and epidemiological conditions suitable for malaria transmission, and 25 million people are at risk of illness or death from it. Human activities such as agriculture, deforestation, and human movement can increase the

risk of malaria. Our objective was to describe the effect of deforestation on the occurrence of malaria. Methods: An ecological study was carried out, using malaria data obtained from the Colombian epidemiological surveillance system SIVIGILA, climate variables from WorldClim, and tree cover from the MODIS satellite. Data were aggregated in space to the municipal level (1,123 municipalities), and climate variables over time to give annual measures. The study period was from January 1, 2007, to December 31, 2018. Spatiotemporal Poisson ICAR regression, in the R-INLA software, was identified as a suitable analysis method. Results: Colombian municipalities had an average of 41,805 population (range 247-8,181,047). The altitudes of their centroids ranged from 1 to 3,350m. Precipitation had an average of 172mm (range 29.7-876.6mm); minimum temperature averaged 16.5ºC (range 2.5-25.8ºC), and maximum temperature 25.9ºC (range 10.1-35.2ºC). Tree cover had an average of 33.0% (range 1.3-83.2%). The average number of malaria cases by municipality was 56.4 (range 0-14,789). The average malaria incidence per 100,000 inhabitants was 264.7 (range 0-36,956.1). Initial correlation analysis showed small (0.14-0.33), but statistically significant, positive associations between the incidence of malaria per municipality and tree cover, precipitation, and minimum and maximum temperature. Regression analysis is underway. Conclusion: The exploratory analysis shows expected associations with environmental variables, and regression analysis will describe the extent of any relation with deforestation.

0927

LOCALLY ACQUIRED MALARIA CASES AMONG SCHOOL-AGED CHILDREN IN THAILAND

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School-aged children (SAC) are consistently Thailand's highest incidence age group for malaria, representing 12% of the population but 22.8% of recent cases. Malaria incidence among SAC dropped from 0.15 cases per 1,000 population in fiscal year 2018 (FY18) to 0.09 in FY21; however, simultaneously, total malaria incidence dropped from 0.09 to 0.04. To support elimination programming, this study used a generalized linear mixed model to examine associations between locally acquired malaria (i.e., transmission within Thailand) and risk factors among SAC. The study used routine surveillance data from FY18-21, with province included as a random effect. Among 18,809 confirmed cases, 16,880 (90.0%) had the required case classification and investigation data for study inclusion. Age groups were defined as 0-4 years (children under 5), 5-14 years (SAC), and 15+ years (adults), representing 4.7%, 22.8%, and 72.6% of cases, respectively. SAC are frequently symptomatic, and from FY18-21, 93.9% were identified via passive surveillance, while another 3.4% were identified via school-based screening. Within the five provinces representing 62.2% of SAC cases, 67.4% of SAC reported travel with a parent or relative, but only 56.4% reported bed net use during travel. Among all confirmed cases, SAC were more likely to have locally acquired malaria than adults ($p<0.01$). Among all acquired cases, SAC had a significant association with Thai nationality (relative risk = 10.54, $p<0.05$). Among all SAC cases, acquired malaria was significantly associated with overnight travel to another village, forest, or cottage (odds ratio [OR] = 2.82, 1.50, 1.31, respectively) and bed net availability (OR = 0.34, $p<0.05$); the association with bed net use was not significant (OR = 1.12, $p>0.05$). These results show that domestic travel is highly associated with malaria among SAC. Because SAC may have unique travel patterns and behaviors, further research could inform interventions to prevent local transmission. Increasing bed net availability and appropriately targeted use, particularly during travel, may also reduce transmission and accelerate malaria elimination.

0928

GLOBAL ESTIMATES OF PREGNANCIES AT RISK OF *PLASMODIUM FALCIPARUM* AND *P. VIVAX* INFECTION IN 2020 AND CHANGES IN RISK PATTERNS SINCE 2000

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Women are at risk of severe adverse pregnancy outcomes attributable to *Plasmodium spp.* infection in malaria endemic areas. Malaria control efforts since 2000 have aimed to reduce this burden of disease. We used data from the Malaria Atlas Project and WorldPop to calculate global pregnancies at risk of *Plasmodium spp.* infection. We categorised pregnancies as occurring in areas of stable and unstable *P. falciparum* and *P. vivax* transmission. We further stratified stable endemicity as hypoendemic, mesoendemic, hyperendemic, or holoendemic, and estimated pregnancies at risk in 2000, 2005, 2010, 2015, 2017, and 2020. In 2020, globally 130.2M pregnancies were at risk of *P. falciparum*, one-half (64·8M, 49·8%) were in areas of stable transmission; 86·7M pregnancies were at risk of *P. vivax*, 72.6% (62.9M) were in areas of stable transmission. An estimated 72·6M pregnancies were in areas with both *P. falciparum* and *P. vivax* transmission. The number of pregnancies at risk of *P. falciparum* or *P. vivax* worldwide decreased between 2000 and 2020, with the exception of sub-Saharan Africa where the total number of pregnancies at risk of *P. falciparum* increased from 37·4M in 2000 to 52·4M in 2020. Our results and methods will also be discussed in relation to World Malaria Report estimates of pregnancies at risk of *P.falciparum* in sub-Saharan Africa. Historic investments in malaria control have reduced the number of women at risk of malaria in pregnancy in all endemic regions except sub-Saharan Africa. Population growth in Africa has outpaced reductions in malaria prevalence. Interventions that reduce the risk of malaria in pregnancy are needed as much today as ever.

0929

SPATIAL DISTRIBUTION AND RISK FACTORS ASSOCIATED TO MALARIA INFECTION AND HEALTH SEEKING BEHAVIOR IN MOPEIA DISTRICT, MOZAMBIQUE, AFTER THREE ROUNDS OF IVERMECTIN MASS DRUG ADMINISTRATION

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A cluster randomized clinical trial to assess the safety and efficacy of the mass drug administration (MDA) of ivermectin on reducing the burden of malaria is ongoing in the district of Mopeia, Mozambique. Mopeia is one of the districts with the highest malaria burden in the country and has also suffered adverse climatic events leading to extremely adverse environmental conditions. After three rounds of MDA (June-July 2022), a cross-sectional malaria prevalence survey will be

conducted, in all age groups (0-<5, 5-<15, and >=15-year-olds). After administering informed consent, rapid diagnostic tests will be used to assess *Plasmodium falciparum* infection in 1590 individuals in 159 study clusters. Demographic, socioeconomic and malaria-related variables will be collected individually through a survey.GIS will be used to describe and visualize the spatial distribution of malaria infection in Mopeia after three rounds of MDA. Moran's I will be used to assess the existence of non-homogeneous disease distribution in the study area, and scan statistics will be employed to identify "hotspots'" locations. Risk factors for infection will be analyzed through a multivariable logistic regression including environmental and meteorological variables (enhanced vegetation index, rainfall, dry season length and proximity to large water bodies), socio-economic variables (village size, literacy rate, proximity to a primary road and migration history) and malaria related variables including coverage of mosquito nets at household level, Indoor Residual Spraying in the previous campaign, and whether the clusters' inhabitants received Ivermectin or control. The spatial distribution of health seeking behavior in Mopeia district will also be described on the basis of self-reported healthcare seeking in the formal system in the previous fever episode. Environmental and socio-economic variables will be explored as risk factors for seeking healthcare. Contrasting the distribution of health seeking behavior and the distribution of malaria infection will be employed to understand the potential effect of climatic events on health seeking behavior.

0930

RELATIONSHIP BETWEEN NUTRITION STATUS AND MALARIA OUTCOMES IN RWANDA

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Undernutrition and severe malaria remain important public health issues. If correlated, improving nutritional health in children under 5 years might help prevent adverse malaria outcomes. The present study aimed at assessing the association of stunting, wasting, and undernutrition with malaria outcomes. We extracted data of children aged between 6 to 59 months from 3 Demographic and Health Surveys (DHS) conducted in Rwanda in 2010, 2014-15, and 2019-20 in which malaria diagnosis has been confirmed by blood smear. Logistic regressions were used to assess odds ratio of stunting, underweight, and wasting on malaria outcome, without and with adjusting on age, sex, mother education, wealth index, type of residence, province, within each survey. Overall, malaria test was performed in 15,009 children under five and anthropometric measures were available for 14,871. The overall malaria prevalence represented 1.31% (197/15009). Moderate stunting (Z-score <-2.0) was observed in 4089 (25.0%) and severe stunting (Z-score <-3.0) in 2001(12.2%) children. Adjusted odds ratio (AOR) indicated that severe (AOR=2.11, 95% confidence interval (CI)=[1.45;3.08], p<0.001) and moderate (AOR=1.55, 95%CI=[1.11;2.18], p=0.01) stunting children had a higher risk of presenting with malaria respectively. Underweight children had also an increased risk of malaria (AOR=1.65, 95%CI=[1.04-2.62], p=0.03), malaria risk was also increased in children aged over 24 months (AOR=1.95, 95%CI= [1.36-2.82], p<0.001), and children living in the richest families were protected from malaria, p<0.001 in all 3 DHS. Findings from this study shows that undernutrition variables are risk factor for malaria, therefore, a close follow-up of the nutritional status in children under five is required.

0931

MAPPING THE ECONOMIC BURDEN OF MALARIA IN MOZAMBIQUE

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The World Health Organization's High Burden to High Impact (HBHI) targeted malaria response strategy recognizes the need for a country-owned and country-led approach to malaria control, characterized by packages of malaria interventions implemented at the sub-national level to achieve the greatest impact. As countries consider how to more efficiently and effectively direct current control strategies, and deliberate if and when novel control strategies should be integrated into country plans, comparing cost-effectiveness of various strategies becomes critical. In the context of sub-national stratification, an important first step in cost-effectiveness analysis is determining the economic burden of malaria at the scale in which any intervention would be deployed. Mozambique holds over 4% of the global malaria burden and is one of the countries targeted by the WHO's HBHI strategy. In this study, we estimate and map the economic burden of malaria across Mozambique at the district level to provide a useful database for future malaria control planning. To generate this map, detailed survey data collected for the district of Mopeia during two separate malaria intervention trials will be applied to a demographic based model and projected to country-level scale. Household costs are estimated from surveys of 2,200 households over a period of 6 months, to include information on demographics, malaria incidence, cost of treatment, wages and time lost due to illness, indirect burden on family members when a dependent is sick with malaria, missed school days, and preventive costs. Health system costs are estimated from information collected on clinical resources used during malaria outpatient visits and hospital admissions in the 13 district health facilities. The demographic based model will be informed by the Demographic and Health Survey (DHS) and Malaria Indicator Survey (MIS). Results on the economic burden of malaria will be presented for all of Mozambique to the district level, with discussion of how the economic burden is split within households, and which strata of the society carry the most burden.

0932

ASSOCIATIONS BETWEEN *IN UTERO* HIV EXPOSURE OR OTHER DELIVERY CHARACTERISTICS AND AGE OF MALARIA INFECTION IN A COHORT OF KENYAN INFANTS

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We aimed to identify the effects of *in utero* HIV exposure and delivery characteristics on an infant's susceptibility to malaria infection. Between 2011-2015, a cohort of pregnant women from Chulaimbo, Kenya were enrolled at their first ANC visit and followed through delivery. Maternal HIV status determined at enrollment was used to categorize children as HIV-exposed uninfected (HEU) or HIV-unexposed uninfected (HUU). Child sex, birthweight, and gestational age was collected at delivery. Children delivered at the study hospital were seen at routine follow-up visits at age 6, 8, 10, 14 weeks, and tri-monthly from 6-24 months. At each visit a clinical assessment was done and venous blood drawn and tested for

Pf DNA by qPCR. Guardians were instructed to bring sick children for clinical assessments and treatment. Cox proportional hazard (PH) was used to model associations between *in utero* HIV exposure, child sex, low birthweight (<2500g), and preterm delivery (<38weeks) with age of first malaria infection by 1) clinical diagnosis and 2) qPCR. Of 360 pregnant women enrolled, 226 delivered children with at least one follow-up. Of those, 33% were HEU, 3% had low birthweight, 30% were pre-term, and 51% were female. Over a two-year follow-up, 39% of children had at least one clinical episode diagnosed as malaria and 31% had at least one *Pf* DNA detection. No associations were found between preterm birth, birthweight, or child sex and age of malaria infection. HUU were at significantly increased hazards of earlier malaria infection by qPCR than HEU [Hazard Ratio=2.34, (95%CI: 1.36-4.02, p=0.002). HUU also had higher hazards of receiving an earlier clinical malaria diagnosis than HEU children, though not statistically significant [Hazard Ratio=1.32 (95%CI: 0.96-1.83), p=0.0907]. Later malaria acquisition by children born to HIV-positive mothers may be due to their receipt of Bactrim, an antibiotic with known anti-malaria activity given prophylactically through 18 months of age, to improved healthcare through HIV clinics, or other unknown factors which may protect against earlier malaria infections.

0933

MALARIA SURVEILLANCE AND REPORTING SYSTEM: A REAL TIME REPORTING AND VISUALIZATION TOOL USED TO ENHANCE MALARIA SURVEILLANCE EFFORTS IN SOUTHERN-EASTERN TANZANIA

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Over the years, the National Malaria Control Program (NMCP) and stakeholders have lacked a tool to assist with real-time reporting of malaria surveillance data, resulting in an inability to make timely and informed decisions on which interventions to implement in specific areas. The health facility is the lowest level unit under DHIS2. DHIS2 provides enhanced data accessibility, allowing it to be used to examine spatial patterns and temporal trends. While temporal variations in transmission are captured and seasonality patterns clearly differ from one location to the next, the ability to map malaria transmission back to the source from a central reporting location is lacking. In response, we have developed a Malaria Reporting and Surveillance System that collects, analyzes, and displays real-time malaria surveillance data. Malaria cases from health facilities are collected and reported to the system on a daily basis, which automatically calculates and visually displays the malaria incidence ratio (MIR) of the individual villages. As a result, Community Health Management Teams (CHMT), NMCP, and other stakeholders can easily identify villages with the highest malaria cases and provide immediate assistance as needed. Other system capabilities include automated analysis and presentation of health facility reporting rates, MIR analysis for all villages in a district for the current and previous week, and aggregated display of malaria cases on a monthly, weekly, and daily basis. The system is freely accessible online, and a mobile app is available. A malaria reporting and surveillance system was successfully implemented in the Rufiji area of Southern Eastern Tanzania, with data collection and focal point village identification, to support the 1,7-malaria reactive community-based testing and response (1, 7-mRCTR) technique. Malaria Reporting and Surveillance System has proven to be an effective tool to assist with decision making by using real time malaria case data reported from health facilities.

0934

DEVELOPING A SAMPLING STRATEGY FOR ESTIMATING WARD-LEVEL MALARIA PREVALENCE AND RELATED RISKS IN NIGERIAN CITIES: HOW FEASIBLE ARE MACHINE LEARNING ALGORITHMS?

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Unplanned urbanization in sub-Saharan African countries like Nigeria has contributed to large heterogeneities in malaria risk requiring malaria control programs to tailor interventions to the smallest administrative units. However, prevalence and other malaria indicator estimates are not available at this level. Nigerian cities are subdivided into numerous administrative units (wards) and sampling each of them may be practically infeasible, thus requiring the development of a cost-effective sampling methodology. Using machine learning algorithms, similar geographic areas can be grouped using data on the determinants of disease to enable extrapolation of findings. We apply a clustering algorithm built on Gaussian finite mixture models, an unsupervised machine learning technique, to categorize 59 and 66 wards in Ibadan and Kano metro areas, respectively, and inform selection of wards for a cross-sectional study designed to estimate ward-level malaria prevalence and associated risks. Variables considered for clustering included population density, road accessibility, housing quality, enhanced vegetation index and the number of dump sites. An optimal number of clusters was determined by selecting the model with the lowest bayesian information criterion. Four and five clusters were identified in Ibadan and Kano metro areas, respectively. Housing quality and the number of dumpsites were identified as the best variable set that improved cluster partitioning in Ibadan while housing quality was the most optimal variable for cluster partitioning in Kano. Model inputs and clustering results were validated through consultation with local experts and "ground-truthing". Two wards were visited per cluster and qualitative observations suggested that visited wards were correctly clustered in 2 out of 4 cases in Ibadan and 3 out of 5 in Kano. We present a valuable technique for improving the extrapolation of findings to unsampled locations in heterogenous settings. Our study highlights the interconnected role of local knowledge and machine learning algorithms in facilitating the development of cost-effective sampling strategies.

0935

INCIDENCE OF NON-FALCIPARUM MALARIA INFECTION AMONG CHILDREN AND ADULTS IN KINSHASA PROVINCE, DEMOCRATIC REPUBLIC OF THE CONGO

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Non-falciparum malaria is increasing in select regions of sub-Saharan Africa, although its epidemiology remains poorly understood. In a longitudinal study of malaria in seven sites in Kinshasa Province, Democratic Republic of the Congo (DRC), we screened samples for *Plasmodium ovale* spp. (*Po*) and *P. malariae (Pm)* infection using a duplex real-time PCR assay to determine the incidence of any (mixed or mono) infection over time and characterize associated risk factors. Rapid diagnostic tests, questionnaires, and dried blood spots were collected

at bi-annual household visits (active surveillance), and at any time a participant presented to a study health center with malaria symptoms (passive surveillance). Cumulative incidences were estimated through Kaplan-Meier methods and stratified by covariates of interest. 9,007 samples collected from 1,565 participants during the 2015-2017 study period were tested. *Pm* infections were detected in 10% of participants and *Po* infections in 5% during the 20-month active surveillance period, compared to a 63% prevalence of *Pf*. Total prevalences remained stable across the study period; however, in the Kimpoko health area, *Po* prevalence increased over time from 0% to 4% (n=16). During passive surveillance (n=1,033), 12% of participants had an episode of symptomatic *Pm,* and 8% of *Po*, compared to 76% with *Pf* over 34 months of follow-up. One-year crude risks of *Pm* and *Po* infection during active surveillance were 5% and 4%, respectively, with slight increases through end of follow-up. During passive surveillance, risks of *Pm* and *Po* increased over time from 9% and 6% at 12-months, to 15% and 11% by 24-months. The risk of *Pm* and *Po* infection over time differed across age, village, and wealth strata; no differences were detected by gender. While *Pf* remains the primary driver of malaria morbidity and mortality in the DRC, our findings confirm that non-falciparum species are a common cause of infection and are frequently detected among symptomatic cases across diverse study sites in Kinshasa. As *Pf* interventions gain traction in high-burden settings like the DRC, non-falciparum malaria may warrant increased attention.

0936

STRATIFICATION OF MALARIA IN NEPAL BASED ON RISK OF TRANSMISSION AND ELIMINATION FOCI

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Nepal has taken the challenge of eliminating all forms of malaria by 2025. In 2021, total malaria cases reported were 391, with 32 indigenous cases only. Since, heterogeneity and focalization are the most common epidemiological characteristics of Nepal, we used wards as the administrative unit. This was a descriptive and retrospective study using cumulative malaria cases at the ward-level conducted in 2021. To classify the receptive areas we used the spatial distribution of key determinants of transmission risk and assigned them weights. These included climate, ecology, the presence or abundance of key vector species and vulnerability in terms of human population movement. Disease burden, receptivity, vulnerability were given scores of 0.6, 0.3 and 0.1 respectively. Furthermore, the API of imported cases and API of indigenous cases was considered 0.1 and 0.5 respectively. The area occupied by the receptive wards, the cumulative burden, and the at-risk population in the regions were calculated. The study showed that the total population at high risk was 77,680, at moderate risk was 4,28,414, at low risk was 1,139,655 and 1,87,17,649 were at no risk. Nine high-risk districts were identified: Banke, Bardiya, kalikot, Mugu, Humla, Bajura, Kanchanpur, Dadeldhura, Baitadi. There were 22 wards in 9 districts at high risk and 69 wards in 12 districts at moderate risk located mainly in the West. There was wide variation in the distribution of the risk wards in seven different provinces. Lumbini, (2 wards) Karnali (6 wards) and Sudurpaschim (14 wards) provinces had the highest number of high and moderate-risk wards, with 22 and 67 high and moderate-risk wards respectively. The total malaria burden in provinces 1 (3 cases), Bagmati (5 cases) and Gandak (15 cases) constituted mainly of imported cases. In Madesh province in Saptari district, there were two moderate-risk wards. No high or moderate risk wards were found in Provinces 1, Bagmati and Gandaki. The majority of high-risk and moderate-risk wards were in the upper-hilly districts which are geographically difficult to access areas posing an additional challenge to the malaria program.

0937

QUANTIFYING THE DRIVERS OF *PLASMODIUM FALCIPARUM* TRANSMISSION ACROSS A HETEROGENEOUS LANDSCAPE USING RESISTANCE SURFACE ANALYSIS

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Despite the advent of new interventions and preventive tools in the last decade, progress towards malaria eradication has stalled. Achieving local elimination requires a comprehensive understanding of the transmission environment, but most efforts to characterize malaria transmission drivers fail to consider the state of environmental factors beyond the immediate vicinity of transmission foci. The application of landscape genetics, specifically resistance surfaces, allows quantification of the degree to which the landscape obstructs or permits malaria transmission for every grid cell in the study domain. In our study, we use this holistic, spatially-refined method to determine environmental drivers of malaria transmission in western Kenya. Our microsatellite dataset covers 44 locations, which represents an unprecedented level of spatial coverage in a study of this type. Consistent with previous work, our population genetics analyses showed only weak spatial structure, with a pattern of isolation-by-distance that disappears over long distances. Clustering analysis revealed a distinct group of parasites in the lowlands north of the Winam Gulf of Lake Victoria. We then estimated resistance surfaces to explain these findings in the context of environmental drivers such as elevation, temperature, and rainfall. The best fitting surfaces show paths of high transmission and barriers to gene flow. These results allow for better parameterization of epidemiological models and improved targeting of interventions.

0938

MALARIA RISK FACTORS ASSOCIATED WITH INFECTIONS AND CLUSTERING OF CASES BY HOUSEHOLDS IN MUHEZA DISTRICT, NORTH EASTERN TANZANIA

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Malaria remains a major cause of morbidity and mortality in Tanzania despite recently scaled-up control interventions. In the current transition, malaria burden has become heterogeneous with higher burden in some regions compared to others. Thus, stratification and mapping of malaria risk and burden is critical to guide proper use of current and future interventions. This cross-sectional study was undertaken in June 2021 to assess the risk factors associated with malaria infections and spatial clustering of cases at a micro-geographic level in three villages of Muheza district in Tanga region. Finger prick blood samples were taken from 1,060 individuals for parasite detection by rapid diagnostic tests and microscopy. Socio-economic status and GIS data were also collected. Generalized estimation equation (GEE) for assessing clustering of cases by households was used to identify risk factors associated with malaria infections**.** Males (AOR=1.08 95%CI: 1.03 -1.13, p=0.001) and children aged 5 to 14 years (AOR=1.17, 95%CI: 1.09-1.26, p < 0.001) had higher risk of malaria infections. Febrile individuals (temperature ≥37.5^{0}C) were more likely to have malaria (OR=1.35; (95%CI: 1.13-1.63, p=0.001) while those living in households with closed eaves had lower risk of infections (AOR=0.93; 95%CI: 0.89-0.98, p=0.012); irrespective of their socio-economic status. Over 90% of participants were using bed nets and there was no significant difference in the risk of malaria infections which was associates with bed net use. These findings show high risk of malaria infections in school children (aged 5 to 14yrs) and individuals living in houses with open eaves. Despite high coverage and use of bed nets, malaria interventions targeting these groups are urgently needed.

0939

USING MALARIA GENETICS TO PREDICT NATIONAL MALARIA CONTROL PROGRAM MEASURED INCIDENCE IN SENEGAL

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Genomic surveillance of the Plasmodium falciparum parasite shows great promise for helping National Malaria Control Programs (NMCPs) assess local parasite transmission. Genetic metrics such as the frequency of polygenomic (multiple strain) infections, genetic clones, andthe complexity of infection (COI, number of strains per infection) are correlated with transmission intensity. However, it is unclear how closely these metrics correlate with transmission or whether genetics alone is sufficient for estimating epidemiological incidence. Here, we examined parasites from 2,917 clinical infections sampled between the years 2012-2019 through passive case detection across 15 clinic sites spread throughout Senegal. Samples were genotyped with a 24 SNP molecular barcode that uniquely identifies parasite strains and distinguishes polygenomic from monogenomic (single strain) infections. To determine whether genetics can predict incidence, we developed a Poisson generalized linear mixed effects model that predicts the reported NMCP-measured incidences of each clinic site using a set of genetic metrics designed to measure parasite clonality, superinfection, and cotransmission rates. We show that genetics alone can predict incidence in moderate to high transmission regions where NMCP-measured incidence is greater than 10. While all examined metrics were needed to accurately predict NMCP-measured incidence, the frequency of polygenomic infections was the strongest individual predictor of incidence. Metrics that evaluate the impact of clonal transmission, superinfection, and cotransmission must be evaluated in concert as each measures a different biological aspect of malaria transmission. However, the model failed to accurately predict incidence when the NMCP-measured incidence was less than 10. This could be because parasite genetics are disproportionately impacted by importation in low transmission settings, are more sensitive to site-specific differences in epidemiological conditions, or represent outbreak dynamics whose genomic epidemiology differs from higher transmission or endemic regions.

0940

ESTIMATING THE POTENTIAL GEOSPATIAL MALARIA EXPOSURE RISK FOR DIFFERENT OCCUPATION GROUPS IN YALA, THAILAND

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Great efforts have been made toward malaria elimination in South-East Asia. Thailand has set a goal of halting malaria transmission by 2025. Despite overall lower malaria transmission, Yala is situated in Southern Thailand and is one of the provinces with the highest burden of malaria. Estimating a geospatial malaria exposure risk surface can provide local health officials with information useful for targeting the remaining foci of transmission, as well as reducing the risk of exposure for local populations, promoting malaria elimination.

To estimate a geospatial malaria exposure risk surface for the province of Yala, we use data on age, gender, occupation, mode of travel to work, type of malaria, and home and work village locations collected through a survey administered by a team of researchers from The Armed Forces Research Institute of Medical Sciences (AFRIMS) in Yala from January 2019 to April 2020. From this survey, there were a total of 54 cases, 36 *Plasmodium vivax* (*P. vivax*) malaria, 15 *Plasmodium falciparum* (*P. falciparum*) malaria, and 2 negative cases. In addition to the 54 infections identified through the AFRIMS study, we collected data on over 1401 *P. vivax* positive cases and 180 *P. falciparum* malaria cases and their village locations from the Ministry of Public Health of Thailand during the same time period. Remotely sensed environmental data was collected including minimum, maximum, and average temperature, precipitation, land cover, elevation among other variables. A detailed road network was also captured from OpenStreetMap. We used a maximum entropy modeling tool (Maxent) to simulate and generate an estimate of the potential malaria exposure risk for Yala. The resulting probability surface captures the spatial variability of malaria risk within this province. We then use this risk surface to analyze the risk of exposure for different occupation groups, and how factors relating to local occupation-based travel are related to the risk of exposure to both *P. vivax* and *P. falciparum* malaria in this province.

0941

IMPROVEMENT OF THE HEALTH INFORMATION MANAGEMENT SYSTEM THROUGH MALARIA DATA QUALITY ASSESSMENT SITE VISITS IN PMI SUPPORTED HEALTH ZONES IN THE DEMOCRATIC REPUBLIC OF THE CONGO (DRC)

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The National Malaria Control Program in the Democratic Republic of the Congo (DRC) in collaboration with partners implements regular data quality assessments to improve the quality of malaria surveillance data. The Malaria Routine Data Quality Assessment (mRDQA) tool was developed to standardize assessment of malaria data quality at health facilities (HF) level. An initial assessment was conducted in December 2020 and a follow up assessment in August 2021 in 80 HF from 27 health zones (HZ) in 7 provinces. The team assessed the performance of the health information system to manage and produce quality data. And reviewed variables linked to human resources and technical capacity to manage data. This included the presence of staff to compile and review quality of data, existence of data management tools and directives, patients' data archiving, capacity of a HF to define targets, analyze data and track malaria indicators progress. At each level, a recovery plan was developed, followed up in between the two assessment and written feedback were sent to HF and HZ. Results revealed that the system management improved significantly, this include the increase of the proportion of HF with staff designated to compile data from 68% to 79%, HFs with standard malaria data collection tools from 57% to 74%, HFs with archive of historical patient diagnostic data from 74% to 90%, HFs with updated dashboards to track malaria indicators from 27% to 45%, HFs with written directives from 41% to 45% and HFs holding data review meeting from 40% to 45%. Results suggest that implementation of recovery plan that meets clearly identified weaknesses following the mRDQA process is effective in improving the health information management system in the DRC and consideration may be given to how the use of this tool may be further expanded to a maximum number of HFs in the country to improve the quality of routine data.

0942

ASSESSMENT OF 5 YEAR MALARIA EPIDEMIOLOGY PATTERNS IN PATHOGEN DIVERSITY NETWORK AFRICA (PDNA) COUNTRIES TO ADDRESS PUBLIC HEALTH INTEGRATED INTERVENTIONS INCLUDING GENETICS FOR THE REDUCTION OF MALARIA BURDEN

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The Pathogens Diversity Network Africa is established across 15 countries in sub-Saharan Africa to ensure that genetics is enabled to play a key role in the global effort for tracking and responding to this public health threat. Objective : To assess the evolution of epidemiological characteristics of malaria in PDNA sites for the design of public health integrated interventions which will include genetic patterns of parasite and hosts. Methods and expected resuts. The dynamics of malaria patterns and level of intervention coverage between 2015 and 2020 will be assessed and compared according to PDNA sites. This will include prevalence and incidence rates, entomological data, rapid diagnostics tests, larviciding, bed-net use, indoor residual spraying, and treatment or prevention tools in accordance with the country's Ministry of Health (MOH) guidelines. Using modelisation, new design of control strategies which will integrate existing knowledge on parasite genetics will be proposed.

0943

APPLICATION OF GC3, A LOCUS READ COVERAGE ASSESSMENT TOOL, TO IDENTIFY GENE DUPLICATIONS OF *PFMDR1* AND *PLASMEPSIN-2* AMONG *PLASMODIUM FALCIPARUM* STRAINS

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A computation tool called "Gene Coverage Count and Classification" (GC_3) was developed to process genome-wide coverage data from whole genome sequencing (WGS) reads. GC_3 was originally designed to identify samples with targeted gene deletions and provide informative figures and tables. This first iteration was successfully applied to the locus encoding histidine-rich protein 2 (*hrp2*), a key antigen for most malaria rapid diagnostics tests. An update to GC_3 is underway to extend its application to identify gene duplications among WGS data, specifically focusing on *Plasmodium falciparum* multidrug resistant protein 1 (*Pfmdr1*) and *Plasmepsin-2*, genes associated with antimalarial drug resistance. Artemisinin-based combination therapies (ACT) are the current frontline treatments for malaria. Artemisinin acts quickly to clear parasites in the blood, but has a short half-life. A partner drug with a longer half-life is administered to clear surviving parasites and to avoid the emergence of resistance to artemisinin. Of concern is the expansion of *P. falciparum* strains with increased copy number of *Pfmdr1* and *plasmedpsin-2*, which are associated with drug resistance against some ACT partner drugs. Duplications of *Pfmdr1* are strongly associated to treatment failures among ACTs with arylaminoalcohol (MQ) or lumefantrine (AL), whereas duplications of *plasmepsin-2* are associated with resistance to ACTs with piperaquine (PPQ). Gene duplications are more common in Southeast Asia, but have been observed in sub-Saharan Africa, jeopardizing efficacy of malaria treatments. We are currently using GC_3 to screen ~1400 P. *falciparum* WGS datasets, collected in 24 countries in South America, Africa, Southeast Asia and Oceania, for the presence of these duplications. GC_3's performance will be validated using representative strains with known gene duplications. Our study will demonstrate the feasibility of applying a bioinformatics pipeline to accurately measure frequency of gene duplications and to screen WGS data for properties associated with drug resistance.

0944

UNMASC (UGANDA MALARIA ACTIONABLE SURVEILLANCE IN THE TIME OF CORONAVIRUS): USING HEALTH FACILITY AND CROSS-SECTIONAL SURVEY DATA TO ASSESS THE EFFECTS OF THE COVID-19 PANDEMIC ON MALARIA BURDEN AND CARE

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To understand the impact of the COVID-19 pandemic on malaria transmission, burden, and care in Uganda, we conducted the UnMASC study. Cross-sectional surveys were performed in April-May 2021 and in February-March 2022 in communities surrounding 12 malaria reference centers (MRCs) that are part of a country-wide malaria sentinel surveillance network. In target areas surrounding each of the 12 MRCs, 50 households with at least one child 2-10 years of age were enrolled. We obtained a thick smear for microscopy and collected dried blood spots from all children in enrolled households, allowing us to estimate parasite prevalence and seroprevalence of malaria and COVID-19 using a multiplex Luminex assay. In addition, we collected data at the household and household member level on healthcare seeking behavior, COVID-19 beliefs and attitudes, and COVID-19 vaccination status. In the April-May 2021 survey (conducted post-Alpha wave), we found that overall seroprevalence for COVID-19 was 10.9% (range 3.0% to 30.6% by MRC). COVID-19 seroprevalence was highest in MRC target areas in the northern districts of Kitgum and Lamwo near the border with South Sudan. Levels of knowledge about COVID-19 were generally high and not associated with MRC-level COVID-19 seroprevalence. COVID-19 serology results from the February-March 2022 survey, and malaria serology results from both rounds, are pending but will be available by time of presentation. Given that the February-March 2022 surveys were conducted post-Omicron wave, data from the second round of surveys will enable us to estimate the attack rate of the Omicron wave of the pandemic in these 12 communities and relate this information to routine malaria indicators collected at the health facility, changes in parasite prevalence/seroprevalence measured in the community, vaccination levels in the community, and changes in healthcare-seeking behavior as measured by questionnaire. Combining data from the 12 MRCs and associated cross-sectional community-based surveys will allow for assessment of the effects of the COVID-19 pandemic on routine malaria care and prevention at these sites.

0945

DETERMINANTS OF MALARIA INFECTION AMONG CHILDREN UNDER FIVE IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Malaria is the leading cause of death among children under five in the Democratic Republic of the Congo (DRC). This study examines malaria infection determinants among children under five in four DRC provinces in 2017. A cross-sectional survey was conducted in 2017. Multivariable logistic regression was used to assess the association between malaria infection in children aging between (6-59) months and plausible determinants at the individual, household, and environmental levels. A total of 2,530 De Facto children, aged between (6-59) months, and who were malaria tested using a rapid diagnostic test (RDT) were included in the study. Of malaria cases, 55 % were from Maniema / Tshopo provinces,

and 71% were living in households that own at least one insecticide-treated bed net (ITN), yet only 48% used an ITN overnight. The majority of ITN Non-users of 65 % were from Manemia / Tshopo provinces, while 60 % of ITN users were from Nord / Sud Ubangi provinces. The odds of having malaria were higher in Maniema / Tshopo [AOR 1.72; 95 %CI: 1.39 to 2.13] compared to the Nord / Sud Ubangi provinces. Per each one-unit increase in the normalized difference vegetation index (NDVI) towards greenness, the predicted log odds of malaria infection increased by a factor of 2.60 [Coefficient 2.60; 95% CI: 1.34 to 3.85]. Odds of the infection showed an upward trend in terms of age, with the highest prevalence in children aging (48-59) months [AOR 4.28; 95% CI: 3.03 to 6.04] compared to those aged (6-12) months. Children residing in the wealthiest households [AOR 0.59; 95% CI: 0.43 to 0.82], and those who slept under a bed net the night before the survey [AOR 0.56; 95% CI: 0.45 to 0.70] were less likely to be infected. While this paper contributes to the understanding of determinants of malaria infection in the most vulnerable group of children under five, further research is needed to identify other factors not captured in this study contributing to high odds and prevalence in central provinces, and factors underlying the observed gap between owning an ITN and not using it within the DRC context.

0946

UTILITY OF MALARIA HISTIDINE RICH PROTEIN2 RAPID DIAGNOSTIC TEST FOR MALARIA SURVEILLANCE IN FEDERAL CAPITAL TERRITORY, NIGERIA

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Malaria surveillance in populations provide monitoring indicator data for measurement of progress with interventions. Malaria indicator surveys (MIS) rely on malaria microscopy though some countries have used malaria rapid tests (RDTs). Malaria microscopy is cumbersome and expensive but the RDTs with histidine rich protein 2 (HRP2) antigen that has been used alongside quality microscopy in some surveys are cheaper and easy to operate but show higher prevalence because of persistent antigenemia that may not fully capture the presence or absence of active malaria infection. The ultrasensistive HRP2 has proved useful in asymptomatic individuals but are expensive. We assessed the utility of HRP2 RDT for malaria surveillance among asymptomatic individuals in the Federal Capital Territory (FCT), Nigeria. A total of 528 children and adult participants from five communities in three Area Councils using a cross-sectional study design. Malaria RDTs and blood smear microscopy were prepared and processed following standard protocol. Questionnaires were administered to collect demographic and other malaria information. CareStart™ Malaria HPR2 RDT was the rapid diagnostic test used, while Giemsa staining technique was used for the malaria microscopy. The median age of the sampled group was 19 years and 212 of the study participants were male while 316 were female. 41.5% (219) of the entire study population were positive by the HRP-2 malaria RDT while Forty-six (8.7%) were positive by malaria microscopy. The performance of the HRP-2 RDT evaluated were: 14.2%, 95.1%, 67.4% and 61.0% for sensitivity, specificity, PPV, and NPV respectively.There was a higher positivity rate recorded by the HRP-2 RDT compared to microscopy. False positivity rate is a major challenge for the adoption of HRP2 RDTs for malaria surveillance while also noting that submicroscopic parasitaemia and low density parasitaemia are major challenges with microscopy. Field adaptable and less expensive tests for malaria surveillance will enhance regular malaria surveillance for programme monitoring and deserves great attention.

0947

FACTORS ASSOCIATED WITH IGG ANTIBODY RESPONSE TO *ANOPHELES ALBIMANUS* SALIVARY GLAND EXTRACT AMONG 6- AND 7-YEAR-OLD CHILDREN: HAITI, 2016

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Malaria prevalence is low across Haiti and heterogeneous by region and age, indicating a need for accurate, precise estimates and understanding of exposure. Serological assays can aid in population exposure estimates to the primary vector, *Anopheles albimanus*, and the primary malaria species, *Plasmodium falciparum*. From February to August 2016, children ages 6 and 7 were enrolled at schools with blood samples assessed for rapid diagnostic testing of active *P. falciparum* malaria infection and later serological analysis of vector and malaria parasite exposure. Among 11,541 children enrolled at 350 schools, a multiplex bead-based assay included targets for IgG against *An. albimanus* whole salivary gland extract (SGE) and four *P. falciparum* antigens. Logistic regression estimated odds of above-median ("high") anti-SGE IgG levels, adjusting for individual- and environmental-level covariates. Environmental data were matched to school GPS coordinates and averaged across the temporal study period. Significant spatial clustering of schools showing increased numbers of children with high SGE IgG levels were detected using a Bernoulli model. Seropositivity to CSP, LSA-1, *Pf*AMA1, and *Pf*MSP-1_{19} were 3.8%, 0.8%, 0.4%, and 4.9%, respectively. Girls had 12% (95% CI: 1%, 23%) increased odds of high SGE IgG levels compared to boys, while children seropositive to *Pf*MSP-1_{19} had 53% (95% CI: 17%, 101%) higher odds compared to *Pf*MSP-1_{19} seronegatives. For every 50 mm increase of mean monthly rainfall, a 29% (95% CI: 12%, 49%) increase in odds of high anti-SGE IgG was observed. Compared to the lowest quartile, quartiles 2, 3, and 4 of higher elevation were associated with successively lower odds of high anti-SGE IgG: 0.82 (95% CI: 0.59, 1.13), 0.43 (95% CI: 0.29, 0.64), and 0.35 (95% CI: 0.22, 0.54), respectively. One significant spatial cluster of children enrolled with high anti-SGE IgG was detected in southern Haiti, and six clusters identified in northern. The ability to estimate population exposure to *An. albimanus* through salivary antigen serology among children has strong associations with various individual and environmental factors.

0948

HEME-INDUCED EXPRESSIONS OF IL-6R, TLR4 AND NFκB IN HUMAN BRAIN ENDOTHELIAL CELLS (HBEC-5I) AND MACROPHAGES (THP-1) ARE MODULATED BY MIR-451A AND LET-7I-5P-LOADED EXTRACELLULAR VESICLES (EVS)

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Plasmodium, a genus of parasite involved in malaria pathogenesis, infects and injures erythrocytes, releasing cytotoxic heme into circulation, similar to sickle cell disease (SCD). Excess heme is linked to the release of proinflammatory cytokines which increase morbidity and mortality associated with malaria. The mechanisms mediating heme-induced

inflammation have been linked to microRNAs (miRNA) such as miR-451a and let-7i-5p activity. MiR-451a targets interleukin-6 receptor (IL-6R) and let-7i-5p targets Toll-Like Receptor 4 (TLR4); two heme-induced receptors associated with nuclear factor kappa B (NFκB) signaling. MiRNAs carried in extracellular vesicles (EVs) such as exosomes impact malaria pathogenesis. We hypothesized that delivery of miR-451a or let-7i-5p in EVs to vascular endothelial cells (HBEC-5i) and macrophages (THP-1) could alter heme-induced inflammation *in vitro*. To test this, we treated HBEC-5i or THP-1 cells with liposome (artificial EV)-loaded miR-451a or let-7i-5p mimic oligonucleotides concurrently with heme and proper controls for 24 hours. Liposomes have been shown to be as effective as exosomes. In HBEC-5i, gene expression of IL-6R and TLR4 was gaged by RT-qPCR and NFκB protein was analyzed by Western blot. Griess and arginase assays verified if THP-1 shifted to proinflammatory (M1) or immunosuppressive (M2) phenotypes. Statistical significance was defined by student's t-test and ANOVA. Our results showed that miR-451a or let-7i-5p-loaded liposomes significantly ($p<0.05$) reduced IL-6R, and TLR4 heme-induced inflammatory responses in HBEC-5i and we found that NFκB was reduced when treated with miR-451 and heme. In THP-1, let-7i-5p reduced the M1 phenotype. These results suggest that both miR-451a and let-7i-5p-loaded liposomes can deliver miRNA to attenuate cellular stress in vascular endothelial cells and the heme-induced proinflammatory response in macrophages. Future studies will focus on defining the mechanism(s) whereby miRNA-loaded EVs reduce cellular stress caused by excess heme. Such an approach could be enhanced to reduce morbidity and mortality linked to malaria infection and SCD.

0949

HETEROLOGOUS EXPRESSION AND EARLY CHARACTERIZATION OF *PLASMODIUM VIVAX* SPOROZOITE ANTIGENS ESSENTIAL FOR LIVER-STAGE INVASION

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Plasmodium vivax is the most geographically widespread cause of malaria and poses some unique challenges for malaria eradication. Most importantly, P. vivax dormant liver-stages, termed hypnozoites, lead to relapse blood-stage infections weeks to years after the initial infection. Since drug treatment options can be limited, vaccines targeting the pre-erythrocytic (PE) stage of P. vivax represent a potential approach to prevent relapse infections. Antibodies to the circumsporozoite protein (CSP) can prevent infection and coupling CSP with other PE antigens are anticipated to improve strain-transcending, broadly neutralizing efficacy of a potential P. vivax vaccine. To guide selection of potential vaccine candidates, we identified infection-related targets that are upregulated with infectivity and accessible to neutralizing antibodies to block infection. This study identified the conserved surface sporozoite protein 3 (SSP3) as one of several genes upregulated upon activation of infectivity of P. vivax sporozoites. Other studies in P. yoelii identified SSP3 to be important for gliding motility and may provide a synergistic target when combined with CSP. To investigate its potential as a multivalent component of a P. vivax PE vaccine, we produced recombinant SSP3 antigen and determined that some patient sera from malaria-endemic provinces of Thailand had strong serological reactivity. Bioinformatic analysis revealed multiple predicted B-cell and T-cell epitopes on selected antigens and dN/dS analysis was used to correlate with potential sites under immune selection pressure. Further analyses are underway to validate the potential of P. vivax SSP3 as a component of a multivalent PE vaccine as a preliminary step in the characterization of potential multivalent P. vivax vaccine.

0950

ROLE OF ANTIMALARIAL ANTIBODIES IN FUNCTIONAL MODULATION OF THE NATURAL KILLER CELL RESPONSE TO MALARIA

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Studies of natural killer (NK) cells have mainly focused on their role in viral infections. There is an increased interest in understanding the role of NK cells in the control of *P. falciparum* malaria infection. It was recently shown that NK cells inhibit *P. falciparum* growth and kill *P. falciparum* infected red blood cells opsonized with malaria-specific IgG antibodies through antibody-dependent cellular cytotoxicity (ADCC). However, prior studies utilized *P. falciparum* laboratory strains that have undergone prolonged culture, and it is important to explore NK cell-mediated ADCC utilizing freshly cultured *P. falciparum* parasites from an African setting. We hypothesized that NK cell-mediated ADCC will be greater in freshly cultured *P. falciparum* parasites compared to lab-adapted strains, and that NK cell-mediated ADCC will be greater using plasma obtained from children living in high vs. low transmission settings. We purified NK cells obtained from adults living in malaria-endemic Uganda, cultured these cells with lab-adapted 3D7 or freshly cultured *P. falciparum* parasites in the presence of pooled plasma from malaria exposed individuals or controls, and measured levels of CD107a, the classical marker for NK cell degranulation. We also compared levels of NK cell degranulation using pooled plasma from populations with varied malaria transmission intensity. Preliminary results indicate that NK cells only minimally reacted to *P. falciparum* 3D7 or freshly cultured *P. falciparum* parasites in the absence of plasma, but levels of degranulation following opsonization with malaria-exposed pooled plasma were similar between freshly cultured *P. falciparum* parasites and lab-adapted 3D7 (20.1% vs. 29.7% CD107a+ NK cells). Experiments comparing ADCC utilizing age-matched plasma from participants living in populations with high vs. low malaria transmission is ongoing. These results highlight an important role for ADCC by NK cells in immunity against malaria and suggest an important new mechanism for the evaluation of malaria vaccine candidates.

0951

UNDERSTANDING THE ROLE OF INNATE IMMUNITY IN CONFERRING RESISTANCE TO MALARIA IN MALI

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Malaria is responsible for nearly half a million deaths every year, and a highly efficacious vaccine is currently unavailable. The immune correlates of clinical protection from malaria remain elusive. Further, years of repeated exposure to the parasite does not typically confer sterilizing protection from parasitemia. We have previously observed a unique subset

of children living in Kalifabougou, Mali who remained free of *Plasmodium falciparum* parasitemia during a single malaria season as assessed by intensive PCR-based surveillance. These children seemed to have acquired sterile immunity despite being naturally exposed to malaria. We found certain gene signatures which were associated with this resistance to malaria[ref1]. In this study, we compared the immune landscape between malaria resistance and susceptibility. We carried out CITE-seq of peripheral blood mononuclear cells (PBMCs) from malaria resistant and susceptible children. Using a panel of 36 antibodies, we profiled ~6000 PBMCs from four children in each category with concomitant B cell receptor (BCR) sequencing. We observed that multiple clusters of monocytes that were different in malaria resistant children as compared to susceptible children. In addition to monocytes, there were differences in the frequencies of other innate-like immune subsets such as gamma delta (γδ) T cells and mucosal-associated invariant T (MAIT) cells. We are currently trying to understand the role of these innate immune cells in conferring resistance to malaria.

0952

ANTIBODY RESPONSES TO PVMSP8 IN ASYMPTOMATIC *PLASMODIUM VIVAX* INFECTED INDIVIDUALS FROM THE PERUVIAN AMAZON

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Plasmodium vivax Merozoite Surface Protein 8 (PvMSP8) has been described as a good biomarker for detection of recent exposure to *P. vivax* infection in individuals from the Peruvian Amazon. For this study, we tested the hypothesis that *P. vivax* (Pv) asymptomatic infected individuals (Asym) feature different antibody signatures against PvMSP8, in comparison to Pv Symptomatic infected individuals (Sym), predictors of clinical immunity. A small case-control study was carried out for the enrollment of Sym, Asym Pv infected individuals and control healthy individuals across 13 riverine communities from the Peruvian Amazon from 2018 to 2021. Overall, 29 individuals were enrolled as Pv Asym, 49 as Pv Sym, and 30 as healthy controls. Once enrolled, individuals were follow-up during the third and sixth months. IgM, total IgG, and IgG subtypes (IgG1, IgG2, and IgG3) levels against PvMSP8 baculovirus expressed recombinant protein, were not significantly different between Sym and Asym, but were higher in comparison to control healthy individuals. Interestingly, IgG2 antibodies responses against PvMSP8 were negatively associated with parasitemia as determined by qPCR. High IgG2 levels had been previously reported in Pv Sym from South Korea but never studied in Pv Asym individuals or correlated to parasitemia. Antibody levels during the third and sixth months of follow-up significantly declined in the case of total IgG, IgG1, and IgG2 but not for IgM and IgG3. Pv Asym individual's antibody levels against other biomarkers will be assessed, still remains to be explored the functional role of antibodies from Pv Asym and their correlation with common low parasitemias observed in this endemic setting.

0953

A SYSTEMS SEROLOGY APPROACH TO CAPTURE THE COMPLEXITY OF THE IMMUNE RESPONSE TO SEVERE *PLASMODIUM FALCIPARUM* MALARIA AND IDENTIFY THE KEY CORRELATES OF PROTECTION

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Sequestration of *Plasmodium falciparum* infected erythrocytes (IE) is an important contributor to severe malaria in children and is mediated by a family of proteins called *P. falciparum* erythrocyte membrane protein 1 (P*f*EMP1) that are displayed on the IE surface. Antibody responses to multiple *PfEMP1* have been associated with protection against severe malaria however the functional features of antibodies targeting P*f*EMP1 that correlate with protection are poorly defined. Whilst traditional studies attempt to correlate total levels of IgG with protection, 'systems serology' involves measuring a large range of antibody targets and Fc characteristics to capture the complexity of the immune response, combined with machine learning to identify key targets and features of antibodies that are associated with clinical outcomes. In our previous work, we have applied a systems serology approach to identify a set of PfEMP1 antibody targets and Fc characteristics associated with protection from cerebral malaria in Malawian children. In this study, we evaluate the PfEMP1 targets and Fc characteristics of antibodies in a case control study of Papua New Guinean children (PNG) with severe malaria (predominantly severe anaemia) or uncomplicated malaria (157 and 82 children, respectively), including convalescent plasma from many children. Antibody responses are being measured by bead-based multiplex array for 33 recombinant *P. falciparum* domains that have been associated with severe or uncomplicated malaria. We are profiling antibody isotypes and subclasses (IgG, IgM, IgG1-4), Fc receptor binding (FcγRIIa, IIb, IIIa, IIIb) and complement fixation (C1q) for each antigen and will use machine learning techniques to identify the key correlates of protection. Differences between acute and convalescent responses will be identified and findings will be compared to our previous observations in Malawi. Data is currently being evaluated and results will be discussed.

0954

ELEVATED INNATE IMMUNE RESPONSES IN FEMALE MICE CONTRIBUTE TO PROTECTION INDUCED WITH RADIATION-ATTENUATED *PLASMODIUM BERGHEI* SPOROZOITES

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Sex-related differences in immune responses to infections and vaccines have been observed; females have elevated reactivity as compared to males. Both humans and mice display a male bias to Plasmodium prevalence, incidence, and parasite load. With an exception of a single study showing that testosterone reduces adoptive immunity and contributes to sex differences in protection, no sex-related differences have been observed in responses induced with radiation-attenuated sporozoites (RAS). We considered the possibility that multiple RAS doses needed to induce lasting sterile protection may obviate potential sex-related differences in immune responses and protection. Therefore, we asked if sex-related differences could become apparent following a single dose of RAS immunization. Male and female C57Bl/6 mice received one dose of *Plasmodium berghei* (Pb) RAS; following infectious sporozoite (spz) challenge, males became parasitemic by day 5, while female mice remained sterile protected. Results from *in vivo* imaging of liver parasite burden (LPB) after challenge with luciferase expressing Pb spz confirmed that females controlled liver stage infection earlier than males. At 48hrs post challenge, Pb RAS immunized female mice had significantly lower LPB as compared to infectivity controls, while Pb RAS immunized male mice did not. This suggests that early immune responses in the livers of females controlled or eliminated LPB. Analysis of gene expression in livers sampled at 6 hrs and 30 hrs post challenge confirmed sex-related differences among 49 genes ($p<0.01$), with 15 genes up-regulated ≥2-fold in female compared to male mice. Among the up-regulated transcripts, IFN-γ, IL-4, CCL5, and T-bet are associated with liver resident γδ T cells

and/or expansion of NKT cells. We propose that sterile protective immunity in female C57BL/6 mice stems from elevated innate immunity that appear to be linked to the dose of RAS. These results show for the first time that innate immune response impact sex-related protective immunity induced with RAS. These observations need to be considered in developing malaria interventions.

0955

TRANSCRIPTOME ANALYSES REVEAL DISRUPTIONS IN THE HSP60-HSP70-TLR SIGNALING PATHWAY ARE CENTRAL TO THE PATHOGENESIS OF SEVERE MALARIAL ANEMIA IN KENYAN CHILDREN

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Malaria remains a significant health burden in sub-Saharan Africa. In holoendemic *Plasmodium falciparum* transmission regions, such as western Kenya, severe malaria manifests primarily as severe malaria anemia (SMA, Hb<5.0g/dL) in children (<5 years). Our previous study using a candidate gene approach discovered that heat shock protein 70 (HSP70) transcripts and protein are significantly suppressed in children with SMA, as are their primary activator, glutamine (GLN). To further define signaling pathways that are central to the pathogenesis of SMA, we performed Next-Generation Sequencing for the entire expressed transcriptome on samples collected from Kenyan children (3-36 months) with acute malaria prior to antimalarial treatment. Children were stratified into non-SMA (Hb>5.0 g/dL, n=39) and SMA (n=25). Enrichment analyses were performed using MetaCore™ with a false discovery rate (FDR)-adjusted $P<0.05$ for differentially expressed genes (log_2) in the models (total=6,862 genes). These investigations revealed HSP60 and HSP70/TLR signaling pathway as one of the top-ranked pathway maps ($P=2.538x10^{-11}$, FDR=$6.325x10^{-9}$) with 32 of 54 nodes for the differentially expressed genes. HSP-70 (HSPA1A) and HSP60 (HSPD1), signals for the inflammatory response through cytokine production, were downregulated. TLR4 and MD-2, which activate downstream signaling via HSP60, were also downregulated. Consistent with TLR4 suppression, IRAK1/2 and IRAK4 were downregulated. E3 ubiquitin-ligase, and the E2 conjugating complex gene, UEV1A, which activate TAB2 and TAB3 for ubiquitination were all upregulated. IKK-alpha was downregulated as were its downstream targets IkB, NF-kB1, and NF-kB2. This resulted in a pattern of increased expression for CD80, CD86, and MHC class II, and decreased transcript levels for IL-1β, ICAM1 and MHC class I. Although signaling through MEK1/2, ERK1/2, MEK3, and AP-1 were upregulated, subsequent changes in their target genes, IL-10, TNF-α, and IL-6 were not observed. Collectively, these results show that altered signaling through the HSP60/HSP70/TLR pathway are central to the pathogenesis of SMA.

0956

A LONGITUDINAL ASSESSMENT OF *PLASMODIUM FALCIPARUM* TRANSMISSION-BLOCKING IMMUNITY IN AREAS OF INTENSE AND DECLINING MALARIA TRANSMISSION INTENSITY IN UGANDA

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Naturally acquired antibody responses to gametocyte antigens can reduce *Plasmodium falciparum* transmission to mosquitoes. We studied the longitudinal kinetics of transmission reducing activity (TRA) and the associated immune profile in an all-age Ugandan cohort. Between 2013 and 2019, plasma samples were taken every 1 to 3 months from a cohort of participants in Tororo, Uganda, during a time transmission declined following effective malaria control. 2484 plasma samples (4 time points over 3 years) were analysed by ELISA for reactivity against total gametocyte lysate and gametocyte antigens Pfs48/45 and Pfs230-CMB, and for gamete recognition by surface immune-fluorescence assays (SIFA). Purified IgG was tested for functional TRA by standard membrane feeding assay (SMFA), using cultured NF54 gametocytes, *An. stephensi* mosquitoes, and a threshold for functional activity at >80% reduction in oocyst intensity (TRA>80%). A custom-made protein microarray was used to identify TRA-associated antigens. We observed high levels of TRA (>80%) in 9.7% (23/236) of samples. TRA>80% was strongly associated with antibody responses against Pfs48/45 ($p<0.001$) and to a lesser extent Pfs230 ($p=0.137$). The strongest predictor of TRA>80% was reactivity in the gamete SIFA ($p<0.001$), allowing discrimination between blockers and non-blockers with 100% sensitivity and 79% specificity. From 11 individuals whose sera strongly blocked transmission on at least one occasion, we are currently performing repeated SMFA with up to 10 samples per donor. Preliminary results show persisting transmission blockade for >1 year in a minority of donors, others display fluctuating TRA over time. Their samples are currently being probed on a protein microarray with 567 gametocyte specific genes. We uncovered high recognition of recombinant gametocyte antigens and stable levels of high TRA in a minority of individuals. Our longitudinal study is the most comprehensive assessment of anti-gametocyte immunity to date and supports the development and deployment of transmission-blocking interventions.

0957

CHARACTERIZING SEROLOGICAL RESPONSES TO VARIANT SURFACE ANTIGENS IN FIRST *PLASMODIUM FALCIPARUM* INFECTIONS IN MALAWIAN INFANTS

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Immunity to *Plasmodium falciparum* variant surface antigens (VSAs), including erythrocyte membrane protein1s (PfEMP1s), RIFINs, and STEVORs, may determine whether the host experiences malaria symptoms. Constitutive PfEMP1 extracellular (EC) domains are highly diverse, allowing the parasite to escape the host immune response. We evaluated first malaria infections in infants from a cohort study conducted in Malawi and assessed serological responses to VSAs among 81 infants who had malaria infection in the first year of life. Asymptomatic infection was defined as a lack of symptoms with a positive RT-PCR for *P. falciparum* 18S rRNA or a parasite-positive blood smear; clinical malaria was defined as any malaria symptoms with a positive rapid diagnostic test. Protein microarrays with 243 PfEMP1 fragments and 9 RIFINs/STEVORs from reference genomes and field isolates were probed with sera collected at quarterly visits between 6 and 12 months. We assessed seroreactivity (mean fluorescent readout) and serorecognition (>2 standard deviations above naïve seroreactivity) at the time of asymptomatic infection, clinical disease, and uninfected visits to establish if serological profiles varied by infection type. The proportion of

infants with serorecognized EC PfEMP1s was higher during asymptomatic infection (46%) than during clinical disease (40%). Seroreactivity to three EC PfEMP1 fragments and one STEVOR was significantly higher during asymptomatic infection than at uninfected visits; seroreactivity to only one EC PfEMP1 fragment was significantly higher during asymptomatic infection than during clinical disease. When assessing serological response following infection, greater changes in seroreactivity to EC PfEMP1s were observed following asymptomatic infection, with significant fluctuations in 27 PfEMP1s (15 increased and 12 decreased), compared to only four PfEMP1s following clinical disease (one increased, three decreased). Broader serological responses to PfEMP1s appear to be associated with asymptomatic infection as compared to clinical disease; this may be due to malaria treatment at the time of clinical disease diagnosis.

0958

*PM*RBP1A SEROPREVALENCE IN GHANA

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Regarded as the Olympic champion of persistence, *Plasmodium malariae* infection is more prevalent than generally perceived. Although it is considered to cause a milder form of malaria, it has been implicated in nephrotic syndrome, inflammation of the gall bladder and anaemia-related deaths. How this parasite contributes to the pathogenesis of these complications remains to be `understood. Possible factors include its unique biology of a longer life cycle, typical low parasitemia and chronic-promoting factor(s) which permit its persistence in the human host. Coupled with the current neglect of *P. malariae* by malaria elimination programmes which can lead to its persistence prompts the need to study it. *P. falciparum* reticulocyte binding-like homologue 5 (*Pf*Rh5) is the leading blood-stage vaccine for Plasmodium falciparum while *P. vivax* reticulocyte binding protein 2b is proving to be an effective vaccine candidate for *P. vivax* vaccine. It has been shown that *P. malariae* reticulocyte binding protein 1a (*Pm*RBP1a) is the most divergent among the PmRBPs suggestive of being a/the host-determining factor. A sequence homology search revealed the presence of nucleotide-binding and erythrocyte-binding domains in *Pm*RBP1a, this suggests the protein is involved in both sensing and anchorage to erythrocytes when invading the cell. *Pm*RBPs genetic analysis using data from South-East Asia and Africa revealed that the sampled strains have limited genetic sequence variation and also showed evidence of the genes undergoing purifying selection. ELISA data on human serum samples from coastal regions of Ghana showed evidence of the antigen being immunogenic with relatively high titres to the N-terminus, a region that overlaps with its erythrocyte-binding domain.

0959

CLINICAL FINDINGS AND DYNAMICS OF CYTOKINES AND CHEMOKINES IN HOSPITALIZED PATIENTS WITH *PLASMODIUM VIVAX,* CÓRDOBA COLOMBIA

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Cytokines and chemokines play an important role in the clinical course of malaria. Eighteen patients hospitalized for *Plasmodium vivax* were studied. A sample was taken on the day of admission (day 1) and on day 3 of hospitalization. Were determine hematological parameters (blood count), blood chemistry (Glycemia, urea, creatinine, total bilirubin, direct bilirubin, GOT transaminase, GPT transaminase and alkaline phosphatase) and the plasma concentration of cytokines (IL-4, IL-2, IL-1B, TNFα, IL-17A, IL-6, IFNγ, IL-12p70 IL-10, TGF-b1) and chemokines (IP-10, MCP-1, IL-8). The patients showed anemia and thrombocytopenia, on day 1 66.6% of the patients presented mild anemia and 22% moderate anemia and on day 3 of follow-up it was evidenced that 70.5% presented mild anemia and 17.6% moderate anemia and 5.8% severe anemia. The platelet counts of the patients on day 1, showed thrombocytopenia (94.4%), on day 3, the platelet counts increased, however, the values remained below 150,000 x10³/ul. Glycemia on day 1 showed that 33% had hyperglycemia and 16% had hypoglycemia, at follow-up on day 3, 39% had hyperglycemia and 22% hypoglycemia, however, the determination of the mean ($\bar{x}$) of glucose showed in the result that on day 1 with $\bar{x}$= 92.3, on day 3 with $\bar{x}$= 87.9, there is no significant difference. It was found that the plasma concentration of proinflammatory cytokines and chemokines on day 1 were altered compared to day 3, finding a significant difference in all molecules (IL4, p=0.0094; IL2, p=0.0006; TNF, p=0.0032, IL6, p=0.0001, IL17, p=0.0037, IL1b, p=0.040, IFNg, p=0.0001, IL12, p=0.032, IP10=0.0094, MCP1, p = 0.0001, IL8, p = 0.0049). IL-10 and TGF-b1 decreased, IL-10 showed a significant difference between day 1 and day 3 (P=0.0001), however, TGF-β1 did not show a significant difference (p= 0.1131).This study suggests that treatment of vivax malaria patients generates homeostasis of the proinflammatory cytokine/chemokine response and of the IL10.

0960

DETERMINANTS OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY UPTAKE IN CÔTE D'IVOIRE: A MIXED-METHODS ASSESSMENT BASED ON THE OPPORTUNITY CAPACITY MOTIVATION FRAMEWORK

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In Côte d'Ivoire, malaria is the number one reason for consultation in health facilities and pregnant women are among the most vulnerable. Only 47% of pregnant women receive the WHO-recommended three doses of intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP). To address these issues, we sought to determine opportunity, capacity, and motivation factors (using the Opportunity Capacity Motivation Framework) associated with the IPTp-SP uptake. A mixed-methods assessment was conducted in 83 health districts of Cote d'Ivoire. Women 15-49 years old who had a live birth in the past two years (N=3402) were surveyed using a structured questionnaire and qualitative data were gathered through in-depth interviews with health workers, community leaders, and religious leaders and focus group discussions with mothers in urban and rural areas. Data triangulation of the qualitative and quantitative data was conducted. SP was available in health centers during ANC visits for 50.9% of respondents and 45.6% mentioned that it was given free of charge. Only 52.2% found the quality of services and SP administration at health centers adequate and 41.7% mentioned they can afford SP. The majority of mothers (79.5%) said they liked SP; 72.5% preferred SP over other means of prevention; and 84.5% stated high confidence in SP to prevent malaria during pregnancy. Additionally, 71.6% said that those around them encourage them to use SP, 65.8% said their friends would be willing to teach them how to use it, and 25.6% mentioned that their friends would be disappointed if they did not use SP. Only 4.3% of women reported that taking SP is harmful to the baby and 8.1% believe that SP is not effective. Qualitative data from IDIs and FGDs with health workers, community leaders, religious leaders and mothers confirmed these findings and it will be also be presented. Our study showed that problems with the delivery of IPTp-SP are linked to weaknesses within the health system, such as insufficient resources to provide free drugs, provider behavior and poorly trained staff, and ineffective procurement and supply chain management.

0961

NOVEL METHOD TO QUANTIFY INFRASTRUCTURE DAMAGE FOLLOWING SEVERE STORMS IN MOZAMBIQUE

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Increases in the frequency and severity of storms is a hallmark of climate change. Climate change will have impacts on the incidence, prevalence, and geographic range of infectious diseases, particularly malaria and other vector borne diseases. One mechanism for these impacts is through changing the environmental suitability of vector habitats in endemic areas. Another mechanism is through infrastructure damage to households, schools, and healthcare facilities. This infrastructure damage leads to increased risk for interaction with infectious vectors and decreased access to community and health services. However, these infrastructure damages are difficult to quantify in the aftermath of storms, particularly outside of areas of direct storm impact (coasts). We conducted a retrospective study to quantify the infrastructural impacts of Cyclone Idai (2019) in the central corridor of Mozambique. As of 2019, Cyclone Idai was the largest tropical storm to make landfall in the southern hemisphere and the range of damage outside of the coastal region is still largely unquantified. We used satellite imagery in Google Earth Pro to determine the number of schools and healthcare facilities damaged due to Cyclone Idai. We used a database of schools in the central corridor of Mozambique from OpenStreetMap and healthcare facilities from an open-source database of health facilities in sub-Saharan Africa. These databases included 71 schools and 98 healthcare facilities. These databases were supplemented with results from Google Earth Pro searches. We created a database of damage to these facilities, documenting the severity of the damage (completely destroyed, partially destroyed) and time frame until fully repairing the damage. We will spatially and temporally join these data with malaria incidence data at the health facility level throughout the corridor of Mozambique. Using these databases, we will construct a geospatial model to quantify associations between infrastructure damage and malaria incidence in the aftermath of severe storms in Mozambique.

0962

EXPLORING A NEW MALARIA SBC APPROACH—TARGETING COUPLES TO IMPROVE ITN USE IN MALAWI

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The shift to universal insecticide-treated nets (ITN) coverage in Malawi brings opportunities for effective social and behavior change (SBC) interventions targeted to general populations, including couples, to improve overall ITN use. We explored couple dynamics related to ITN use in Malawi to inform if couple-centered SBC approaches may be used to improve consistent ITN use. Analysis focused on 1,213 couple-dyads (married or cohabitating men and women), a subset of a nationally representative survey conducted in 2021. Key variables for both members of the couple-dyad included i) consistent ITN use and ii) ITN ideation—the combination of cognitive, social, and emotional factors related to behaviors—measured as a composite score of several psychosocial factors. Concordance between men and women in the couple-dyad was assessed using Cohen's Kappa statistic (k). Logistic regressions analysis generated adjusted odds ratios (aOR) and associated 95% confidence intervals (CI) for any association with concordant couples' consistent ITN use and ITN ideation, adjusting for household and couple characteristics. Over half (54%) of couple dyads reported consistent ITN use for men and women (k=0.81). Concordance in ITN ideation (aOR: 1.66; 95% CI: 1.08-2.55) was a statistically significant predictor of consistent ITN use among couples. Factors statistically significantly associated with couples' concordance in high ITN ideation included residence in Central (aOR: 2.27: 95% CI: 1.59-3.25) or Southern (aOR: 2.35; 95% CI: 1.42-3.91) regions of Malawi compared to the North; wealthier households (aOR: 2.05; 95% CI: 1.20-3.51) and having at least primary education (aOR: 1.59; 95% CI: 1.15-2.20). Our study demonstrated that couples are likely to jointly use or not use ITNs consistently, suggesting that a couples' approach may be worth exploring in the design and implementation of SBC programs to promote consistent ITN use.

0963

EXPLORING THE CULTURAL NORMS, BELIEF, PERCEPTION AND PRACTICES THAT CAN INFLUENCE IPTI IMPLEMENTATION IN NIGERIA: A QUALITATIVE STUDY APPROACH

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Malaria continues to be one of Africa's public health issues. In Nigeria, as in most sub-Saharan countries, children under 5 are at highest risk of severe malaria and mortality. The risks and consequences of malaria disease vary across the first five years of life. Nigeria is responsible for 27% of the global malaria cases. Children, mostly infants are more prone to malaria. WHO has recommended IPTi to run alongside EPI services. Still, only Sierra Leone has scaled it up. Exploring cultural norms, beliefs and practices that influence malaria service uptake is critical for developing effective malaria prevention, control strategies and closing the gap between efficacy and effectiveness. This study was conducted in Ebonyi and Osun States, Nigeria, and aimed to explore cultural norms, beliefs, and practices that could influence IPTi implementation in Nigeria. It employed an exploratory research design with the use of various qualitative data collection techniques including focus group discussions (FGDs), in-depth interviews (IDIs), and Key Informant Interviews (KIIs). Interviews were conducted with different stakeholders in the states' health sector, community leaders and caregivers of infants. Six FGDs, 13 IDIs, and seven KIIs were conducted in each state. Participants were selected purposively. Data were analyzed using content analysis. Factors that could facilitate IPTi uptake include cultural norm like "nnenji ulo" which ensure newborn babies are well protected against mosquitoes, belief that immunization is beneficial to the growth and development of children, and practices like community mobilization of members to embrace government programs. Also, caregivers show positive perception to general immunization for children. But, adverse reactions to drugs and additional workload on implementers are the beliefs and perceptions that could inhibit the uptake of IPTi. In conclusion, there are cultural norms, beliefs, and practices about immunization that could promote or inhibit IPTi implementation. Improving the community's understanding of the childhood immunization is imperative for the successful implementation of IPTi.

0964

ASSESSING HEALTH SEEKING BEHAVIOUR OF CAREGIVERS IN MANAGING FEVER AND MALARIA ILLNESSES AMONG NIGERIAN INFANTS: A QUALITATIVE STUDY

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Malaria remains one of Africa's most worrisome public health issues. Children are disproportionately affected by malaria in Nigeria, as they are in most Sub-Saharan countries. Nigeria accounts for about 25% of the world's malaria cases. Assessing the health seeking behaviour (HSB) of caregivers is essential, as the findings will be useful to design interventions in the context of implementing preventive and control measures for childhood illnesses such as malaria. Qualitative research was carried out in Ebonyi and Osun, Nigeria. Focus group discussions (FGDs), in-depth interviews (IDIs), and key informant interviews (KIIs) were conducted. Interviews were done with various stakeholders in health sector, with community leaders and caregivers. In each state, 6 FGDs, 13 IDIs, and 7 KIIs were done. Thematic analysis was conducted to identify and interpret the patterns of HSB as reported by caregivers. The results show that majority of the caregivers took their children to orthodox sources, such as hospitals (both private and public), pharmacies, and patent medicine store. Some of the caregivers in Osun State expressed dislike for traditional sources and strongly believe in orthodox sources for the treatment of childhood illness such as malaria. However, some caregivers were found to patronize traditional sources such as herbalists for the treatment of malaria infections in infants in Ebonyi and Osun. In most cases, caregivers patronized traditional sources before proceeding to orthodox sources. When the illness does not subside or there is no positive response, they then resort to taking them to health sources. The caregivers do not only patronize orthodox and traditional sources; they also patronize religious centres. Other methods reported include the use of un-prescribed over the counter drugs as well as religious and home care services. The findings suggest concerted efforts are required to improve the HSB of caregivers to adopt orthodox methods in treating or preventing childhood illnesses including the uptake of intermittent preventive treatment in infants.

0965

REDUCING HEALTH SHOCK, HOUSEHOLD SAVINGS AND INVESTMENTS IN EDUCATION CASE OF MALARIA IN MALI

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The findings of several research show that malaria has a negative impact on the standard of living of households, but few studies have looked at the immediate effect of malaria reduction on household savings and investments in human capital. The aim of this study was to assess the impact of malaria reduction through interventions during the period of high malaria transmission that coincides with the start of the school year in Mali, on household savings and investment in children's education. We have constituted four randomized controlled groups of households in Birga village, Mali in 2016: i-Control group: only seasonal malaria chemoprevention (SMC) campaign, ii-Full intervention group: SMC, Insecticide treated nets (LLINs) and maternal Information on malaria prevention, iii-SMC + LLINs and iv-SMC + Information. We carried out two surveys in July (pre-intervention) and December (post-intervention) on the same sample to collect information on household characteristics, education expenditures, bed net use, and medical indicators among children under 5 years old. We used the difference-in-difference methods to estimates the effects of our intervention by the intention-to-treat (ITT) approach to draw accurate conclusions and local average treatment effect (LATE) to estimate the effect for the compliers. The ITT estimates imply that, savings and education expenditures had increased by 5,37 USD and 4.82 USD respectively among households in the intervention group. The LATE estimates found 3.7 USD household savings and 3.62 USD education expenditures. While these effects were due to an increase in bednet use (28%) among children under 5 years of age, which led to a decrease in clinical malaria prevalence (9.1%) in ITT, the mechanism of transmission in LATE could not be clearly demonstrated. In Conclusion**, r**educing the level of malaria allows households to save and invest in children's education. Although the results of this study imply that effective malaria control is associated with a positive return on human capital, large-scale and long-term studies are needed to better understand this issue.

0966

DATA COACHING OF HEALTH WORKERS IMPROVES MALARIA SERVICE DATA QUALITY AND USE FOR PLANNING AND DECISION MAKING IN GHANA

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The monitoring and use of data for planning and decision-making are essential for malaria service delivery. Quality data is crucial to assess the burden of malaria in order to develop interventions for the pre-elimination of malaria in Ghana. Findings from facility assessments and supervisory visits in February 2021 show poor malaria data quality, health workers lack clarity on data elements in registers and do not use data in planning. To improve malaria data quality, U.S. President's Malaria Initiative (PMI) Impact Malaria supported the National Malaria Control Program to implement a facility-based data coaching program. A total of 270 peripheral facilities were prioritized (based on a high data error and lack of completeness in reporting in DHIS2) from 45 districts in nine of the 16 regions in Ghana. Regional and District Malaria Focal Persons and Health Information Officers were trained to visit selected facilities to offer coaching on the job. In the visit, health workers were trained on the malaria-related registers and reporting forms, tools for data validation, and the use of facility data wallcharts for planning. A standardized data quality tool was applied to assess facilities' performance and the use of quality improvement approaches to develop interventions to address gaps identified. The coaching visits reached 833 health workers in 211 facilities from five regions (coaching is underway in 59 facilities in the remaining four regions). Data quality checks showed improvement in the integrity of data from 54% to 90%, reliability of data being reported by facilities from 29% to 65%, and precision of data from 48% to 78% after six months of implementation. In the same period, data reported in DHIS2 indicated a reduction in data error from 50% to 10% and an improvement in completeness of reporting from 35% to 91%. Also, 68% of the facilities use the data wallcharts for planning the stock of malaria commodities and reviewing indicator performance during clinical meetings. Facility data coaching visits build and sustain the competence of health workers to improve malaria data recording, reporting, and validation as well as the use for planning.

0967

BARRIERS AND MOTIVATING FACTORS TO THE USE OF MALARIA SERVICES AND THE ROLE OF COMMUNITY HEALTH ACTORS IN MALARIA SERVICE PROVISION IN COTE D'IVOIRE

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Malaria remains the leading cause of morbidity and death in Côte d'Ivoire, where the uptake of preventive measures is low and communities have poor access to treatment services. We conducted a comparative mixed-methods study in four malaria strata from 2018 to 2020 to understand the barriers and motivating factors for the use of health services provided by community actors in rural and peri-urban areas. Mothers of children under 5 years old and pregnant women (N=1200) were surveyed using a structured questionnaire. Additionally, In-depth interviews (n=80) and focus groups discussions (n=80) were conducted with traditional chiefs, elderly women, religious leaders, health workers, mothers-in-law, midwives, and community health workers (CHWs). Our results showed that in very high endemic areas, pregnant women who were suffering from malaria were the most reluctant to visit a health facility (7% and 16%). Barriers included the cost of malaria treatment, shortages and stock out of commodities, and distances to health facilities. Mothers and pregnant women preferred accessing malaria services through community health actors. The most influential factor for the use of malaria services were community actors (i.e. community leaders, CHWs, village chiefs, and women leaders). Motivational factors included the relationship between health actors and the population, communication channels, and the quality of medical procedures. Community actors were the preferred choice of malaria service provision by mothers and pregnant women. They play a critical role in reaching Cote d'Ivoire's national malaria targets. However, problems within the health system are likely to contribute to the high malaria incidence in Cote d'Ivoire.

0968

REDUCTION IN MALARIA CASE FATALITY RATE AFTER IMPLEMENTATION OF AN EMERGENCY PLAN FOR IMPROVED CASE MANAGEMENT IN THE BITTOU HEALTH DISTRICT, BURKINA FASO

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In Burkina Faso, malaria remained the leading cause of death between 2014 and 2021. In the Centre Est region, uncomplicated malaria cases among children under five years of age were 11% of the country's total (3,679,128 cases) and severe malaria cases were 9% of the country's total (211,093 cases) in 2014. This region, is subdivided into 7 health districts including Bittou. In 2014, the malaria case-fatality rate (CFR) among children under five years of age in Bittou (1.39%) was higher than the average for all districts in the Centre Est region (1.08). To remedy this situation, the Bittou health district management team (HDMT) implemented an emergency plan in 2016. The plan included five components: i) sensitization of health facility staff to enable the rapid referral of severe malaria cases to the district hospital (CMA); ii) reorganization of CMA pediatric emergency management to make a physician the first point of contact; iii) Ensuring availability of supplies for severe malaria case management, including the availability of blood; iv) daily medical check-ups of hospitalized patients, and v) reinforcement of skills all HFs. Other improvements in the health system that were introduced around the same time, but were not part of the emergency plan, included: i) free care for children under 5 years of age; ii) municipal financing of ambulance fuel for transferring patients referred; iii) free blood collection; iv) free telephone calls between the health structures; v) the presence of 5 doctors at the CMA, and vi) coaching and increased dynamism of the HDMT. After implementation of the emergency plan, the malaria CFR in Bittou went from 1.39% in 2014, and 1.52% in 2015 to 0% in 2016 and 2017, 0.2% in 2018, 0% in 2019, 0.07% in 2020 and 0.05% in 2021. Malaria control remains a challenge in Burkina Faso. However, the improved CFRs seen in Bittou show that effective involvement of HDMT could potentially contribute to substantial reductions in malaria mortality.

0969

STRENGTHENING DATA SCIENCE RESEARCH CAPACITY IN MALI THROUGH SCIENTIFIC SYMPOSIA

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The West African Center of Excellence for Global Health Bioinformatics Training program is a multi-institutional partnership supported by the National Institutes of Health Human Heredity and Health in Africa (H3Africa) initiative. This program has delivered annual bioinformatics and data science symposia in Mali since 2019. This work summarizes their highlights and details challenges incurred in their development and sustainability approaches to foster the growth of local symposia in West African settings. The inaugural bioinformatics and data science symposium was held in March 2019 and included 106 student, faculty, researcher, and collaborator participants, 19 student oral presentations, eight student poster presentations, and four panel discussions. Each symposium was complemented with workshop training on computationally intensive topics, including statistical programming, bioinformatics analyses, and spatial data science. Participant home countries included Mali, Tunisia, France, Burkina Faso, Morocco, and the United States. Because of the COVID-19 pandemic, the symposium was not offered in 2020 and was reintroduced in a virtual format in June 2021. The focuses of the student presentation topics were malaria, drug resistance, and genome-wide association studies. Workshop training leveraged computer infrastructure provided by the National Institutes of Health African Center of Excellence in Bioinformatics in Mali. Notable symposia strengths included high student participation rates, high English fluency rates, high administrative involvement, and a relatively low operating budget. The primary challenges were the limited availability of large teaching computer laboratories and the lack of an academic software portal to provide discounted commercial software. Increased coordination of local symposia across West Africa is needed to regionalize capacity-building efforts and exchange local insights and perspectives. Longitudinal follow-up studies of local symposia and short-term training participants would assist in quantifying their impact.

0970

FAMILIAR VS KNOWLEDGEABLE: TREATMENT ADHERENCE MONITORING PREFERENCES OF PATIENTS TAKING 14-DAY PRIMAQUINE FOR VIVAX MALARIA IN PAPUA, INDONESIA

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One of the main factors leading to poor adherence to the 14-day primaquine radical cure for *Plasmodium vivax* is that the duration of the treatment exceeds the acute malaria symptoms. Home monitoring of treatment can increase adherence but requires communication between health facilities and communities. We assessed 2 different approaches in 5 health centers in a malaria endemic area of Indonesian Papua. Clinic catchment areas were either villages inhabited by indigenous populations and agricultural migrants, or more urbanized areas with a mix of indigenous populations, agricultural migrants, and other migrant workers. Approaches were: home visits by community health workers (CHWs) and standardized phone calls by a study nurse. Qualitative methods were used to evaluate both approaches from a patient perspective. Home visits were largely accepted in villages where 78.3% of the patients were successfully visited at home by CHWs as compared to only 32.6% in the urbanized areas. Having a local CHW in the village or belonging to the same ethnic group increased the effectiveness.In urbanized areas, the intervention was less effective due to operational difficulties such as locating patients' residence, patients declining interaction with CHW they perceived as strangers, and patient mobility. Phone calls by study nurses were preferred to home visits since nurses were perceived as a legitimate source of health information, calls could be received without being home, and the encounter took less time than a home visit. Phone ownership was 53.7% in urban populations compared to 42.3% in villages. Understanding social relations at the microlevel was key to identifying the effectiveness of the public health approach that required creating linkages between health facilities and communities. Multi-faceted strategies that consider different social structures have the potential to improve adherence to antimalarial treatment.

0971

LONG TERM FORECASTING OF MALARIA COMMODITIES AND DEVELOPMENT OF NOVEL POLICY TOOLS

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The COVID-19 pandemic has highlighted that abrupt changes to global supply chains and volatile markets can have significant impact on the availability of key health commodities. Forecasting demand and need can ensure malaria endemic countries are supplied with un-interrupted access to commodities such as bed nets, sprays for campaigns, treatments (ACTs) and diagnostics (RDTs), whilst trying to strategically anticipate possible restrictions and/or market opportunities. To improve the quality and transparency of information about how malaria commodity markets will evolve over the next decade, a modelling framework was built to extrapolate key epidemiological metrics (malaria prevalence and incidence, fevers) and intervention coverages (ITN, IRS, RDT, AM) to feed into estimations of future commodity need for vector control and case management under different scenarios. Additionally, an interactive web-based policy tool, intended for donors, manufacturers, and policy makers, has been developed specifically for ITN distribution campaigns. The tool estimates the number of new nets required per country over a future time span to meet policy objectives set by the user. It provides flexibility for users to set target coverage objectives for a given adjustable campaign period, define target population in rural and urban setting based on parasite prevalence and amplify/supress distributional efficiency such as net retention rates, overallocation and usage rate. The result of this work feeds into a larger consortia framework that estimates long-term commodity demand under various budget scenarios and emergence of global threats such as insecticide and drug resistance.

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SUPERVISION, PERFORMANCE ASSESSMENT, AND RECOGNITION STRATEGY (SPARS) APPROACH LEADS TO IMPROVED PERFORMANCE IN MALAGASY DISTRICT PHARMACIES

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In Madagascar, the health commodity supply chain faces many challenges, including for malaria products. Past assessments indicated that district pharmacies (Pha-G-Dis) face challenges including adhering to the Central Medical Store's cyclical order schedule, accurately quantifying the commodities they need, comprehensive and timely reporting of stock status data, and infrequent supervision and evaluation due to the limited capacity of the Ministry of Public Health. To address this, the Improving Market Partnership and Access to Commodities Together (IMPACT) project adapted the Supervision, Performance Assessment, and Recognition Strategy (SPARS) approach from Uganda, implementing in 78 Pha-G-Dis (of 114 or 68%) supported by the U.S. President's Malaria Initiative since 2020, to improve pharmaceutical management practices. SPARS is an indicator-based, multi-pronged strategy that combines supervision, on-the-job training, and provision of tools and guidelines with structured performance reviews to identify and prioritize issues and encourage progress by rewarding improvements. All 78 IMPACT-supported Pha-G-Dis received at least one supervision visit between April and September 2020 and at least one follow-up visit. Among the 78 Pha-G-Dis, the proportion of the Pha-G-Dis classified as "performing" (score of 90% or higher) increased from 5% to 27% (4 to 21 Pha-G-Dis), and the proportion classified as "weak" (score of 75% or less) decreased from 29% (23 Pha-G-Dis) to 5% (4 Pha-G-Dis). These results corroborate with the end-user verification survey in 2021, which found that none of the 20 Pha-G-Dis surveyed were out-of-stock of any antimalarial products for 3 or more consecutive days, a marked improvement compared to 2020 when up to 50% of the Pha-G-Dis surveyed were out-of-stock of certain formulations of Artesunate/Amodiaquine for 3 or more days. This demonstrates the utility of SPARS to effectively improve district-level supply chain management of malaria products.

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LIVESTOCK OWNERSHIP AND MALARIA INCIDENCE: EMPIRICAL EVIDENCE BASED ON A CLUSTER-RANDOMIZED TRIAL IN RURAL MOZAMBIQUE

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The dynamic relationship among humans, peri-domestic livestock, and partially zoophagic mosquitoes has been investigated to determine if co-location of humans and livestock in malaria endemic areas might affect malaria incidence. At this time, there is no consensus in the scientific literature as some studies suggest ownership of peri-domestic livestock leads to a reduction of malaria due to vector diversion (i.e., zooprophylaxsis), while others suggest peri-domestic livestock lead to an increase in malaria transmission when livestock support vector survival (i.e., zoopotentiation) and a few describe no clear relation between peri-domestic livestock and malaria transmission. In Mozambique, a country that carries 4% of the global burden of malaria, small observational studies have looked at this relationship and found evidence of a correlation between livestock proximity to the household and an increase in malaria incidence. Given the need to develop novel vector control tools in the fight against malaria, an innovative One Health approach was proposed by the BOHEMIA project to take advantage of peri-domestic livestock through the administration of ivermectin to human and livestock populations for malaria vector control. Here, we use data collected during the cluster-randomized trial that takes place in Mopeia, a highly endemic district in the Zambezia province of Mozambique, to present empirical evidence of the impact of livestock ownership, proximity, and density on malaria incidence at the household and community level. Data will be generated from an active case detection cohort of children under five years of age and a longitudinal household economic and animal health survey administered during the intervention. Multivariate regression models will be used to determine the relationship of selected independent variables related to livestock with malaria incidence, and will include known confounding socioeconomic variables.

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HARNESSING SMARTNET INITIATIVE MOBILE TECHNOLOGY AS PART OF COMMUNITY ENGAGEMENT TO SUPPORT MALARIA CONTROL IN MALAWI (2020-2021)

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Malaria is a serious public health challenge in Malawi with 6,914,975 cases in 2020 and 18% of reported hospital deaths. Malaria control efforts require timely accurate data collection and community engagement. Mobile technology use in Malawi has increased from 21.4 mobile phone subscriptions per 100 people in 2010 to 52.3 in 2020. Although rural phone ownership in Malawi is lower than urban (40% vs 81%, respectively), rural mobile phone ownership is increasing and households often share phones. The Malawi SmartNet Initiative leverages mobile technology to reach malaria insecticide-treated nets (ITN) users in real-time. In March 2020, 300,000 ITNs with a short code were distributed in 28 districts via antenatal clinics with multiple nets often going to a single recipient. Among these recipients, 54,682 people from all 28 districts voluntarily dialed in the shortcode and responded to the first survey that included questions on socio-demographics, net usage, malaria-like illnesses, and location. As of March 2022, through four surveys and an intensified recruitment campaign using local radio and other media in a single district, the SmartNet Initiative network has grown to 125,957 respondents with a unique phone number. Of whom 47,291 (38%) have answered at least three questions in a survey. A comparison of demographics between respondents and the Malawi 2017 MIS survey and 2018 Census shows that respondents were more likely to be male (70% SmartNet vs 49% Census) and were similar in age (SmartNet 62% were 15-29 years of age vs MIS 2017 58% vs Census 60%). Comparisons of reported household size, ITN possession and usage, and malaria-like illnesses are in preparation. Limitations and potential biases include low participation of respondents in multiple surveys over time, lack of generalizability of convenience sampling approach including a greater likelihood of participation by those who are literate, urban dwellers, and mobile phone owners. Although the data is not generalizable, this network provides an opportunity for large-scale community engagement and further research on its use as a means to collect strategic information in near real-time.

0975

IMPROVING QUALITY OF SERVICES FOR MALARIA CASE MANAGEMENT INCLUDING MALARIA IN PREGNANCY THROUGH INTEGRATED SUPPORTIVE SUPERVISION IN 10 DISTRICTS OF RWANDA

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Rwanda has made progress in malaria control through evidence-based approaches guided by the National Malaria Strategy (2020-2024) and is committed to improving the quality of malaria case management including malaria in pregnancy (MIP). Malaria integrated supportive supervision (ISS) tool was introduced to assess the implementation of malaria control interventions such as behavior change communication; malaria case management; availability of insecticide-treated nets (ITN), malaria drugs, malaria guidelines, and job aids; data quality checks and use at health center (HC) level. After the ISS visit the Malaria and Other Parasitic Diseases Division (MOPDD) and health facilities implemented recommendations to address the gaps identified. From October 2020 to December 2021, the program conducted capacity building of health care providers (HCPs), including malaria diagnostic and case management trainings, provision of updated guidelines and job aids, monthly data review and validation meetings, and strengthened ITN distribution at HC level. A comparative analysis of findings from 2 rounds of ISS (baseline 2020, second visit 2021) was conducted. In total, 52 of 204 HCs with low performance in malaria case management in 10 districts were selected, for a total of 104 ISS visits over the two rounds. The findings showed an increase in the availability of updated malaria guidelines in consultation rooms from 63% to 77%, and an increase in HCP's competency scores in the prevention of MIP from 61% to 83%, and HCP's competency scores in the treatment of MIP from 68% to 70%. The competency in classifying malaria cases correctly also increased from 82% to 93%. The quality of malaria diagnosis increased from 92% to 94% at HCs and 91% of visited HCs had staff trained in malaria case management. However, only 44% of the visited HCs had social behavior change materials to support malaria prevention and counseling for pregnant women attending ANC. ISS tool was useful in assessing malaria control interventions and guiding the MOPDD, health facilities, and stakeholders to improve and maintain quality malaria services.

0976

HEALTH WORKER PRACTICES IN DATA REPORTING, ANALYSIS, AND USE: RESULTS FROM POST TRAINING SURVEY IN MADAGASCAR

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Under the U.S. President's Malaria Initiative and in partnership with the National Malaria Control Program, the Measure Malaria project trained 30 data managers from 13 of Madagascar's 22 regions in malaria surveillance, monitoring, and evaluation (SME) in March 2021. We conducted a follow-up survey six months after the training to assess trainees' knowledge and practices regarding SME activities using quantitative and qualitative methods. We used a self-administered, structured questionnaire to collect information from participants on skills in developing a malaria strategic and monitoring and evaluation (M&E) plan, data analysis, use of data for decision making, factors underpinning reporting system performance, and opinions on the training content. All 30 trainees responded to the survey. Just over two-thirds found that the training was relevant to their daily activities (67%) and 83% reported having the skills to develop the strategic and M&E plans. For the 60% of districts with a strategic plan including an M&E plan, all 18 trainees from those districts were involved in developing them. Regarding data analysis, most respondents (93%) reported conducting weekly reviews of data submitted by health centers, in addition to monthly report verification, prior to entering the data into the District Health Information System, version 2 (DHIS2), and 80% performed data validation prior to entry into DHIS2. For data use, 97% of respondents reported performing weekly data analysis of surveillance data to identify potential malaria outbreaks and undertaking prompt response. Additionally, 90% of respondents analyzed malaria commodities data (rapid diagnostic tests, artemisinin-based combination therapies) to anticipate stock outs. Although SME training improved health worker practices regarding SME activities, some factors such as weak communication network, workload and HCs remoteness were reported by health workers as underpinning reporting system.

0977

IMPROVING COMMUNITY HEALTH WORKERS PERFORMANCE THROUGH COMMUNITY SUPPORTIVE SUPERVISION IN NYAMASHEKE AND RUSIZI DISTRICTS IN RWANDA

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Supportive supervision (SS) is the process of guiding, monitoring, and coaching community health workers (CHWs) to promote compliance with standards of practice and assure the delivery of quality care. The Rwanda Ministry of Health (MoH)'s Community Health Policy recommends at least 4 quarterly supervision visits per CHW per year (once a quarter). The supervisory process allows health staff, mainly community and environmental health officers (CEHO) and nurses, the opportunity to work as a team, maintaining the link between CHWs and the health system. However, a joint needs assessment exercise conducted by MoH and the U.S. PMI Impact Malaria (IM) project in Nyamasheke and Rusizi districts, demonstrated that only 62.5% of CHWs received a quarterly SS visit in 2020. The assessment highlighted challenges to implementing SS mainly due to the constrained logistics including transport, staff shortages, and the COVID-19 pandemic. In order to address these issues, IM supported orientation in SS of 1 CEHOs and 1 nurse at each Health Center of Nyamasheke and Rusizi districts and supported activity preparation and logistical support and participated in quarterly SS visits with CEHOs for identified poor performing CHWs. A total of 2,360 CHWs, who were trained on malaria case management, were assessed through quarterly SS over 12 months from October 2020 to September 2021, using a tool developed by the MoH, where 85% of CHWs received at least one SS on a quarterly basis. Performance scores evaluated the completeness of registers, availability of drugs and other commodities, and CHW knowledge at the time of the visit. Register completeness improved from 72% (first visit) to 82% (third visit). The knowledge among CHWs increased from 78% to 93%, while the score of availability of drugs and other commodities improved from 65% to 88% in the third visit. These findings show that quarterly SS is a key component in strengthening the performance of CHWs. Therefore, implementation of the SS should be done regularly by all community health program stakeholders.

0978

WHY USING BED NETS IS A CHALLENGE AMONG MINORITY POPULATIONS IN CENTRAL VIETNAM

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Despite the distribution of insecticide-treated bed nets (ITNs) and their proven health benefits, malaria transmission persists in forested areas in Vietnam. We conducted a mixed-methods study among the Ca Dong and M'nong populations in Central Vietnam to assess factors limiting ITN use, combining ethnographic methods in four villages and a cross-sectional survey of all households (n=141) in one theoretically selected village with the highest malaria cases to quantify factors for appropriate bed net use. The Ca Dong and M'nong's livelihood was dependent on swidden agriculture in the forest. Poverty-related factors, including the lack of beds, blankets, the practice of sleeping around the kitchen fire and deteriorated bed nets in open housing structures, were reasons for not using ITNs or using them as blankets and alternative purposes. The slash-and-burn farming required overnights outside of the official villages in plot huts or homes at fields where ITNs were unavailable and easily deteriorated. 72.5% of households reported having received one net for every two people, and 82.2% of participants reported to have used ITNs the night before the survey. However, after accounting for the deteriorated/torn state of theITNs and ITN use as blankets -at both villages and fields- only 18.4% of participants were estimated to be effectively protected by ITNs. Multi-variable logistic regression showed the effect of being female, being aware of mosquito bites as the only cause of malaria, not sleeping around the kitchen fire, and having sufficient nets in the household as significant factors for appropriate net use. The results show that poverty, related mobility patterns and multiple residences linked to slash-and-burn agriculture limited ITN use and their expected product's lifespan. Despite high coverage and high self-reported net use, only one-fifth of the population was estimated to be effectively protected by ITNs. The results also show the importance of examining existing assumptions using exploratory qualitative research and the inclusion of all relevant variables for the quantitative operationalization of ITNs as a complex concept.

0979

MOLECULAR EVALUATION OF THE FORCE AND MULTIPLICITY OF INFECTION IN CHILDREN AGED 1.5-12 YEARS LIVING IN THE MALARIA ENDEMIC AREA OF BANFORA, BURKINA FASO

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Genotyping *Plasmodium falciparum* parasites in longitudinal studies provides a robust approach to estimating force of infection (FOI). The molecular force of infection is defined as the number of new *P. falciparum* clones acquired over time. It has been described as a suitable for measuring outcomes of interventions. This study was designed to explore molecular measures (molecular FOI and Multiplicity of Infection) of *P. falciparum* burden in children 1.5–12 years.This was a prospective cohort study conducted during malaria transmission season. Children 1.5 to 12 years of age were enrolled. At screening, dried blood spots were collected from finger prick, and supervised curative doses with either Artesunate (AS) or Dihydro-artemisinin-Piperaquine (DHAPQ) was administered to clear any existing parasites. Parasite DNA was extracted and then analyzed by a nested PCR for the detection and the genotyping of *P. falciparum* parasites. Children were seen 21 days later and a PCR done to confirm parasites clearance. Only children with negative PCR were enrolled into the longitudinal follow up. At screening, before the treatment, prevalence of *P. falciparum* infection by PCR was 32.3% (95% IC 28.3-36.6) among the 513 eligible participants. At Day 21 post the radical cure, 458 (89.3%) of them were free of *P. falciparum* malaria infection; 87.3% (226/259) in the AS group vs 91.3% (232/254) in the DHAP group (P=0.05). During the course of the 6 months follow up, the incidence of *P. falciparum* infection detected by PCR was 28.2/1000 person-time at risk in the AS arm compared to 19.5/ 1000 person-time at risk in the DHAPQ arm. The incidence rate ratio was 1.45 (95% CI 1.07-1.96). The genotyping of these infections is in process and full results will be presented. These findings confirm the persistent high transmission intensity of malaria in our study area despite the currently deployed malaria control tools.

0980

CLINICAL OUTREACH TRAINING AND SUPPORTIVE SUPERVISION PLUS IN HAUT KATANGA, DEMOCRATIC REPUBLIC OF CONGO SHOWS IMPROVED RESULTS

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The U.S. PMI Impact Malaria project has supported the National Malaria Control Program of the DRC with laboratory outreach training and supportive supervision plus (OTSS+) for many years. In 2021, the clinical OTSS+ component was added to the laboratory OTSS+ in Haut Katanga. Three rounds of clinical OTSS+ were completed from March to September 2021. Round 1 (R1) was held in March, Round 2 (R2) in July and Round 3 (R3) in September. OTSS+ Visits were held at 42 referral hospitals and 38 lower-level health facilities in the province of Haut Katanga. The facilities selected were those that were accessible, had high patient volume and use the health zone data reporting system. Provincial supervisors collected data using the Health Network Quality Improvement System (HNQIS) tool. The first-round data served as a baseline. Data were tracked on wall charts at the health facilities to enable review and discussion of trends in between visits. Monitoring meetings and focus group discussions were held to identify gaps and discuss solutions. Results from the three rounds showed improvement in malaria testing and treatment; by R3, 99% of malaria cases treated had been confirmed with a diagnostic test vs 91% in R1 and 88% of health workers prescribed the recommended drugs for uncomplicated malaria in R3 versus 79% in R1. Confirmation of malaria by rapid diagnostic test or microscopy reached 93% in R3, versus 86% at R1. Health workers correctly diagnosing severe malaria rose to 64% in R3 from 58% in R1. Also, 84% of providers administered the appropriate treatment to malaria-positive pregnant women in R3 versus 74% in R1. Finally, 21% of providers scored 90% or greater in adherence to national case management guidelines in R3 versus 10% in R1. External causes may have limited improvements, notably stock outs and public sector strikes that lasted several months. Using clinical OTSS+ helped to understand and address gaps in malaria service delivery.

0981

COST-EFFECTIVENESS ANALYSIS OF SEASONAL MALARIA CHEMOPREVENTION IN BENIN

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Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine is recommended for eligible children aged 3-59 months to prevent Plasmodium falciparum. This study assessed the cost-effectiveness of two methods of monthly SMC administration in northern Benin, comparing three-days of directly observed treatment (3-day DOT) by a trained provider versus one-day of directly observed treatment (1-day DOT) by a trained provider with the subsequent two doses provided by the child's caregiver. The study focused on the 2020 SMC campaign which targeted four health zones - Tanguiéta Matéri Cobly (TMC), Malanville Karimama(MK), Banikoara (BNK), and Kandi Gogounou Ségbana (KGS) - targeting 304,772 children aged 3-59 months. Zones BNK and KGS utilized the 3-day DOT strategy and zones TMC and MK utilized the one-day DOT strategy. The financial and economic costs were captured from expenditure reports, microplans, and in-person interviews and were analyzed from both the program and household perspectives. The main effects measures were malaria cases, deaths, and disability-adjusted life-years (DALYs) averted which were estimated using a decision analytic model. The cost per monthly SMC cycle delivered to a child was $3.71 (FCFA 1,983) in the 1-day DOT zones compared with $3.13 (FCFA 1,673) in the 3-day DOT zones. The 3-day DOT strategy was the most cost-effective across all effects outcomes with an incremental cost-effectiveness ratio (ICER) of $446 (FCFA 238,409) per discounted DALY averted. One-way deterministic sensitivity analyses demonstrated that the ICER remained cost-effective under the most conservative estimates. Both 1-DOT and 3-DOT are low cost and cost-effective strategies for SMC administration. This evidence should help in guiding future program planning and resource allocation for SMC in Benin and other SMC-eligible countries.

0982

EFFECT OF SEASONAL MALARIA CHEMOPREVENTION IMPLEMENTATION FOR FIVE MONTHS VERSUS FOUR MONTHS IN MALARIA INDICATORS IN DABOLA, GUINEA

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In most eligible districts in Guinea, Seasonal Malaria Chemoprevention (SMC) is implemented over a 4-month period aligned to the rainy season. However, in some of those districts, malaria transmission starts earlier than the SMC campaign schedule, where the rainy season lasts for up to 5-6 months. In these areas, the number of SMC cycles does not match the real transmission risk and children may be left unprotected for part of the season. Starting the campaign in June by adding a fifth monthly cycle at the start of the malaria season to extends the duration of protection and potentially averts a significant number of additional severe malaria cases and deaths in at-risk children. In collaboration with Guinea's National Malaria Control Program and local health authorities, with funding from the Global Disease Eradication Fund from KOICA, Catholic Relief Services and Medicines for Malaria Venture had supporting an additional month of SMC in June in Dabola. This ensured to 41,140 additional treatment courses and lead to 36,944 children covered by five SMC cycles. Total confirmed malaria cases in Dabola in June 2021 decreased by 36% in comparison to June 2020 and by 65% for severe malaria cases among the under-five years old population. In neighboring districts, where only 4 cycles of SMC were implemented in 2021, there were minor reductions in malaria cases in children with a decrease of 5% in Dinguiraye, 11% in Faranah, 24% Mamou and 12% in Kouroussa. In Dabola, malaria positivity rates dropped from 82% in June 2020 to 60.3% in June 2021, corresponding to a 26% reduction whereas in neighboring districts the decrease in malaria positivity rate was between 6% to 13%. Extending SMC to 5 cycles in Guinea reached 83% of eligible children and averted an estimated 65% of severe malaria cases, leading to $831 savings in treatment of severe cases and an overall $3,739 savings in Dabola in June 2021. This project will continue to be implemented in 2022 and 2023 to have sufficient data for a comparative outcome analysis of 5 versus 4 cycles of SMC and versus no SMC to demonstrate potential improvement in the protection of children living in these areas over a period of 7 years.

0983

INTEGRATING GENDER INTO THE PROCESS EVALUATION OF SEASONAL MALARIA CHEMOPREVENTION IN KARAMOJA, UGANDA: RESULTS AND FUTURE DIRECTIONS

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Seasonal malaria chemoprevention (SMC) is the intermittent administration of antimalarials to children in areas where transmission is highly seasonal. While mainly implemented in the Sahel, SMC is recently being expanded to new geographies, including areas of Uganda. Qualitative findings from the SMC pilot conducted in 2021 in Karamoja, Uganda found that, female caregivers had to often convince reluctant husbands to give SMC drugs to their children. Female caregivers were overall more accepting of the intervention as they bear much of the burden once a child gets sick, their responsibilities including seeking care for the children, sleeping with them in health facilities, providing food and performing other chores for their family while caring for sick children. Rural women were overall more accepting of SMC than urban women. These findings hint to complex gendered dynamics at play during SMC implementation, whereby gender and other social determinants can affect bargaining and decision-making within households, caring roles, time-poverty as well as acceptability of the intervention. In 2022, Malaria Consortium are conducting a hybrid SMC effectiveness-implementation study in five districts in Karamoja. Tackling the lack of systemic evidence on gendered barriers to, and outcomes of SMC, the process evaluation will adopt gender integration through mixed methods. Focus group discussions will be conducted with caregivers, community members in the area, and village health workers, while interviews will be conducted with key informants involved in SMC implementation, programme management and policy making, including gender experts and/or advocates in the study sites. These will explore stakeholders' experiences of SMC, including roles in drug administration, as well as surrounding gendered norms and outcomes. Routine end-of-round survey will include variables on gendered intra-household dynamics, household composition, as well as roles in health-related decision-making. Preliminary results will be presented. Findings will shape future implementation and adaptation of SMC in Karamoja.

0984

TIMING OF INFECTIVE ANOPHELINE BITING AND HUMAN BEHAVIOUR UNDER HIGH INDOOR RESIDUAL SPRAYING (IRS) AND INSECTICIDE TREATED NET (ITN) USE IN ULANGA, TANZANIA

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In areas where insecticide treated nets (ITNs) or indoor residual spraying (IRS) of insecticides coverage is high, exposure to *Anopheles* bites outdoors or indoors but out of bed has been thought to play an important role in residual malaria transmission. However, there has been no clear link between exposure to *Anopheles* biting in such contexts and the risk of malaria parasite transmission. We investigated hourly human exposure to infective anopheline bites in an endemic area in rural Tanzania where high ITN use was reported and a community-wide IRS program had been implemented. Mosquito surveys by hourly indoor and outdoor human landing catch (HLC) were conducted in the frame of an indoor residual spraying (IRS) trial in Ulanga District, southeast Tanzania. In the same area and over corresponding seasonal periods, trained members of selected households recorded the hourly whereabouts and activities of their householders (outdoors, indoors and awake or asleep). Nightly human and mosquito behavioural data were summarized by hour for the period 6 PM to 6 AM to assess outdoor and indoor exposure to infective mosquito bites. In our findings, individuals spent most of the time preceding 10 PM outdoors, but nearly everyone (94%) was indoors between 11 PM and 6 AM. The vector population consisted of *An. funestus* and *An. arabiensis*. The prevalence of malaria sporozoite infection was 4% and 1% indoors, and 1% and 0% outdoors, in *An. funestus* and *An. arabiensis*, respectively. A pooled estimate for *An. funestus* and *An. arabiensis* showed that 87% of the exposure to infective bites was indoors between 10 PM and 5 AM. The high ITN use of 98.4% was estimated to avert nine out of ten (90%) of all indoor and outdoor infective bites. In conclusion, the bulk of infective mosquito bites occurred indoors and at a time when individuals are usually asleep. Therefore, ensuring high ITN use is essential to contain malaria transmission in this area, while innovative approaches targeting outdoor biting may have a complementary effect.

0985

DOING MORE WITH THE SEASONAL MALARIA CHEMOPREVENTION CAMPAIGN: SAFETY, EQUITY AND COST OF FULL INTEGRATION WITH VITAMIN A SUPPLEMENTATION IN NIGERIA

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Given the increasing scale in the Sahel region and expansion into new geographies, seasonal malaria chemoprevention (SMC) could provide a community-based platform for reaching children under five with additional life-saving interventions, including vitamin A supplementation (VAS). Following initial implementation research in 2019 on the feasibility and acceptability of co-implementing VAS with SMC campaign in one local government area (LGA) in Sokoto state, Nigeria, we conducted a follow-up study in two LGAs in Bauchi state in 2021 to answer additional questions on safety, equity, feasibility in rural and urban settings and cost of integration, targeting 165,000 children under five. We conducted cross-sectional surveys at baseline (cycle 3 SMC only) and end line (cycle 4 integrated SMC+VAS campaign) with 540 children aged 6-59 months to assess coverage (previously reported, ASTMH 2021), adverse drug reactions (safety) and background demographics of household members among others. A programmatic cost analysis from health care sector perspective using the ingredient method was carried out comparing cost of SMC delivery at baseline with the integrated campaign cost. There was no significant difference between children who did or did not receive SMC and VAS at endline in terms of age, sex, wealth index, caregiver's educational status or religion. However, children living in urban areas had lower odds of receiving either SMC or VAS compared to those living in rural areas (SMC, OR=0.21 [95% CI = 0.10 to 0.41]; VAS, OR=0.58 [95% CI=0.37 to 0.92]). Adverse drug reactions (ADRs) reported for VAS was 1.6% and 4.1% for SMC at endline [p-value=0.032]. Types of reactions reported: vomiting, skin rash, loss of appetite, fever, diarrhea did not differ between baseline and endline. It cost $0.9 to reach each child with SMC only and $1.1 to reach the same child with both SMC and VAS. This study demonstrates the viability of the SMC platform to deliver VAS safely and equitably at a mere additional cost of $0.2 per child. It also highlights the need to explore factors responsible for limited reach of children in urban areas using the current delivery approach.

0986

WHAT GAPS EXIST IN ROUTINE NET DISTRIBUTION AT ANTENATAL CARE AND MATERNITY CHANNELS? A MALAWI CASE STUDY

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In Malawi, it is national policy to distribute insecticide-treated nets (ITNs) to pregnant women free of charge at first antenatal care (ANC) visit and at delivery. However, the 2017 Malawi Malaria Indicator Survey showed that among households with an ITN, the percentage of pregnant women who slept under an ITN decreased from 85% in 2014 to 73% in 2017. We assessed if, and when, pregnant women attending ANC and delivering at the maternity ward who were eligible for ITNs received nets in three districts. We conducted a record review of stock cards and ANC, maternity, and ITN registers at a random sample of 24 health facilities in PMI-supported districts: Kasungu, Nkhata Bay and Mchinji. Data from four cohorts of pregnant women who initiated ANC in October 2019, January 2020, July 2020, and January 2021, were abstracted using a structured questionnaire programmed in Kobo-Collect. Most of the eligible pregnant women (91%) received an ITN at ANC, ranging from 88% in Kasungu to 94% in Nkhata Bay. The majority of pregnant women (93%) received an ITN during the 1st ANC visit, as per policy, while 4.5% and 1.8% received an ITN at ANC2 and ANC3, respectively. Only 14.6% of pregnant women received an ITN during the 1st trimester, while 75.2% and 10.2% received an ITN between 13-28 weeks and after 28 weeks, respectively. Only 37% of newborns were documented to have received an ITN in labor wards, however data were not captured in postnatal wards where most newborns receive an ITN, as there is no documentation field in the postnatal registers. The average number of ITN stock-out days in the 3 months preceding the visit was 2.7, ranging from 0.3 in Nkhata Bay to 7.1 in Mchinji. A high percentage of eligible women receive nets; infants are less well covered. However, gaps still exist both at ANC and maternity. Updating the postnatal register to enable documentation of ITN distribution would assist in monitoring appropriate ITN distribution in newborns. Further supportive supervision and mentorship efforts in postnatal wards would improve reporting and increase the number of newborns who receive nets.

0987

EARLY SEASONAL MALARIA CHEMOPREVENTION (SMC) IMPLEMENTATION CONTRIBUTED TO REDUCING MALARIA INCIDENCE IN SUD-OUEST REGION IN BURKINA FASO

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In Burkina Faso, malaria remains a major public health problem. According to 2020 health statistics, malaria accounted for 40% of health service consultations, 54% of hospitalizations, and 27% of deaths. Children under 5 years of age account for 72% of malaria deaths. To help reduce this burden, the Ministry of Health, with the support of its partners, has organized annual Seasonal Malaria Chemoprevention (SMC) campaigns since 2014 during the high malaria transmission period (July, August September, and October). In 2021, the U.S. PMI Impact Malaria project provided support to the National Malaria Control Program to implement SMC in 19 districts from three regions (Centre-Est, Centre-Ouest, and Sud-Ouest). One of the innovations of the 2021 SMC campaign was the introduction of five cycles in 7 of these 19 districts, compared to four cycles elsewhere. Therefore, SMC started earlier (in June) while all the others started in July. We compared the incidence of malaria (in the 5 districts of the Sud-Ouest region) in 2020 to that of 2021 when the SMC started earlier. The malaria incidence is estimated based on the weekly disease surveillance form where the number of malaria cases is recorded, using updated population census data as a denominator. In 2020, the average malaria incidence from May 31 to October 6 in the Sud-Ouest region was 51.44/1000. In 2021, during the same period malaria incidence was 40.94/1000 (a decrease of 20%) The SMC coverage was 103% and 104% respectively in 2020 and 2021. Starting SMC early can contribute to reduced malaria incidence but key challenges need to be addressed: i) Underestimation of the target population due to IDPs and gold miners; ii) youngest children are with their mothers on the farm so cannot be found at home; iii) insufficient cards for the SMC.

0988

FEASIBILITY &LT ACCEPTABILITY OF EXTENDING SEASONAL MALARIA CHEMOPREVENTION TO CHILDREN AGED 5-10 YEARS &GT CHAD

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The World Health Organization recommends seasonal malaria chemoprevention (SMC) for children aged 3-59 months in areas of highly seasonal transmission across the Sahel. In Chad, malaria is endemic and routine household surveys conducted to evaluate the coverage and quality of SMC delivery found that administration of SPAQ to children over 59 months appears to be common. We conducted a mixed-methods study in the health district of Massaguet (Chad) to determine the extent of, and reasons for, this occurrence. We collected qualitative data through 15 key informant interviews with SMC stakeholders including donor representatives, program managers, policy makers and those in charge of SMC drug distribution and supervision at different levels of the health system. We also conducted eight focus group discussions with community distributors and caregivers in three rural villages and one urban settlement. We collected quantitative data via two types of household surveys: i) end-of-cycle surveys, using lot quality assurance sampling in SMC cycles one and three; ii) an end of-round coverage survey, measuring implementation performance for cycles one, three and four. Among community distributors who acknowledged that older children do sometimes receive SMC, many identified pressures from caregivers who demand SMC for their older children and difficulty determining a child's age which results in SMC being unintentionally administered to over-fives. The perceived feasibility of extending SMC to children aged 5-10 years was mixed among community distributors, caregivers, and key informants. While extending SMC to older children is acceptable to all participant groups, key informants prioritized closing the coverage gap among under-fives before extending SMC to older children. Many also highlighted the need to consider intervention sustainability prior to extending the age range of SMC.

0989

CONTRIBUTION OF SEASONAL MALARIA CHEMOPREVENTION (SMC) TO THE REDUCTION OF MALARIA BURDEN IN CHILDREN UNDER 5 YEARS OF AGE IN THE SUD-OUEST REGION, BURKINA FASO

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According to health statistics for 2020, in Burkina Faso, malaria accounts for 40% of medical consultations and 27% of deaths. Children under 5 years of age account for 72% of malaria deaths. In 2021, the US PMI Impact Malaria project implemented Seasonal Malaria Chemoprevention (SMC) in collaboration with the National Malaria Control Program (NMCP) of Burkina Faso in 3 regions. SMC consists of the administration of three days of monthly treatments of amodiaquine plus sulfadoxine-pyrimethamine to all eligible children (3-59 months of age) during the high malaria transmission season (June to October). The objective is to maintain therapeutic concentrations of these antimalarials during the period of high transmission. In 2021, 19 of 70 health districts (27%) were supported by the project to implement SMC with more than 838,000 children under 5 years treated, including 180,000 from the Sud-Ouest region (Dano, Batie, Kampti, Gaoua, and Diebougou health districts). In this region of high rainfall, the number of severe malaria cases in children under 5 years decreased from 17,760 in 2017 (before SMC) to 14,609 in 2021 with SMC after 4 years of SMC implementation, i.e. a reduction of 17%. The number of malaria deaths also decreased from 133 in 2017 (before SMC) to 118 in 2021, a reduction of 11%. Kampti health district recorded the highest reduction of deaths of 78% [33 to 7 deaths] between 2017 and 2021 and Dano district had a reduction in severe malaria cases by 28% between 2017 and 2021. The main challenges with SMC include a delay in referral of fever cases by community distributors to health facilities during the campaign, management of vomiting during the 2nd or 3rd dose, and failure to retain the treatment cards by the parents. Seasonal Malaria Chemoprevention is a proven intervention and appears to be an important component of the malaria prevention strategy in Burkina Faso but consideration should be given to address ongoing implementation challenges.

0990

MY NET WILL GO ON: MODELING THE COST-EFFECTIVENESS OF MORE DURABLE INSECTICIDE-TREATED NETS VS MORE FREQUENT DISTRIBUTIONS IN SUB-SAHARAN AFRICA

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Insecticide-treated nets (ITNs) are one of the most widespread and cost-effective malaria prevention tools in sub-Saharan Africa, but maintaining high net coverage has proven challenging in many settings. Shorter-than-expected retention times are a major driver of low net coverage, as

many households discard nets due to physical damage well before they are scheduled to receive new ones. There is an ongoing conversation in the policy sphere about the best solution to this problem-- should manufacturers produce more durable nets? Or should countries distribute existing, less-durable nets more frequently? Both approaches have significant costs, and it is unclear what type of burden reduction each strategy might present. This study uses a microsimulation transmission model to explore the potential burden impact and cost-effectiveness of a three-year distribution schedule with more durable nets compared to two-year distribution schedule with existing nets. We explore this question across transmission intensities and seasonalities. Taking into account the cost of a mass net distribution as well as the unit costs of nets, we show that the optimal strategy depends on transmission intensity and the expected unit cost of a more durable net. These results contribute to a crucial and time-sensitive paradigm shift in the production, procurement, and distribution of one of the most important malaria interventions in the world.

0991

CHALLENGES IMPLEMENTING DISTRIBUTION SHORTLY AFTER HOUSEHOLD AUTHENTICATION AS PART OF THE 2021 LONG-LASTING INSECTICIDE-TREATED NETS (LLIN) MASS CAMPAIGN DISTRIBUTION

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In August 2021, to maintain universal coverage (one Long-Lasting Insecticide-treated Net [LLIN] per two people), Madagascar conducted a mass campaign distribution (MCD) of 13.7 million LLIN in 101 districts of the country. During previous MCDs (2010, 2013, 2015 and 2018), population was quantified at the household level two months before the MCD to inform allocation of LLINs. During the two months between authentication and distribution, Community Health Volunteers conduct malaria prevention sensitizations at households through home visits, hence the possibility to have more than four contacts between these actors and households. In 2021, given the COVID-19 context, Madagascar conducted a census two weeks before distribution to reduce the need for sensitization visits and therefore contacts between actors to minimize infectious risks. In addition, to prevent COVID-19 spread, all actors wore personal protection equipment (PPE), and were sensitized to respect social distancing. Household authentication occurred from 26 July to 14 August 2021. During this period, coupons were also distributed. All the data collected during authentication were used for developing the micro pre-positioning plan (MPP) and sent to the district level for validation and then validated by the National Coordination Committee. After MPP validation, 15 Civil Society Organizations transported the LLINs to the distribution sites. Once the LLINs were available, for 10 days, community actors ensured the distribution to all authenticated households. The results of the authentication showed that the population increased by 23.8% and authenticated households by 24.5% compared with the population in the 2021 sectorization of the Ministry of Health; the population was 22,497,234 and the number of households was 5,219,572. Due to limited time, a verification of the data quality could not be carried out. For future campaigns, to avoid discrepancies between the number of population vs LLINs available, monitoring and evaluation system (data collection, reporting and validating) should be strengthened.

0992

FACTORS INFLUENCING THE ACCEPTABILITY OF A COMMUNITY-BASED DISTRIBUTION OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY: FINDINGS FROM AN ANTHROPOLOGICAL STUDY IN 4 SUB-SAHARAN COUNTRIES

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Increasing uptake of intermittent preventive treatment in pregnancy with sulphadoxine-pyrimethamine (IPTp-SP) is key to improving maternal health indicators in malaria endemic countries, yet current coverage rates remain low. An anthropological study has been carried out as part of a broader project aiming to evaluate a community-based approach to the delivery of IPTp (C-IPTp) through community health workers (CHWs) in four SSA countries: the Democratic Republic of Congo (DRC), Madagascar, Mozambique, and Nigeria. The main objective of the study was to understand the social context in order to identify key factors that could influence C-IPTp acceptability where the project has been implemented. Between March 2018 and August 2021, a total of 796 in-depth interviews and 257 focus group discussions were carried out in the four country sites with pregnant women, relatives, women of reproductive age, community leaders, CHWs, and health providers (3235 participants). These were combined with direct observations (388) of both community and facility based IPTp delivery, among other scenarios. Grounded theory guided the overall study design and data collection, and data were analysed following a combination of content and thematic analysis. Research findings suggest that a series of key factors have influenced the acceptability of the strategy. These consisted of the alignment of the intervention with local norms surrounding pregnancy; the engagement with existing socio-political structures and the active involvement of influential actors in implementation activities; the perceived improvement of pregnant women's self-efficacy concerning access to IPTp-SP, and a reinforced trust in CHWs as legitimate SP providers. Although factors related to IPTp uptake, such as perceptions of SP as an undesirable drug or ANC access barriers still persist and could negatively impact the adherence to the strategy, results show that C-IPTp has been widely accepted by its beneficiaries in project areas. These findings provide meaningful insights into how community-based interventions could be framed to ensure their acceptability.

0993

MODELLING TO SUPPORT THE IMPLEMENTATION OF MASS DRUG ADMINISTRATION DURING A COMPLEX EMERGENCY - CABO DELGADO, MOZAMBIQUE

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The humanitarian emergency in the northern Mozambique province of Cabo Delgado has caused large population displacement and disrupted

malaria services, threatening to increase malaria transmission. To mitigate this, the National Malaria Control Programme deployed mass drug administration (MDA) in two districts in 2021, and is considering deployment in three high burden districts with the greatest disruption and population influx. In order to aid campaign planning, we used mathematical modelling to explore how the level of effective case management, and number and timing of rounds of MDA, can help mitigate the effects of the conflict. We simulated deployments of two or three rounds of MDA every six weeks with 75% coverage and varied the timing around the seasonal peak in early 2022. The effect of the conflict on case management was modeled by reducing the effective treatment (ET) of uncomplicated malaria, by assuming a reduction in provider's compliance to first-line anti-malarial drugs proportional to population increase. Prior to the conflict, ET was estimated to be 48% in Cabo Delgado. We estimated ET to have reduced to 14%, 35%, and 37% in the districts of Ibo, Ancuabe, and Mecufi. We calculated the number of cases averted by comparing each MDA scenario with two counterfactuals (no MDA scenarios): the estimated number of malaria episodes under pre-crisis conditions and the estimated number of cases with an enlarged population and reduced ET. The model predicts an increase of up to four-fold in malaria cases due to the crisis. Deploying three rounds of MDA may be sufficient to counteract the effect of the conflict on malaria in two of the three districts. In Ibo, the district with the greatest increase in population, three rounds of MDA may avert around 57% of the additional malaria cases estimated due to the conflict. Timing of rounds had shaped MDA impact to a far lesser extent than number of rounds. As decisions and planning are still taking place, this type of modelling exercise allows policy-makers to add a layer of rationale to a complex process whilst providing quantitative evidence to funding bodies.

0994

USING DYNAMICAL MODELLING TO GUIDE THE REDESIGN OF AN UNDERUSED MALARIA INTERVENTION

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Perennial malaria chemoprevention (PMC) is a long-ignored malaria intervention which is currently being revitalised and reimagined. We used dynamical modelling to help inform the planning of PMC implementation pilots in Cameroon, Benin, and Cote d'Ivoire, as part of the IPTi+ project. We aim to explore how both setting and PMC deployment characteristics may affect the number of cases averted. Using the OpenMalaria modelling suite, we developed a series of PMC deployment scenarios: varying the number of rounds from three to eight, coverage levels from 20% to 100%, and timing rounds to align either with transmission seasons, or with infant age. These scenarios were deployed across 54 archetypal settings, with varying prevalence, bednet usage, case management levels, and seasonality patterns (perennial or dual-peak). We calculated the number of cases averted (per 1,000 children <2 years/year) compared to the scenario with no PMC in the same setting. We found that the number of cases averted may approximately double with a doubling of either the number of rounds, or of intervention coverage. It is likely advantageous to align timing with seasonality when few rounds are deployed, but timing makes little difference when deploying 5+ rounds. More than twice as many cases may be averted in high (40%) prevalence compared to low (10%) prevalence settings. Slightly more cases may be averted in settings with low (15%) case management, while the level of bednet usage and setting seasonality seemed not to influence the number of cases averted. Model findings prioritised planning discussion on ways to increase number of rounds and coverage, and deprioritised other considerations e.g., aligning delivery with seasonality. National policy-makers decided to deploy five (Cote d'Ivoire) or eight rounds (Benin and Cameroon) extended into the second year of life, and aim to maximise coverage by involving community health workers in awareness raising and/or delivery. As exemplified by its use in the IPTi+ project, dynamical modelling can play an instrumental role in developing the flexible, problem-solving approach needed if malaria burden is to decrease once more.

0995

A HYBRID OF SCREEN-AND-TREAT AND INTERMITTENT PREVENTIVE THERAPY FOR THE PREVENTION OF MALARIA IN PREGNANCY: A RANDOMIZED CONTROLLED TRIAL

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Despite the increase in *Plasmodium falciparum* resistance to sulfadoxine-pyrimethamine (SP), intermittent preventive treatment in pregnancy with SP (IPTp-SP) remains the only recommended chemoprevention for malaria in pregnancy (MIP). Alternative chemopreventive strategies are urgently needed. We conducted a phase IIIb open-label, two-armed randomized controlled superiority trial to assess the safety and efficacy of an IPTp approach that incorporates screening with rapid diagnostic test (RDT) and treatment with dihydroartemisinin-piperaquine (DP) at the first antennal care (ANC) visit. The study was conducted in Nchelenge District, Luapula Province, Zambia. 392 HIV-negative pregnant women without signs or symptoms of malaria out of 850 screened were recruited and randomized to either standard IPTp-SP or hybrid IPTp-SP plus screening and treatment (IPTp-SP+). In the IPTp-SP+ arm, participants who screened positive by RDT were treated with DP at the first ANC visit while those who screened negative received SP. Participants in the control arm were administered IPTp-SP per current guidelines. All received SP on days 35 and 63. Participants were followed biweekly up to day 63 and then monthly until delivery. Infants were followed until 1 year after delivery. The primary endpoint was incident PCR-confirmed MIP at day 42. Secondary endpoints included incident MIP at other time points, placental malaria determined from histology of placental biopsies, congenital malaria determined from cord blood smears, hemoglobin trends, birth outcomes, and incidence of adverse events in infants. The last infant follow-up visit was completed July 2021 and data analysis is underway. This trial assesses the safety and efficacy of a hybrid approach combining standard IPTp-SP with screening and treatment using DP at the first ANC visit. Over 50% of *P. falciparum* infections diagnosed during pregnancy can be detected at the first ANC visit, and higher density infections that occur early in gestation may pose the most harm, therefore focusing on detection and treatment at the first ANC visit may improve birth outcomes in a cost-effective manner.

0996

IMPLEMENTATION AND ACCEPTANCE OF GOVERNMENT-SPONSORED MALARIA CONTROL INTERVENTIONS IN MEGHALAYA, INDIA

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India has made considerable progress in malaria reduction over the past two decades, with government-sponsored indoor residual spraying (IRS) and long lasting insecticidal nets (LLIN) being the main vector-related prevention efforts. Few investigations have used non-participant observational methods to assess malaria control measures while they are being implemented, nor documented people's perceptions and acceptance of these measures in India, and none have done so in the northeast region. We evaluated household (HH)-level distribution of IRS and LLIN by the

National Vector Borne Disease Control Program (NVBDCP) in 50 villages of Meghalaya state, and documented people's acceptance and use of these measures in this malaria-endemic state. In 2019-2020, our research teams accompanied the NVBDCP teams to observe deployment of LLIN, and record HH-level data on net numbers and use. In addition, NVBDCP spray teams were followed during 2019-2021 to observe the preparation and administration of IRS, after which HH members were interviewed to better understand reasons for acceptance or refusal of spraying. A total of 8386 LLIN were distributed to 2727 HHs in 24 villages, representing 99.5% coverage of what was planned. Interviews with a sub-sample of 80 HHs indicated that they were appreciative of the LLIN distribution, and generally made appropriate use of LLIN, except during overnight travel or when working in agricultural fields. However, of 1,079 occupied HHs that were visited by the spray team for IRS treatment, 632 (58.6%) refused to allow any spraying, only 198 (18.4%) agreed to be sprayed, comprising 152 (14.1%) HH that were only partly sprayed, and 46 (4.3%) that were fully sprayed. Reasons for refusal included: not enough time to rearrange HH items, young children were present, the smell was annoying, walls would be stained, and their beekeeping or Eri silk moth cultivation would be threatened. This study represents the first in northeast India that independently evaluated the government's IRS and LLIN programs for malaria prevention, and provides insights that are critical to India's goal of malaria elimination by 2030.

0997

RAISING THE FLOOR ON NETS: UPDATES FROM A CONVENING ON ITN QUALITY

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Significant reduction in malaria over the past fifteen years is largely due to universal coverage of vector control tools, especially insecticide treated nets (ITNs). Despite this success, progress against malaria has plateaued, and lapses in quality assurance mechanisms mean that the highest quality products are often unavailable to end users. Identifying the gaps in the current quality assurance framework for ITNs and identifying solutions is therefore a priority. However, this endeavour is complicated by the involvement of numerous partners at multiples stages, and a joined-up approach is needed. We therefore organised a convening on ITN quality to gather the views of stakeholders from across the ITN quality life cycle, co-create solutions to the gaps identified, and plan activities to sustainably raise the quality of ITNs. Participants included representatives from the WHO, ITN suppliers, product development partnerships, national malaria control programmes, researchers, non-governmental organisations, and financiers. Everyone was asked to complete a brief pre-meeting survey on ITN quality. All participants met virtually using Microsoft Teams over three 3-hour sessions in December 2021. Sessions included standard presentations, panel discussions, and group work. Over half of the convening was dedicated to a group brainstorming exercise using the Charette procedure to efficiently consolidate the group's opinion on solutions to the key challenges identified. Group work was facilitated by the Mural whiteboarding and Menti polling tools. The convening facilitators reviewed group outputs, synthesized findings, and presented priorities back to plenary for confirmation of agreed actions. Participants identified many challenges in the areas of communication and trust, quality and performance metrics, incentives for quality and innovation, and the global quality assurance process. The group identified several priority actions: link product specifications with performance, revise product testing guidelines, enhance procurement to reward quality and innovation, clarify roles, and improve transparency of data.

0998

EPITOPE-SPECIFIC DIFFERENTIAL ANTIBODY RESPONSES TO *PLASMODIUM FALCIPARUM* CIRCUMSPOROZOITE PROTEIN ARE ASSOCIATED WITH PROTECTION FROM MALARIA INFECTION IN MALIAN ADULTS

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Circumsporozoite protein (CSP) coats the *Plasmodium falciparum* sporozoite surface and is the target of multiple vaccines and monoclonal antibodies in development. In studies of RTS,S, antibodies to the immunodominant central repeat region correlated with protection. However, RTS,S-induced protection remains modest, and monoclonal antibodies targeting the R1-NANP junction were found to be highly efficacious in preventing infection in controlled human malaria infection studies. We examined CSP antibody responses in vaccinated adults who subsequently developed malaria (infected) compared to those who did not (uninfected) in a double-blinded randomized, placebo-controlled clinical trial of fully active sporozoites administered with chloroquine prophylaxis (PfSPZ-CVac (CQ)) in Mali to further define potential correlates of protection. Sera from 31 Malian adults, 15 uninfected and 16 infected, were probed on a peptide array with coverage of 81 CSP variants as 16-amino acid peptides overlapping by 12. Compared to the infected group, the uninfected group had lower mean of the mean $\log_2$ fold change in fluorescence intensity (FI) across CSP variants in the central repeat region at day 71 post-vaccination compared to baseline. 95% confidence intervals (CIs) estimated by bootstrapping across the region did not overlap, suggesting a strong differential signal. In contrast, the uninfected group had higher antibody responses at the R1-NANP junction. CIs did not overlap with the mean antibody signal for the infected group, confirming a differential signal for this region as well, albeit in the opposite direction. We hypothesize that the immunodominant central repeat region may elicit antibodies that are not as effective as R1-NANP junction antibodies, which may be more specific for blocking hepatocyte invasion by sporozoites. It is also possible that responses to the central repeat region may inhibit responses to the R1-NANP junction. Future analyses will include assessing cross-reactivity between allelic variants of CSP and analyzing vaccine escape by comparing CSP sequences from infecting parasite strains to CSP antibody responses.

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IDENTIFICATION OF NOVEL GENETIC VARIANTS IN THE MALARIA VACCINE CANDIDATE PFRH5: STRUCTURE-GUIDED INSIGHTS INTO POTENTIAL FUNCTION

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The recent stall in the global reduction of malaria deaths has made the development of a highly effective vaccine essential. A major challenge to developing an efficacious vaccine is the extensive diversity of *Plasmodium falciparum* antigens. While genetic diversity plays a major role in immune evasion and is a barrier to the development of both natural and vaccine induced protective immunity, it has been under-prioritized in the evaluation of malaria vaccine candidates. This study uses genomic approaches to evaluate genetic diversity in next generation malaria vaccine candidate PfRH5 (Reticulocyte Binding Protein Homologue 5). We used targeted deep amplicon sequencing to identify non-synonymous Single Nucleotide Polymorphisms (SNPs) in PfRH5 in 189 *P. falciparum* positive samples from Southern Senegal and identified 74 novel SNPs. We evaluated the population prevalence of these SNPs as well as the frequency in individual samples and found that only a single SNP, C203Y, was present at every site. Many SNPs were unique to the individual sampled, with over 90% of SNPs being found in just one infected individual. In addition to population prevalence, we assessed individual level SNP frequencies which revealed that some SNPs were dominant (frequency of greater than 25% in a polygenomic sample) whereas most were rare, present at 2% or less of total reads mapped to the reference at the given position. Structural modelling uncovered 3 novel SNPs occurring under epitopes bound by inhibitory monoclonal antibodies, potentially impacting immune evasion, while other SNPs were predicted to impact PfRH5 structure or interactions with the receptor or binding partners. Our data demonstrate that PfRH5 exhibits greater genetic diversity than previously described, further emphasizing the power of next-generation sequencing in assessing genetic diversity at population levels. The structural studies reveal that novel SNPs could have functional implications on PfRH5 receptor binding, complex formation, or immune evasion, supporting continued efforts to validate PfRH5 as an effective malaria vaccine target and development of a PfRH5 vaccine.

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INITIAL EVALUATION OF *ESCHERICHIA COLI*-PRODUCED RECOMBINANT EPA (ECREPA)

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Recombinant ExoProtein A (rEPA), the mutant and detoxified toxin of *Pseudomonas aeruginosa,* was produced by the *Escherichia coli* expression system (EcrEPA). EcrEPA has been used by the Laboratory of Malaria Immunology and Vaccinology (LMIV) as a carrier protein for malaria antigens Pfs25, Pfs230D1M, Pfs28, Pvs25, Pvs230D1M and Pvs28 to increase immunogenicity in mice, monkeys, and/or humans. Although EcrEPA itself does not directly contribute to antigen-specific protection against malaria, as an important component of the conjugated malaria transmission-blocking vaccine, extensive evaluation of EcrEPA is required by the regulatory agencies prior to further studies in human clinical trials. In this study, EcrEPA was manufactured in conformance with current good manufacturing practices (cGMP). The initial evaluation for this cGMP EcrEPA lot included purity by visual inspection (appearance), limulus amebocyte lysate (LAL) for endotoxin, microbial enumeration tests for bioburden, rabbit pyrogenicity test, qPCR for residual DNA, slot blot analysis for residual host cell proteins (HCP), and High-performance liquid chromatography (HPLC) for residual isopropyl β-d-1-thiogalactopyranoside (IPTG). Additional evaluations also included protein content by UV spectrum (A_{280}), identity by amino acid composition, pH, SDS-PAGE with Coomassie blue staining, capillary gel electrophoresis (CGE), N-terminal sequencing, electrospray mass spectrometry, Western blotting, and integrity (percent as a single/monomeric band/peak) by SDS-PAGE, CGE, reverse phase ultra-performance liquid chromatography (RP-UPLC) and size-exclusion ultra-performance liquid chromatography (SEC-UPLC). Our results showed that EcrEPA manufactured following cGMP passed all of the release specifications and is suitable for use as a vaccine carrier protein in human clinical trials.

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MAPPING WITHIN-HOST ANTIGENIC ESCAPE AND ALLELE-SPECIFIC IMMUNITY OF *PLASMODIUM FALCIPARUM* VACCINE ANTIGENS

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An understanding of pathogen antigenic diversity and strain-specific immunity can identify critical epitopes and prioritize alleles for vaccine development. Here, we integrated multiplexed serological assays measuring antibody responses (total IgG) against a panel of 28 antigens including AMA1, MSP2, and novel long-read targeted sequencing assays, to explore the turnover of alleles and acquisition of allele-specific immunity for each antigen. These assays were applied to consecutively collected samples from two longitudinal cohorts of 700 Papua New Guinean school-aged children (5 - 14 years old). We developed a bioinformatics pipeline, a novel algorithm to determine antigenicity of polymorphic sites, and a 'shot-noise process'-based mathematical model combining classic statistical approaches to understand the dynamics of antibody responses and antigenic diversity. We found breakthrough infections with variant alleles at specific polymorphic sites, but some residues such as those from the AMA1 cluster 1 loop were more likely to change than others. Amongst antigens that are known to result in allele-specific immunity such as AMA1, MSP2, the dynamics of antibody responses was influenced by the turnover rate of antigenically relevant polymorphisms. This study provides a classification system to define polymorphisms associated with antigenic escape of *P. falciparum*, knowledge which is essential to develop broadly effective vaccines.

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STRATEGIC INTRODUCTION OF THE RTS,S/AS01 MALARIA VACCINE RELATIVE TO SCALE-UP OF EXISTING INTERVENTIONS

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The World Health Organization has recommended a 4-dose schedule of the RTS,S/AS01 (RTS,S) vaccine for children in regions of moderate to high *P. falciparum* transmission, as part of a comprehensive malaria control strategy. Faced with limited supply, global funders and domestic malaria control programs will need to examine the relative cost-effectiveness (CE) of RTS,S sub-nationally to consider how implementation compares with scale-up of existing interventions. Using an individual-based mathematical model of *P. falciparum*, we modelled the CE of RTS,S across a range of settings in sub-Saharan Africa, incorporating various rainfall patterns, insecticide-treated net (ITN) use, and parasite prevalence bands. We

compare the cost-effectiveness of RTS,S administration through both age-based and seasonal vaccination, to that of alternative strategies including increasing ITN usage, switching to next generation ITNs in settings with insecticide-resistance, and introduction of seasonal malaria chemoprevention (SMC). Increasing ITN use by 10% was estimated to be the most cost-effective strategy in 97% of non-insecticide-resistance settings with a median incremental CE ratio (ICER) of $71 (IQR: 28-187) per DALY averted. A switch to next generation ITNs was estimated to be the most cost-effective strategy in 87% of insecticide-resistance-settings, with a median ICER of $18 (9-65). Introduction of RTS,S was estimated to be cost-effective in areas of at least 40% parasite prevalence and/or 75% ITN usage with a median ICER of $119 (103-127) for age-based and $75 (36-93) for seasonal vaccination. Addition of RTS,S to strategies involving 75% ITN use and SMC, if eligible, led to significant marginal case reductions, with a further 5,985 (4,676-9,163) cases averted per 100,000 people annually. Use of RTS,S results in additional reductions in malaria cases and deaths when layered upon existing interventions. When comparing relative CE, scale up of ITNs, introduction of SMC (where eligible), and switching to new technology nets should be prioritized in most scenarios where ITN usage is not yet maximized or where insecticide resistance is a threat.

1003

A NOVEL MALARIA MULTISTAGE VACCINE BASED ON VACCINIA VIRUS-PRIME/AAV5-BOOST ELICITS STERILE PROTECTION AND TRANSMISSION BLOCKING EFFICACY

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A leading malaria vaccine RTS, S/AS01 is the first malaria vaccine to be recommended to use for children in sub-Saharan Africa with moderate to high *P. falciparum* malaria transmission, although it has only modest efficacy and short durability, and it must be administered in a four-dose schedule to achieve high efficacy. The development of more efficacious vaccines is still needed. Viral vectored vaccines have a key advantage over Protein-in-Adjuvant vaccines like RTS, S, because they are capable of inducing cytotoxic $CD8^+$ T cell responses that are critical for the elimination of intracellular pathogens like malaria parasites. Adeno-associated virus (AAV) is being utilized as an attractive vehicle for delivering genes to various target cells with a minimum level of toxicity in clinical trials. Here, we examined the efficacy of Adeno-associated virus serotype 5 (AAV5), as a malaria booster vaccine after a prime of replication-competent vaccinia virus, LC16m8Δ, harboring a fusion gene encoding the pre-erythrocytic stage protein, *Plasmodium falciparum circumsporozoite* (PfCSP) and the transmission-blocking sexual stage (Pfs25). The result shows that vaccination using the heterologous regimen, LC16m8Δ-AAV5, induces robust anti-PfCSP and anti-Pfs25 malaria functional antibodies. Remarkably, LC16m8Δ-AAV5 achieves sterile protection (100% protection level) against challenge with transgenic *Plasmodium berghei* sporozoites expressing PfCSP (PfCSP-Tc/Pb). In addition, LC16m8Δ-AAV5 also induces a high level of transmission-reducing activity (TRA: > 99%) and transmission-blocking activity (TBA: > 95%). Our data indicate that AAV5 based multi-stage malaria vaccine is an efficacious vaccine when administered as a booster of an LC16m8Δ based vaccine. These results support the further evaluation of this regimen as a novel and cost-effective malaria vaccine platform in clinical trials.

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IN-SILICO AND FUNCTIONAL CHARACTERIZATION OF *PLASMODIUM MALARIAE* RETICULOCYTE BINDING PROTEIN 2B

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Plasmodium malariae are widely spread in the tropical and sub-tropical areas, and have an overlapping presence with *P. falciparum* (*Pf*) especially, in sub-Sahara countries. Due to its low parasitaemia, *P. malariae* infections usually go undetected during diagnosis. This enables it to live within an individual for a long period of time and tend to cause several rare complications such as nephrotic syndrome, acute cholecystitis, severe anaemia, and convulsions. Thus, emphasizing the need to study this species and as well, identify molecular targets to aid in the development of an efficacious malaria vaccine. *P. malariae* Reticulocyte Binding Protein 2b (*Pm*RBP2b) is a secretory protein from *P. malariae* merozoites that might be involved in the invasion of human RBCs. Fragments of *Pm*RBP2b were assessed of sequence and structural conservation, then recombinantly expressed before they were purified to assess their sero-prevalence among individuals living in Ghana. Computationally, *Pm*RBP2b was found to be highly conserved, has both erythrocyte and nucleotide binding regions. ELISA assay showed that people living in malaria-endemic areas have antibodies elicited against *Pm*RBP2b with an increasing titre against increasing age.

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PROTEIN INTERACTION ANALYSIS OF *PLASMODIUM FALCIPARUM* CIRCUMSPOROZOITE PROTEIN VARIANTS WITH HUMAN IMMUNOPROTEINS EXPLAINS RTS,S VACCINE EFFICACY

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The world's first malaria vaccine, RTS,S construct contains part of the central repeat and the complete C-terminal regions of the *P. falciparum* 3D7 circumsporozoite protein (*PfCSP*). Prior clinical trial studies have shown that RTS,S provides 36% protection against falciparum malaria and the explanation for such low efficacy is unclear. *PfCSP* has been shown to be highly polymorphic and may impact human immuno-responses. This study employs computational modeling and *in vitro* assays to examine the associations of *PfCSP* variants with binding affinity of the CSP peptides to human immunological proteins including human leukocyte antigen (HLA) and T cell receptors (TCR). The multiplicity of infections was determined by amplicon deep sequencing of *PfCSP* C-terminal region and merozoite surface protein 1 (PfMSP1). Among 88 *P. falciparum* samples collected broadly across Ghana where RTS,S rolls out, 27 *PfCSP* haplotypes was detected. Majority of the samples are polyclonal with multiple *PfCSP* haplotypes within a sample. Haplotypes do not cluster by high and low transmission regions. There was a significant correlation between CSP molecular weight and its binding affinity to the HLA. However, the number of genetic differences in *PfCSP* between 3D7 and non-3D7 variants does not influence the recognition of the HLA/CSP complex by the TCR. Ongoing study validates the CSP-HLA-TCR binding performance by *in vitro* binding assays on a subset of most common CSP peptides in Ghana. It is possible that the prevalence of multiple non-3D7 *P. falciparum* strains impacts the effectiveness of RTS,S. Longer CSP peptides may elicit a stronger immune response and should be considered in future versions of RTS,S.

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MOSQUITO-BITE INDUCED CONTROLLED HUMAN INFECTION WITH *PLASMODIUM VIVAX* IN MALARIA-NAÏVE STUDY PARTICIPANTS - CLINICAL PROFILE AND UTILITY OF MOLECULAR DIAGNOSIS

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Controlled human infection (CHI) studies, the deliberate infection of healthy adults, have been performed for over a century, with early studies utilizing deliberate infection with live pathogens as a mode of vaccination. In addition to being used to evaluate vaccine and drug efficacy, CHI can provide information on pathogen safety, tolerability, biology, pathogenesis, immunogenicity etc. With close to 3000 subjects, controlled human malaria infections (CHMI) with *Plasmodium falciparum* are only behind infections with Rhino and influenza viruses in terms of the number of subjects participating in CHI. This has led to advancement in evaluation of drugs and vaccines for malaria and additionally has led to a collection of information on the clinical symptoms post exposure. In contrast, *P. vivax* CHMI (*Pv*CHMI) studies are in their infancy, with less than 200 subjects exposed to a controlled infection to date. We report clinical and laboratory data collected, to include hematological and biochemical profiles and adverse-events, following mosquito-bite induced *Pv*CHMI in 33 malaria-naïve study-participants. Following exposure to the bite of *P. vivax* infected *Anopheles dirus* mosquitoes clinical, hematological and biochemical profiles as well as adverse events (AEs) were collected from the time of infection to immediately following malaria diagnosis. Overall, all biochemical and hematological deviations, as well as AEs were mild to moderate and majority of the symptoms were transient, resolving within 48hours. Using exploratory molecular-diagnostic methods detected parasitemia in 100% of study-participants before malaria diagnosis using microscopy. Additionally, majority of subjects were detected by molecular methods prior to the appearance of symptoms. Almost all the symptoms appeared after the initiation of treatment. We will present data to indicate that *Pv*CHMI is safe with majority of the infections being detected prior to the appearance of clinical symptoms, which can be further alleviated by using sensitive molecular methods for clinical diagnosis.

1007

THE IMPORTANCE FOR AGE-STRUCTURE AND DOSE SPACING TOWARDS THE EFFECTIVENESS OF THE RTS,S VACCINE TO REDUCE MALARIA BURDEN: A MATHEMATICAL MODELLING STUDY

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Despite intensive efforts in diagnostics, treatment and prevention, Malaria remains a major public health issue killing about 400,000 people a year, mainly children under five in sub-Saharan Africa. The RTS,S vaccine targets the liver stage of the parasite life-cycle and comprises three doses with a booster, administered between the ages of 5 and 38 months. Following promising results of efficacy trials with an estimated 30% reduction in severe Malaria in infants, WHO has recently recommended to include this vaccine into national Malaria prevention portfolios.The vaccine represents an important scientific advance, but to ensure its effectiveness, we need to investigate how intended vaccine deployment plans interact with existing disease control efforts. What would be the optimal spacing of the four doses? What would be tolerable levels of risk compensations (i.e. vaccinating children would result in neglecting early diagnostics, bed nets or treatment)? Focusing on Burkina Faso, we utilize an age-structured mathematical formalism (i.e. partial differential equations) to address these questions while taking into account the host age, the time since infection and vaccination for Malaria dynamics. Furthermore, we apply control theory to devise vaccine deployment plans minimizing the number of severe Malaria cases with constraints informed by local knowledge.

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DIFFERENTIAL PATTERN OF IGG SUBCLASS RESPONSE AND IGG AVIDITY TO PMRBP 1A

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The biased focus of vaccine and drug development programs on *Plasmodium falciparum* and *P. vivax* at the expense of other human malaria-causing *Plasmodium* spp. has an evolutionary impact on non-falciparum and non-vivax spp.- this could stymie global malaria elimination and eradication efforts. As a result, there is a rising support for the development of a species-transcending vaccine against human malaria parasites. *P. malariae* is one of the neglected species whose prevalence is believed to be underestimated due to its characteristic low parasitemia presentation. Though it causes mild malaria, it is implicated in nephrotic syndrome and other complications such as anemia, convulsion and death. *P. malariae* reticulocyte binding protein (PmRBP1a) has been shown to potentially be a major player during the invasion of erythrocyte by *P. malariae*. This calls for the need to assess this antigen as potential vaccine candidate.Hence, this study sort to evaluate the functional affinity of the naturally acquired IgGs to *P. malariae* reticulocyte binding protein, a potential vaccine candidate. And to also assess to the differential pattern of IgG subclass responses to this antigen. An ELISA-based avidity and subclass typing will be employed for the evaluation. The results will provide insights to the poorly understood transmission dynamics of *P. malariae* and inform the vaccine candidacy of PmRBP1a.

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PROTECTION-FORWARD SCREENING STRATEGIES TO IDENTIFY PROTECTIVE LIVER-STAGE ANTIGENS IN A MODIFIED PRE-CLINICAL RODENT MALARIA INFECTION MODEL

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Immune responses to multiple antigens may be needed to achieve reliable sterile protectionagainst the *Plasmodium* liver-stage. Identifying protective antigens is difficult because manyantigens are immunogenic but ultimately prove to be non-protective in pre-clinical mousemodels. We modified our 'two-dose challenge' protection-forward screening strategy to enhanceour ability to detect partially-protective antigens. Briefly, mice were gene gun-immunized withplasmid DNA encoding *P. yoelii* candidate antigens. Primed mice were gene gun boosted and thenadministered a low dose ($2x10^3$) of radiation-attenuated sporozoites (RAS) to recruit memory$CD8^+$ T cells to the liver. Mice were then challenged soon thereafter with wild-type sporozoites($\leq 1x10^4$) and monitored for sterile protection by blood smears. The interval between RAS andwild-type sporozoite administration can be varied from 2-4 days, thereby extending the parasiteliver-stage antigen exposure to a total of 4-6 days, more closely mimicking the natural liver-stageduration of human *P. falciparum* infection. By first vaccinating with plasmids encoding *P. yoelii*circumsporozoite protein with or without other candidate antigens and then varying the intervalbetween RAS and wild-type dosing, we can better assess the contribution of non-CSP antigens toliver burden reduction at the time of wild-type challenge. Several protective antigens have beenidentified in this manner with significant liver burden reductions compared to naïve animals givenRAS alone. Such candidates are then evaluated in single antigen vaccination

using prime-and-trapvaccines to prioritize them for further development. These approaches have the potential tospeed the development of a more effective malaria vaccine targeting the liver stage.

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EFFICACY AND IMPACT OF THE RTS,S/AS01E MALARIA VACCINE ADMINISTERED ACCORDING TO DIFFERENT FRACTIONAL AND FULL DOSE REGIMENS UNDER CONDITIONS OF NATURAL EXPOSURE IN AFRICAN CHILDREN: INTERIM RESULTS FROM A PHASE 2B RANDOMIZED CONTROLLED TRIAL UP TO MONTH 32

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RTS,S/AS01$_E$ (RTS,S) malaria vaccine is recommended by WHO in areas of moderate to high malaria transmission. Malaria challenge studies suggested that fractional (Fx) dose regimens may increase vaccine efficacy (VE). We present month (M) 32 VE and impact of the RTS,S vaccine from an ongoing phase 2b trial (NCT03276962) using different immunization regimens with or without Fx doses. 1500 Kenyan and Ghanaian children aged 5-17M were randomized (1:1:1:1:1) to receive RTS,S or a rabies control vaccine. Children in the RTS,S groups received 2 full doses of RTS,S at M0, M1 followed by either full doses at M2, M20 (group R012-20, standard regimen) or M2, M14, M26 (R012-14-26), or Fx doses (1/5 of full dose) at M2, M14, M26 (Fx012-14-26) or M7, M20, M32 (Fx017-20). As previously presented, we were unable to show a superior VE of Fx012 *vs* R012 regimen 12M post-dose 3 (primary objective), but all vaccine regimens showed significant VE against clinical malaria *vs* control group over 20M of follow-up. All vaccine regimens continued to be immunogenic, well tolerated with no safety signals observed, and showed statistically significant reduction of clinical malaria *vs* control group, with VE ranging from 38% (R012-20; 95% confidence interval [CI]: 24-49) to 53% (R012-14-26; 95%CI: 42-62). Translating VE into impact of RTS,S was done by expressing cumulative malaria cases averted/1000 children vaccinated: this ranged from 1344 (R012-20) to 2450 cases (R012-14-26) over 32M of follow-up. However, in the context of our trial, different number of vaccine doses and dosages (Fx *vs* full dose) should be considered to derive the impact. Therefore, we estimated malaria cases averted/1000 full dose equivalent vaccine doses by factoring in the amount of vaccine administered (Fx *vs* full dose): this ranged from 336 (R012-20) to 874 cases (Fx012-14-26). Expressing malaria cases averted/1000 vaccine doses administered may be an important measure for vaccine impact when different vaccine regimens and doses are administered across arms. The trial continues until study end (M50) and may provide further insight into longer term VE and impact of the different RTS,S regimens evaluated.

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CHARACTERIZING THE EFFECTS OF MONTHLY VERSUS DELAYED-BOOST VACCINATION REGIMENS ON HUMORAL RESPONSES INDUCED BY THE *PLASMODIUM FALCIPARUM* BLOOD-STAGE VACCINE RH5.1/MATRIX-MTM IN TANZANIAN INFANTS 5-17 MONTHS OF AGE

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Reticulocyte-binding protein homologue 5 (RH5) is the leading blood-stage *Plasmodium falciparum* vaccine candidate. Previous studies indicate protection is strongly associated with anti-RH5 serum IgG antibody and *in vitro* functional growth inhibition activity (GIA). Clinical trials have also shown that IgG responses are 10X higher with protein/adjuvant delivery as compared to viral vectors (UK adults), in Tanzanian infants as compared to UK adults (viral vectors), and are more durable with delayed fractional booster dosing as compared to monthly booster dosing (UK adults). Here we assess the RH5.1 soluble protein vaccine formulated in Matrix-M^{TM} (MM) adjuvant in an age de-escalation Phase Ib clinical trial in Tanzania. Adults and infants (5-17months old) received three doses of RH5.1 administered in one of the following schedules: 10 µg doses in a "monthly" regimen (0-1-2mo), 10 µg doses in a "delayed" booster regimen (0-1-6mo), or in a "delayed fractional" booster regimen (50 µg 0-1mo doses, 10 µg dose 6mo) in MM. An additional infant group was enrolled from highly endemic areas to allow assessment of the impact of malaria pre-exposure (confirmed by anti-schizont ELISA). All vaccine doses were well tolerated and there were no safety concerns. All infant groups showed greatly improved humoral responses as compared to Tanzanian adults and historical UK adult data. Antibody functionality - measured by GIA assay - was consistent with previous work and there was no effect of pre-exposure status on antibody quantity. The infant delayed regimen showed the highest anti-RH5.1 IgG responses to date, suggesting that previously observed improved antibody titres (as compared to monthly dosing regimen) are due to the delay of the final booster rather than fractionation of dose. Consistent with the positive impact of delayed booster dosing on humoral immunity, RH5.1-specific long-lived plasma cells were detected in the bone marrow of vaccinated adults at a higher frequency in delayed versus monthly regimens. These data support the progression of RH5.1/Matrix-M candidate for 5-17 month old infants into Phase IIb efficacy trials against clinical malaria.

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OPTIMIZATION OF *PLASMODIUM FALCIPARUM* MULTISTAGE VACCINE BASED ON THE HETEROLOGOUS VIRAL-VECTORED PLATFORM IN A MURINE MODEL

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Very recently, we have developed a multistage *Plasmodium falciparum* vaccine based on LC16m8Δ (m8Δ)/adeno-associated virus (AAV) effective both for pre-erythrocytic (100% protection) and sexual stages (>99% transmission blocking; TB). The present study aims to optimize the Prime-Boost immunization strategy of m8Δ/AAV vaccine. We assessed various immunization regimens including promoter stringency, sequence of immunization and vaccine delivery devices to optimize m8Δ/AAV vaccine

harboring the fusion gene encoding the pre-erythrocytic stage antigen PfCSP and the sexual stage antigen of Pfs25. The timing of expression of heterologous antigens in the vaccinia virus system affects the capacity to induce antigen-specific T-cell immune responses. We made three kinds of m8Δ vaccines harboring the Pfs25-PfCSP fusion gene under the control of three kinds of vaccina virus-derived promoters P7.5, Early-Late synthetic and mPH5 promoters. The mPH5 promoter with strong activity at the early phase expressed the most abundant Pfs25-PfCSP fusion protein both at early (8.1 times) and late (7.0 times) infection phases. We will show whether the enhanced early phase expression of the fusion antigen increase the quality of the antigen-specific T-cell response, resulting in high protective efficacy in C57BL6 mice that are highly susceptible to malaria infection. We will also show whether sequence of immunization and vaccine delivery devices can improve vaccine efficacy. Our results may provide a guideline for desirable immunization regimen of m8Δ/AAV vaccine, especially as these concepts move toward clinical trials.

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SYMPTOMATIC MALARIA IS ASSOCIATED WITH ENHANCED PROTECTION FROM REINFECTION WITH HOMOLOGOUS *PLASMODIUM FALCIPARUM* CIRCUMSPOROZOITE PROTEIN EPITOPES

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A hallmark of functional protection against malaria is the delayed acquisition or decreased risk of infection when exposed to homologous parasites. Cataloging homologous reinfections and measuring associations with host and parasite factors in a natural setting can provide insights into the process by which anti-parasite immune memory is inscribed. We hypothesized that, as a proxy for a functional immune response, symptomaticity during an infection with *P. falciparum* would be associated with a decreased risk of reinfection with homologous parasites. We investigated the risk of reinfection with parasites bearing homologous parasite CSP types after symptomatic and asymptomatic infection in a longitudinal cohort of 239 people tested monthly for parasites over 14 months in Western Kenya. We recorded 69 symptomatic and 275 asymptomatic infection episodes, from which we amplified polymorphic regions of *csp* and genotyped using deep sequencing. We observed 155 unique *csp* haplotypes, which we defined by 8 amino acid positions that clustered in the known T-cell epitopes. Specifically, we observed 27 unique Th2R and 14 unique Th3R epitope types. Irrespective of parasite sequence, the risk of reinfection was not affected by symptomaticity of the previous infection. However, when classified by observed epitopes, symptomatic infections, compared to asymptomatic infections, were associated with significantly reduced hazard of reinfection with parasites harboring homologous Th2R (aHR 0.63, 95% CI: 0.45 - 0.89) and Th3R epitope types (aHR 0.71, 95% CI: 0.52 - 0.97). Notably, this decreased hazard after symptomatic exposure was not observed for reinfections with heterologous CSP epitope types. The reduced hazard of reinfection with homologous parasites following symptomatic infection suggests that symptomatic malaria provides more robust protective immunity than asymptomatic infections. Future studies can leverage the delay in reinfection following symptomatic disease to identify new non-*csp* targets of functional immunity.

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DIVERSE ANTIMALARIALS TARGET *PLASMODIUM FALCIPARUM* DEVELOPMENT IN THE *ANOPHELES* MOSQUITO

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Although extensive research has focused on identifying and characterizing asexual blood stage (ABS) *Plasmodium falciparum* drug targets, less is known about the parasite during the mosquito portion of its lifecycle. We recently demonstrated that parasite development within its vector can be completely inhibited by allowing *Anopheles gambiae* mosquitoes to rest on a surface coated with the potent cytochrome bc1 (cyt b) Q_o site inhibitor atovaquone prior to infection. We have since undertaken an *in vivo* screening approach to identify additional, diverse antimalarial compounds that have a similar antiplasmodial effect when applied directly to the mosquito cuticle prior to infection. To date, we have tested approximately 100 compounds spanning 25 distinct modes of action and identified multiple *P. falciparum* targets amenable to drug perturbation in the mosquito stages of development, including cyt b Q_o and Q_i sites, P-type ATPase 4 (ATP4), dihydrofolate reductase (DHFR), and elongation factor 2 (EF2). Both hits and inactive compounds provide key insight into parasite pathways that are essential during mosquito development, and reveal intriguing differences relative to asexual blood stages. For example, multiple, potent dihydroorotate dehydrogenase (DHODH) inhibitors were found to be inactive. This was surprising, as cyt b inhibitors are highly effective and their activity during *P. falciparum* ABS is due to their downstream inhibition of DHODH and subsequent pyrimidine biosynthesis, rather than a direct result of impaired ATP production by the mitochondrial electron transport chain (ETC). This may indicate that DHODH is not essential during the early parasite stages exposed in this assay, and that the activity of cyt b inhibitors in our assay is in fact due to their disruption of the ETC. Alternatively, the DHODH compounds tested may be unsuitable for mosquito uptake and bioavailability. Further chemical biology approaches are ongoing to identify additional mosquito-stage targets, elucidate optimal parameters for mosquito pharmacokinetics, and better understand critical steps in *P. falciparum* development in the *Anopheles* vector.

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INFECTIVITY OF *PLASMODIUM OVALE* CARRIERS TO *ANOPHELES GAMBIAE* MOSQUITOES IN TANZANIA

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Plasmodium ovale (*Po*) causes low density infections and often accompanies *P. falciparum* (*Pf)* as part of mixed species infections. In a previous pilot study among *Pf*/*Po* co-infected participants, we showed efficient transmissibility of *Po* from humans to mosquitoes in direct

skin feeding assays (DFAs). Six of eight asymptomatic individuals who underwent DFAs successfully transmitted *Po* parasites to *An. gambiae*, confirmed via PCR of oocyst-positive mosquito midguts and/or mosquito thoraces 14 days after blood-feeding. We are now pursuing a larger prospective cohort study. Among 122 asymptomatic individuals (> 5 years) enrolled within a median of 2 days after screening *Po* positive by 18s real-time PCR, 105 successfully underwent DFAs on the day of enrollment with >25 engorged mosquitoes surviving to midgut dissection. However, only 21/105 (20%) had *Po* parasitemia detectable on the day of enrollment. An additional 29 participants separately enrolled had *Po* parasitemia detectable on the day of enrollment despite having only *Pf* detected at screening. Out of these combined 50 individuals, 10/35 (29%) with *Pf/Po* parasitemia infected mosquitoes, with parasite oocysts visualized at midgut dissection; while 3/15 (20%) with *Po* parasitemia without *Pf* co-infection infected mosquitoes. In general, few mosquitoes were infected at each DFA, with only 3/13 positive feeds resulting in more than 10% mosquitoes infected. Oocyst-positive midguts are undergoing PCR to determine the *Plasmodium* species present. Screening and enrollment will continue through June 2022. Additionally, data from DFAs conducted at participant follow-up will be presented. In summary, we have found that *Po* parasitemia among asymptomatic parasite carriers is remarkably transient. When present, infection is transmitted to biting *An. gambiae* roughly 20% of the time, comparable to the rate of asymptomatic *Pf* transmission we have observed in the same population. Understanding the infectivity of *Po* parasite carriers with and without *Pf* co-infection is a critical step towards understanding the rising prevalence of *Po* throughout Sub-Saharan Africa.

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COMMUNITY-BASED SURVEILLANCE: A KEY PROCEDURE FOR CONTINUOUS FIELD ENTOMOLOGICAL DATA COLLECTION IN AREAS OF DIFFICULT ACCESS IN MALI

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Since 2017, the PMI VectorLink Mali project has been conducting monthly longitudinal entomological monitoring in Mopti, a central region of the country where indoor residual spraying (IRS) is implemented (Mopti, Djenné, Bankass and Bandiagara health districts). Unfortunately, the North and the Center of Mali were increasingly affected by the activities of organized armed groups, resulting in unpredictable security conditions that prevented nighttime supervision of human landing catches data in the IRS districts. To overcome the challenges and still provide sound entomological data for vector control decision-making, VectorLink Mali and the National Malaria Control Program in 2020 launched a community-based surveillance (CBS) monitoring pilot in two sites (Sarema sprayed with Fludora Fusion WP-SB and Toguel unsprayed) in Mopti District. Collectors and supervisors were selected from each host community and trained on basic entomology and mosquito collection methods using Centers for Disease Control and Prevention (CDC) light traps (LT) and pyrethrum spray catch (PSC). CDC-LT collections were done in 15 houses/week for 20 nights/month (60 houses/month) and PSC in 6 houses/week for 24 houses/month. Mosquito samples preserved by CBS collectors were identified and preserved individually by VectorLink entomology staff for further laboratory analysis. A total of 5,202 *Anopheles* mosquitoes, including 5,186 (99.7%) *An. gambiae* s.l. were collected in Sarema with 99.7% (5,186) *An. gambiae* s.l. using CDC -LT and 2,464 *An. gambiae* s.l. (100%) collected by PSC over a 5-month collection period. In unsprayed Toguel, 5,278 *Anopheles* mosquitoes were collected including 5,267 *An. gambiae* s.l. (99.8%) using CDC-LT and 11 (0.2%) using PSC. Higher numbers of mosquitoes were caught by CDC-LT than PSC. The implementation of CBS enabled continuous entomological vector surveillance, despite security challenges. Additional benefits included increasing number of sentinel sites, greater community engagement and scaling up of local capacities. The data collected will support the IRS impact analysis for further vector control decision making.

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SUSCEPTIBILITY STATUS OF MALARIA VECTORS TO INSECTICIDES COMMONLY USED FOR MALARIA CONTROL IN DIFFERENT GEO-ECOLOGICAL AREAS OF NEPAL

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The rapid spread of insecticide resistance is a major challenge to malaria elimination; hence, updated information on commonly used insecticides is important for planning and implementing national insecticide resistance management strategies. This study was conducted to map the insecticide susceptibility status of *Anopheles fluviatilis* and *An. annularis* in malaria high-risk areas of Nepal. In 2018 and 2021, wild-caught adult female *An. fluviatilis*, *An. annularis* were collected from provinces 1, 2, 3, 5 and 7 and in Sudurpashchim Province representing different geo-ecological areas (plain cultivated terrain, forest and forest fringe and inner terrain) of Nepal. Susceptibility tests were conducted using test kits as per WHO's methodology. Mortality rates (MRs) and knockdown times were calculated for 5 insecticides commonly in all provinces of Nepal (alpha-cypermethrin [0.05%], deltamethrin [0.05%], lamda-cyhalothrin [0.05%], permethrin [0.75%] and bendiocarb [0.1%]) on a total of 4393 specimens. *An. fluviatilis,* the major vector in Nepal, was susceptible to all insecticides tested in all study areas (98% in 2018 and 100% in 2021). However, in provinces 7 and 5, *An. annularis* showed resistance to alphacypermethrin (88.46% in 2018) and, in 2021, it showed increased resistance (59.7%) in Sudurpashchim Province. In provinces 7 and 5, *An. annularis* showed marginal susceptibility to deltamethrin (94.03% in 2018) and lambdacyhalothrin (94.31% in 2018) and possible resistance to *An. annularis* (91.5% in 2021) in Sudurpashchim Province. In province 1, *An. annularis* showed resistance to deltamethrin (35.9% in 2018). Whereas in province 2, in 2018, it showed resistance to lambdacyhalothrin (40%), lambdacyhalothrin (86.7%), alphacypermethrin (40.6%). The sustained susceptibility of malaria vectors to pyrethroids and carbamates in Nepal makes LLINs and IRS effective tools. However, the development of insecticide resistance in *An. annularis* to pyrethroids is of concern and it calls for continued monitoring to fill knowledge gaps on resistance mechanisms and the impact of current insecticide resistance management approaches.

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SPECIES COMPOSITION AND SEASONAL PREVALENCE OF MALARIA VECTORS IN RISK AREAS OF NEPAL

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Nepal aims to eliminate all forms of malaria by 2025. Entomological surveillance is essential to implement a targeted approach for malaria control interventions in Nepal which are long lasting insecticide-treated nets and indoor residual spraying. The aim of this study was to understand *Anopheles species* abundance and malaria vector seasonal occurrence in risk areas of Nepal. Entomological surveys were conducted in provinces 1,

6 and 7 of Nepal during the pre-monsoon and monsoon seasons in March and August 2018. In each locality, the collection spots faced different directions and random collections were performed from every possible mosquito habitat. Adult mosquitoes sampling was carried out as per WHO guidelines and identified morphologically. The dipping method was used to collect larvae. *Anopheles* mosquitoes resting indoors and outdoors were collected using aspirators with the support of flashlight. In total, 3193 *Anopheles* were captured, 442 (13.8%) mosquitos in the pre-monsoon season and 2751 (86.2%) mosquitos in the monsoon season. *Anopheles fluviatilis*, *Anopheles annularis*, *Anopheles maculatus complex (Anopheles pseudowillmori*, *Anopheles willmori* , *Anopheles maculatus*) were were identified from all three provinces. *Anopheles fluviatilis* (38.24%) was the most abundant species followed by *Anopheles maculatus* (17.7%) in the pre-monsoon season. Whereas in the monsoon season, *Anopheles subpictus* (39.48%) was the principal species followed by *Anopheles vagus* (34.21%). This study identified that *Anopheles fluviatilis* was the the dominant species in the pre-monsoon season, which indicates that prevention interventions must take place in March and April. Although, the peak of *Anopheles* density was in the monsoon season, there was relative high abundance of malaria vector species in the pre-monsoon season. *Anopheles fluviatilis,* the primary vector of malaria in Nepal, was predominant in the pre-monsoon season. In the monsoon season, *Anopheles annularis* was the most abundant malaria vector species. Longitudinal studies on vector bionomics are required in order to develop more effective vector control strategies.

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THE USE OF NEXT GENERATION INSECTICIDES FOR INDOOR RESIDUAL SPRAYING OF TEMPORARY STRUCTURES

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The development of resistance to most Insecticide classes are hampering the elimination effort in many countries. The residuality of Insecticides are also influenced by the surfaces onto which it is sprayed. Following disasters, people are often housed in make-shift shelters and are at risk of malaria. The option most effectively used for malaria prevention is indoor residual spraying. In most southern African countries, galvanized iron (tin) is most often the material used to build temporary housing in the aftermath of natural disasters. This study was conducted to investigate the residual life of Fludora®Fusion (Bayer), Actellic (Syngenta), SumiShield (Sumitomo) and DDT (HIL) when sprayed on tin surfaces. The study was conducted in northern KwaZulu-Natal, South Africa. Spray operators from the control programme sprayed the insecticides onto tin structures. The WHO cone bioassay method was used to determine mortality among fully susceptible mosquitoes that had been exposed to the insecticide. For each insecticide, mortality was observed every 24 hours post-exposure until 100% mortality was achieved. The data obtained showed that all chemicals were effective in controlling mosquito populations, with all insecticides resulting in 100% mortality between 1- and 5-days post exposure. DDT exposure resulted in mortality within a maximum of 4 days post-exposure in the latter months but could result in total mortality within 3 days, except for months and 5. Both Fludora®Fusion and Actellic have the same trend in terms of duration to 100% mortality, with total mortality being achieved in 5 days for months 10-12. The duration to 100% mortality when exposed to SumiShield was 5 days in months 11 and 12. Although comparing between insecticides was not an objective of the study, it clearly shows that DDT is still the most effective insecticide available for IRS. The chemical manufacturers maintain that delayed mortality is accompanied by feeding inhibition but this still needs to be ascertained. Nevertheless, all four insecticides can effectively be used for IRS since exposure to these insecticides results in 100% mortality up to 12 months post-spray.

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THE IMPACT OF LARVICIDING AS A SUPPLEMENTARY TOOL FOR MALARIA VECTOR CONTROL IN RUFIJI, TANZANIA

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WHO recommends larviciding with a reservation that it should be conducted in an area where LLIN's and IRS have attained optimal coverage, but Malaria transmission still exists. National Malaria Control Program (NMCP) in Tanzania in line with WHO has indorsed the use of larviciding in many areas in the country through a programme called TOWARD. The plan is to implement larviciding for four years in five regions in Tanzania and the program has already started. The project was implemented in Rufiji, southern-eastern of Tanzania from November 2020 to October 2021, the study took place in two wards and included 19 villages. Coverage of LLIN's and IRS was 80%-85%. Malaria vectors were collected indoors using CDC-light traps, clay ports were used for both indoor and outdoor collection. Biolarvicides, Bacillus thuringiensis israelensis (Bti) and Bacillus sphaericus (Bs), were applied to waterbodies surrounding human habitats. We fitted liner model to determine the effectiveness of larviciding and the result shows there is significant decline in average number of mosquitos with time (p-value < 0.001, CI= 0.67, 0.89) which is 88.2% reduction in average mosquito due to larviciding management. Through treatment of the larvicides the mortality impact observed for over nine months for immature anopheles was 87% and 92% for larvae and pupae respectively, where this indicates the approximation of 100% impact in the usage over a long period of time. The mortality impact of larviciding to the adult mosquito is said to be 98% to the Anopheles Gambiae which is the most dangerous species in the Rufiji area. Biolarviciding received high acceptance from both the government and community members in southern eastern Tanzania due to its ability to target immature mosquitoes and reduce the rate of fecundity, which makes it an efficient tool to be adopted as a supplementary measure for malaria vector control.

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ECOLOGY, DISTRIBUTION AND INSECTICIDE SUSCEPTIBILITY STATUS OF THE MAJOR MALARIA VECTOR *ANOPHELES FUNESTUS* S.L. IN GUIDIMOUNI, EASTERN NIGER

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Longitudinal vector surveillance conducted in 2021 in Guidimouni, Niger revealed *Anopheles funestus* s.l. as the main malaria vector. Species' breeding sites and density vary according to climatic conditions, so characterizing ecology and insecticide susceptibility status will enable targeted vector control interventions .Adult mosquitoes were collected using human landing catches (HLC, 2 nights/month) and pyrethrum spray catches (PSC, 10 houses/month) from July to December 2021 to determine *An. funestus* s.l. composition, human biting rate (HBR), indoor resting density (IRD), parity rate, and entomological inoculation rate (EIR).

Susceptibility to alpha-cypermethrin (0.05%), deltamethrin (0.05%) permethrin (0.75%), pirimiphos-methyl (0.25%) and chlorfenapyr (100 ug/bottle) was determined using the WHO insecticide susceptibility kits and CDC bottle assays on mosquitoes collected by HLC. Resistance intensity (5x, 10x diagnostic doses) and PBO (4%) synergist assays were conducted for pyrethroids. Potential larval habitats were sampled to assess their physio-chemical characteristics.. *An. funestus* s.l. represented 62% (n=2912) of the total *Anopheles* collected and PCR analysis showed *An. funestus s.s.* (92%) and *An. leesoni* (8%). The mean HBR and IRD were 29.8 bites/person/night and 8.3 females/house, respectively, with a mean parity rate of 54% (n=375/698). The mean EIR was 17.9 infected bites/person/month. *An. funestus* s.l. was resistant to all pyrethroids (22% mortality for alpha-cypermethrin, 55% for deltamethrin and 85% for permethrin, low resistance intensity for all three, susceptible to pirimiphos-methyl and chlorfenapyr. PBO restored full susceptibility to all pyrethroids. Sixteen larval habitats were surveyed; 93% were more than 50 cm deep and had vegetation. About 23% (11/48) of the collected larvae were *An. funestus* s.l. found only in one site. The findings revealed that the *An. funestus* s.l. population in Guidimouni is highly involved in malaria transmission and is resistant to pyrethroids. The results suggest that PBO or Interceptor G2 nets may be appropriate to reduce malaria transmitted by this vector.

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ESTIMATING INSECTICIDAL CONCENTRATION IN AN INDOOR RESIDUAL SPRAYING CAMPAIGN USING A HANDHELD X-RAY FLUORESCENCE ANALYZER

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Indoor Residual Spraying (IRS) reduces vector densities and malaria transmission; however, the quality of IRS operations is not often assessed because of the limited choice of methods available for quantifying insecticide content in the field. This study evaluates a less than one minute field deployable X-ray fluorescence spectrometry (XRF) analysis for detecting insecticidal content on sprayed walls. XRF can be used for this purpose as it can detect characteristic chemical elements such as bromine (Br), sulfur(S) and chlorine (Cl) present in various insecticides used in IRS. Our study consisted of proof of principle experiments using surfaces (plywood and masonite) sprayed with Fludora Fusion insecticides. A standard curve was constructed with known insecticide concentrations and an established liquid chromatography mass spectrometry assay to quantify the respective insecticides. XRF was then used in a small real world pilot IRS implementation study with Fludora Fusion in two villages in Papua New Guinea. Eight treated and four control houses were selected for the XRF analysis. For each house, six dedicated spots were marked for longitudinal analysis (3 indoors and 3 outdoors). Insecticide content was measured before spraying, 24 hours after spraying and then in monthly intervals by pointing the analyzer directly on the surface of the wall. We observed a very distinct and statistically significant increase in target element (Br, S and Cl) concentrations on the surfaces after spraying indicating that XRF quantified insecticides on sprayed walls. These observations were confirmed in our small village study, where sprayed houses could clearly be distinguished from unsprayed houses using XRF before and after spraying. Monthly longitudinal measurements after spraying showed a characteristic exponential insecticide decay pattern indicating an IRS chemical half-life of 3-4 months. XRF is a promising and rapid technique to quantify insecticides under field conditions. Provided further development, XRF has the potential to be applied for routine quality control in malaria control programs in Papua New Guinea and globally.

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CHARACTERIZING PHENOTYPIC RESISTANCE TO INSECTICIDES IN VECTORS: INTRODUCING A NOVEL STATISTICAL FRAMEWORK FOR ANALYSIS OF INTENSITY BIOASSAY DATA

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Insecticide resistance is a growing problem that threatens the success of vector-borne disease control interventions across the world, particularly in sub-Saharan Africa. Historically, phenotypic resistance was monitored by discriminating dose bioassays. WHO now recommends intensity bioassays (IBs) to measure the level of resistance in regions where the discriminatory concentration indicates its presence. However, mosquito data can be highly variable and it is unclear how IB data should be analysed, which metrics can be reported and what these represent. Here, a novel statistical framework for analysis of IB data is introduced. This framework consists of a Bayesian binomial model using a flexible logistic function and is tested on data from susceptible and resistant laboratory mosquito colonies with defined genetic background, as well as highly resistant wild mosquitoes collected in Burkina Faso. A base model is developed, quantifying the amount of background mortality, the median lethal concentration, and heterogeneity and within-assay variability in mortality. The model is then extended to add a time covariate to explore temporal variation in insecticide resistance. We find that the framework developed is suitable for the analysis of IB mortality data in laboratory colonies as well as field samples. Whilst observed mortality is more heterogeneous in resistant strains, the framework captures both susceptible and resistant trends suitably. Within- and between-assay variability can be quantified, indicating which species, insecticides or locations are more heterogeneous. The time model enables the characterisation and quantification of temporal changes in resistance, with the potential to be extended to other covariates of interest. The framework introduced here provides guidance for the analysis of IB data as well as insights into novel ways of describing phenotypic insecticide resistance. It is highly adaptable and describes vector resistance more precisely than traditional statistical models, with the potential to be applied to other types of dose-response data.

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APPLICABILITY OF NANOPORE SEQUENCING AS POINT OF NEED TEST FOR DIARRHEA PATHOGENS

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The need for fast detection of etiological agents outside the narrow target range of pathogens that may cause an event of infectious disease epidemic necessitates rapid sequencing technologies to be implemented in routine diagnostic procedures. We tested the performance of a PCR-free rapid nanopore barcoding assay to detect microbial species by analyzing genomic contents extracted from acute diarrheal case specimens. Sequenced reads were processed in automated analysis module for species identification, whereas pathogenic sub-species detection was aided by sequence similarity search against a gene-specific database. Evaluation of assay and analysis parameters (e.g., run-time, sequence length, and species hit abundance level) were carried out using a standard bacterial community for assessing detection accuracy. It was observed that longer sequence length (≥ 500 nucleotide) along with higher species abundance level (≥ 1%) can be critical for exclusion of false-negative outcomes, while increased sequencing run-time can affect proportional abundance

of true-positive species. Under optimal parameters, the sensitivity of the rapid assay remained 100% for the detection of a target species in a background of non-target fecal (diarrheal) DNA that weighted up to 64 times of DNA of the target species. The method was applied to acute diarrheal samples. Among these, 62% were in agreement with target-specific traditional diagnosis methods for the presence/absence of pathogenic agent(s), 12% in disagreement, and pathogenic agents that were not targeted by the traditional methods were revealed by sequencing for 25% of samples. These observations suggest that further optimization and evaluation of the rapid nanopore sequencing method can potentiate widening of the range of pathogens that can be detected in acute diarrheal samples in the context of regular diagnostic needs as well as epidemics.

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PREVALENCE OF BACTERIAL AND PARASITIC ENTEROPATHOGENS IN CHILDREN UNDER FIVE DURING A HIGH TRANSMISSION PERIOD IN A COMMUNITY SETTING IN OUAGADOUGOU, BURKINA FASO

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The introduction of rotavirus vaccine in Burkina Faso has led to the control of the main cause of diarrhoea in children. Although bacterial and parasitic are an important cause of children diarrhoea, they remain under targeted by vaccination. This study was undertaken, prior to the implementation of clinical trial of *Shigella* vaccine candidate, to assess the burden of enteric bacteria, and intestinal parasitosis. A community-based cross-sectional survey was conducted from June 15 to September 8, 2021, during the high transmission period, among children under five living in the peri-urban areas (Nioko2 and Polesgo) of Ouagadougou, the capital of Burkina Faso. Fresh stool samples collected were aliquoted and those for culture were placed in Cary-Blair medium and transported at 2-8°C. By microscopy, fresh stools were examined for intestinal parasites. Enteric bacteria were isolated on selective agar media. Bacterial identification was performed using BD Phoenix M50. Sensitivity of the isolated bacteria to antibiotics was tested by Kirby Bauer's method.The mean age of the children was 2.56 ± 1.24 years. From 610 stool samples collected, the prevalence of enteric bacteria was 12.13% (74/610). *Shigella spp* and *Salmonella spp* had the same prevalence, 34.13% (26/74), *Enteropathogenic Escherichia coli* was present in 29.72% (22/74). *Shigella flexneri* was the most prevalent 42.30% (11/26) in the *Shigella* species. The most common resistant antibiotics to the enteric bacteria were to tetracycline, cotrimoxazole and amoxicillin. The prevalence of intestinal parasites was 29.01% (177/610). 82.48% (146/177) of intestinal parasitosis were due to *Giardia intestinalis*; 5.64% (10/177) to *Trichomonas intestinalis*, 5.17% (9/174) to *Entamoeba histolytica* and 6.71% to other parasites The present study revealed a high prevalence of enteric bacteria and intestinal parasites. This could be explained by the poor socio-economic conditions of the population and the inadequacy of hygiene and sanitation measures.

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RAPID GENERATION AND SELECTION OF ANTI-CHAPERONE SCFV-ANTIBODIES AGAINST THE ESSENTIAL EXPOSED ELEMENTS OF LISTERIA MONOCYTOGENES AND STREPTOCOCCUS

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Gram-positive bacteria are causative agents of serious and often fatal infections in both hospital and community settings, however many fundamental aspects of their physiology and pathogenesis remain poorly studied in comparison to their Gram-negative counterparts. The fundamental process of Gram-positive secretion, critical for the delivery of virulence factors, is one of these largely understudied physiological facets. We have focused on post-translocation secretion chaperones in the human Gram-positive pathogens *Listeria monocytogenes* and *Streptococcus pneumoniae* so as to better understand the process underlying protein secretion, folding, and activity following membrane translocation. We present a simple robust approach for the generation of panels of recombinant single-chain antibodies against the essential exposed elements (PrsA1 and PrsA2) of *Listeria monocytogenes* and *Streptococcus pneumoniae* that may inhibit virulence factor secretion and increase antibiotic susceptibility studies. *In vitro* combinatorial antibody ribosome display libraries were assembled from immunoglobulin transcripts rescued from the spleens of mice immunized with chaperone proteins PssA1 and PrsA2. The libraries were used in a single round of selection against chaperone proteins, PrsA1 and PrsA2, resulting in the isolation of a panel of recombinant antibodies. The potential use of selected anti- chaperone antibodies was demonstrated by the successful application of the two antibodies in an enzyme-linked immunosorbent assay (ELISA), and a Western blot assay. These immortalized *in vitro* recombinant single-chain antibody libraries against the essential exposed elements (PrsA1 and PrsA2) of Listeria monocytogenes and Streptococcus pneumoniae are a resource for the antimicrobial resistance and virulence research community that may be readily accessed for the isolation of antibodies against a plethora of Listeria monocytogenes and Streptococcus pneumoniae surface-exposed antigenic molecules.

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FILLING IN THE BLANKS: DEFINING EPIDEMIOLOGICALLY-RELEVANT UNITS OF CHOLERA TRANSMISSION IN AFRICA

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Recent molecular evidence on Vibrio cholerae introductions into Africa has provided insights into cholera transmission dynamics; however, there are still large gaps in our understanding of cholera transmission in Africa. Combining epidemiologic and molecular data can provide valuable information on cholera dynamics and epidemiologically-relevant transmission units, which is critical for developing regional approaches to cholera control. We obtained data on annual cholera incidence reported to the World Health Organization (WHO) from 52 African countries (1970 to 2019) and whole-genome sequence data from >900 V. cholerae isolates collected from 42 African countries (1970 to 2019). Given that cholera isolates from all countries in all years with cholera epidemics are not available, we first developed models to infer the pandemic V. cholerae lineage in unsequenced country-years using inverse Euclidean distance and correlation in annual cholera incidence between country pairs as a measure of closeness. We assessed model performance using the area under the curve (AUC) and leave-one-out cross-validation (LOOCV). We then used predictions from these models and cholera incidence data to group countries into transmission units. Models performed well in predicting lineage co-occurrence in country-year pairs (LOOCV accuracy=0.76, AUC=0.85) and in assigning pandemic V. cholerae lineage (multi-class AUC>0.90), allowing us to infer likely pandemic lineages for unsequenced country-years with reported cholera cases. Distance was most influential in predicting whether a lineage would co-occur in two countries in a given year, with near countries more likely to have co-occurring lineages ($\beta = 3.78$, SE = 0.21, $p<0.001$). We will continue to refine our models and update our analyses with additional sequence data as they become available. Results from this work can be used to define geographic areas of transmission, improve risk assessments during outbreaks, aid in cholera prevention planning, and target resources for sequencing in unsampled areas where additional phylogenetic data would improve inference of likely lineages.

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COST ANALYSIS OF NIRUDAK CLINICAL DIAGNOSTIC MODELS FOR VOLUME DEFICIT IN PATIENTS WITH ACUTE DIARRHEA

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With over 6.5 billion cases and 1.4 million deaths in 2019, diarrheal diseases are a major cause of morbidity and mortality and place a heavy burden on healthcare systems worldwide. This study aims to compare simulated treatment costs of acute diarrhea management using the World Health Organization (WHO) guidelines or the recently developed NIRUDAK machine learning model to the actual cost of care in patients over 5 years old. Cost of care for each patient included fluid administered, hospital costs, and equipment for patients presenting to icddr,b's Dhaka Hospital from March 2019-2020. Total costs of resuscitation along with cost of fluid required for initial resuscitation (within first 6 hours of admission) were calculated and reported as median and interquartile range (IQR) in USD. Using the NIRUDAK model, patients had a median projected total cost of $5.18 (IQR:0-25.56), while median projected total costs using the WHO guidelines were $5.23 (IQR:5.09-22.17). Actual total cost of care was $37.75 (IQR:15.69-45.00). When isolating costs for initial fluid resuscitation, the median projected cost per patient was $3.27 (IQR:0-4.27) using the NIRUDAK model and $4.55 (IQR:0-5.76) using the WHO guidelines, while actual costs of care were $5.43 (IQR:4.16-5.43). When using the NIRUDAK model to predict dehydration severity, patients had lower projected median total cost of care and cost of initial resuscitation compared to both the WHO guidelines and current clinical practice. Implementing the most cost-effective approach to diarrhea management will help optimize allocation of resources, which is especially critical in low resource settings.

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THE GUT MICROBIOME IN HAITIAN CHILDREN AND EXPOSURE TO FREE RESIDUAL CHLORINE IN DRINKING WATER

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In Haiti, diarrheal illness is a major cause of morbidity in children. Following a deadly cholera outbreak that began in 2010, efforts to improve water, sanitation, and hygiene (WASH) have been emphasized. How these interventions impact the gut microbiome is not well understood. We assessed WASH practices, free chlorine residue (FCR) levels in drinking water, microbiome composition, and enteric pathogen burden in Haitian infants and young children. We enrolled 131 children (0-5 years old) from the Centre department of Haiti. WASH practices were collected using a questionnaire and FCR levels in household drinking water were measured. Enteric pathogen burden was defined using a multiplex RT-PCR and microbiome samples from rectal swabs were analyzed using shotgun sequencing. Detection of enteric pathogen DNA in stool was common in our study population, including enteroaggregative *E. coli*, which was found in 88% and 71% of infants under 1 year and young children 1-5 years, respectively. FCR in household drinking water was not associated with pathogen burden. Comparisons of FCR levels and the microbiome composition in infants (nearly all breastfed) trended toward significance (Analysis of Molecular variance, P=0.056). Infants from high FCR households had a high abundance of *Bifidobacteriaceae* while infants from low FCR households had a more diverse microbiome composition, including *Peptoniphilaceae* and *Streptococcacceae*. We tested microbes from these families for chlorine susceptibility using the Kirby-Bauer disk method and found gut commensals *Finegoldia magna* (P=0.02, t test, from the family *Peptoniphilaceae*) and *Streptococcus salivarius* (P=0.0007) were susceptible to chlorine in a dose-dependent manner, while *Bifidobacterium* species were not inhibited even at high chlorine levels (P=0.3). In our cohort, chlorine treatment of drinking water impacted the gut microbiota in infants but did not reduce the burden of enteric pathogen by RT-PCR.

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ASSOCIATION BETWEEN ANTIBIOTIC USE AND LENGTH OF HOSPITAL STAY AMONG CHILDREN PRESENTED WITH ACUTE WATERY DIARRHEA IN A TERTIARY CARE HOSPITAL, KARACHI

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Responsible for at least one in nine pediatric deaths, diarrheal diseases are the leading, global cause of death. Further abetted by improper antibiotic use in a children hospital setting, children with acute watery diarrhea can see prolonged hospital stays, and unwanted adverse effects such as antibiotic resistance. Hence, this study is aimed to identify the association between antibiotic usage for the treatment of acute watery diarrhea in children, and the impact this line of management has on the duration of their hospital stay. A retrospective review was conducted at the Aga Khan University Hospital in Karachi. 305 records of children aged 6 months to 5 years, admitted with a diagnosis of acute watery diarrhea from June 2017 – December 2018 were screened. A predesigned questionnaire was used to collect demographic information, comorbidities, and clinical features, severity of dehydration, clinical examination, treatment received, and laboratory investigations. The primary outcome of this study was the length of hospital stays measured against the number of hours a child stayed in hospital for treatment of acute watery diarrhea. 175 patients presented with acute watery diarrhea, of which 106 (60.6%) did not receive antibiotics. In both groups, there were more males than females, less than 15% of the patients were severely malnourished (WHZ score -3SD) and less than 10% of the patients were severely dehydrated. The median (IQR) length of hospital stay (hours) was 32.0 (25.0-43.0) respectively for the group that did not receive antibiotic and 41.0 (31.0-62.0) for the group that did receive antibiotic therapy. The expected length of hospital stays for the group that received antibiotic therapy was 0.22 hours higher than the group that did not. Finally, as compared to females, hospital stay for males was longer by 0.25 hours. In conclusion, antibiotic use was associated with a prolonged hospital stay in children with acute watery diarrhea as compared to children who did not receive antibiotics.

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IMMUNOGENICITY OF PSORALEN INACTIVATED WHOLE CELL CAMPYLOBACTER VACCINE

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Campylobacter is the most common bacterial cause of diarrhea in the world and a priority target for vaccine development. Psoralen plus UVA (PUVA) inactivation is a promising strategy for viral and bacterial pathogens. PUVA inactivation results in the development of killed but metabolically active (KBMA) bacteria, potentially enhancing immunogenicity. The purpose of this study was to assess the immunogenicity of a PUVA inactivated *Campylobacter jejuni* vaccine compared with a whole cell inactivated vaccine using a standard formalin method with and without the mucosal adjuvant dmLT. *Campylobacter jejuni* was inactivated using either a psoralen derivative

4-aminomethyl-4,5', 8-trimethylpsoralen (AMT) and irradiation with 1 Joule/cm^2 UVA (2 cycles required for inactivation) or with formalin. Four treatment groups of 7-8 BALB/c mice each were given an intramuscular injection of PUVA or formalin inactivated *C. jejuni* (1x10^8) with or with dmLT (0.25 µg/mouse) on days 0, 21, and 35. Pan-campylobacter (whole cell as coating agent) serum IgG titers were measured by ELISA using whole *C. jejuni* as the coating antigen. All mice had serum IgG titers above baseline and IgG titers increased with each booster dose. The addition of dmLT significantly boosted response to formalin inactivation at days 35 (p=0.006) and 49 (p<0.001), but only showed a non-significant effect with the PUVA inactivated vaccine. At day 42, the IgG titer induced by the formalin+dmLT vaccine was greater than that of the PUVA+dmLT vaccine (p<0.001). This study demonstrates a proof of concept for a PUVA inactivated *Campylobacter* vaccine. The vaccine elicited a strong humoral response in the mouse model when adjuvanted with dmLT but less than that elicited by a formalin inactivated whole cell vaccine. Future studies will evaluate other dosing regimens and specific *Campylobacter* antigen targets.

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EVALUATION OF THE INHIBITION OF THE GROWTH OF ENTEROPATHOGENIC BACTERIA IN THE PRESENCE OF PROBIOTIC AGENTS

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Probiotic agents, live microorganisms with beneficial effects for the host, may offer an alternative to conventional antimicrobials in the treatment and prevention of enteric infections. In this study, the growth inhibition of enteropathogenic bacteria (*Salmonella enterica subsp enterica* ATCC 14028, *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, *Yersinia enterocolitica* ATCC 23715, *Shigella flexneri* ATCC 12022 and *Listeria monocytogenes* ATCC 19115) was evaluated in the presence of two probiotic agents (*Lactobacillus plantarum* and *Lactobacillus delbrueckii* spp *delbrueckii*).Briefly, the Kirby-Bauer method or agar diffusion method was established, performing the following procedure: a sterile cotton swab was submerged in the bacterial suspension of each study strain and the cotton was pressed against the inner walls of the tube to remove excess liquid. Then, using the same swab, it was massively inoculated on the surface of Müeller-Hinton agar. Subsequently, after 5-10 minutes, a disc of 6mm diameter filter paper impregnated with the liquid culture of the two probiotic agents was placed. Each culture was refrigerated at 4°C for 1 hour and then incubated at 37°C for 24-48 hours in an anaerobic atmosphere. After this time, the presence or absence of growth inhibition halos around the impregnated discs was verified by the formation of transparent zones around the disc. It should be noted that the zones of inhibition were measured in millimeters (mm) and the inhibitory effect was calculated by the diameter of the halo measured in mm.The two probiotic agents evaluated were shown to inhibit growth against one or more microorganisms except *L. monocytogenes*. It can be concluded that the in vitro growth inhibition for a variety of enteropathogenic bacteria by these two probiotic agents is useful to support future clinical investigations that contemplate their use in antimicrobial therapeutics.

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MOLECULAR CHARACTERIZATION OF CARBAPENEM-RESISTANT AND EXTENDED-SPECTRUM B-LACTAMASES (ESBL) PRODUCING *KLEBSIELLA PNEUMONIAE* ISOLATED FROM HOSPITAL ENVIRONMENTS AND PATIENT SAMPLES IN BANGLADESH

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In nosocomial infections, extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) cause significant morbidity and mortality. Furthermore, these bacteria are well-known for their propensity to create biofilms, which aids persistence in the hospital setting. From environmental and patient samples of three district hospitals in Bangladesh, 67 ESBL-KP were isolated from 275 suspected *K. pneumoniae*. The isolates were subjected to molecular typing using Enterobacterial Repetitive Intergenic Consensus (ERIC) sequences, antibiotic susceptibility testing, PCR amplification of the virulence and drug resistance-associated genes, and quantitative adherence assays. All of the isolates had ESBL generating potential as well as multidrug resistance (MDR) to β-lactams, aminoglycosides, quinolones, macrolides, and sulfonamides at high levels. Carbapenem-resistant *K. pneumoniae* isolates made up 62.68 % of the total. *bla*CTX-M-1 (91%) was the most frequent β-lactam resistance gene, followed by *bla*TEM (76.1%), *bla*SHV (68.7%), *bla*OXA-1 (29.9%), *bla*CTX-M-9 (11.9%), and *bla*CTX-M-2 (4.5 %). *fimH* (65.7 %), *ugeF* (55.2 %), *wabG* (52.2 %), and *ureA* (46.3 %) were the most often found virulence-associated genes. The majority of the strains were able to produce biofilms, with 96.2 % of the environmental isolates and 100% of the patient isolates being able to do so. A link between environmental and patient samples was discovered using ERIC-PCR analysis and genotypic profiles of *K. pneumoniae* isolates. *K. pneumoniae* from hospital-associated samples had a significant prevalence of resistance to numerous types of antibiotics, as well as the presence of virulence factors and MDR genes. Our study suggests a link between the hospital environment and patients' isolates in Bangladesh; this information may have a profound effect on patient treatment, infection control measures, and public health policies for hospital-associated infections.

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THE IMPACT OF THE COVID-19 PANDEMIC ON THE CHOLERA CONTROL PLAN IN BANGLADESH

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The control of the Covid-19 pandemic has been possible by quick detection, treatment, behavior change and vaccination strategies. Our attempt has been to work with the policy makers to facilitate the rapid testing, seroprevalence and immunological studies as well as design vaccine trials and study the effectiveness of vaccines that are being deployed in the country as well as the changing genomic characteristics of SARS-Cov-2. Recently, when vaccines have become available for us, there is the need to see their suitability in the different socioeconomic and varying age groups and in terms of boosters that will be needed.Cholera an acute, diarrhoeal, infection caused by is another global public health challenge being faced especially in Asia, Africa and in fragile settings for decades. The GTFCC has launched a control plan entitled "Ending cholera by 2030" in 2017. Bangladesh has been aligned with this goal whereby both oral cholera vaccine (OCV) and WASH strategies will be implemented

in high risk areas of the country. Bangladesh has now a national cholera control plan that is approved by the WHO. Based on the plan, OCV together with other preventive measures will be delivered to eliminate cholera by 2030. A demonstration campaign was conducted in six areas of Dhaka city with 1.2 million doses of OCV given as first dose just prior the Covid-19 pandemic. The delivery of the second dose was halted subsequently. Cholera is known to have a biannual seasonal peak, one between April to May and the second peak from August to September. This year in 2022, the major cholera spring surge started in early March. The rate of culture-confirmed cholera has increased from 11% in early March to 34% by end March and the peak continued to rise in April. Outbreaks are also being detected to other settings in Bangladesh. The pandemic of Covid-19 has also had a negative impact on other infectious diseases for which control measures could not be implemented due to the diversion of time and resources. Cholera control measures are now being implemented to prevent future epidemics by the use of available vaccines.

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PARTIAL DOSES OF LIVE ORAL CHOLERA VACCINE CVD 103-HGR (PXVX0200) INDUCE SERUM VIBRIOCIDAL ANTIBODIES (SVA) IN CHILDREN

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The attenuated recombinant *Vibrio cholerae* O1 strain CVD 103-HgR, redeveloped as PVXV0200 [Vaxchora® (Cholera Vaccine, Live, Oral)], elicits a rapid SVA response in children and adults as soon as 7 days after vaccination, and protected against cholera-induced diarrhea in adult volunteer challenge trials. A previous study with CVD 103-HgR in a developing country documented SVA seroconversion, defined as a four-fold or higher rise above baseline, in children who received partial doses of vaccine. The immunogenicity of partial dosing has not been evaluated in children in developed countries. In a phase 4, placebo-controlled, double-blind, multi-center study performed to assess the safety and immunogenicity of a single oral dose of PXVX0200 in children and adolescents aged 2-17 years, volunteers were randomized 6:1 to receive 1 x 10^9 colony forming units of PXVX0200 or placebo as 100 mL (6-17 years) or 50 mL (2-5 years) oral suspension. The primary endpoint was SVA seroconversion on day 11. In the subset of subjects who consumed <80% of the vaccine dose, seroconversion rates were calculated and stratified by amount consumed. Of 468 subjects dosed in the larger study, a subset of 33 (7%) received <80% of the vaccine dose. SVA seroconversion occurred in 75.8% of these subjects, including 100% (7/7) of those who took 50-80% and 69.2% (18/26) of those who took <50%, versus 98.5% of those who consumed 80% or more. Vaccination with PXVX0200 produced an immune response in most children who received partial dosing. Since SVA seroconversion is a strong correlate of protection, PXVX0200 may protect against cholera infection in children who ingest only part of the vaccine dose.

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A NOVEL MULTIPLEX REAL-TIME PCR ASSAY FOR THE MOLECULAR DIAGNOSIS OF METACESTODE INFECTIONS IN HUMANS

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For the clinical outcome of larval cestodiases in humans such as neurocysticercosis (NCC), cystic echinococcosis (CE) and alveolar echinococcosis (AE), fast therapeutic treatment based on early differential diagnosis at the initial stage of infection is key. Despite remarkable development of imaging technologies and serology for the diagnostic identification of invasive cestodiasis, a reliable high-throughput molecular method on biopsy or cytology specimens would ensure a more rapid species identification. This holds specifically true for diagnosing NCC, CE and AE in patients with unusual imaging data and/or negative serology due to immunosuppression, or diagnosing rare taeniid species. A broad variety of PCR protocols for the detection and differentiation of taeniid species have been published. However, most approaches are based on conventional PCR techniques and either require gel electrophoresis, an additional sequencing step or are limited to certain *Echinococcus* or *Taenia* species, taxa or genotypes. In the present study a quadruplex real-time PCR has been established which allows the differentiation of *E. granulosus sensu lato (s.l)*, *E. multilocularis* and *Taenia spp.* but also the detection of an internal control in a single processing step. Subsequent Sanger sequencing of *E. granulosus s. l.* and *Taenia spp*. amplicons further allows the differentiation of all *Echinococcus* and *Taenia* species including recently reported human infecting species such as *T. crassiceps*, *T. serialis*, *T. martis* and *Versteria sp*. This simple, fast and reliable multiplex real-time PCR has been successfully assessed for the specific detection of *E. granulosus sensu lato (s.l)*, *E. multilocularis* and a broad spectrum of *Taenia spp.* cyst fluids and fine-needle biopsies of clinical and veterinarian cases. All reference samples were from clinical cases well documented upon imaging, serological and morphological means. To our knowledge, this is the first report of a quadruplex real-time PCR, which can be routinely used in a clinical microbiology lab on biopsy or cytology specimens for the detection of *E. granulosus s.l*, *E. multilocularis* and *Taenia spp.*

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ASSESSING THE SPATIAL TRANSFERABILITY OF A LOCAL-SCALE *TAENIA SOLIUM* TRANSMISSION MODEL USED TO ESTIMATE RESULTS OF CONTROL INTERVENTIONS IN RURAL VILLAGES IN NORTHWEST PERU

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Models can be used to study and predict the effect of interventions aimed at controlling the spread of infectious agents, such as *Taenia solium,* a zoonotic parasite which causes epilepsy and economic losses in many rural areas of the world. While the process of model calibration against observed data is needed to enhance the credibility of model estimates, it may also produce a paradoxical dependence of model parameters on location-specific data, hence limiting the model's transferability to other endemic settings. We adopted a non-local model calibration approach to assess whether it can enhance the spatial transferability of *CystiAgent*, our agent-based model of local-scale *T. solium* transmission. The dataset used to calibrate *CystiAgent* comprised cross-sectional human taeniasis, pig cysticercosis and pig serology data collected in a group of 8 villages in Northwest Peru. After calibration, the model was then transferred to a second group of 23 villages in the same area, without recalibrating model parameters. The outputs of the transferred model were then compared to longitudinal pig serology data collected during a trial of *T. solium* control interventions, based on mass and spatially targeted human and pig treatments. Considering the uncertainties associated with empirical data, the model produced simulated pre-intervention pig seroprevalences that were successfully validated against data observed in 85% of destination villages. Moreover, model outputs, when compared to the longitudinal data obtained during the interventions, were also able to reproduce the correct decline of pig seroprevalence in 85% of destination villages. The results of this study show that the *CystiAgent* model, if calibrated using

a non-local calibration approach, can be successfully transferred among villages located in the region of Northwest Peru to simulate both baseline pre-intervention situations and the results of control interventions.

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IMPLEMENTING AN EVIDENCE-BASED FOCAL CONTROL STRATEGY FOR *TAENIA SOLIUM* CYSTICERCOSIS IN NORTHERN PERU, PHASE 1: A FORMATIVE EVALUATION WITH THE PUBLIC HEALTH AND ANIMAL WELFARE SYSTEMS IN PREPARATION FOR SCALE-UP

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Taenia solium (pork tapeworm) cysticercosis was declared eradicable over 30 years ago, yet it continues to impose severe health and economic harms across Latin America, Africa, and Asia. This zoonotic parasite is a leading cause of epilepsy, causing one-third of all seizure disorders in endemic regions. The World Health Organization's 2021-2030 roadmap identified critical needs in the areas of planning, program management, monitoring, evaluation, access and logistics in order to control this neglected disease. Ring treatment, developed and rigorously tested in Northern Peru, is a highly effective and efficient control strategy that takes advantage of local geospatial clustering of human and pig hosts, allowing treatment to be targeted to focalized risk areas. We are now working to develop a process by which ring strategy can be adopted as a feasible, scalable, and sustainable public health program. Using the Consolidated Framework for Implementation Research (CFIR), we conducted a formative evaluation with 341 participants from public human and animal health agencies in three health districts in Northern Peru. Our activities included mapping organizational networks, identifying barriers and facilitators for implementation, and developing processes and procedures for a health-system-managed ring strategy control program. The results of our formative evaluation will be summarized in this presentation. This work sets the foundation for a community-based pilot study (phase 2), which will inform a three-year trial in multiple health districts (phase 3) to evaluate the cost, reach, effectiveness, approach, implementation, and maintenance of the intervention. This work demonstrates the application of the CFIR to a One Health project, to improve integration of human, animal, and environmental health to support healthy communities in Peru.

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THE RISE IN CAESAREAN SECTIONS OVER TIME IN THE DOMINICAN REPUBLIC

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The Dominican Republic has one of the highest prevalence rates of cesarean sections (CS) in the world. This study aimed to examine the pattern of change in the CS rate over time by birth order (first versus subsequent) and facility type where the delivery occurred (public versus private). Data from six Demographic and Health Surveys (1986-2013) and two Multiple Indicator Clustery Surveys (2014, 2019) from the Dominican Republic were used for this study. The percentage values are based on women who gave birth in the two-year period prior to each survey, weighted to provide national estimates. The overall national CS rate increased from 18.1% based on the 1986 survey to 64.3% based on the 2019 survey, an increase of 1.4%/year. The change over this same time period for first births was 24.2% to 63.5% (a rate increase of 1.2%/year) compared to subsequent births that increased from 15.6% to 64.8% (i.e., an increase of 1.5%/year). The larger slope for the latter potentially reflects the growing impact of the need for repeat CS among the expanding pool of women who had had initial CS. Health facility information was available from 1991-2019 demonstrating an increase over this time period from 15.1% to 47.1% for public facilities versus 45.3% to 90.8% in private facilities with corresponding slopes of 1.1%/year versus 1.6%/year, respectively. The steepest increase occurred between 1996 and 2002 for private health facilities with a rate increase of 3.3%/year. A slight drop in the rate in public health facilities between 2014 and 2019 (47.6% to 47.1%) may reflect government initiatives to curb the excessive use of CS. Further investigations of the practices and policies related to CS in the Dominican Republic are warranted with a particular focus on private health facilities.

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MAD DOGS, MISSIONARIES, AND NOONDAY SUNS: AVOIDING SUNSTROKE AND SUNBURN IN COLONIAL AFRICA

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Mad Dogs, Missionaries, and Noonday Suns: Avoiding Sunstroke and Sunburn in Colonial AfricaBy the turn of the 20th century, thousands of British troop, civil servants, and missionaries had arrived in sub-Saharan Africa. What they often found, however, were climates that were strikingly different from those they had left behind in the United Kingdom. This presentation examines contemporary—largely anecdotal—information about that medicos and laypersons disseminated among civilian and military personnel. Drawing on archival and published diaries and medical-scientific literature of the late 19th century, this presentation will show how imperfectly they appreciated the solar hazards that awaited them.

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TROPICAL TROUBLES: NEURASTHENIA AMONG EX-PATS IN AFRICA AND INDIA, 1900-1914

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Tropical Troubles: Neurasthenia among Ex-Pats in Africa and India, 1900-1914Discussions of "tropical neurasthenia" (TN) abounded in early 20th century medical journals. TN provided specialists in the emerging field of tropical medicine with a diagnostic classification to explain the vague symptoms that North American and European ex-pats often complained of in tropical climates. The condition was also used to account for high rates of invaliding among colonial staff and missionaries. One 1913 report in the *British Medical Journal* estimated that NT invalided 20% of all missionaries at tropical posts. Climate-based theories concerning the aetiology of NT abounded during the early 20th century. Some experts blamed not simply "tropical light" itself but exposure to its different spectra in tropical regions. Others blamed climate, heat, humidity, and altitude, while others cited ex-pats' contacts with "diseased or depraved indigenous peoples or simply the sense of loneliness and despair." Symptoms included irregular heartbeat, irritability, loss of appetite, sexual dysfunction, depression, and even suicide. Relying primarily on archival and published primary sources, this presentation will examine the rise and fall of NT as a clinical entity during the first quarter of the 20th century.

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VACCINATION COVERAGE AND ITS DETERMINANTS AMONG CHILDREN IN CAMBODIA, MADAGASCAR, AND SENEGAL CHILDREN IN CAMBODIA, MADAGASCAR, AND SENEGAL

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Vaccination reduces infectious diseases burden, the leading cause of under-five mortality, occurring mainly in low- and middle-income countries (LMICs). The latest Global Vaccine Action Plan has set a target of 90% immunisation coverage for all vaccines included in national programmes by 2020. National reports and demographic and Health Surveys, which are main sources of vaccine coverage data in LMICs, presents some limitations. Here, to estimate coverage of vaccines included in national programmes among children in three LMICs (Cambodia, Madagascar, and Senegal) and to identify determinants associated with incomplete immunization, we used data from a community-based cohort which complement the main sources of vaccine coverage data. The BIRDY study was a mother-and-child cohort (2012-2018) conducted both in urban and rural areas of these 3 countries. Children were followed-up from birth up to the age of 24 months with at least one home visit monthly. Immunizations received since the last visit were collected after verification in the child's vaccination card. Risk factor analysis was performed with logistic regression models. Among the 3606 children followed-up, all vaccine coverages were below the 90% threshold, except for BCG vaccine coverage in Cambodia. They were higher for vaccines recommended at birth and a decrease in coverage with age was observed for vaccines requiring several doses in all countries. For example, the decrease in coverage between the first and the third dose of pentavalent vaccine ranged from 20% to 40% ($p<0.001$). Low birth weight (<2500g) was an important risk factor for non-vaccination for vaccines recommended at birth (BCG and oral polio vaccine) in all three countries (aOR ranging from 1.93 [1.11-3.38] to 4.28 [1.85-9.37]). Also, high maternal education (from 0.38 [0.24-0.60] to 0.61 [0.38-0.97]) and high antenatal care attendance (from 0.39 [0.25-0.63] to 0.66 [0.52-0.84]) were identified as protective factors. Vaccination coverage is still low in these countries. A multi-disciplinary approach is needed to improve coverage and thus reduce the burden of vaccine-preventable infectious diseases in LMICs.

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SICKLE CELL DISEASE IN ANGOLA. A PUBLIC HEALTH PROBLEM. GENETIC VARIABILITY AND DISEASE SEVERITY IN A COHORT OF PREGNANT WOMEN

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With a prevalence of about 2% in Angola, Sickle Cell Anaemia (SCA), a monogenic disease, has a remarkably high clinical heterogeneity in its phenotypic expression. Several factors have been shown to modulate the clinical manifestations of SCA, namely genetic markers that can modulate biological parameters like the degree of haemolytic anaemia or the levels of HbF. Pregnancy in women with SCA is associated with an increase in adverse outcomes. This study aims to determine the complications in pregnant women with SCA and study the association between genetic variability and phenotype. The patient's clinical history was registered. Biochemical, and hematological data was also collected. All samples were genotyped for the HbS mutation by PCR-RFLPand 4 SNPs were genotyped in the β-cluster to determine the HbS haplotype.The presence of the 3.7kb deletion of the α-globin gene was determined by Gap-PCR. Cerebral hemodynamics was assessed using Transcranial Doppler (TCD) the middle cerebral arteries (MCA) and basilar artery (BA). A total of 52 SCA patients (all SS) have been study until now, with ages ranging from 18 to 36 years old (mean of 25.6±5,0). The observed frequency of homozygous for 3.7kb α-thalassemia deletion was 16.7. The CAR/CAR haplotype was the most prevalent in our population There is a significant difference in symptoms experienced by SCA patients that co-inherit the α-thalassemia deletion, and in the ones with the CAR haplotype. We observed an apparent more severe symptomatology in CAR/CAR patients, especially pain crisis, blood transfusions, hospitalizations, premature births, and miscarriages. On the other hand, a significant reduction in these parameters was evident in patients that co-inherited the 3.7kb α-thalassemia deletion. At the MCA level, TAMMx reached between 62cm/s and 105cm/s, whereas the PSV was between 96cm/s and 155cm/s. The BA showed TAMMx between 38cm/s and 64cm/s, with the PSV ranging 55cm/s to 93cm/s. With this project, we seek to support a cohort of SCA pregnant women in Angola to improve their quality of life and reduce problems during pregnancy, but also maternal mortality and neonatal outcomes in Angola.

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MONOCLONAL ANTIBODY USE IN TRAVELER MEDICINE: EXPENSIVE LUXURY?

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Monoclonal antibodies (mAbs) used to prevent or treat infectious diseases are on the rise: a couple of years ago only two mAbs were registered; per 2022, more than 75 mAbs are registered or are granted emergency use authorization. Due to the covid-19 pandemic, mAbs have been put in the spotlight although multiple phase 1 studies were already on its way in 2020 for other infectious diseases such as malaria and yellow fever. Monoclonal Abs could function as prophylaxis before travelling abroad (i.e., malaria) which is called passive immunization (in contrast to the active immunization done by vaccination), or could be used to treat (tropical) infections (i.e., rabies, dengue, yellow fever). The use of mAbs in travel medicine could have its benefits compared to a standard vaccination and prophylaxis strategy. For example, using mAbs to prevent a malaria infection, as recently demonstrated by Gaudinsky et al [NEJM, 2021], would mean one dose administered intravenously or intramuscular before departure, inducing immunity lasting at least 12 weeks without significant side effects compared to daily or weekly oral drug intake with gastro-intestinal or psychiatric side effects. Other examples would be the use of single dose mAbs for hepatitis A or yellow fever for the immunocompromised travelers who could not be given live-attenuated vaccines or are unable to produce an antibody response at all. Furthermore, successful effort has been put in the treatment of diseases with a high mortality and morbidity such as Ebola and yellow fever using mAbs, and newer therapeutic options are being developed for rabies and dengue. However, the use of mAbs could also lead to more pressure on the health care systems and especially higher costs, is this a luxury we do want to afford for our travelers or should we use our resources to eliminate infectious (tropical) diseases on a global scale? In this presentation, we will discuss the prospects of using mAbs in the prevention and treatment of (tropical) infectious diseases seen in the returning traveler.

1045

PERSONS WITH NODDING SEIZURES HAVE A MORE SEVERE FORM OF ONCHOCERCIASIS ASSOCIATED EPILEPSY WITH HIGH LEVELS OF *ONCHOCERCA VOLVULUS* INFECTION

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In onchocerciasis-endemic communities in Maridi County, South Sudan, a high prevalence of epilepsy was reported (overall 4.4%, range 3.5–11.9%). The highest prevalence (11.9%) was observed in communities living nearby the Maridi dam, a blackfly breeding site with high ongoing onchocerciasis transmission. We aimed to investigate the association between the level of *Onchocerca volvulus* infection, epilepsy and related outcomes. In December 2018, a study was conducted in Maridi County, in which 318 persons with epilepsy (PWE) enrolled, and two skin snips were taken from each posterior iliac crest of the participants using the Holt-type punch for microscopic detection of *Onchocerca volvulus* microfilariae. Seizure history was obtained for all PWE and their autonomy assessed using the modified Rankin disability scale. Almost all (84.9%) PWE had detectable microfilariae (mf) in their skin snips. Onchocerciasis-infected PWE experienced nodding seizures more often than uninfected PWE (p=0.034). Moreover, persons with nodding seizures had more frequent seizures (p<0.001), higher disability scores (p<0.001), were more often cognitively impaired and started seizures earlier (9 years vs 12 years, p<0.001) compared to other PWE. In multivariate models, nodding seizures were associated with higher mf densities (aOR 1.022, 95% CI 1.005-1.041) and the presence of nodules (aOR 8.870, 95% CI 1.554-167.658). Epilepsy-related outcomes were negatively associated with the age of participants. In conclusion, PWE with nodding seizures have a more severe form of onchocerciasis-associated epilepsy with seizures that start at an earlier age and with a higher level of *O. volvulus* infection. Younger PWE were prone to worse epilepsy outcomes.

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IS RIFT VALLEY FEVER A PUBLIC HEALTH THREAT IN EASTERN DEMOCRATIC REPUBLIC OF THE CONGO? PRELIMINARY RESULTS OF THE CREID-ECA NETWORK

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Serologic evidence suggests that Rift Valley Fever (RVF) virus circulates in livestock in the Democratic Republic of the Congo (DRC), but no related hemorrhagic fever in humans have been documented although outbreaks occur in neighboring countries as Uganda last January. In November 2021, we established a 2 year prospective study of acute fever in Virunga Hospital, Goma, Eastern DRC. Subjects aged ≥12 years, presenting with fever (≥37.5°C) or reported fever are enrolled and serum is collected for molecular and serologic testing for RVF and other arboviruses (Dengue, Chikungunya, Zika, Yellow fever), besides sampling for routine testing of malaria (rapid diagnostic test and thick smear) and typhoid (Widal's test). Clinical, risk and behavioral data are collected at enrollment and 4-6 weeks later. As of March 2022, a total number of 319 subjects have been enrolled (mean age 33 years, 95% CI 31.5-34.5, female 59%). Although only 7 subjects reported working with animals, 85.9% referred domestic contact with mainly poultry (50.4%) and goats (27.2%); handling of raw meat (79.6%), drinking unboiled milk (9.4%) and consuming bushmeat regularly (7.5%). Fifty percent of the population regularly used a mosquito net. At moment of inclusion, fever was detected in 64.6% of cases and 57.7% reported previous self-medication. The main symptoms were headache (91.8%), weakness (66.5%) and musculoskeletal pain (51.4%); 14 subjects reported bleeding (1 miscarriage). In 27.9% of cases hospitalization was required. After routine testing for common pathogens, the main diagnoses were gastrointestinal infection (29.7%) including enteric fever (23.8%), malaria (23.3%) and undifferentiated fever (23%). Antibiotics were used in 84.9% of cases and antimalarials in 26.3%. Laboratory analysis is ongoing and by October 2022 we expect a complete characterization of approximately 700 cases linked to the study-related diagnostic RVF and arbovirus testing results. The complete statistical analysis of results will give an initial estimate of local RVF circulation in the region, supplemented by clinical and risk behavior characterization, to guide control efforts.

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A CASE DEFINITION FOR THIAMINE RESPONSIVE DISORDERS: RESULTS FROM A PROSPECTIVE COHORT STUDY AMONG INFANTS AND YOUNG CHILDREN IN LAO PDR

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Thiamine deficiency disorders (TDD) are the broad clinical conditions associated with thiamine deficiency, of which beriberi is best known. Due to the non-specific manifestations and the observation that infantile TDD can present in the context of acute infections, TDD may go unrecognized and untreated. This study aimed to develop a case definition for thiamine responsive disorders (TRD) to determine in hospitalized children which clinical features and risk factors identify those who positively respond to thiamine. Children (aged 21 d -18 mo) were eligible if they presented with symptoms suggestive of TDD. Children were treated with parenteral thiamine (100mg daily) for ≥3 days alongside other treatments. Physical examinations and recovery assessment were conducted 0, 4, 8, 12, 24, 36, 48, and 72 hrs after administration of the initial thiamine dose. Individual case reports were generated and independently reviewed by 3 pediatricians who assigned a TRD score that was used as the dependent variable in logistic regression models to identify predictors of TRD. Clinical prediction model performance was quantified by empirical area under the receiver operating characteristic curve (AUROC). In total, 449 children (mean±SD age 4.3±3.4 mon; 61% male; 70% exclusively/predominantly breastfed) were enrolled. The majority presented with signs of cardiac and respiratory distress (71% difficulty breathing; 62% tachycardia; 45% tachypnea) and were hospitalized for a median (Q1, Q3) of 3 (2,6) days. TRD prevalence was high (61%). The AUROC (95% CI) was 0.82 (0.78, 0.86) indicating excellent discriminative capacity. Variables selected as most predictive of TRD were exclusive/predominant breastfeeding, hoarse voice/loss of voice, cyanosis, no eye contact and no diarrhea in the previous 2 weeks. In this study population, there was a high prevalence of TRD, and the consensus recommendation would be that all children presenting with clinical signs suggestive of TDD in this and similar settings with high risk of thiamine deficiency should be treated with thiamine. The usefulness of the case definition in other contexts requires exploration.

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A VERBAL AUTOPSY ANALYSIS OF CHILDHOOD DEATHS IN RURAL GAMBIA

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In low-resource settings it is challenging to ascertain the burden of under 5 mortality as many deaths occur outside health facilities and are unaccounted for. Verbal autopsy (VA) is an important tool which provides data on causes of death in communities with limited access to health care. We used the WHO standard questionnaire to conduct VAs for deaths under 5 years of age in the Basse and Fuladu West Health and Demographic Surveillance Systems in rural Gambia between 2019 and 2021. Two physicians assigned a cause of death and discordant diagnoses were resolved by consensus. Causes of death were classified using International Classification of Disease 10th edition codes. VAs were conducted for 89% (647/727) of deaths. Of these deaths, 49.5% (n=319) occurred at home, 50.1% (n=324) in females, 37.1% (n=240) in neonates, and 27.1% (n=175) in infants aged 1-11months. Pneumonia (17%, n=110), diarrhoeal diseases (14.7%, n=95) and sepsis (13.6%, n=88) were the three commonest primary causes of death. In the neonatal period, unspecified perinatal causes of death (29.6%, n=71), birth asphyxia (23.8%, n=57) and prematurity/low birth weight (17.1%, n=41) were the commonest causes of death. Outside the neonatal period, pneumonia (27.0%, N=110), diarrhoeal diseases (23.3%, n=95) and sepsis (21.6%, n=88) were the commonest primary causes of death. Severe malnutrition (28.6%, n=185), Unspecified perinatal deaths (10.7%, n=69), Pneumonia (10.2%, n=66), and Prematurity/Low Birth Weight (10.2%, n=66) were the commonest underlying causes of death. Most of the respondents were aware that the deceased needed medical care (72.2%, n=464), lived within 2hrs of a health facility (88.2%, n=569) but care was not sought outside the home in 63.7% (n=421). According to VA analysis, half of deaths amongst children under 5 in rural Gambia occur at home. Pneumonia and severe acute malnutrition are the commonest primary and underlying causes of death respectively. Though most respondents were aware of the need for medical care and lived close to health facilities, most did not seek medical care. Improved health seeking behaviour may reduce childhood deaths in rural Gambia.

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MAPPING DISTRICT-LEVEL MEASLES-CONTAINING VACCINE COVERAGE VIA COMBINED ROUTINE AND SUPPLEMENTARY IMMUNIZATION IN LOW- AND MIDDLE-INCOME COUNTRIES

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From 1980 to 2019, global coverage of at least one dose of the measles-containing vaccine (MCV) increased from 38.5% [35.4-41.3] to 83.6% [82.3-84.8]. However, coverage gains for MCV have plateaued in the past decade and measles outbreaks continue to affect many low- and middle-income countries (LMICs). Identification of subnational gaps in coverage of MCV are crucial for effective provisioning of vaccination services and outbreak prevention. Existing subnational coverage estimates often account only for vaccinations administered via routine immunization (RI). However, supplementary immunization activities (SIAs) also play a major role in measles vaccination strategies in many LMICs. To effectively identify gaps in vaccine coverage and optimally plan interventions, granular estimates of MCV coverage from both RI services and SIAs are needed. Here, we present a novel cohort modeling method to estimate combined RI and SIA coverage by age and subnational location over time. This method incorporates geospatial estimates of RI-only MCV coverage, demographic data derived from the Global Burden of Disease and Worldpop, World Health Organization-reported SIA information, and post-campaign coverage survey results to distribute MCV doses via both RI and SIAs to individuals by age and district over time within a country. SIA doses were distributed among previously-RI-vaccinated and previously-RI-unvaccinated individuals according to SIA-specific dose information and campaign-efficiency estimates derived from survey data. With this method, we estimated dose-specific combined RI and SIA coverage for 101 low- and middle-income countries at the district level by age for the years 1980-2020. These estimates aim to provide a more complete picture of MCV coverage and patterns of MCV-zero-dose children compared to estimates of RI coverage alone.

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TICK-BORNE RED MEAT ALLERGY: A SURVEY OF DIAGNOSED ALPHA-GAL SYNDROME IN SOUTH CAROLINA

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Galactose-alpha-1,3-galactose (alpha-gal) is a polysaccharide found in mammalian meats and by-products such as milk. The development of an allergy to alpha-gal is also known as red meat allergy or alpha-gal syndrome (AGS). Recent literature has implicated bites from Amblyomma americanus, the Lone Star Tick, in AGS development, but the prevalence of AGS cases in South Carolina is not yet well understood. Increased understanding of high-incidence geographical clusters is critical for public health prevention, especially given the morbidity and mortality risks stemming from the wide variety of symptom presentation, which ranges from mild irritation to anaphylaxis. Chronic elevation of IgE antibodies in humans following tick bites can prompt an allergy-induced immune response to the consumption of red meats and other animal products containing alpha-gal, which has significant implications for diet and lifestyle of those afflicted. This study aimed to describe and identify cases of AGS diagnosed within the PRISMA Health healthcare system encompassing the Midlands and Upstate regions of South Carolina through a retrospective chart review. Our long-term objectives were to better understand the case load of AGS in the targeted regions of South Carolina, to identify clusters where AGS was most prevalent, and to ultimately explore and quantify tick-borne AGS transmission in these areas through collection and testing. Abstracted review of associated variables, including demographics, hospital information, allergy information and history, co-morbidities, disease presentations, acquisition factors and history of tick exposure, diagnostic tests including IgE levels, and treatment administered was accomplished through a standardized chart abstraction form and view-only access to the appropriate electronic health record system. Lastly, we used ArcGIS Pro to execute hotspot analysis to identify geographical case clusters compared to tick surveillance data, producing a heatmap to inform future public health response.

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ETIOLOGIC INVESTIGATION OF PATIENTS DIAGNOSED WITH BACTERIOLOGICALLY UNCONFIRMED TUBERCULOSIS IN NORTHERN TANZANIA

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Approximately half of patients beginning treatment for pulmonary tuberculosis (PTB) globally are diagnosed clinically without bacterial

confirmation. Limited evidence suggests some do not have tuberculosis, but rather other diseases that mimic PTB. The prevalence of these non-tuberculosis diseases is uncertain. We aimed to estimate the proportion of patients with clinically diagnosed PTB that could be confirmed by inducing sputum, and the prevalence of diseases that mimic PTB. We recruited consecutive adult patients beginning treatment for PTB, in Moshi, Tanzania, 2019, whose diagnosis was not bacteriologically confirmed. We conducted systematic investigations testing two induced sputum samples using mycobacterial smear, Xpert MTB-RIF Ultra, and mycobacterial, fungal and bacterial culture; fungal serology; and computed tomography chest scans. We followed participants up to two months after enrolment. Of 125 patients who began treatment for PTB, 57 (46%) were not bacteriologically confirmed. Of these, 36 (63%) consented to participate. The median (interquartile range) age was 55 (44-67) years; 6 (17%) were HIV-infected, all had a cough with 19 (53%) reporting spontaneous sputum production, 20 (56%) reported fevers, and 17 (47%) weight loss. We bacteriologically confirmed tuberculosis in 2 (6%) of 36. We identified pneumonia in 11 (48%) of 23, bronchiectasis in 8 (35%) of 23, interstitial lung disease in 5 (22%) of 23, chronic pleural collections in 5 (22%) of 23, lung malignancy in 1 (4%) of 23, and chronic pulmonary aspergillosis in 1 (3%) of 35. At two months follow up, 4 (11%) were dead, 21 (58%) had persistent symptoms, 6 (17%) had recovered, and 5 (14%) were lost to follow-up. We obtained bacteriologic confirmation of PTB in a minority of those beginning treatment for clinically diagnosed PTB, and identified a high prevalence of non-tuberculosis diseases. Improving diagnostic tools for PTB and its mimics may improve patient outcomes.

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USE OF SPATIAL-TEMPORAL SEROPREVALENCE ESTIMATES AS A PRE-TEST PROBABILITY FOR IMPROVING INDIVIDUAL-LEVEL CLINICAL PREDICTION FOR DENGUE VIRUS INFECTION.

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Acute febrile illness (AFI) is a common reason for seeking healthcare in low- and middle-income countries (LMIC). Determination of AFI etiology is often limited by diagnostic testing capacity, given the wide spectrum of potential infectious agents. Misallocation of limited testing and treatment resources contributes to high case fatality rates in admitted AFI patients (>5-20%). Dengue virus (DENV) is a major cause of AFI in LMICs (estimated 390 million infections, 96 million illnesses, 2 million severe cases, and 21,000 deaths per year) that requires resource-intensive treatment. Clinical decision support tools using clinical prediction models is one strategy to optimize the appropriate use of diagnostic testing. Our objective was to develop an improved clinical prediction model for DENV by including location-specific parameters. We use DENV spatial-temporal seroprevalence data as a pre-test probability, integrated with climate and clinical data using a post-test odds formulation, to derive a clinical prediction model for DENV test positivity. We use force-of-infection estimates based on sero-surveillance of a multigenerational cohort, featuring fine-scale spatial and temporal data, from Kamphaeng Phet province (KPP), Thailand. We fit random forest models using clinical data from KPP hospital to identify a set of patient characteristics that provided the best discrimination between DENV and non-DENV patients. Using a Bayesian approach, we combine the seroprevalence pre-test odds with the likelihood ratios from the clinical model to determine the odds of having DENV. We also examine whether updating the model with weather data and seasonality data improves discriminatory performance. In preliminary analysis, we found that the use of temporal seroprevalence data alone achieved better performance than spatial data alone. We are continuing our analysis and will present a complete model at the time of presentation.

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CASE-STUDIES AND WORK FLOW INTEGRATION: HOW TO ENCOURAGE PRIMARY CARE PROVIDERS TO SCREEN FOR CHAGAS DISEASE

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Chagas disease is a neglected disease of poverty that affects 8-10 million people worldwide. In the United States, it chiefly affects Latinx immigrants and their children. Commonly asymptomatic for decades, patients with untreated disease can suffer significant morbidity, particularly from chagasic cardiomyopathy, that may result in death. Primary care providers (PCPs) are the first, and sometimes only, point of contact in the healthcare system for many vulnerable populations in the US. We set out to address how to engage PCPs in learning about and screening for Chagas disease and other neglected tropical diseases (NTDs) with which they may be unfamiliar. We conducted group interviews via Zoom with providers in Massachusetts, New York, California, and Florida who work with Latinx immigrants to learn more about their attitudes and preferences towards professional educational activities and to identify current barriers to their screening for Chagas disease. We developed a discussion guide using the theoretical framework of acceptability to identify educational priorities. We spoke with physicians (n=19), nurse practitioners and physician assistants (n=4), and midwives (n=2). Themes that emerged from the interviews included the importance of timing (i.e., holding educational sessions during regularly scheduled meetings), an overwhelming preference for case-based materials, and the fact that social media (e.g., Twitter) was not seen as a useful educational tool. Barriers to screening for Chagas disease included unfamiliarity with diagnostic tests and discomfort with a lack of national screening guidelines. Preliminary results also suggest that PCPs are interested in learning about NTDs that affect their patient population and that they want materials that clearly explain how to integrate screening and care into existing practice, not just information about the diseases. These study results will help create a guide for creating educational materials on Chagas disease and other NTDs in the US to enhance awareness, screening, and treatment.

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CHARACTERIZING THE CO-INFECTION OF TYPHOID AND MALARIA AND ASSOCIATED RISK FACTORS IN AN ENDEMIC REGION OF PAKISTAN

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Acute febrile illness is a serious public health issue, which requires an accurate diagnosis for the proper management and improved antimicrobial resistance stewardship. Studies of AFI in Pakistan have been focused on the emerging viral pathogens rather than endemic diseases that may be lacking in appropriate confirmatory diagnosis. Two of the most important epidemic-prone diseases associated with fever in Pakistan are malaria and typhoid. Unfortunately, there is a lack of data on the prevalence of circulating strains of typhoid and malaria, and particularly co-infection, in Sindh province in Pakistan, despite the region being the epicenter of an on-going typhoid outbreak. We designed a study to investigate the prevalence of malaria and typhoid including their co-infection among hospital patients in Karachi and characterize the risk factors associated with the co-infection of circulating *Plasmodium* species and *Salmonella* typhi serotypes. This pilot cross-sectional disease prevalence study recruited patients (≥ 2 years old) presenting with fever (≥ 37.5ºC) or respiratory illness at two tertiary hospitals in Karachi. Rapid diagnostic tests were used to screen patients for both malaria and typhoid fever, and confirmed

by RT-PCR. Pathogen strain variation and relatedness was explored via sequencing. A short questionnaire was administered to capture and characterize medical history and socio-economic-behavioral data to identify risk factors associated with exposure and infection with malaria and/or typhoid. Here, we present preliminary results and recommendations for future directions. Overall, this study contributes to broadening knowledge about the extent of both infections and simultaneously co-infection of malaria and typhoid in Pakistan and is helping to foster the development and implementation of guidelines and recommendations for better case identification and diagnostic algorithms for malaria and typhoid in Pakistan.

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STANDARDIZATION OF DATA WITH ANNOTATED CASE REPORT FORMS FOR USE IN VISCERAL LEISHMANIASIS CLINICAL TRIALS IN PATIENTS WITH AND WITHOUT HIV CO-INFECTION

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Visceral Leishmaniasis (VL) remains an important cause of morbidity and mortality in several tropical regions. In collaboration with the VL research community, IDDO conducts curation from historical datasets to standardise data into a common format to enable individual patient data meta-analyses. Past trials have shown large heterogeneities in the methodology used to assess drug efficacy, making comparability between studies challenging. In order to facilitate comparison of studies, optimise data quality and maximise re-use of future datasets, dissemination of common standards should be promoted. A group of experts was convened by IDDO and the Drugs for Neglected Diseases *initiative* (DND*i*) in 2020 to develop a standard annotated Case Report Form (aCRF) for uncomplicated VL efficacy trials to optimise data quality and comparability for prospective research, aiming to disseminate a common terminology across endemic regions. We use Clinical Data Interchange Standards Consortium (CDISC) compliant terminology. It was recognised that with falling numbers of leishmaniasis, patients with HIV coinfection were going to have increasing importance in control of VL. Capitalising on the work done for the uncomplicated VL aCRF, an aCRF for HIV-VL coinfection has been developed in 2022 in collaboration with the Rajendra Memorial Research Institute of Medical Sciences, an institute of the Indian Council of Medical Research, DND*i*, Médecins Sans Frontières and other global stakeholders from academia, NGOs, WHO, pharmaceutical industry and drug regulators. These aCRFs are the first for a neglected tropical disease to have been developed based on CDISC compliant terminology, allowing for efficient generation of clinical data with downstream impact via adherence to CDISC standards recognised by national drug regulatory agencies. A key consideration has been to develop a tool that can be adapted to the data requirements of individual trials. We will present the benefits and impact of data standardisation, and discuss the challenges associated in deciding what data to capture and how, and the need to tailor aCRFs depending of the study population.

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LONG-TERM MORTALITY IN A PROSPECTIVE ADULT SEPSIS COHORT IN WESTERN UGANDA, 2017 TO 2022

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Long-term mortality in sepsis survivors has been insufficiently characterized in Sub-Saharan Africa. To describe factors associated with long-term mortality, we performed a survival analysis with baseline factors in a prospective cohort study with 12-month follow-up in Western Uganda. Hospitalized adults with ≥ 2 modified systemic inflammatory response syndrome (SIRS) criteria (temperature < 36°C or > 38°C, heart rate ≥ 90 beats per minute, or respiratory rate ≥ 20 breaths per minute) were enrolled at a tertiary care center between October 2017 and January 2021. Clinical parameters including malaria rapid diagnostic test and sputum tuberculosis PCR results were performed. Baseline demographics were evaluated for risk of death by 12-months using Cox proportional hazards regression. Among 356 participants, the median age was 43.0 years (interquartile range [IQR]: 28.0, 56.0) years, 40.2% were male, and 27.0% were living with HIV. The majority were followed to one-month (N=338, 94.9%), 6 months (N=282, 79.2%) and one-year (N=239, 67.1%). Malaria (15.7%) followed by tuberculosis (4.8%) were the most common causes of illness identified. Overall, 35 (9.8%) participants died. By one-month, 18 (5.7%) participants died, and 17 deaths occurred between one month and one year (48.6% of deaths and 4.5% of the cohort). Death occurred a median of 14.0 (IQR: 7.0, 79.0; range: 1, 281) days from enrolment and 45.7% of those that died had known or newly diagnosed HIV. Overall, male sex was associated with an increased risk of death (unadjusted hazard ratio [HR]: 2.48; 95% confidence interval [CI] 1.26, 4.89) but age was not associated with an increased risk (p=0.7). After adjustment for age and sex, HIV remained associated with an increased risk of death at 12 months (aHR: 2.38; 95% CI: 1.20, 4.69; unadjusted HR 2.19, 95% CI: 1.12, 4.26). In conclusion, a high proportion of deaths after sepsis occur between one month and one year after hospital discharge in Western Uganda. The burden of sepsis may be underestimated in Sub-Saharan Africa due to limited long-term follow-up.

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COINFECTIONS IN PATIENTS WITH ACUTE FEVER SYNDROME IN A TROPICAL AREA OF COLOMBIA

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Acute febrile syndrome (AFS) of infectious etiology occurs due to multiple infections such as dengue, malaria, leptospirosis, rickettsiosis, brucellosis and typhoid fever, among others. Colombia is a country located in the tropical zone, with a great ecological diversity; the geographical, climatic and epidemiological conditions enhance the transmission of infectious diseases, about 60% of the Colombian population is at risk of becoming ill or dying from infectious diseases. The aim of this study was to determine the presence of coinfections in patients with AFS in a tropical area of Colombia. A cross-sectional prospective descriptive study was carried out using non-probabilistic convenience sampling between February and December 2014. A total of 160 patients with AFS were obtained from the emergency department of Hospital San Jerónimo from Montería-Colombia. Two blood samples were taken at two different times. For the

first sample, 10 mL of venous blood was collected, 4 mL in a tube with EDTA K3 anticoagulant to perform thick blood smears, peripheral blood smears, and polymerase chain reaction (PCR) for malaria. The tube without anticoagulant (6 mL) was used to perform febrile antigens, ELISA for dengue (IgM) and microagglutination for leptospira. The second sample was collected 10 to 15 days after the first, and ELISA was performed for dengue (IgM) and microagglutination for leptospira. The frequency for dengue was 31.87%, 11.87% of the patients had malaria, leptospirosis was detected in 6.87% and 3.76% of co-infections between these 3 etiological agents. All patients were negative for brucellosis and typhoid fever. 2.5% of the patients presented coinfection between dengue and leptospira, 0.63% between dengue and malaria (P.vivax) and 0.63% co-infection between malaria (P.vivax) and leptospira. Although coinfections were not highly prevalent in the study population, they can create difficulties in diagnosis and delays in timely treatment of patients, since all these diseases share common endemic areas. Concurrent infections with similar clinical manifestations remain a challenge for diagnosis and treatment.

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COMMUNITY-BASED TRIAL ASSESSING THE IMPACT OF ANNUAL VERSUS SEMIANNUAL MASS DRUG ADMINISTRATION WITH IVERMECTIN PLUS ALBENDAZOLE AND PRAZIQUANTEL ON HELMINTH INFECTIONS IN NORTHWESTERN LIBERIA

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We assessed the impact of three annual vs five semiannual rounds of mass drug administration (MDA) with ivermectin plus albendazole followed by praziquantel for the control or elimination of lymphatic filariasis (LF), onchocerciasis, soil-transmitted helminth (STH) infections and schistosomiasis in Lofa County, Liberia. The study started in 2012 and was interrupted in 2014 during the Ebola virus outbreak. Repeated cross-sectional surveys were conducted in individuals 5 years and older to measure infection markers. *Wuchereria bancrofti* antigenemia prevalences decreased from 12.5% to 1.2% (90% reduction) and from 13.6% to 4.2% (69% reduction) one year after three rounds of annual or five rounds of semiannual MDA, respectively. Mixed effects logistic regression models showed decreases in odds of antigenemia positivity were 91% and 74% at that time in the annual and semiannual treatment zones, respectively ($p < 0.001$). Semiannual MDA was slightly more effective for reducing *Onchocerca volvulus* microfiladermia prevalence and at follow-up 3 were 74% (from 14.4% to 3.7%) and 83% (from 23.6% to 4.5%) in the annual and semiannual treatment zones, respectively. Both treatment schedules had similar beneficial effects on hookworm prevalence. Thus, annual and semiannual MDA with ivermectin and albendazole had similar beneficial impacts on LF, onchocerciasis, and STH in this setting. In contrast, MDA with praziquantel had little impact on hyperendemic *Schistosoma mansoni* in the study area. Results from a long-term follow-up survey showed that improvements in infection parameters were sustained by routine annual MDA provided by the Liberian Ministry of Health after our study endpoint.

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CHARACTERIZATION OF THE GENETICS AND EPIDEMIOLOGY OF A *BRUGIA* SP. IN DOMESTIC DOGS IN CHAD, AFRICA

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Domestic animals can serve as reservoirs for certain zoonotic parasitic infections, including Guinea worm disease and lymphatic filariasis. This project aimed to characterize *Brugia* sp. infections in dogs from Chad, Africa. During a canine pathogen surveillance project in 2019-2020, we identified *Brugia* sp. infections in 46 out of 428 dogs (10.7%) sampled. We found high levels of sequence similarity to *B. malayi* and *B. pahangi* based on amplification of 18S rRNA, 5.8S rRNA, and ITS-2 regions. Phylogenetic analysis of 18S rRNA gene sequences placed the Chadian *Brugia* sp. in a clade with other *Brugia* spp. but grouped it separately from *B. malayi* and *B. pahangi*. Analysis of *Hha* I sequences showed the greatest similarity with *B. patei*, a parasite previously reported from dogs, cats, and wildlife in Kenya. Epidemiologic analysis found significantly higher odds of *Brugia* sp. detection among dogs in southern Chad compared to those in the northern region; within the northern region, there were higher odds of detection in the dry season, compared to the wet season, which is consistent with the ecology of a presumably mosquito-borne parasite. No association was noted between *Brugia* infection and a dog being positive for *Dirofilaria immitis* antigen using a commercial assay, with only seven of 119 dogs positive for *D. immitis* antigen being *Brugia*-positive. This is the first report of *Brugia* sp. in domestic dogs in Chad and additional research is needed to definitively identify the species present, elucidate transmission, and understand potential risks to canine and human health.

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GEOSPATIAL MODELING OF THE BASELINE *ONCHOCERCA VOLVULUS* NODULE PREVALENCE IN ETHIOPIA ASANAID TO ELIMINATION

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With almost half a century of onchocerciasis control efforts, the World Health Organization is now focusing on onchocerciasis elimination. Onchocerciasis, predominant in sub-Saharan African countries, shows much spatial heterogeneity: high endemic areas are close to low endemic areas, posing the risk of sustaining transmission because of movement of people and/or vectors between them. While control efforts were focused on highly endemic areas, unmapped areas have been identified with onchocerciasis transmission potential in Ethiopia. We used a Bayesian geostatistical approach on pre-intervention nodule prevalence data from 916 unique locations collected from 25,077 people to create a baseline nodule prevalence map for Ethiopia. We accounted for several ecological and socio-demographic variables and quantified the uncertainty associated with the model output. Onchocerciasis nodule prevalence was higher in southwestern and northwestern parts than in central and eastern Ethiopia. Modeling revealed some areas with predicted high mean prevalence but large uncertainty, which might need to be prioritized for elimination mapping. In addition, hydrological variables such as distance to the nearest river (mean coefficient: -0.015, 95% BCI: -0.025 - -0.005), precipitation seasonality (mean coefficient: -0.017, 95% BCI: -0.032 - -0.001), flow accumulation (mean coefficient: -0.042, 95% BCI: -0.07 - - 0.019), and soil moisture (mean coefficient: 0.0216, 95% BCI: 0.014 - 0.03) were found to be significantly associated with prevalence. Thus, significant environment variables reflect the association of high prevalence locations with areas suitable for vector breeding and biting. Finally, this approach

could be used to create baseline prevalence maps accounting for ecological variables in other onchocerciasis endemic areas, and these could be used as a reference to prioritize areas for mapping and monitoring.

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PERSISTENCE OF THE PREVALENCE AND ASSOCIATED CLINICAL MANIFESTATIONS OF LYMPHATIC FILARIASIS IN THE BONO REGION OF GHANA

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In Ghana, lymphatic filariasis, a neglected tropical disease of the poorest of the poor, is endemic in 114 out of the 260 districts of 12 of 16 regions, with the at-risk population estimated to be more than 9.9 million. Though the disease has been earmarked for elimination as a public health burden by 2025, there is inadequate monitoring of the effectiveness of the control programme which is mainly the mass drug administration of ivermectin. This study aimed at evaluating the prevalence of LF and its associated clinical manifestations in selected communities in Ghana to understand the effectiveness of the control programme. A cross-sectional survey was conducted in the Odumase, Chiraa, Antwikrom, and Twerekrom communities in the Bono Region of Ghana. A total of 104 consenting individuals were recruited for the study. The participants were examined for clinical manifestations of lymphatic filariasis including hydrocele and elephantiasis. Venous blood was also taken to determine their infection status by microscopy. The results from the microscopic examination of blood samples from participants demonstrated a microfilaria prevalence of 26% (6/23) in Chiraa, 33.3% (12/36) in Odumase, 15.3% (4/26) in Antwikrom and 36.8% (7/19) in Twerekrom. The findings from the clinical examinations demonstrated the prevalence of lymphedema as 26.1% (6/23) in Chiraa, 5.6% (2/36) in Odumase, 3.8% (1/26) in Antwikrom and 10.5% (2/19) in Twerekrom with individuals having lymphedema at stages 1-6. Meanwhile, the prevalence of hydrocele was 8.7% (2/23) in Chiraa, 3.8% (1/26) in Antwikrom, 5.3% (1/19) in Twerekrom and 0% (0/36). This study demonstrated that most of the study communities are still hyperendemic for LF infection, with its associated clinical manifestations persisting despite more than a decade of LF control in the Bono Region of Ghana. The findings from this study underscore the need for further investigations into reasons for persistence of the disease in these communities and to regularly evaluate the LF control programme in the race to achieve the 2025 targets.

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ONCHOCERCA VOLVULUS VECTORS *SIMULIUM SPP.*: PERSPECTIVES ON RESEARCH, BIONOMICS, AND IMPLICATIONS FOR ELIMINATION OF ONCHOCERCIASIS IN NIGERIA

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Onchocerciasis (river blindness), caused by the filarial nematode *Onchocerca volvulus* and transmitted by blackflies of the genus *Simulium*, is widely endemic in sub-Saharan Africa. Nigeria has the largest burden with an estimated 50 million people at risk. The World Health Organization (WHO) recommends the drug ivermectin as the main treatment strategy for interrupting transmission but recognises that to achieve the elimination goals an ambitious research agenda is needed to support programme progress. One of the priority areas identified by the WHO includes demonstrating the programmatic utility of vector control measures. However, to achieve this, an understanding of the research conducted hitherto, and the vector distribution and bionomics is essential. This study, therefore, aimed to examine published research on *Simulium* spp. in Nigeria. Information was compiled into a database on the publication (e.g., authors, institution, journal), study locations, duration, field sampling, laboratory methodologies, and the results related the species composition, spatial-temporal distributions, transmission indicators (e.g., biting and infection rates), habitats, ecology, impact of interventions and/or changes in environment. In total, 105 publications from the scientific literature were identified from 1950 to 2021 (1950-60s=8; 1960-70s=5; 1970-80s=1; 1980-90=12; 1990-00=10; 2000-10s=21; 2010-2021=48) with 466 locations geolocated to an administrative level (e.g., zone, state, implementation unit). Detailed analysis is ongoing, however preliminary results indicate that most studies reported the *S. damnosum* complex, focused on both adult/larvae blackfly stages, used human bait for adult fly collections, sampled for different durations across different seasons, and used both dissection/molecular methods to detect infection. When completed, this comprehensive information database will be an important resource and facilitate future research to assist the onchocerciasis elimination programme in Nigeria.

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DISTRICT AND SUB-DISTRICT PREVALENCE ESTIMATES OF LYMPHATIC FILARIASIS IN LEOGANE AND GRESSIER, HAITI, 2021: A CASE FOR DECISION-MAKING AT THE SUB-DISTRICT LEVEL

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Haiti's lymphatic filariasis (LF) Elimination Program was established in 2001. That year during the national baseline survey, circulating filarial antigen (CFA) prevalence was 23% among children ages 6-11 years in Leogane, and 25.3% in neighboring Gressier. The first LF mass drug administration (MDA) campaign in Haiti was piloted in Leogane in 2000, with 17 rounds conducted through 2021. In Gressier, 10 rounds were conducted from 2008-2021. The most recent campaign in December 2020 was followed by a coverage and prevalence survey. Using probability proportionate to estimated size sampling, census enumeration areas were divided into segments of 50 households (HH); 30 segments were selected in each of 4 strata defined by district (Leogane and Gressier) and topographical zones (mountains and plains). HH were approached to participate based on a skip pattern. In each HH, members ages 2 years and older were eligible to participate, and 2 were randomly sampled for blood sample collection and testing by filariasis test strip (FTS). In total, CFA was detected in 63 (1.8%) of 3,560 participants with valid results. Weighted prevalence estimates for Leogane-overall, -plains, and -mountains were: 1.7% (95% CI: 1.1-2.6), 2.0% (1.3-3.1), and 0.4% (0.1-1.5), respectively. Similarly for Gressier: 1.4% (0.8-2.5), 2.2% (1.2-4.1), and 0.8% (0.3-2.1), respectively. In each district, the mountains strata had lower estimates than the plains. Leogane-mountains was the only stratum with an upper confidence limit beneath the World Health Organization stop-MDA threshold of 2% CFA. Three individuals, ages 22, 26, and 68, tested CFA-positive in this sub-district; none had circulating microfilaria detected by microscopy from night blood samples. These results indicate the absence of LF transmission in the sub-district. The Pan-American Health Organization's Regional Program Review Group approved the program to stop-MDA in Leogane-mountains and to start post-treatment surveillance meaning an estimated 36,892 persons no longer require MDA. Sub-district evaluations may be useful to make efficient use of limited resources in Haiti and other countries.

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PRELIMINARY REPORT ON PCR DETECTION OF BRUGIAN FILARIAL DNA IN BLOOD SMEAR NEGATIVE HUMAN BLOOD SAMPLES IN SRI LANKA

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Lymphatic filariasis (LF) is a Neglected Tropical Disease caused by filarial nematodes including *Brugia malayi*, which affects 859 million people worldwide. Post-elimination surveys have reported the re-emergence of Brugian filariasis in Sri Lanka after four decades of quiescence, threatening the LF-elimination status achieved in 2016. This study investigated the prevalence of Brugian filarial parasites within the human population in Wattala (Gampaha district) and Maggona (Kalutara district) based on two Brugian filariasis positive human cases reported to the Anti-filariasis Campaign in 2021. Humans and animals within a 500m radius of the respective index human cases of Brugian filariasis were screened for microfilaria using Giemsa-stained Thick Blood Smears (TBS). Microfilaria were not detected in any of the 96 and 9 human blood samples screened from Maggona and Wattala respectively. Of the 28 (Maggona) and 12 (Wattala) animal blood samples screened, *Brugia* microfilaria were detected only in 2 samples from Wattala. Molecular characterization targeting the *Brugia* specific *Hhal* repeat region (Bm*Hhal*rr) confirmed these parasites to be of *Brugia* spp. Molecular analysis of 20 randomly selected microfilaria negative blood samples, elicited a band of the expected size (322bp) for the Bm*Hhal*rr except one from Maggona, suggestive of the presence of Brugian parasite DNA in these samples. Interestingly, all of the animals except 1 from Kalutara yielded similar results. Dissection of head and thorax regions of 67 and 44 mosquitoes from Maggona and Wattala respectively identified 30 and 4 parasite positive mosquitoes from each area, all of which were confirmed by the Bm*Hhal*rr PCR. The gold standard for the detection of Brugian infections is microscopic examination for the presence of microfilaria. However, our results indicate that TBS might be less sensitive in detecting low levels of microfilaraemia. The presence of infective vector mosquitoes in these locations is suggestive of active transmission of these parasites. Hence, the actual state of infection in the animal reservoirs and humans need immediate investigation.

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ONCHOCERCIASIS ELIMINATION PROGRESS AFTER TWO DECADES OF TREATMENT: LAST MILE CHALLENGES IN MAHENGE, TANZANIA

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Onchocerciasis is a parasitic disease caused by the nematode *Onchocerca volvulus*, transmitted through repeated bites from infected blackflies of the genus *Simulium* that breed in fast flowing rivers and streams. The disease is targeted for elimination by 2030 through mass drug administration (MDA). Mahenge Focus includes 4 highly endemic onchocerciasis district councils; the area recorded the highest baseline prevalence in Tanzania, (nodular palpation of 45-95% conducted in 1997). Mass treatment following the Community-Directed Treatment with Ivermectin (CDTI) approach reduced the prevalence to up to 2.8% OV16RDT, however there is evidence of continued transmission despite more than two decades of MDA. This survey was conducted to explore challenges related to the elimination of onchocerciasis targeted by 2030. A Social Ecological Model (SEM) survey was conducted in four councils of Mahenge Focus in November 2021 to explore factors affecting Onchocerciasis MDA implementation from community members, CDDs, and Frontline Health Workers and District NTD teams. A total of 24 in-depth interviews with District NTD teams, frontline health workers, and community leaders/ influential personalities were conducted. Moreover, 24 focus group discussion were conducted with community drug distributors and community members. The major challenges identified to reaching the last mile for elimination of onchocerciasis in Mahenge Focus are interrelated. These include the need for strengthened context-specific planning, greater materials and human resources, increased coordination among key players during MDA, and robust community sensitization efforts to combat misconceptions among community members. The CDTI at operational level in Mahenge focus faces obstacles which negatively affect transmission interruption. Intensifying advocacy for resource mobilization both from the government and development partners to improve planning, strengthening coordination during MDA, enhancing community sensitization and mobilization to address misconception as well as shifting to microplanning may overcome the observed challenges.

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TOWARDS ONCHOCERCIASIS ELIMINATION: PROMISING TREND ON EPIDEMIOLOGICAL EVALUATION RESULTS IN TANZANIA

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Onchocerciasis is endemic in 28 districts of Tanzania with six million people at risk. Between 1997 and 2004 recorded prevalence ranged from 29% to 95%. Ivermectin mass drug administration (MDA) following a Community Directed Treatment with Ivermectin (CDTI) began in 1997. Following MDAs, evaluation surveys were conducted. We report results of surveys undertaken from 2009 to 2018 to assess progress towards onchocerciasis elimination in CDTI areas with ≥10 years treatment. The surveys are grouped into two categories. The first category used microfilaria skin snip test, undertaken from 2006 to 2013 in purposeful sampled villages to determine the prevalence of *O.volvulus* microfilariae. Around 150-200 Individuals aged 5 and above years were tested in each village and the decline in prevalence was compared against the baseline surveys. The second category involved finger prick blood samples to determine prevalence of IgG4 antibodies against the Ov16 antigen, conducted between 2014 and 2018, either district-wise adopting a random selection in children aged 6-9 years, or purposeful in 3 first-line villages enrolling individuals aged 5-90 years. Analysis was done to determine if stopping criteria was being approached. In the first category, 23,638 people from 132 villages in 28 district councils were examined. The microfilaria skin snip prevalence indicated reduction of infection from 29-95% at baseline to 0-9.8%. The decline in prevalence was satisfactory in 5 district councils (0-0.03%), on track in 19 councils, and delayed in 4 district councils. In the second category, children aged 6-9 years or individuals aged 5 years and above were examined in 22 district councils, of which 5 councils met the epidemiological criteria for conducting stop MDA surveys. The recorded prevalence ranged between 0-3.5%. Overall, 5 district councils were close to the elimination threshold, 19 district councils were on track but required more rounds of treatment, and in 4 district councils progress was unsatisfactory. Nine councils (4 with unsatisfactory progress and 5 which were on track) changed the modality from annual to bi-annual MDA to accelerate elimination.

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MAXIMIZING THE POTENTIAL OF MOLECULAR XENOMONITORING TO SUPPORT FILARIASIS ELIMINATION

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Molecular xenomonitoring (MX) is recommended as a supplemental surveillance strategy to inform filariasis elimination efforts. However, there are essential knowledge gaps which limit the implementation of MX and the interpretation of MX data. Through a series of systematic reviews, meta-analyses, and entomological and epidemiological surveys, we determined the sensitivity of MX to detect the presence of filariasis and the predictive power of the MX rate in the model of microfilaria (mf) prevalence. We found that MX was 100% sensitive at mf prevalence 0.5-1% when 1,000 mosquitoes were screened in pools. With mf prevalence <0.5%, 2,000 mosquitoes were needed to achieve the same sensitivity. The correlation between MX rate and mf prevalence is dependent on MDA status with the strength of the relationship increasing after MDA. The correlation was the highest when consistent entomological sampling approaches were used in a given area (R^2= 0.78, p<0.001). We compared sensitivity with different mosquito trap types, sampling intensity and vector genus. We found that methods which target recently fed mosquitoes (indoor resting, pyrethrum spray catch, exit trap) yielded significantly higher MX rates compared to those that target unfed mosquitoes (light traps, human landing catch) [RR 3.5 95%CI 1.52-8.24]. The screening of anopheline mosquitoes yielded a rate ratio of 6.91 [1.73-27.52] in areas where anophelines are the primary vector compared to culicines. Interestingly a similar trend was also observed in areas of culicine-transmitted filariasis, though these data are limited. Finally, we demonstrated the scope of multi-helminth surveillance by reporting the prevalence non-mosquito borne pathogen DNA in mosquitoes, including *Mansonella perstans* and *Loa loa*.

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COTE D'IVOIRE INTERRUPTS TRANSMISSION OF LYMPHATIC FILARIASIS FOR THE FIRST TIME IN 37 DISTRICTS DESPITE THE SARS-COV-2 PANDEMIC

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Lymphatic filariasis(LF) is endemic in 99 of 113 districts in Cote d'Ivoire. World Health Organization(WHO) recommended annual mass drug administration(MDA) for elimination of LF as a public health problem was initiated in the country in 2013. Ivermectin and albendazole are co-administered to persons ≥ 5years in endemic districts during MDA. In 2019, 46 LF endemic districts with a baseline Wuchereria bancrofti antigen prevalence of 2.0% to 70.0%, completed the required five effective (≥ 65% total population coverage) annual MDAs and were eligible for assessment of MDA on infection prevalence and transmission. Despite disruptions to planned technical assistance by WHO and partners by the SARS-CoV-2 pandemic; local expertise, virtual training platforms, modified field strategies, and strict adherence to SARS-CoV-2 prevention measures enabled successful implementation of the first LF pre-transmission assessment surveys(pre-TAS) in August 2020 and transmission assessment surveys(TAS) in November-December 2021 according to WHO guidelines. In the pre-TAS, a convenient sample of ≥ 400 persons (≥ 5years) were surveyed in one sentinel and spot check site in each district. In the TAS, cluster and random sampling were used to select 30 primary schools and enroll 1376-1556 children in grades 1 and 2(proxy for 6-7 years old) per evaluation unit(EU) for the survey. In both surveys, 75µl of finger stick blood was tested using the filarial test strip(FTS), a rapid point of care diagnostic test, to detect antigens to the adult parasite. 37 districts where both sentinel and spot check sites recorded a prevalence of < 2.0% (0.0 to 1.5%) passed the pre-TAS, while nine districts where at least one site recorded a prevalence of ≥ 2.0% (2.0 – 6.2%) failed. The 37 districts were constituted into 24 EUs for the TAS. A total of 40,023 children were surveyed in the 24 EUs. In all, only eight FTS positive cases were found(overall prevalence of 0.02%) in 6 EUs; below the 16-18 cut-off value per EU. All 24 EUs(37 districts) passed the TAS and have stopped MDA. Despite the challenges, Cote d'Ivoire is on a trajectory to stop LF MDA in endemic districts and achieve elimination.

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PROGRESS TOWARDS LYMPHATIC FILARIASIS ELIMINATION IN ETHIOPIA

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Lymphatic Filariasis (LF) elimination program in Ethiopia was started in 2009 in 5 districts of Gambella region and has since expanded to 95 endemic districts, which have received anywhere from 2 rounds of MDA in newly established areas to more than 10 rounds of mass drug administration (MDA, here an annual treatment of ivermectin combined with albendazole) to date. Impact and follow-up surveys were conducted in 53 districts that received at least five rounds of MDA and achieved treatment coverage of 65% and above. This review documents the efforts made towards LF elimination in the country. Transmission assessment surveys (TAS) and Pre-TAS are key milestones to evaluate the epidemiological status of LF. Purposive and random cluster sampling were used to select sites for Pre-TAS and TAS respectively. The sample sizes for each assessment were determined per the World Health Organization's criteria and procedures for Pre-TAS and TAS. Community-based TAS was the norm due to low school enrollment, and each district is considered its own evaluation unit (EU. EUs persist through redistricting decisions, which are relatively common in Ethiopia. Both Immunochromatographic tests (ICT) and Filarial Test Strips (FTS) were used to test blood samples collected from people ages ≥5 years and 6-7 years for Pre-TAS and TAS, respectively. Fifty-three districts were assessed for treatment impact in both sentinel and spot check sites and 16,460 people were tested, and out of which 37 districts passed (70%) and 16 districts failed (30%) when one or more sites per district showed antigen prevalence at 2% or above. To date, of the 95 endemic districts, 26 (27%) have completed TAS-1, 12 (13%) districts TAS-2, and 3 (3%) districts are on track to complete TAS-3 by the end of 2022. Hence, 3.4 million people no longer require MDA for LF. Further investigation is required for districts that have repeatedly failed pre-TAS studies.

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INVESTIGATION INTO POSSIBLE CAUSES FOR CONTINUED ONCHOCERCIASIS HIGH PREVALENCE IN THE WENCHI MUNICIPAL OF GHANA

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For over 15 years, ivermectin Mass Drug Administration (IVM MDA) against river blindness (onchocerciasis) has been uninterrupted in Wenchi Municipal of Ghana, with reported effective coverage >65% of total population. This should have greatly reduced or interrupted transmission, but impact evaluation indicated microfilariae (mf) prevalence increased

in Kwanware community in the Wenchi Municipal from 5% in 2012 to 29% in 2017. This study verified the level and extent of onchocercal infection and contributing factors in Kwanware and surrounding areas. Verification was made through: (1) review of past treatment records and community registers for the preceding IVM MDA; (2) treatment coverage survey (TCS) of preceding IVM MDA; (3) qualitative assessment of IVM MDA participation; (4) entomological prospection for blackfly vector larvae in rivers and assessment of blackfly infectivity rates; and finally, (5) parasitological survey by skin snip microscopy test for mf in people aged 20 years and above. The results revealed that for entomology, two close communities, Kwanware and Ottou, out of 19 had a positive blackfly infectivity rate (0.59% and 0.67); and for parasitology, 10 of 17 communities surveyed had a positive onchocercal mf prevalence, with the highest rates (29.9 and 36.6%) corresponding to the two communities with positive blackfly infectivity rate. This confirms persistent, high and ongoing onchocerciasis transmission which were considered the focus of high transmission (hotspot). Seasonal migratory farming communities, including Kwanware and Ottou situated near highly productive breeding sites have ten times risk of mf infection than the settled communities. Suboptimal programmatic performance related to inexhaustive census and reach issues revealed by qualitative assessment might have been contributing to the ongoing transmission as well. These results have prompted the programme and the Ghana Onchocerciasis Expert Committee to call for further exploration to identify and characterise all other at-risk communities in the vicinity of Kwanware and Ottou in order to inform strategy adaption to address the situation.

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INVESTIGATING URBAN TRANSMISSION OF LYMPHATIC FILARIASIS IN MONROVIA

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Considering the progress and goal of elimination, the Ministry of Health (MoH) in Liberia is keen to establish the prevalence and need to treat Lymphatic Filariasis (LF) in urban areas. As urban areas are large and expensive to treat, and it is difficult to achieve good coverage, the decision to treat needs to be carefully reached. This study in urban Monrovia aimed to determine if there was onward *Wuchereria bancrofti* (causative parasite of lymphatic filariasis) transmission through testing for circulating filaria antigen (CFA) using filarial test strips (FTS) in children and through molecular xenomonitoring (MX). Thirty (30) schools in four health districts (HD) were selected using probability proportionate to sample size. Within the schools, 1799 children aged 9-14 years were tested for LF using FTS. Across eight communities in two HD, mosquitoes were collected using exit traps (ET) for 5 days and gravid trap (GT) for four days each month from May to October, 2019 representing a total of 3361 trapping events which caught a total of 3006 and 17751 *Anopheles* and *Culex* mosquitoes, respectively. FTS analysis revealed an overall positivity rate of 5.3% (CI:4.3, 6.5%); ranging from HD prevalence of 1.1% to 13.3%. All the mosquitoes analyzed by PCR returned negative test. There was no complete spatial overlap in MX and FTS sampling sites - notably the HD with the highest CFA prevalence had MX sites. The results bring into question whether there is ongoing transmission in Monrovia and highlight the need to optimise spatially the configuration of sites for epidemiological and MX. In addition, sub-optimal sampling of mosquitoes could also have contributed. Furthermore, it is plausible that the FTS positive persons are the result of migration as opposed to local transmission. Therefore, further investigation is needed to understand the reasons for the discording FTS and MX results.

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PREDICTIVE RISK MAPPING OF LYMPHATIC FILARIASIS RESIDUAL HOTSPOTS IN AMERICAN SAMOA TO INFORM SURVEILLANCE AND CONTROL STRATEGIES

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American Samoa successfully completed seven rounds of mass drug administration (MDA) from 2000-2006 for lymphatic filariasis (LF). The territory passed the recommended school-based transmission assessment survey (TAS) in 2011 and 2015 but failed in 2016. A community-based survey of 2,710 people in 2016 found an overall adjusted antigen (Ag) prevalence of 6.2% (95% CI: 4.5–8.6%), confirming resurgence. One of the key challenges after the implementation of MDA is the identification of residual hotspots of transmission to minimise the risk of potential resurgence. Based on data collected in the 2016 community survey, separate Bayesian geostatistical models with environmental factors were developed for LF Ag, and Wb123, Bm14, Bm33 antibodies (Abs) to predict spatial variation in infection markers. In the Ag model, males had a 15.0% (95% CrI: 1.7–29.8%) higher risk of being Ag-positive than females. There was a 2.3% (95% CrI: 1.8–2.9%) increase in the odds of Ag positivity per year of age, and 0.6% (95% CrI: 0.06–1.1%) increase for each 1% increase in forest cover within 20-meter (m) buffers around household locations. The odds of Ag-positivity decreased by 0.1% (95% CrI: 0.01–0.3%) with each 1m increase in elevation. All Ab models showed similar significant associations as the Ag model for sex, age, forest cover and elevation. Spatial correlation occurred over greater distances for Abs. The results indicate that after accounting for the effect of covariates, the radii of the clusters for Ag, Wb123, Bm14 and Bm33 Abs were approximately 1.0, 1.1, 1.5 and 1.2 km, respectively. The predictive maps showed that Ab-positivity was more widespread across the territory, while Ag-positivity was more confined to western villages. The findings may facilitate the implementation of post-MDA surveillance activities by targeting those areas at higher risk of infection to ensure the territory achieves and maintains the LF elimination goals.

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MOLECULAR CHARACTERIZATION OF *WUCHERERIA BANCROFTI* IN NEPAL - A COUNTRY EMBARKING FOR LYMPHATIC FILARIASIS ELIMINATION

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Although Nepal has made substantial progress in the elimination of lymphatic filariasis (LF), few districts failed to achieve the goal even after recommended rounds of mass-drug administration (MDA) which led to substantial extension of the elimination deadline. Potential movement of *Wuchereria bancrofti* strains across Nepal-India borders might pose a challenge to elimination programs. This study attempted to address the gap in genetic information of circulating strains required to understand parasite movements and genetic variability in Nepal. *W. bancrofti* was recovered from blood samples of microfilaraemic individuals from LF endemic districts of Nepal. *W. bancrofti* abundant larval transcript (*alt-2*) fragment and internal transcribed spacer (*its*) region of 18S ribosomal DNA were PCR-amplified from gDNA and sequenced. The resulting sequences were analyzed for polymorphism in the 29 bp Short Tandem Repeats (STR) in intron-1 of *alt-2* gene and haplotype mapping of the *its* region. Phylogenetic trees were constructed for evolutionary relationships

of strains. Over hundred polymorphic sites were recognized in the *its* sequence (58 in Nepal alone) indicating strain variation. STR analysis of *alt-2* revealed two distinct polymorphism patterns in Nepal and India. Parasite strains were largely mixed up within Nepal (across different regions and districts) and also between two countries as evidenced by phylogenetic trees of *its* and *alt-2* sequences suggesting potential movement of parasites. Moreover, *Alt-2* phylogenetics also demonstrated at least three distinct lineages/clades of *W. bancrofti* strains circulating in Nepal. To conclude, *W. bancrofti* strains circulating between Nepal and India are genetically closely related which suggest a potential cross-border parasite movement through porous borders. This information has important implications in LF elimination since they share a long open border. Therefore, monitoring by molecular tools should be emphasized in countries - like Nepal embarking LF elimination.

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A SYSTEMATIC REVIEW OF THE GLOBAL DISTRIBUTION OF HUMAN HOOKWORM SPECIES AND DIFFERENCES IN THEIR MORBIDITY EFFECTS

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Diagnostic approaches for soil-transmitted helminth (STH) infections that are used in control programmes worldwide do not allow identification of hookworm genera or species. As a result, detailed information on the global distribution and morbidity effects of the different species of hookworms is not available. This limits the ability for effective programmatic decision-making on the best suite of interventions for locally effective STH control. The aim of the current study was to obtain a contemporary estimate of the global distribution and morbidity effects of the major hookworm species. Systematic reviews were conducted for the proportion of hookworm isolates of each species and genus by region of the world and other study attributes; and associations between hookworm species-specific infections and morbidity outcomes, particularly severe anaemia. the most prevalent hookworm species was Necator americanus (pooled proportion 79%; 95% confidence interval (CI): 67, 89%) whereas the proportion of hookworm-infected people that had Ancylostoma spp. infection was significantly lower at 32% (95% CI: 20, 45). N. americanus and Ancylostoma spp. were present in all regions of the world, although at different ratios. Lower proportions of people were infected with *Ancylostoma* spp. and mixed infections in the 2000s and 2010s compared to the 1990s. No clear evidence was found for differential morbidity effects for different hookworm species. Diagnostic that differentiate hookworm species, including molecular methods, need to be developed for widespread use in control programmes to elucidate key features of hookworm epidemiology and control.

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GIT PARASITIC INFECTIONS IN BETA-THALASSEMIA MAJOR ADULT POPULATION, LAHORE, PAKISTAN

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Parasitic infections are worldwide in distribution. In developing countries intestinal parasitic infections occur at high frequency. The factors that are associated with intestinal parasitic infections are Poverty, illiteracy, poor sanitation, lack of clean water and humid tropical climate. In Pakistan it is still a highlighted public health problem despite of improved socio-economic conditions and elevated living standards. Throughout the world and in Pakistan Beta thalassaemia is one of the commonest inherited disorders and an autosomal recessive hemoglobinopathy. Our objective of study was to check the prevalence of GIT parasitic infections among Beta thalassemic patients. This type of the work was not available in Punjab. 200 stool and blood samples were collected from male and females patients from which 100 was the experimental thalassemic and 100 was the control haemophilic. Then stool samples were analyzed for various parasites and blood samples to determine the various changes in the blood as well. Data regarding the patients were obtained with the help of Questionnaire. Statistical analysis was done by using SPSS. Prevalence of parasitic infections in Beta thalassemic patients was found 27% and in normal adults 24% . So this kind of study emphasizes the necessity of regular screening for such infections in Beta thalassemic patients to aware them about their health.

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CIRCULAR RNA EXPRESSION AND SECRETION IN *ASCARIA SUUM* TISSUES AND EXTRACELLULAR VESICLES

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Circular RNAs (circRNAs) are a recently identified RNA species with emerging functional roles as microRNA (miRNA) and protein sponges, regulators of gene transcription and translation, and modulators of fundamental biological processes including immunoregulation. circRNAs have been found in a variety of species including plants, animals, and model genetic organisms such as the free-living nematode *Caenorhabditis elegans*. Relevant to this study, circRNAs have recently been described in the parasitic nematode, *Haemonchus contortus*, suggesting they may have functionally important roles in parasites. Given their involvement in regulating biological processes, a better understanding of their role in parasites could be leveraged for future control efforts. Here, we report the use of next-generation sequencing to identify 1,997 distinct circRNAs expressed in adult female stages of the gastrointestinal parasitic nematode, *Ascaris suum.* We describe spatial expression in the ovary-enriched and body wall muscle, and also report circRNA presence in extracellular vesicles (EVs) secreted by the parasite into the external environment. Further, we used an *in-silico* approach to predict that a subset of *Ascaris* circRNAs bind both endogenous parasite miRNAs as well as human host miRNAs, suggesting they could be functional as both endogenous and exogenous miRNA sponges to alter gene expression. There was not a strong correlation between *Ascaris* circRNA length and endogenous miRNA interactions, indicating *Ascaris* circRNAs are enriched for *Ascaris* miRNA binding sites, but that human miRNAs were predicted form a more thermodynamically stable bond with *Ascaris* circRNAs. These results suggest that secreted circRNAs could be interacting with host miRNAs at the host-parasite interface and influencing host gene transcription. Lastly, although we have previously found that therapeutically relevant concentrations of the anthelmintic drug ivermectin inhibited EV release from parasitic nematodes, we did not observe a direct effect of ivermectin treatment on *Ascaris* circRNAs expression or secretion.

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RESISTANCE TO SINGLE-DOSE ALBENDAZOLE AND REINFECTION WITH INTESTINAL HELMINTHS AMONG CHILDREN AGES 2 TO 11 YEARS FROM THE PERUVIAN AMAZON REGION

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Soil-transmitted helminths (STH) are widely distributed and adversely impact child growth, especially in resource-limited countries. Studies have documented very high rates of STH infections in the Department of Loreto in the Peruvian Amazon, but national deworming programs are inadequately implemented in many communities. We aim to describe the frequency of reinfection with STH and clinical resistance to anthelmintics

following treatment in accordance with Peruvian Ministry of Health (MOH) guidelines using albendazole 400 mg administered every six months. Children ages 2 to 11 years from the district of Belén in Iquitos, Peru who received albendazole per MOH guidelines had stools examined for helminth ova pre-treatment and at 20 days, three months, and four months post-treatment. Following each stool examination persistent STH infections were re-treated with albendazole alone or, for Trichuris trichiura, with albendazole plus ivermectin. Stools were examined for ova by direct observation, quantification by Kato-Katz, and confirmation by qPCR. Initial stool samples (n=230) demonstrated a prevalence of 37.8% for Trichuris and 37.4% for Ascaris, while second samples (n=203) collected 20 days post treatment demonstrated a prevalence of 38.6% for Trichuris and 10% for Ascaris. Trichuris was the parasite with the highest frequency of clinical resistance to albendazole. After 90 days, during the third sampling period (n=131) the prevalence of Trichuris was 19% and 20.6% for Ascaris, and after 130 days with the fourth specimen (n=61) the prevalence of Trichuris was 19.7% and 15% for Ascaris. The cure rate for Trichuris and Ascaris after initial treatment was 33.7% and 88%, and after a second dose 71.7% and 68.6%, respectively. Participants to date (46% boys and 54% girls) had an average age of 6.5 years (SD +- 2.8). Age and sex did not correlate with prevalence of infection. These preliminary data suggest that while every 6-month dosing of albendazole established by MOH guidelines works in most cases, quarterly dosing would provide greater protection, and cure rate could be increased by using combination therapy of albendazole plus ivermectin.

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SPATIO-TEMPORAL DISTRIBUTION OF HELMINTH INFECTION AMONG A POPULATION OF THE KINTAMPO DISTRICT IN THE MIDDLE BELT OF GHANA

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An estimate of 2.7 billion people who live in low-income countries in Africa, South America, and Asia are thought to have some type of helminth infection. Such infections remain the most common in over 230 million preschool-aged children. This exploratory analysis was set up to assess spatially the influence of factors identified to affect helminth infection among a population in two districts in the middle-belt of Ghana, West Africa to advise on the implications for helminth control and elimination programmes. The exploratory analysis used data from 1543 consented and recruited participants that were positive at baseline with helminths and were followed up at 14 days post-treatment. We fitted and compared univariate and multivariate models. The models had similar structures except the structures for the spatially structured and non-structured random effects. The risks of soil transmitted helminth (STH) infections in younger age groups were higher compared to older individuals. Decrease in body mass index (BMI) was found to relate to increasing risk of STH infection. The residual spatially correlated and uncorrelated effects for periods 1 and 2 reveals pronounced high risks at the central parts and low risks at the peripheries of the study region. The residual correlated risks that remained after the intervention suggests that STH infection control measures and programmes need to be continued in the study area. The uncorrelated effects from the model revealed a random distribution of the risks contributing to the spread of STH infections in sub-districts in both Kintampo North and Kintampo South.

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NOVEL DIAGNOSTIC TOOLS FOR SOIL TRANSMITTED HELMINTHS WITH NON-INVASIVE CAPABILITY. THE NEAR-INFRARED SPECTROSCOPY AND ARTIFICIAL INTELLIGENCE

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Soil transmited helminths affect more than 1.5 billion people around the world. A majority of these infections are reported among school-aged children in resource challenged settings. Current diagnostic tools such as optical microscopy, Kato-Katzo and formol-ether concentration tests can be low in sensitivity in areas with low parasite endemicity whereas alternative techniques such as FLOTAC and mini-FLOTAC can be costly and time consuming for programmatic monitoring of these infections in areas under elimination. The near-infrared spectroscopy (NIRS) technique involves shining a beam of light (700-2500nm) on samples to produce a reflectance spectrum. Artificial intelligence (AI) is applied on the spectrum to determine diagnostic features. It does not require reagents or sample procesing procedures to operate and it only takes 5-10 seconds to scan a sample allowing thousands of samples to be assesed in a day by unskilled personnel. We assessed the capacity of NIRS coupled with AI to differentiate mice infected with *Trichuris muris* from those without the infection. To do this, we orally infected 10 mice with 30 *T. muris* eggs (low dose group), 10 mice with 200 eggs (high dose group) and 10 naive mice. All mice were non-invasively scanned using a malvern panalytical NIR spectrometer prior to infection and again after 24 hrs, 2 , 4, 6 and 7 weeks post infection. Faecal samples were collected at 24 hrs, 3 weeks and 4 weeks post infection whereas whole blood was collected 3 and 7 weeks post infection. Machine learning algorthms to detect the presence/absence of infection in the 3 groups were developed using artificial neural networks. NIRS detected *T. muris* with predictive accuracy of 92%, 97% and 90%, predictive sensitivity of 90%, 93% and 91% and predictive specificty of 95%, 100% and 80% non invasively, in faecal samples and in whole blood, respectively. This is the first study to demonstrate that NIRS and AI have potential to be applied as a diagnostic tool for STH. The non-invasive capacity of the technique makes it even more attractive for large scale screening of populations at risk. Further assessment of NIRS/AI in the field is recommended.

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STRONGYLOIDES STERCORALIS INFECTIONS IN THE MILITARY HEALTH SYSTEM

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This study reports the burden, clinical course, and outcomes of *Strongyloides stercoralis* infections within the military health system (MHS) from 2012-2019. Over this time period, 243 individuals were given a diagnostic code consistent with a *Strongyloides stercoralis* infection. Manual review of clinical notes from 243 charts demonstrated 210 confirmed diagnoses (coding positive predictive value 86.4%). Among confirmed diagnoses 56.7% were male, 25.7% represented active duty individuals while 26.7% were retired service-members, and 31.4% were patients 65 years old or over. Regarding geographic exposure risk, 25.2% were born in an endemic region, 19.5% had been deployed or stationed in an endemic region, and 12.4% had visited an endemic region. The

risk ratio for *Strongyloides stercoralis* infection based on region of birth was compared to overall foreign-born MHS members not from that region. The risk ratio was 1.40 for patients from Sub-Saharan Africa, 1.35 for patients from Latin America and the Caribbean, and 0.87 for immigrants from East Asia and the Pacific. In active duty patients, risk ratio based on military occupation was assessed by comparing the incidence risk within each occupation category to members outside that category. Servicemembers in the healthcare community had the highest risk ratio at 2.31, while the second highest was in the naval transport/operations realm at a ratio of 2.22. When the Special Forces community is examined alone, the risk ratio for infection is a striking 8.45 when compared to active duty service members outside of Special Forces. The clinical course of documented *Strongyloides stercoralis* infections including presentation, diagnosis, treatment, and follow-up is also described. In the Military Health System, both occupational exposures and country of birth serve as important risk factors for *Strongyloides stercoralis* infection. Personnel in the Special Forces community, in particular, appear to be at very high risk. As infections may be chronic and can lead to life threatening hyper-infection, the impact of targeted screening programs to complement routine medical care should be considered.

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ASSESSMENT OF CETHYLTRIMETHYLAMMONIUM BROMIDE (CTAB) BASED METHOD FOR THE EXTRACTION OF GEO-HELMINTH DNAS FROM STOOLS FOR MOLECULAR DIAGNOSTIC OF GEO-HELMINTHIASIS

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Although several protocols have been developed to extract DNA for the diagnostic of soil-transmitted helminths (STHs), amplifying these extracts remains a challenge due to DNA polymerase inhibitors. This study aimed to determine stool mass, the type of DNA polymerase and assess a DNA extraction method for efficient molecular detection of STHs. Stool samples were collected from school-aged children and Kato-Katz enabled to search for STH infections. DNA was extracted from 10, 20, 40 and 80 mg of stool using commercial kit and/or cetyltrimethylammonium bromide (CTAB)-based method. From extracts of 20 samples, the amount of stool for STHs diagnostic was determined by amplifying specific DNA fragments of *Ascaris lumbricoides*. Performance of three DNA polymerases as well as CTAB-based method were assessed by amplifying specific fragments of different STH species. The cost linked to each DNA extraction was estimated. In total 141 stools harbouring STHs' eggs (94 with *A. lumbricoides*, 39 with *Trichuris trichiura* and 15 with hookworm) were subjected to molecular detection of STH species. DNA extracts from 97.9% of stools revealed the presence of at least one STH species. The number of amplified DNA extracts from 10 and 20mg of stool was significantly higher (X^2 = 14.6; P = 0.0001) than those of 40 and 80 mg. The "Q5 high fidelity DNA polymerase", the "One taq DNA polymerase" and "Standard DNA polymerase" amplified respectively 97.9%, 54.6% and 34.8% of infected stools. Whatever the STH species, the "Q5 high fidelity DNA polymerase" amplified significantly more stool samples than other polymerases. Single PCR confirmed co-infections of *A. lumbricoides* with either *T. trichiura* or *Necator americanus.* Amongst hookworm infections, 10 and 13 were respectively due to *N. americanus* and *Ancylostoma duodenale*. CTAB-based method ($1.45) appeared 3 times less expensive than commercial kit. The CTAB-based method appears cheap and reliable to extract from 10 or 20 mg of stool samples, the DNA from STHs' eggs. Its combination with the "Q5 high fidelity DNA polymerase" highlighted its ability for the molecular detection of different STH species in stool samples.

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COMPARISON OF MICROSCOPY-BASED METHODS AND QPCR FOR QUANTITATION OF HOOKWORM INFECTIONS IN AN ENDEMIC COMMUNITY IN SOUTHERN INDIA

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Soil transmitted helminths (STH) are associated with a substantial global burden and a high morbidity particularly in children and women of the reproductive age. Sensitive and specific diagnostic methods for accurate assessment of infection prevalence and intensity are essential for monitoring control programs. Conventional microscopy-based methods such as the Kato Katz smear have been the mainstay of diagnosis and although they are simple and cost-effective especially in low resource settings, they are sub-optimal due to variability in egg excretion rates, uneven distribution of ova in samples and inability to detect very low intensity infections. Furthermore technical skill and delays between collection and examination also impact results especially for hookworm. Here we compare microscopy-based methods and qPCR with samples (n=52) that tested positive for hookworm by direct microscopy from a previously published cross-sectional community-based survey in southern India conducted between January to March 2017. Kato Katz and McMaster methods were carried out for quantitation of eggs per gram (EPG) and qPCR for the hookworm species *Necator americanus, Ancylostoma duodenale* and *A. ceylanicum* using previously published primers based on high copy number non-coding repetitive DNA sequences. Out of 52 samples, 51 samples were positive for *N. americanus* and 1 sample was positive for both *N. americanus* and *A. duodenale.* The EPG assessed by Kato Katz and McMaster methods showed a good correlation with Lin's correlation being 0.98, 95% CI 0.97 - 0.99. The EPG as assessed by Kato Katz and McMaster microscopy was further compared with DNA concentration (based on Ct values) from qPCR. Both methods individually showed good correlation when compared to qPCR with Spearman correlation being rho (ρ)=0.81, p<0.001 and 0.78, p<0.001 for Kato Katz and McMaster respectively. Knowing the performance of qPCR-based methods in comparison to more widely applied microscopy-based methods will be essential in implementation during larger scale community surveys.

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PREVALENCE, INTENSITY OF SOIL TRANSMITTED HELMINTH AMONG INDIVIDUAL LIVING IN RURAL AREA IN SOUTH OF GABON

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Soil-Transmitted Helminth infection (STH) remain major Negleted Tropical Diseases in sub-Saharan Africa. This study aimed to determine the prevalence, intensity of STH and associated risk factors among rural communities in south of Gabon. A prospective study was conducted between January and February 2020 in five communities in south of Gabon. Faecal specimen were analysed using merthiolate iode formaldehyde solution, Kato-katz and stool culture. The intensity of STH was determined according to WHO recommendations. Data were analyzed using SPSS. STH were the most common intestinal parasites found with light and moderate intensity (62.2%) in studies communities. *A. lumbricoides* prevalence and eggs density were higher in women (50.5%). Participants aged below 45 years were frequently were more frequently infected (69.7% and 71.4%). Antihelminthic self medication was associated with lower *A. lumbricoides* and *N. americanus* (49.7% and 14.7%). *A. lumbricoides* eggs densities significantly decreased with the level of education. STH are highly prevalent in rural settlements in Gabon. The intensification of control strategy intervention is needed to achieve the WHO objectives by 2030.

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PROFILE OF INTESTINAL PARASITES INFECTIONS AMONG PATIENTS IN HEALTH CARE SERVICE IN GABON

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Intestinal parasites infections are still a serious public health problem in poor and developing countries in sub-Saharan Africa. Local epidemiological data is crucial to design and monitor prevention and control strategies. The aim of this study was to determine the profile of intestinal parasites detected in patients consulting in health care service according to lifestyle and demographic factors in Gabon. This was a retrospective study based on records collected from patients having carried out a stool examination at the Department of Parasitology and at the Laboratory of Paul Moukambi Hospital (LPMH). Demographic and socioeconomic data as well as the results of the stools examinations were collected on a standardized sheet. Data from 606 patients were selected during the study period. The age of the patients varied between 16 and 95 years. Intestinal parasites were detected in 69% (n=420) of the patients, of whom more than 80% (n=405) were infected by protozoa. *Blastocystis sp* was the predominant species with (n=214; 51%). *Trichuris trichiura* was only detected in patients from LPMH (n=10) as *Cryptosporidium* (n=1) and *Isospora belli* (n=1). These data underline the predominance of protozoa among the intestinal parasites infections diagnosed in patients, with a high frequency of *Blastocystis sp*. Helminths frequency tends to decline. These data may contribute to adapt control strategies of intestinal parasites infections.

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THE TIMIRI EFFECT OF DEWORMING ON IMMUNE RESPONSES (TEDI) BIRTH COHORT STUDY-UPDATES FROM THE FIRST YEAR

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Community-wide deworming to potentially break transmission of soil-transmitted helminths (STH) in endemic areas could reverse the effects of these infections on host immune responses. In this study, the effect of large-scale, community-wide deworming with albendazole as part of the ongoing cluster randomized trial, Deworm3 in rural communities in southern India (6 rounds of community-wide deworming carried out from February 2018 to November 2020), on immune phenotype and vaccine response will be studied by comparing children born into intervention and control clusters. A birth cohort targeting 250 children each in intervention and control clusters with a three year follow up is currently being established by recruiting antenatal women in the community since November 2020 (n=369 enrolled so far). Inclusion criteria are children born to mothers residing in intervention clusters and recorded to have been treated during at least 4 preceding rounds of deworming and children born to mothers residing in control clusters. The study protocol includes monthly household visits with anthropometric assessments (1841 visits so far), collection of stool samples for assessment of STH and microbiome (every 3 months and at birth with 1269 collected so far) and collection of cord blood and venous blood for immunophenotyping and vaccine response (at 0, 6, 12 and 24 months with 465 samples collected so far). Meta-data on household demographics, socio-economic status, WASH, weaning, illness, immunization status, home environment and, exposure to animals and animal handling behaviors are being collected. Analysis of the impact of community-wide deworming on immune phenotype, vaccine responses, microbiome maturation and nutritional status in the context of covariates including biological (mode of delivery, breast feeding, parity, gestational age, gut inflammation etc) and environmental (such as socioeconomic status, siblings and animal exposures) factors will extend our understanding of host-helminth interactions, their effect on the growth, developing immune responses and microbiome in early childhood.

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HIGH THROUGHPUT PHENOTYPIC SCREENING FOR ANTHELMINTIC DRUG DISCOVERY

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Soil Transmitted Nematodes (STNs; hookworms, whipworms, large roundworms, threadworms) are the most prevalent multicellular parasites of humans, farm, and companion animals. STN infections perpetuate poverty and challenging development via its impact on humans' health especially children and pregnant women. Together, these parasites are responsible for >5 million years lived with disability (YLDs). STN infections are associated with, or leading to growth stunting, cognition impairment, malnutrition, anemia, loss of income, increased rates of school dropout, and weakened immune response to other infectious diseases. The WHO has set forth the ambitious goal to eradicate STNs by 2030 yet we clearly do not currently have the drugs to do so. Clearly, new, and effective drugs with new mode of actions are highly needed to replace those facing drug resistance. A major challenge in the development of new drugs has been a lack of a proper screening pipeline with sufficient throughput. To combat these parasites, we have developed an effective screening pipeline to detect safe and broad-spectrum anti-nematode compounds. Our screening pipeline includes a human hookworm parasite used as a primary screening model followed by screening against an evolutionary distant whipworm parasite. Here we will present a revised screening pipeline and our results in screening >33,000 compounds from known bioactives libraries and diversity scaffolds. Our goal is to define lead candidates for SAR by library. Following screening at single and multiple doses against parasitic adults and cell tox studies in mammalian cells, prioritized compounds were tested for in vivo efficacy. As part of this new STN pipeline, we have to date identified four novel compounds that have significant impact on parasitic infections *in vivo*.

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USING IN-DEPTH PROCESS MAPPING TO IDENTIFY OPPORTUNITIES TO OPTIMIZE MASS DRUG ADMINISTRATION FOR SOIL-TRANSMITTED HELMINTHS

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Several studies are testing the feasibility of interrupting transmission of STH using community-wide mass drug administration (cMDA). Yet, many programs do not achieve coverage high enough to maximize health and economic benefits. The purpose of this study was to develop a detailed understanding of the steps needed to deliver high coverage MDA, how implementation processes change over time, and how closely implementation adheres to baseline plans (e.g. fidelity). This study was embedded within the DeWorm3 Project, a cluster randomized trial testing the feasibility of interrupting transmission using cMDA compared to school-based MDA in Benin, India, and Malawi. Eighteen clusters

participated in in-depth process mapping and were recruited based on having historically high or low coverage. Baseline implementation plans were developed and updated annually to visualize the implementation process and track adaptations and fidelity to implementation over three years. We separately examined fidelity to implementation timelines and targeted benchmarks (ex. number of health workers trained). Descriptive statistics quantified the number of adaptations made and fidelity to activities. Results demonstrated that MDA was implemented with a different cascade of activities in each site. Clusters in India included more activities on average (72) than in Benin (28) and Malawi (31). Most adaptations to baseline plans were made directly after implementation launched but continued over time with less frequency. The average number of adaptations at each round were similar across sites. When comparing programs, cMDA had more activities on average (48) compared to school-based MDA (34) and underwent more adaptations (5 vs 3). Fidelity to baseline implementation plans was higher in sites implementing cMDA. Digitized process maps displayed the cascade of activities necessary to achieve high coverage, and elucidated areas of potential dependency delays and process efficiencies. Process mapping is a simple, low technology tool which can support program microplanning and integration with other campaigns.

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TOXOCARIASIS: AN EMERGING PUBLIC HEALTH CONCERN IN RICHLAND COUNTY, SOUTH CAROLINA?

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Toxocariasis is a parasitic infection caused by intestinal roundworms of either *Toxocara canis* (canine host) or *T. cati* (feline host) and is thought to be the most common helminth infection in the US second to pinworm. Dogs and cats are the principal hosts, but humans become incidentally infected via oral-fecal route, particularly children, through contact with animal fecal-contaminated community parks' soil, playgrounds, and sandboxes. Infections are not frequently considered in the US but were once highly endemic in southern states. Widespread surveillance disappeared with sanitation infrastructure improvements in the early 20th century. Infections are typically asymptomatic or present with non-specific symptomology. Toxocariasis may also resultin cognitive delays and other morbidities, perpetuating cycles of poverty in vulnerablecommunities. Severe infections can occur when larvae spread to vital organs such as the liver, lungs, eyes, or brain. South Carolina's (SC) warm, humid climate coupled with areas of deep poverty and a historically high soil transmitted helminth (STH) burden in humans provides an ideal environment for STH persistence. The focus of this project was to determine the presence of *Toxocara* and other nematodes of public health importance in Richland County, SC. We conducted environmental sampling across 30 parks in Richland County, collecting a total of 300 grams of soil across each site. We performed qPCR to determine parasite presence and load and conducted geospatial analysis via ArcGIS including neighborhood characteristics by zip code. We found parasite DNA present for 3 of 5 STHs in nearly 25% of sampled parks. We found a positive association with seasonality of collection time with higher parasite burden. As expected, we found that Richland County parks in areas of lower socioeconomic status had higher parasite load. Neighborhoods with higher population densities tended to have a higher parasite burden. In conclusion, this project adds evidence for the persistence of STHs in SC. Further studies should be conducted to assess the human transmission risk potential for STHs in SC and across the US.

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THE THERAPEUTIC EFFICACY OF ALBENDAZOLE AGAINST SOIL TRANSMITTED HELMINTHS IN DISTRICTS WITH A VARIED HISTORY OF ALBENDAZOLE MASS DRUG ADMINISTRATION IN NORTHWESTERN TANZANIA

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Towards 2020, the global coverage of albendazole and mebendazole mass drug administration in soil transmitted helminths control reached unparalleled levels. These drugs are administered in a single oral dose which does not achieve 100% efficacy. This has increased the risk of development of anthelmintic resistance. Recent reports from multi-country albendazole efficacy trials have suggested that sites with longer history of albendazole drug pressure have a lower albendazole efficacy. In 2019, we conducted an albendazole efficacy trial in 4 districts with varied history of albendazole mass drug administration in north-western Tanzania. A single Kato-Katz slide was used to determine the efficacy of albendazole against soil transmitted helminths in districts with a varied mass drug administration coverage in 5 years reported on the expanded special project for elimination of neglected tropical diseases database. We screened 3193 primary school children and analysed of 336 complete cases in three out of four districts using the paradrug® efficacy online analysis tool. The efficacy of albendazole against *A. lumbricoides* in Muleba district was 96.3% which was satisfactory. The efficacy of albendazole against *T. trichiura* was -41.2% which was reduced. The efficacy of albendazole against hookworms in Buchosa, Kaliua and Muleba district were 95.5%, 99.3 and 85.5% which were satisfactory for Buchosa and Kaliua and doubtful for Muleba. There is a statistically significant difference in the efficacy of hookworm between Muleba and Buchosa district (P <0.023) and between Kaliua and Muleba (P< 0.001). The efficacy of albendazole against *T. trichiura* is reduced highlighting the need to evaluate new drugs or drug combinations for *T. trichiura* mass drug administration. Results also show a difference in albendazole efficacy against hookworms in the different districts in Tanzania. Muleba district where reduced albendazole efficacy against hookworm is reported had the fewest years history of albendazole use. We are currently applying molecular genetic tools to preserved hookworm ova samples from this trial to explore the cause of these differences.

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GENOMIC ANALYSIS OF *TRICHURIS TRICHIURA* USING OXFORD NANOPORE TECHNOLOGY

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Trichuriasis is a prevalent human whipworm infection caused by a soil-transmitted helminth (STH) *Trichuris trichiura*. In South Korea, the prevalence of soil-transmitted helminthiasis was higher than 60% in the past, but has been curved down to less than 1% prevalence since 1992 and they are considered to be close to elimination of infections. However, unlike other STH infection, the trichuriasis is relatively persistent with prevalence as low as 0.4%. Whipworms show high host specificity in parasitism but recent evidences show cross-infection among different hosts. This then raise the need to perform genetic analysis to better understand the genetic relationship particularly in areas where infection persist although human to human transmission is less likely. Here we report the first Korean *T. trichiura* complete mitogenome sequenced using Oxford Nanopore Technology. This circular complete mitogenome

of *T. trichiura* is 14,451 bp in length. A total of 36 predicted genes were identified and contains 13 protein-coding genes (PCGs), 21 transfer RNA (tRNAs) genes, two ribosomal RNA (rRNA) genes (*rrn*S and *rrn*L), and two non-coding regions. Comparative variant detection and phylogenetic analysis using cox1 and ITS genes confirmed the distinct molecular identity of the newly assembled mitogenome. More importantly, the assembled AT-rich region was 6 times longer than previously published reference mitogenomes and showed high genetic relationship with an unpublished Japan reference sequence. This results emphasize the advantage of third generation long reads (>10kb) sequencing in terms of repeats resolution over the second or next generation short reads (<500bp) sequencing. Using the ONT long-read sequencing this study provided a high-quality complete mitogenome of *T. trichiura* isolated from Korean individual. This new reference mitogenome would be fundamental in understanding the evolutionary relationship, transmission, and diagnostics of key nematode taxa which in turn can be used to come up with better policies that will help control and eliminate these important human parasitic infections.

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GEOGRAPHIC SCREENING FOR CHRONIC PARASITIC INFECTIONS PRIOR TO KIDNEY TRANSPLANT: AN INSTITUTIONAL EXPERIENCE IN A NON-ENDEMIC AREA

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With increasing human mobility, it is important for transplant programs to consider chronic parasitic infections in their patient populations. Currently it is recommended to screen for strongyloidiasis, schistosomiasis, and Chagas disease prior to transplant in the presence of epidemiologic risk factors. Our objective was to evaluate implementation of a parasite screening protocol prior to kidney transplant at a health system in a non-endemic region that serves a large proportion of foreign-born patients. Candidates listed for kidney transplant at Hennepin Healthcare (Minneapolis, MN) between 1/1/2010 and 10/15/2020 were identified using an institutional FileMaker database (Cupertino, CA) and included in the retrospective cohort. Country of birth and serologic screening for strongyloidiasis, schistosomiasis, and Chagas disease were obtained from the electronic medical record with data collection facilitated by REDCap. Frequency of parasite screening and seropositivity was assessed prior to and following implementation of a geographic risk factor-based screening protocol on 7/1/2014 with all analyses performed with R Statistical Software (v4.1.3). Of 907 kidney transplant candidates, 550 (61%) were male, and the mean age was 49. There were 312 (34%) born in the US and 232 (26%) born outside the US, with the remainder missing country of birth information. There were 460 candidates prior to the protocol and 447 following. Following the protocol, fewer candidates had an unknown country of birth (53% to 27%, $p < 0.001$) and screening rates for strongyloidiasis, schistosomiasis, and Chagas disease increased (14% to 44%; 8% to 22%; and 1% to 14%, respectively, $p < 0.001$ for all). There were 14 (7% of screened) candidates seropositive for strongyloidiasis after protocol implementation versus 2 (3%) prior; and 11 (11%) seropositive for schistosomiasis versus 1 (3%) prior. None were seropositive for Chagas disease. Implementing a protocol to screen kidney transplant candidates using geographic risk factors can increase identification of country of birth and chronic parasitic infections in a non-endemic region.

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AN EVALUATION OF MASS DRUG ADMINISTRATION CAMPAIGNS FOR SCHISTOSOMIASIS AND SOIL TRANSMITTED HELMINTHIASIS IMPLEMENTED AFTER COVID-19 LOCKDOWN WERE LIFTED IN TAKUM, NORTHEAST NIGERIA

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Following the recent lifting of COVID-19 lockdown order in Nigeria, mass drug administration campaign (MDA) was implemented in Takum, Northeastern Nigeria, for schistosomiasis (SCH) and soil-transmitted helminthiasis (STH). This study therefore evaluated implementation coverage and associated bottlenecks, with the aim of providing evidence that would inform decisions to strengthen MDA towards elimination targets. We adopted the WHO coverage evaluation survey methodology, involving administration of standardized questionnaires to school-aged children (SAC) and adults across thirty communities. Consenting participants were interviewed in local Hausa language, if they were offered mebendazole (MEB) and praziquantel (PZQ), and if they swallowed it. Reasons why medicines were not offered and swallowed was documented. Data were collected electronically and analyzed. 1757 respondents comprising 1015(57.8%) SAC and 742(42.2%) children/adults above age 15 were recruited. For STH, 44.24% (449/1015) were offered MEB and 41.97% (95%CI: 31.95-52.69) swallowed the medicine, with a compliance of 94.86%. Similarly, for SCH, 53.36% (937/1757) were offered PZQ and 50.28%, (95%CI: 41.13-59.42) swallowed it, with a compliance of 94.19%. Only 30% (9/30) and 20% (6/30) of the communities surveyed met the minimum threshold of 75% PZQ and MEB coverage, respectively. Reasons why medicines were not offered or swallowed were; (1) absenteeism during the MDA, (2) drug distributors never came, (3) fear of adverse reactions and (4) not having enough information about the medicines. Our evaluation showed unsatisfactory coverage rates which were significantly lower than the administrative reported rates for STH (99.27%) and SCH (74.76%). This result raises concerns about the reliability of programmatic data collected following the lockdown era, and highlight the need for data quality assessment and retraining of drug distributors. Other measures targeted at increasing compliance using health educational campaigns, improving the timing of intervention and motivation of drug distributors are also suggested.

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INTESTINAL PARASITE INFECTIONS AND HEALTH HABITS AMONG SCHOOL CHILDREN IN NIBO COMMUNITY, AWKA SOUTH LOCAL GOVERNMENT AREA, ANAMBRA STATE, NIGERIA

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Intestinal parasitic infections are the major causes of high morbidity and mortality especially in children in tropical areas where poor sanitation provides conducive environment for their development and transmission. This study was to determine the prevalence of intestinal parasites and health habits among primary school children between the age 0 to 15 years, in Nibo, Awka South L.G.A., Anambra State, Nigeria. Six schools were randomly selected. Kato-Katz technique was used for parasite identification. Information on health habits of the children were collected using pre-tested questionnaires. Data were analyzed using Chi square. Of 319 pupils examined, 73(22.9%) were positive with Ezinwankwo school 19(47.5%) having the highest prevalence and Olive Child school 7(14%) the least which is significant [P=0.000; P<0.05]. *Ascaris lumbricoides* 53(72.6%) was the highest parasite species recorded while

Trichuris trichuira 3(4.1%) had the least. Prevalence among occupation was significant [P=0.008; P<0.05] with the children whose parents were Farmers 22(34.9%) having the highest prevalence while Civil Servants 17(13.9) had the least. Prevalence in relation to health facilities was significant [P=0.027; 0.000; P<0.05] with those using borehole 22(55.6%) as source of water and children defecating in the bush 28(45.2%) having the highest occurrence of infection while those using well water 24(26.7%) and those using water system 19(11.1%) having the least. Teachers and parents need to improve the healthy living of the pupils through health education and periodic deworming exercise and government should provide more facilities to encourage the hygienic lifestyle of the pupils in the school environment.

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DEFINING OPTIMAL IMPLEMENTATION PACKAGES FOR DELIVERING COMMUNITY-WIDE MASS DRUG ADMINISTRATION FOR SOIL-TRANSMITTED HELMINTHS WITH HIGH COVERAGE

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Emerging evidence suggests that community-wide mass drug administration (MDA) may interrupt the transmission of soil-transmitted helminths (STH) in some settings. To support potential policy changes for STH delivery (e.g., transition from school-based to community-wide MDA), more evidence is needed to understand best practices for effective delivery of an expanded MDA platform. This information could enhance NTD operational guidelines by identifying which activities are most essential for achieving high coverage or how they work together to produce effective intervention delivery. We applied coincidence analysis, a novel cross-case analytical method, to identify the various necessary and/or sufficient combinations packages (i.e., implementation pathways) that result in high coverage of community-wide MDA for STH. Our analysis used process mapping data from the implementation science research component of the DeWorm3 Project, a hybrid cluster randomized controlled trial assessing the feasibility of interrupting STH transmission using community-wide MDA in Benin, India, and Malawi. Our analysis included activities related to drug supply chain, implementer training, community sensitization, intervention duration, and implementation context. We used pooled implementation data from three sites and six intervention rounds, with study clusters serving as analytical cases (N=360). Across all three sites and six intervention rounds, efficient duration of MDA delivery (within ten days) singularly emerged as a common and fundamental component for achieving high MDA coverage, particularly when combined with having a conducive implementation context, early arrival of albendazole before the planned start of MDA or a flexible community sensitization strategy. No individual activity proved sufficient by itself for producing high MDA coverage. Effective MDA delivery can be achieved with flexible implementation strategies. Findings can be used by MDA implementers and policymakers in STH-endemic countries to support effective implementation planning and delivery.

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ASSESSING THE IMPACT OF IVERMECTIN-CONTAINING MASS DRUG ADMINISTRATION FOR LYMPHATIC FILARIASIS ELIMINATION ON SCABIES PREVALENCE IN SAMOA

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Scabies is a common skin disease in Samoa caused by infestation with *Sarcoptes scabei* mite and transmitted by close contact. A localised study of children aged 4-15 years in one district in early 2018 found scabies prevalence of 14.4%, but nationally representative data are limited. Nationwide triple-drug mass drug administration (MDA) for lymphatic filariasis using ivermectin, diethylcarbamazine, and albendazole was conducted in August 2018. Those aged over 5 years received ivermectin, a highly effective treatment for scabies. This study aimed to assess whether the 2018 MDA impacted scabies prevalence in Samoa. We conducted household cluster surveys 1.5-3.5 months (Survey 1) and 6-8 months (Survey 2) after MDA in 35 primary sampling units. We conducted clinical examination for the presence and distribution of scabies-like rash, and estimated scabies prevalence by age groups, gender and region, adjusting for survey design. Multivariable logistic regression was used to assess odds ratios for factors associated with scabies. In Surveys 1 and 2, 2868 and 2796 persons aged 0-75 years were examined in 499 and 544 households, respectively. Adjusted scabies prevalence increased between the surveys for all ages from 2.4% (95% CI 2.1-2.7%) to 4.4% (4.0-4.9%), especially in those aged 0-4 years (from 6.5% [5.6-7.5%] to 11.1% [9.3-13.1%]). Scabies was associated with younger age (adjusted odds ratio (aOR) 3.5 [2.9-4.2] for 0-4 years compared to 16 years and older), male gender (aOR 1.3 [1.1-1.4]), region (aOR range from 1.4-2.5 between regions), larger households (aOR 2.6 [2.0-3.4] in households with >12 people compared to 1-4 people), and not taking MDA in 2018 (aOR 1.3 [1.1-1.7]). Our post-MDA surveys found that overall scabies prevalence was lower than pre-MDA estimates. Our results suggest that ivermectin-containing MDA may have decreased community scabies prevalence, but there was possible increase in prevalence between the surveys. However, limited data on scabies prevalence pre-MDA and differences in study designs limit direct comparisons between studies. Ongoing post-MDA surveillance of scabies prevalence in Samoa is recommended.

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THE NEGLECTED TROPICAL DISEASES AND WATER SANITATION AND HYGIENE DATA MERGE VISUALIZATION FOR EASY DECISION MAKING AND PRIORITIZATION IN TANZANIA

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In Tanzania, the Neglected Tropical Disease (NTD) Control Program coordinated with the Water Sanitation and Hygiene (WASH) Department to understand which districts were facing challenges in both NTDs and WASH. The merging of NTD and WASH indicators to create integrated visualizations within the Ministry of Health system was necessary to

inform the decision-making process when considering focus districts for upcoming interventions. In the Global Strategy on WASH to combat NTDs 2021-2030, the strategy objective 2 indicates the use of integrated data to highlight inequalities and target investments. The data merge was created by a consultant within the National Sanitation Management Information System (NSMIS). In 2020 Helen Keller staff in collaboration with departments focal persons, and consultant selected indicators to create the 32 visualizations. The team worked closely with the department monitoring and evaluation focal persons to generate the range, median, and mean for each indicator, which helped to select high/low cutoffs to provide meaningful visualizations. Four NTD indicators and eight WASH indicators were combined to make 32 joint indicators. A visualization was made for each of the joint indicators, and one final visualization which summarized all 32 joint indicators. In the first iteration, NTD indicators were imported into the database for the visualizations. In 2021, the consultant linked the NTD indicators from the WHO ESPEN website directly into NSMIS, ensuring that the visualizations will update when NTD data is updated in ESPEN. Following the creation of the visualizations, they were presented at a Tanzania WASH-NTDs Forum to share how the data merge operates and to provide feedback for improvements. It was noted that the visualizations which utilized WASH data from schools were not useful, because school WASH data from Ministry of Education portal was not yet linked to NSMIS. This was a key area identified for improvement in the coming year. All visualization that does not include school data will be presented to relevant stakeholders for utilization.

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THE IMPACT OF PRIORITY REVIEW VOUCHERS ON SMALL BIOPHARMACEUTICAL COMPANIES

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Neglected Tropical Diseases (NTDs) are a group of 20 communicable diseases that disproportionately affect 1.7 billion people in Low-and Middle-Income countries (LMICs). They cause immense suffering and significant mortality and morbidity, resulting in 200,000 deaths and 19 million disability adjusted life years (DALYS) lost annually. Despite this, there is a dire shortage of drugs to prevent and treat NTDs, mainly because of the low purchasing power of LMICs. To incentivize biopharmaceutical companies to create drugs for NTDs, the U.S. Congress created the Priority Review Voucher (PRV) program in 2007. The U.S. Food and Drug Administration issues a PRV after the successful review of a drug developed for an NTD. The PRV can then be redeemed to expedite any future drug application review or sold for anywhere from $67 million to $350 million. In 2020, a government audit of the PRV program revealed that it had produced little impact and suggested that more impact could be realized by targeting smaller drug sponsors that could profit from selling them. To test this theory, we conducted a qualitative study utilizing questionnaires to investigate how widely known the PRV program is among smaller biopharmaceutical companies and their sponsors. We also wanted to understand whether knowledge of the PRV program and its benefits is sufficient enough to influence an increase in focus on research and development of diagnostics, vaccines and therapeutics for NTDs. Preliminary results reveal that knowledge of the Priority Review Voucher Program is not widespread among small biopharmaceuticals and their drug sponsors. Results also showed that drug sponsors were particularly interested to learn more about the R&D process for various NTDs as the sale of a PRV could offset some of the high costs incurred during the process of drug production. This study presents an opportunity to provide important information on the impact this policy could have on stimulating an increase in research and development of drugs, vaccines, and diagnostics for NTDs. It also provides evidence to steer R&D advocacy efforts for these diseases in a strategic and impactful manner.

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DATA FOR IMPACT - A REVIEW AND ANALYSIS TO IDENTIFY DATA PRIORITIES FOR THE PREVENTIVE CHEMOTHERAPY NEGLECTED TROPICAL DISEASE (PC-NTD) ELIMINATION SUCCESS IN KENYA

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The NTD program in Kenya is committed to improving data use to control NTDs, ensuring that data is available, accessible and high quality, and is analysed and visualized in a way that informs program functions -resource planning for mass drug administration (MDA), measuring disease burden, planning and implementation of activities and program evaluations. MDA and survey datasets for lymphatic filariasis (LF), onchocerciasis (ONC), schistosomiasis (SCH) and trachoma (TRA) were consolidated. Data from 2015 to 2021 was collated into a centrally managed folder and key NTD variables and indicators extracted. Reporting and variable completeness, timeliness, consistency between key variables and over time were assessed. For available data shared in the original reporting format, consistency of variables collected over time and geographic areas was also assessed (26 key variables were identified and assessed for LF, 2 for ONC, 4 for SCH and 16 for TRA). There is no central data source for NTD data, making collating and assessing data challenging.LF and SCH survey data however was well organized (by year and data type). Overall, reporting completeness and completeness of key variables was high and the LF report had built in calculations for data quality checks. Noted challenges included 1) inconsistent reporting forms across years and administrative units making it difficult to compare key variables over time, 2) targets for SCH in 2015 and 2020 were lower than the number of people reportedly registered or treated during MDAs resulting in program coverage of 104% and 143% respectively, and 3) LF coverage in 2019 was 106% suggesting targets and population denominators need to be updated to reflect current populations eligible to receive interventions. The results highlight the need to improve consistency in data collection and reporting, develop data standards and integrate NTD data into a single database which is linked to the general national public health database, and to improve data quality (specifically to refine population estimates), to ensure effective use of data to target the right people and places with the right PC-NTD interventions.

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MASS DRUG ADMINISTRATION COVERAGE AND DETERMINANTS OF DRUG UPTAKE FOR ELIMINATION OF ONCHOCERCIASIS TRANSMISSION IN ULANGA DISTRICT, TANZANIA

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Ulanga district has been implementing Mass Drug Administration (MDA) against onchocerciasis for the past 20 years. However, there has been limited evidence for transmission interruption while the prevalence of onchocerciasis in both human and vector species has remained persistently high. We conducted a study to assess treatment coverage and explore determinants of drug uptake during the MDA program. A cross-sectional community-based study using a multistage cluster sampling method was carried out in Ulanga District, Morogoro Region from April-June 2019. Study participants were randomly selected from households and

interviewed using a structured questionnaire. Modified Poisson regression was performed to determine independent factors associated with MDA uptake. A total of 502 participants were recruited during the study period with a response rate of 96%. The mean age of the study participants was 37.8 ±15 years, with the majority in the age range of 25-34 years (25.5 %) with females representing 67%. MDA coverage was 68%, 83%, 84% and 79% for Mawasiliano, Uponera, Isongo, and Togo villages respectively. Drug uptake for three villages were below the optimal coverage recommended by WHO (80%) for successful transmission interruption. Being ≤ 24 years old [APR = 3.9(95% CI:1.9-8.3), p < 0.05)]. Living in the village for at least a year [APR = 3.4 (95% CI:2.4-4.8), p <0.05)], and believing IVM prevents onchocerciasis [APR = 13.4(95% CI:2.9-60.9)], p<0.05) were associated with increased chances of ivermectin uptake during MDA. Fear of restriction from drinking alcohol after taking drugs was correlated to decreased drug uptake [APR = 12(95% CI: 2.4-60.9), p<0.05)]. Low coverage of drug uptake indicates that the effectiveness of the MDA activities was not up to the recommended level. These findings highlight the need to intensify the MDA awareness campaign targeting lower compliance groups in the community to reinforce the benefits of ivermectin in onchocerciasis control and address the community misconceptions about MDA.

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COMPARISON OF HOUSEHOLD PARTICIPATION IN COMMUNITY-DIRECTED TREATMENT FOR ONCHOCERCIASIS AND LYMPHATIC FILARIASIS ELIMINATION IN TWO COUNTRIES

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Community participation is a primary pillar in the fight against onchocerciasis, lymphatic filariasis, and other neglected tropical diseases. Community-directed treatment with ivermectin (CDTI) relies on active engagement of community members in the selection of drug distributors and decisions around distribution processes. Expanded investigation nested within routine mass drug administration (MDA) coverage surveys from 2019 to date in Nigeria and Ethiopia explored how households participate in the selection of community drug distributors (CDDs), the selection of distribution locations, and their involvement in MDA. Coverage surveys in 78 districts (34 in Ethiopia, 44 in Nigeria) interviewed 55,892 people from 11,967 households. In both countries, households reported that CDDs were chosen most often by communities (33% in Ethiopia and 33% in Nigeria) followed by health workers in Ethiopia (15%), and village leadership in Nigeria (20%). The location of MDA was decided most often by community members in Ethiopia (24%) and by village leadership in Nigeria (24%), followed by CDDs themselves in Ethiopia (21%) and community members in Nigeria (20%). However, relatively few surveyed households reported participation in choosing CDDs - 36% in Ethiopia and 15% in Nigeria - with substantial regional variation ranging from 1% to 99% of surveyed households, reflecting diverse programmatic histories and orientations. More households in Ethiopia (94%) than in Nigeria (85%) reported at least one household member taking pills during MDA, although the sampling methodology and population may have affected this result. Households that participated in selecting the CDD were much more likely to have at least one person take MDA than those that did not (97% vs. 86%, risk ratio [RR]=1.1, p<0.0001). Household engagement with MDA plays an important role in the success of neglected tropical disease programs, but the nature and degree of that participation is highly varied. Introducing questions on the degree and nature of program participation into routine coverage surveys could be helpful and informative.

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SOCIO-CULTURAL AND MOBILITY FACTORS AFFECTING UPTAKE AND INCREASE OF MASS DRUG ADMINISTRATION COVERAGE AMONG NOMADIC PASTORALISTS IN SOUTH SUDAN

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Consistent high treatment coverage during Mass Drug Administration (MDA) contributes to effective control and elimination of Preventive Chemotherapy Neglected Tropical Diseases (NTDs) in endemic communities. Increasing the participation of pastoralist communities is critical to achieve the NTD targets in South Sudan. Previous MDA data have indicated lower participation of pastoralist communities with no clear evidence for low participation. The study explored the socio-cultural motivators and factors in relation to participation of pastoralist communities in NTD programmes. Using a cross-sectional study design, we collected data from 239 pastoralist community members in five counties through in-depth and key informant interviews, and focus group discussions. We found that nomadic and pastoralist communities' mobility patterns in South Sudan are motivated by search for water, pastures, and livestock disease outbreaks, which in turn influence the access and uptake of MDA. Decision making on health seeking behaviour is largely male dominated, thereby affecting women's participation in MDA and other health interventions. We also found that community members had specific notions and conceptions on the causes and treatment of NTDs. For example, that lymphatic filariasis is caused when one steps on elephants' faeces, trachoma by dust or theft of property, or that soil-transmitted worm infections are caused by overconsumption of food. Similarly, community members also shared their experiences with remedies such as washing the eyes with the cows' urine to treat trachoma. Our study also revealed community member concerns around inadequate information about MDA campaigns, drug expiry, general lack of trust in drug distributors, and concerns around side effects. Perceptions on masculinity that strong men do not need medicines also influenced participation in MDA. These findings reveal that NTD interventions such as MDA require nuanced approach to community sensitization that addresses structural factors such as seasonal mobility, gender norms, traditional leadership structures, and social conceptions on disease and remedy.

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INTERVENTION PACKAGE TO IMPROVE MASS DRUG ADMINISTRATION FOR NEGLECTED TROPICAL DISEASES AMONG MOBILE AND MIGRANT POPULATIONS MALI

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Mobile and migrant populations (MMPs) are highly vulnerable to neglected tropical diseases (NTDs) because of their lifestyle and obstacles faced accessing curative and preventive services, including mass drug administration (MDA). MDA has been recommended for the elimination

of several NTDs. Due to regular movement and poverty levels, MMPs risk being overlooked in MDA which may impede 2030 NTD elimination. This study aimed to develop an intervention package to strengthen current MDA strategies. We conducted a mixed-method study in two districts in Mali with individual in-depth interviews, focus group discussions, and questionnaires to identify current access to MDA. The sample included migrants, internally displaced persons (IDPs), and nomads. The survey tool collected information on participants' movements and their experiences of attending or not the last MDA. Results from 1067 individuals in the baseline sample for their participation in the last MDA: 38.9% (415/1067) migrants, 49.4 % (527/1067) IDPs, 11.7% (125/1067) nomads. Factors associated with access included long-distance, lack of awareness, and absence during MDA. A workshop was organized with stakeholders to develop an intervention package using the data. The package focused on 6 key areas: 1) MMP census prior to start of MDA; 2) information and sensitization through community, religious leaders, and celebrities; 3) identifying contact persons amongst MMPs; 4) targeting of MMPs gathering sites; 5) highlighted shortages of inputs for attention; 6) organization of mini-campaigns dependent on MMP movements. Results in the endline survey demonstrated an increased MDA coverage in the two districts as a result of the interventions. Strengthening NTD control interventions and locally managed surveillance and response mechanisms with health system actors will be more beneficial if MMPs are part of the NTD control and elimination strategy. These innovative strategies linked to multisectoral control mechanisms will contribute to the elimination of NTDs. Recommend to further test and evaluate the process in multiple contexts.

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POST MASS DRUG ADMINISTRATION COVERAGE EVALUATION SURVEYS IN ANGOLA: IMPLEMENTATION AND LESSONS LEARNED AFTER IMPLEMENTATION ACROSS 18 DISTRICTS

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Coverage Evaluation Surveys (CES) are a recognized standardized tool to independently measure coverages achieved after a Mass Drug Administration (MDA) campaign. These surveys, implemented at community level are important to validate reported coverages and better understand processual gaps in MDA implementation. In Angola, 9 CES have been implemented since 2017 in a total of 18 districts. In line with WHO guidelines for these surveys, roughly 1700 children or caregivers are selected per district to report if they took the NTD drugs in the past MDA. Randomly sampled villages are visited and selection of children on site is done using segmentation of areas to be surveyed. Data is cleaned, analysed, and compared against reported MDA coverages. From the 18 districts surveyed, 15 have surpassed the 75% coverage threshold recommended by WHO for effective MDA campaigns, when using CES estimates. CES coverages did not reach the recommended threshold in (Kibala, Cuanza Sul, 2017; Libolo, Cuanza Sul, 2017; Mungo, Huambo, 2021). However, when comparing the reported coverage against the estimates obtained from CES, only 3 reported coverages were validated using the 95% Confidence Intervals from CES estimates (In Kibala, Cuanza Sul, 2017; Cangola, Uíge, 2019 and Bembe, Uíge, 2021). Main reasons reported for not taking the drugs were not being aware of MDA, drug stockouts and fear of drug side effects. Discrepancies between coverages reported and CES coverages are mostly linked to inaccurate denominator (population) data. MoH has been using annual population estimates from 2014 Census which may no longer be accurate. CES are a useful source of information to verify coverages achieved and key issues that may be hindering better MDA implementation.

1104

TRACHOMA AND ONCHOCERCIASIS: THE BURDEN OF NEGLECTED TROPICAL DISEASES IN SOUTH SUDAN

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Trachoma, caused by infection with the bacteria *Chlamydia trachomatis*, and Onchocerciasis, caused by the parasitic worm *Onchocerca volvulus*, are the leading infectious causes of blindness in the world, especially prevalent in developing countries. These neglected tropical diseases are endemic in South Sudan, with an estimated prevalence of 80% and 60% respectively in some communities. Because these infections are common in rural settings and poor communities where access to water, sanitation, and health care is inadequate, the World Health Organization promotes investments in preventing infections with the *Chlamydia trachomatis* through the SAFE (Surgical correction of trichiasis, Antibiotic treatment, Facial cleanliness, and Environmental improvement) strategy and mass drug treatment (MDT) of *Onchocerca volvulus* with ivermectin to reduce and prevent avoidable the diseases. To determine the prevalence of visual impairments caused by trachoma and onchocerciasis, we report on the findings in patients screened at six outreach eye care services in 2019. The sites were in the three regions (2 sites each) in Equatoria (EQ), Bahr El Ghazal (BEG), and Upper Nile (UN). A datasheet was used to collect the relevant variables, including demographics. Data were entered, organized, cleaned, and analyzed using SPSS version 21, and $p<0.05$ was considered statistically significant. 9,032 patients were screened, of whom 4,540 (50%) were in BEG, 3,410 (38%) in UN and 1,082 (12%) in EQ with $p<0.5$. There were 5,239 (58%) females and 3,793 (42%) males. Trachoma accounted for 15% of all causes of eye diseases, with the highest numbers in UN (88%) and EQ (12%). Meanwhile, onchocerciasis accounted for only 9% of cases screened for eye diseases. The highest number of OV was seen in 92% in BEG, with no instances of OV in UN. These results highlight the burden of these neglected tropical diseases in the country, especially trachoma. South Sudan should conduct epidemiological studies to determine the prevalence of the diseases and invest in and expand the SAFE strategy and MDT in the regions affected to reduce and prevent long-term complications.

1105

MOLECULAR DIAGNOSTIC OF *CRYPTOSPORIDIUM* SPP., *GIARDIA DUODENALIS*, AND *ENTEROCYTOZOON BIENEUSI* IN WILD ANIMALS SEIZED BY FOREST AND WILDLIFE SERVICE FROM PERU

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Giardiasis, cryptosporidiosis, and microsporidiosis are three of the most common waterborne diseases worldwide. Pathogens that produce these diseases affect a wide range of hosts, including humans, domestic and wild animals. Also, wildlife trafficking is considered the third most lucrative illegal activity, not only affects the health of ecosystems and populations of wild animals, also can generate outbreaks in humans and livestock due to the closeness that is generated between wildlife and urban/rural life. Given the importance of knowing the diversity of *Giardia duodenalis*, *Cryptosporidium* spp. and *Enterocytozoon bieneusi* that affects our native fauna and the risk that some of these imply in public health due to their zoonotic condition, the aim of this study was to identify molecularly these

pathogens in wild animals seized from Peru. A cross-sectional survey of 396 wildlife animals that include reptiles, mammals, and birds seized by the Forest and Wildlife Service from Peru. DNA was extracted from fecal samples using a commercial kit DNA for soil. PCR-based sequencing was employed, utilizing specific genetic markers: the nuclear ribosomal RNA small subunit (SSU) for *Cryptosporidium*, β-giardin gene for *G. duodenalis* and the Internal transcribed spacer 1 region (ITS-1) for *E. bieneusi*. Of these samples, 11 (2.8%), 14 (3.5%) and 7 (1.8%) animals were positive for *G. duodenalis*, *Cryptosporidium* spp. and *E. bieneusi*, respectively. Only 11 PCR-positive samples could be sequenced. Genotyping of *G. duodenalis* based on β-giardin identified the zoonotic assemblage A in three squirrel monkeys (*Saimiri sciureus*) and one Harris's hawk (*Parabuteo unicinctus*). *Cryptosporidium baileyi* was found in a black vulture (*Coragyps atratus*). *E. bieneusi* sequences identified NCF2 genotype in two parrots (*Brotogeris versicolurus*) and two monkeys (one *S. sciureus* and one *Alouatta seniculus*), Type IV genotype was found in one Harris's hawk (*P. unicinctus*), and a novel genotype was found in a coati (*Nasua nasua*). Our research discovered zoonotic genotypes of *G. duodenalis* and *E. bieneusi* in wild animals seized, raising a significant public health concern.

1106

ESSENTIAL ROLES OF DIVERGENT APICOMPLEXAN ATP SYNTHASE SUBUNITS CONTAINING CHCH DOMAINS

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Apicomplexan parasites include the causative agents of several debilitating global diseases including malaria and toxoplasmosis. Recent work in *Toxoplasma gondii* parasites has revealed that their single mitochondrion, an organelle which hosts essential metabolic pathways, is also a hub of apicomplexan-specific biology. This is exemplified by the ATP synthase: in apicomplexans, over half of the subunits in this energy-generating complex have no homologs outside the phylum. Specifically, the apicomplexan ATP synthase contains proteins with coiled-coil-helix coiled-coil-helix (CHCH) domains, which play integral roles in eukaryotic mitochondria by mediating the function of electron transport chain complexes and mitochondrial morphology. These domains are comprised of specifically spaced cysteine residue pairs in separate α-helices that are oxidized to create disulfide bonds upon mitochondrial import. However, because CHCH-domain proteins have not been identified as part of the ATP synthase in organisms outside the phylum, their role in apicomplexans is unclear. As the ATP synthase is essential for *T. gondii* tachyzoites and *Plasmodium spp.* insect forms, it is critical we advance knowledge of ways it diverges from the mammalian host. To characterize two apicomplexan ATP synthase subunits containing CHCH domains, we generated conditional gene knockdown strains in *T. gondii* and confirmed that both subunits are necessary for tachyzoite survival. Using native gel electrophoresis, mitochondrial volume analysis, and transmission electron microscopy we have shown that these subunits are critical for ATP synthase structure, mitochondrial volume, and cristae density. Current work is focused on evaluating the metabolic importance of these subunits and using exogenous mutant gene copies to determine the role of the cysteine residues in subcellular localization and function. These investigations will elucidate the function of divergent apicomplexan ATP synthase subunits and potentially reveal vulnerabilities that could be targeted by novel drugs against these opportunistic parasites.

1107

*LMJ*PES MAY PLAY A CRITICAL ROLE IN *LEISHMANIA MAJOR* INFECTIVITY

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Leishmaniasis is a neglected tropical disease caused by *Leishmania* spp. The improvement of existing treatments and the discovery of new drugs remain the major goals in control and eradication of this disease. From the parasite genome, we have identified the homologue of the human oncogene *PES1* in *Leishmania major* (*LmjPES*). PES1 is involved in several processes such as ribosome biogenesis, cell proliferation and genetic transcription. Our phylogenetic studies showed that *LmjPES* encodes a highly conserved protein. LmjPES harbours three main domains: PES N-terminus (shared with proteins involved in ribosomal biogenesis), BRCT (found in proteins related to DNA repair processes) and MAEBL-type domain (C-terminus, related to erythrocyte invasion in apicomplexan). We demonstrated the nuclear localization of LmjPES protein. The gene *LmjPES* showed its highest expression level in metacyclic promastigotes. After generating mutant parasites overexpressing *LmjPES*, we observed that these clones displayed a dramatic increase in the ratio of cell infection within macrophages. Furthermore, BALB/c mice infected with these transgenic parasites exhibited higher footpad inflammation compared to those inoculated with non-overexpressing parasites.This work also presents a structure-based drug discovery strategy to validate the BRCT domain of LmjPES as a novel therapeutic target in *Leishmania* spp. The structure of this domain was explored using homology modeling, virtual screening, and molecular dynamics studies. Candidate compounds were validated in vitro using promastigotes of *L. major*, *L. amazonensis*, and *L. infantum*, as well as primary mouse macrophages infected with *L. major*. The novel inhibitor CPE2 emerged as the most active of a group of compounds against *Leishmania*, being able to significantly reduce the viability of promastigotes. CPE2 was also active against amasatigote forms and significantly reduced parasite burden in murine macrophages without exhibiting toxicity in host cells. Our studies suggest new potential therapeutic options against leishmaniasis.

1108

EQUAL CARDIAC TROPISM OF TWO GENOTYPES OF *TRYPANOSOMA CRUZI* IN ZEBRAFISH LARVAE

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Chronic human infection due to *Trypanosoma cruzi* affects mainly heart tissue and less frequently digestive organs such as colon or esophagus. Tissue tropism depends on many host and pathogen factors, such as genetic variability. Seven Discrete Typing Units (DTUs) are described for *T. cruzi*. Several studies have tried to determine an association between TcI infection and heart tissue involvement, and TcII infection and digestive organs implication, but this relationship has not been yet verified. In our research group, the zebrafish model is used in order to study *T. cruzi* motility *in vivo* considering that its transparency allows us to visualize the parasite-host interaction in real time. The goal of this study was to evaluate the possible tissue tropism of TcI and TcII trypomastigotes in the zebrafish larvae model. Fluorescently labelled parasites with either CFSE or FarRed were injected into 48 to 72 hours post-fertilization larvae. Stereomicroscopy was used to acquire videos of the process, and then light-sheet fluorescence microscopy (LSFM) was used to establish the precise location of the parasite inside the zebrafish larvae. Trypsin enzymatic digestion was done in order to determine the presence of labelled parasites by flow cytometry. After TcI injection, trypomastigotes

migrated mainly to atrium, atrioventricular valve and blood vessels. Following TcII injection, parasites also adhered to cardiac tissue, predominantly atrium and atrioventricular valve. However, in some larvae, TcII migrated to the yolk sac extension which will develop into the digestive tract of the zebrafish. When compared TcI to TcII injected zebrafish, a higher amount of TcII trypomastigotes were attached to cardiac tissue. Larvae injected with TcI and TcII simultaneously, had both trypomastigotes DTUs adhered to the zebrafish heart. Lastly, 5 out of 18 trypsin digested larvae had detectable fluorescent parasite. Cardiac tissue tropism was found with both DTUs in this *in vivo* model. Digestive tract tropism was detected in TcII injected larvae. The use of LSFM allows the study of interaction of living organisms in a non-invasively way at high-resolution.

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TRANSMISSION OF AFRICAN ANIMAL TRYPANOSOMIASIS IN THE FOREST ZONE OF GHANA

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The African Animal Trypanosomiasis (nagana) is caused by several species of trypanosome species which results in significant clinical diseases. This consequently leads to huge economic losses. We carried out a cross-sectional survey to investigate the composition of vectors, parasite diversity and intensities in two districts in the Eastern region of Ghana. Cytochrome c oxidase subunit 1 (COI) and internal transcribed spacer (ITS1) dependent PCR assays identified tsetse fly species and trypanosome parasites circulating in the area. A total of 229 tsetse flies, 65 pigs and 20 were sampled. Female and male flies 155 (51.8%) , 74 (32.3%) respectively were collected with biconical traps. The overall vector density of 4.3 flies/trap/day was observed. Typanosome prevalence of 58.9% (95% CI: 52.5-65.1), 46.2% (95% CI: 34.6-58.1) and 0.0% (95% CI: 0.0-16.1) in tsetse flies, pigs and cattle respectively were detected. *Trypanosoma congolense* was the predominant species with a prevalence of 80.7% (95% CI: 73.3-86.5) in flies and 60.0% (95% CI: 42.3-75.4). There was evidence of multiple trypanosome infection with *T. congolense*/*T. simiae* occurring highest with prevalence of 38.0% (95% CI: 30.7-46.9). The parasite prevalence in pigs across the communities was high with significant differences associated between locations (Chi^2 = 28.06, 95% CI: 0.05-0.81, P=0.0009). Blood meal with flies revealed feeding on both domestic *Sus scrofa domesticus* (pig) and *Phacochoerus africanus* (warthog). Tsetse flies in this area remain highly infected with trypanosomes and continue to transmit the parasites to livestock and human populations in the communities.

1110

SEROPREVALENCE AND RISK FACTORS OF *TOXOPLASMA GONDII* IN CHILDREN AGES 0-14 YEARS - NIGERIA

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Human infection with *Toxoplasma gondii,* a unicellular parasite found worldwide, occurs via ingestion of contaminated food or water, undercooked contaminated meat, and congenital transmission. Infection is lifelong and normally asymptomatic; relapse in immunocompromised persons can be fatal. Understanding of the epidemiology of *T. gondii* in Nigerian children is limited. In July – December 2018, a national, population-based survey to assess HIV burden was conducted in Nigeria. Blood samples from selected households were also tested by multiplex bead assay for antibodies against antigens from 19 other pathogens, including SAG2A from *T. gondii.* Multivariate logistic regression analyses of variables associated with seropositivity produced adjusted odds ratios (aOR). Among 31,459 children aged 0–14 years, seroprevalence of SAG2A antibody was 10.9% (95% CI: 10.3–11.4%); all states had evidence of *T. gondii* exposure (seroprevalence range 4.9–28.3%). Seroprevalence was higher among males (aOR 1.11, P=0.019) and increased with age (aOR 1.12, P<0.001). Household factors associated with higher seroprevalence were use of rainwater (aOR 1.61, P<0.001) or surface water (aOR 1.38, P=0.003) and higher wealth quintiles (Q) versus the lowest (2^{nd} Q: aOR 1.32, P<0.001; 3^{rd} Q: aOR 1.85, P<0.001; and 4^{th} Q: aOR 1.73, P<0.001). Lower seroprevalence was associated with improved toilet facilities (aOR 0.80, P<0.001) and owning pigs (aOR 0.55, P=0.002). Higher odds of seropositivity with rainwater and surface water may reflect their contamination by oocytes from the environment. Lower odds seen with improved toilet facilities, owning pigs, and living in a household in the lowest wealth quintile are more difficult to explain. Data on important toxoplasmosis risk factors (e.g., consumption of undercooked meat) not collected in the survey complicate interpretations of these possible associations, which could be explored in future studies. These data present the first national population-based estimate of *T. gondii* seroprevalence in Nigerian children throughout the country and highlight limitations of analyzing data collected for other purposes.

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THE PREVALENCE OF INTESTINAL PARASITES AMONG STOOL OVA AND PARASITE SAMPLES PROCESSED AT TRIPLER ARMY MEDICAL CENTER (TAMC), OAHU HAWAII, 2000 TO 2019

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Infection from intestinal parasites poses a significant health risk to persons living in tropical climates. Little is known about the prevalence of clinically significant intestinal parasites in the tropical climate of Hawaii. This study describes the prevalence of intestinal parasites among stool ova and parasite samples (O+Ps) processed on Oahu, Hawaii and describes demographic factors associated with O+P positivity. Using a retrospective analysis, we evaluated the prevalence of intestinal parasites among O+Ps processed at TAMC between 2000 through 2019 and calculated cumulative monthly prevalence rates per 1000 specimens. Multivariable logistic regression, with 95% confidence intervals (CI), was used to calculate odd ratios (OR) for demographic factors associated with increased odds of O+P positivity. There were 8772 O+Ps, arising from 7972 individuals, included in this analysis. The majority of O+Ps arose from individuals age 18-39 (n= 4012, 46%), males (n=4850, 55%), and family members of active duty military personnel (n=4465, 51%). There were 422 (4.8%) positive O+Ps and the most common parasite recovered was *Blastocystis hominis.* The monthly prevalence of O+P positivity ranged from 34.3 per 1000 to 69.2 per 1000 samples. After controlling for sex and beneficiary category, individuals ages 6-17 years had over two times increased odds (OR =2.44, 95% CI 1.70, p = < 0.001) of a positive O+P as compared to those 0-5 years of age. Beneficiaries from American Samoa had nearly six times increased odds (OR = 5.67, 95% CI 3.11, 10.36, p = < 0.001) of a positive O+P as compared to active duty military members. Our analysis of nearly 2 decades of stool O+P samples processed at TAMC revealed a low prevalence of intestinal parasites among samples. Similar to published studies from temperate climates, we observed a predominance of *Blastocystis hominis,* a parasite for which clinical significance remains unclear. We identified that persons from American Samoa had increased odds of a positive stool sample which likely reflects acquisition of intestinal parasites prior to arrival to Hawaii and may inform preventative strategies in this population.

1112

RISK FACTORS FOR PROGRESSION TO CHRONIC CHAGAS CARDIOMYOPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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About a third of people with *Trypanosoma cruzi* infection develop chronic Chagas cardiomyopathy (CCC), which carries a poor prognosis. Accurate prediction of which individuals will develop CCC remains elusive. We performed a systematic review of the literature comparing characteristics of individuals with chronic Chagas disease with or without CCC. We included cohort studies, case control studies, and randomized trials. This report presents the subset of studies examining age, sex, or parasitic load stratified by clinical form. A meta-analysis of 106 eligible studies indicated that male sex was associated with CCC (Hedge's g: 1.56, 95% CI: 1.07-2.04), and a meta-analysis of 91 eligible studies indicated that older age was associated with CCC (Hedge's g: 0.66, 95% CI: 0.41-0.91). A meta-analysis of four eligible studies did not find an association between parasitic load and disease state. The risk of bias within studies ranged from moderate to high, as assessed by the Joanna Briggs Institute Checklist for Analytical Cross Sectional Studies. The most common limitations were retrospective design and lack of identification of confounders. Our findings are consistent with the fact that most individuals develop CCC 10-30 years after initial infection, as well as the higher risk of cardiac comorbidities among males and older individuals. It is unknown whether cardiac comorbidities synergistically increase the risk of developing CCC. In addition, ischemic cardiomyopathy may be difficult to distinguish from CCC in low-resource settings, which could lead to overestimated prevalence among older males. We did not find an association between parasite load and clinical stage, although our analysis was limited to a small number of retrospective studies, which did not examine parasitic load prior to disease progression. Peripheral parasitemia may also not reflect parasite accumulation in cardiac tissue. In conclusion, older and male patients with Chagas disease appear particularly susceptible to developing cardiomyopathy. Identification and treatment of high-risk individuals with *T. cruzi* infection prior to the development of CCC is key.

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A SCOPING REVIEW OF THE LEISHMANIASES IN KENYA

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The leishmaniases are a group of four vector-borne neglected tropical diseases (NTDs) caused by 20 species of protozoan parasites of the genus Leishmania and transmitted through a bite of infected female phlebotomine sandflies. Endemic in over 100 countries, the leishmaniases put over 1.6 billion people at risk. The four types of leishmaniasis include visceral leishmaniasis (VL) (known as Kala-azar), cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and post-kala-azar dermal leishmaniasis (PKDL). In Kenya, the extent of research on the leishmaniases remains unclear. This knowledge is instrumental in designing appropriate interventions for diagnosis, treatment, and tailoring strategies for elimination. The present study uses the scoping review methodology to determine the state of leishmaniases research and identify existing gaps in Kenya. Online databases including PubMed, Web of Science, Embase, ClinicalTrials.gov, Cochrane CENTRAL, WHO ICTRP, and the Pan African Clinical Trials Registry were searched to identify articles published to date discussing VL, CL, MCL, and PKDL in Kenya. Inclusion criteria: articles about leishmaniasis or NTDs in Kenya, or global research on leishmaniasis and NTDs. A total of 7,486 articles were found. Title and abstract screening was performed to identify studies that discussed the leishmaniases in Kenya or were likely to. 479 articles were selected for the full article review. Full-text screening was performed to identify studies that explicitly discussed leishmaniasis in Kenya. 314 articles were selected for further analysis. The journals with the most articles published include Transactions of the Royal Society of Tropical Medicine and Hygiene (49), East African Medical Journal (37), and Annals of Tropical Medicine and Parasitology (25). Themes most covered were vectors (120), treatment (56), and general epidemiology (47). Additional analysis will analyze the type of leishmaniasis discussed (VL, CL, MCL, PKDL), the type of analysis performed (clinical, epidemiological, etc.), the year published, and more. The review has been registered in Open Science Framework.

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LEISHMANIASIS: DISEASE PATTERN AND RESPONSE TO TREATMENT IN CHILDREN

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Cutaneous leishmaniasis (CL) is endemic in Sri Lanka with nearly one third of the population living at risk of acquiring the disease. Despite its apparent effects in children, there is a dearth of detailed studies on paediatric CL. Country-wide disease incidence data collected from 2001 to 2018 were analysed to investigate the CL distribution. The anthropometric data of 2,379 cases were used to study the age-sex distributions and the age groups affected by CL. Clinical data of 498 CL patients from all 9 provinces from 2016 to 2020 were analysed. There were 15,300 CL cases reported from 2001 to 2018 with 2 disease hotspots in the north-central and southern parts of the country. CL affects all age groups and both sexes though the disease incidence deviated from the census data, in patients <14 years of age, especially boys, with reduced numbers of reported cases. There were 92/498 (18.5%) CL patients under 18 years of age with almost equal male:female ratio (45:47). Highest proportion of patients (43.5%) were in the 11-15 year age group. Majority had single lesions (76.7%) with most on head and neck region (36.3%). Commonest clinical type was ulcers (36.7%) and majority were referred for treatment within 3-6 months of onset of lesions. When compared with adults, occurrence of CL in the head and neck region was higher in children ($p<0.05$). Majority (63.6%) failed to respond to standard weekly intra-lesional sodium stibogluconate (IL-SSG) after 10 weeks of follow up. The highest proportion of treatment failed children belonged to the 6-10 years (38.1%). Childhood CL accounts for a considerable proportion of CL in Sri Lanka, with both sexes affected. Clinical spectrum appears same as in adults, except for the higher involvement of head and neck region in children. High proportion of IL-SSG-failures warrants review of therapeutic protocols. The apparent low case numbers reported in younger age groups, raise concerns of possible underreporting and undiagnosed patients among children, especially boys, which may add to the disease reservoir pool thus contributing to disease spread, hence of potential public health significance.

1115

A CASE SERIES OF AUTOCHTHONOUS CHAGAS DISEASE IDENTIFIED AMONG CALIFORNIA AND ARIZONA BLOOD DONORS

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Chagas disease(CD) is a parasitic infection resulting in cardiomyopathy in 30% of those infected. Few of the estimated 350,000 USA cases have been identified, with low rates of treatment. Early case identification is vital for effective trypanosomal treatment. Increasing interest in autochthonous infection has led to increasing identification of cases acquired within the USA. Due to limited surveillance and physician awareness of this infection, routine blood donation has become a pathway to identify CD cases. This study enrolled 46 individuals screening positive for antibodies to *Trypanosoma cruzi* through respective blood center testing. Consenting participants donated blood samples, completed a lifetime risk-factor questionnaire and home survey, and underwent ECG. A portion of those enrolled consented to allow the study team access to the original blood center *T. cruzi* testing results. Blood samples underwent confirmatory testing at the University of South Carolina (Columbia, SC) and the Center for Disease Control and Prevention (Atlanta, GA). We present three confirmed cases and one probable case of locally acquired CD and participant lifetime risk factors for infection. None of these individuals had Latin American born mothers/maternal grandmothers, >2 weeks travel to an endemic area, prior tissue/organ transplant, and all were born and lived in the USA. Locally acquired CD cases are at particular risk of going undetected and undiagnosed due to the absence of traditionally considered risk factors for this neglected infection. Despite these donors being diagnosed in California and Arizona, several had lived in or traveled to Texas, which has been identified as a potential autochthonous transmission geospatial focus. Physician awareness should be bolstered and access to diagnostic testing increased to aid in diagnosis of both locally acquired and imported cases and clinical management of CD in the USA.

1116

BURDEN OF CRYPTOSPORIDIOSIS IN FAMILIES LIVING IN BANGLADESH DURING THE COVID-19 PANDEMIC

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Cryptosporidium spp are a leading contributor to diarrheal morbidity and mortality in under-5 children worldwide. Cryptosporidium spp are enteric protozoa spread via fecal-oral contact. We have previously demonstrated 40% of children acquired Cryptosporidium infection by age 1 in a birth cohort in Bangladesh. Both diarrheal and asymptomatic Cryptosporidium infection is associated with growth faltering in children younger than two years. There is no vaccine or effective therapy for cryptosporidiosis in young children. Therefore, we aimed to define person-to-person transmission of cryptosporidiosis in a cohort of infants and their families living in an urban area of Mirpur, Bangladesh. From December 2020 to August 2021, we enrolled 100 families with children aged 6-8 months. All household members were surveyed for illness and tested for enteric pathogens weekly. Cryptosporidium was detected in stool via antigen detection. One hundred index children and 242 family members were enrolled. Forty-four percent of index children and 8.2% of family members became infected with Cryptosporidium during the 8-month follow up period. The median duration of Cryptosporidium shedding in stool was 21 days. Two hundred and seventy-two episodes of diarrhea in index children were reported during the follow up period, and the median duration of diarrheal illness was 8.8 days. The majority of Cryptosporidium infections were non-diarrheal, but 37% of infections were associated with diarrhea. Sixty-seven percent of infections in index children were associated with symptoms other than diarrhea including fever (31%), cough (45%), and abdominal pain (2%). The number of Cryptosporidium cases per month were stable except for a spike noted in May 2021, which correlated with a relaxing of COVID-19 related social restrictions, emphasizing the important role of person-to-person transmission in cryptosporidiosis. Our study again established the high burden of cryptosporidiosis in infants in Mirpur. Future directions will include sequencing of Cryptosporidium spp. to evaluate transmission of the parasite between family members and within households.

1117

THE ROLE OF DIHYDROLIPOYL DEHYDROGENASE (DLD) IN THE IMMUNOPATHOGENESIS OF *LEISHMANIA MAJOR*

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Cutaneous leishmaniasis (CL) caused by several species of the protozoan parasite *Leishmania* (including *Leishmania (L) major)*, is a spectral disease ranging from self-healing lesions to chronic disfiguring disease. The current treatment modalities have failed to offer any significant protection against the disease. Dihydrolipoyl dehydrogenase (DLD) is a critical mitochondrial enzyme in eukaryotic cells including *Leishmania* and modulates metabolic activities, thus serving as a promising therapeutic target. The role of DLD in *L. major* immunopathogenesis is unknown. We hypothesize that DLD is a virulence factor and its deficiency in *L. major* will result in an attenuated disease pathology and altered host immune response. To generate DLD deficient *L. major*, a plasmid (pLDCN) containing two short oligonucleotide sequences (guide RNA) complementary to the *DLD* gene in *L. major* was introduced such that upon expression, Cas9 initiates cleavage. Functional validation of *DLD* gene deletion was performed in axenic culture, bone marrow-derived macrophages and in mouse challenge. Deficiency of DLD in *L. major* was confirmed by PCR and *in vivo* by the absence of DLD-specific $CD4^+$ T cells from splenocytes of mice infected with DLD deficient parasites using DLD-specific tetramers. Growth kinetics in axenic culture and macrophages show that deficiency of *DLD* gene products results in reduced proliferation in comparison to wild-type (WT) parasites. Mice infected with DLD deficient parasites did not develop any observable lesion and habor significantly reduced parasite burden compared to WT-infected animals. The frequency of cytokine (IFN-γ and TNF)-producing $CD4^+$ T cells in spleens and dLN of mice infected with DLD deficient parasites was significantly lower than those from their WT-infected counterparts. These findings strongly support the fact that DLD in *L. major* is a critical metabolic enzyme responsible for intracellular survival and its absence alters the quality of the host immune response against the parasite.

1118

PARASITE, MACROPHAGE AND CD8+ T CELLS IN THE PATHOGENESIS OF DISSEMINATED LEISHMANIASIS

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Disseminated Leishmaniasis (DL) is a severe form of *L. braziliensis* infection defined by the presence of 10 up to more than 1,000 skin lesions and is associated with Genotypic differences among isolates of *L. braziliensis*. There is no impairment in T cells response and the inflammatory infiltrate at the lesion site is similar in cutaneous leishmaniasis (CL) and DL. Here we characterize phenotypically $CD8^+$ T cells and the function of monocytes and $CD8^+$ T cells from CL and DL in response to infection with isolates pertaining to both clinical forms of the disease. The percentage of infected cells and parasite load were evaluated by optical microscopy and the respiratory burst, TLRs expression, subsets of $CD8^+$ T cells and cytokine expression were evaluated by FACS analysis. DL isolates infected more monocytes ($P<.05$), induced greater respiratory burst ($P<.01$) and more cytokine production ($P<.05$) compared to CL isolates regardless of the origin of monocytes used (DL or CL). However, TLR-2 and TLR-4 expression were higher ($P<.05$) in monocytes from DL patients compared to CL and viable promastigotes were higher in cell culture supernatants of monocytes

from DL infected with DL isolates. The frequency of $CD8^+CD107^+$ T cells were higher in peripheral blood of DL than CL and the frequency of $CD8^+CD57^+CD107^+$ T cells were higher in blood and tissue of DL than in CL ($P<0.05$). Moreover, when $CD8^+$ T cells were co-cultured with uninfected or infected macrophages increase in the frequency of apoptotic cells ($P<0.05$) were only found in co-cultures of cells from DL. Our results indicate that differences in parasite genotype, macrophages and $CD8^+$ T cells function participate in the pathogenesis of DL.

1119

ASSESSING THE IMMUNOPROPHYLACTIC PROPERTIES OF A NOVEL *TRYPANOSOMA CRUZI* CHIMERIC PROTEIN

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Flagellate protozoan parasite *Trypanosoma cruzi* is the etiological agent of Chagas Disease, that affects over 8 million people around the world. This silent and chronical pathology is the most important parasitic infection of the heart in lower-income countries, where is estimated that represents the principal cause of cardiac disability and mortality among young adults. Despite the scientific community efforts, it doesn´t exist any effective vaccines. Still, the research around vaccines development is improving. In this sense a multi-component vaccine strategy has gained relevant significance. In this work, we constructed a fusion chimeric protein based on two T. cruzi antigens with different goals. On one hand, the N-terminus of Tc52 protein (N-Tc52) develops humoral immune response, and in the other hand a well-characterized epitope of TS protein, TSKB20, possess immunodominance in cellular response against the parasite. Firstly, N-Tc52 was amplified by PCR from *T. cruzi* CL Brener strain and subsequently reamplified to incorporate, with specific primers, two TSKB20 sequences in tandem. Next, this genetic construct was cloned into a bacterial plasmid and finally, we expressed and purified the chimeric protein resulting (N-Tc52/TSKB20). To prove the biological activity of this bivalent antigen, an immunization scheme in mice was diagrammed. Animals were inoculated with chimera protein plus a saponin-type adjuvant 3 times separated between 21 days; controls were added too. Blood was collected before each dose and 21 days after last dose when the half of animals were sacrificed, and spleens were taken to evaluate cellular response. The other half of mice were challenged with a lethal dose of *T. cruzi* trypomastigotes. Parasitemias were recorded twice a week for 25 days to assess vaccine effectiveness. At that point, animals were sacrificed, and hearts, colon and skeletal muscle were taken to measure parasitic load and for histological examination. Remarkably, mice inoculated with chimeric protein were able to control parasitemias and reduce parasitic burden, amastigote nests sizes and immune cell infiltration in target organs.

1120

THERAPEUTIC EFFECT OF HOOKWORM DERIVED ANTI-INFLAMMATORY PROTEINS ON CHAGAS MYOCARDITIS

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Chagas disease, caused by infection with the protozoal parasite *Trypanosoma cruzi*, affects approximately 7 million people worldwide. Parasite persistence causes chronic myocarditis, with increased infiltration of inflammatory cells into the heart, accompanied by increased production of inflammatory cytokines. There are no current antiparasitic drugs that reduce or prevent chronic myocarditis caused by the onset of Chagas disease, thus new therapies are urgently needed. Hookworms are parasitic helminths that induce anti-inflammatory immune responses, including increased CD4+Foxp3+ regulatory T cells and IL-10 production. Hookworm derived recombinant proteins AIP-1 and AIP-2 have been shown to reduce inflammation in mouse models of inflammatory bowel disease and inflammatory airway disease by inducing CD4+Foxp3+ cells and IL-10 production. Therefore, the impact of AIP-1 and AIP-2 on myocarditis was investigated in a mouse model of chronic *T. cruzi* infection. Female BALB/c mice infected with bioluminescent *T. cruzi* H1 strain trypomastigotes for 70 days were treated once daily for 7 days with 1mg/kg AIP-1 or AIP-2 protein by intraperitoneal injection. Control mice were left untreated or treated once daily for 14 days with 25mg/kg aspirin in drinking water. At 84 days of infection, splenocytes, cardiac tissue and serum were collected for evaluation. Both AIP-1 and AIP-2 proteins significantly reduced cardiac parasite burdens, and AIP-2 protein showed a trend toward reduced cardiac cellular infiltration. Both AIP-1 and AIP-2 increased CD8+IFNγ+ and Foxp3+ cells in the spleen, and antigen specific serum IgG. Pilot *in vitro* studies suggest that AIP-1 and AIP-2 inhibit *T. cruzi* invasion of target cells. Ongoing studies are evaluating cardiac specific immune responses. These data suggest that hookworm derived recombinant proteins boost both effector CD8+IFNγ+ cells to reduce parasite burdens, and Foxp3+ cells to reduce inflammation. We conclude that hookworm derived proteins are a potential novel therapeutic treatment for Chagas myocarditis.

1121

SALIVARY GLAND PROTEINS OF *PHLEBOTOMUS ARGENTIPES* AND DETECTION OF ANTI-SALIVA ANTIBODIES BY OPTIMIZED INDIRECT ELISA ASSAY

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Antibody responses against salivary proteins are promising biomarkers of sandfly exposure in human & animal reservoirs. Studies on immune responses against salivary proteins of *Phlebotomus argentipes* are lacking & a specific assay is important to measure the antibody response. The present study aimed to characterize the proteins of salivary gland homogenate (SGH) of *Ph. argentipes* & to optimize an indirect ELISA assay using crude SGH. Salivary glands were dissected from female sandflies (5-7 days old) & placed in phosphate-buffered saline (PBS). SGH was prepared by sonicating the pellet for 2 minutes followed by 8000 rpm centrifugation for 2 minutes. The checkerboard titration method was used to optimize the indirect ELISA assay. The cut-off value was determined using absorbances corresponding to 20 clinically confirmed cutaneous leishmaniasis (CL) patients & 15 individuals from non-endemic areas. The SGH equivalent to 40 pairs of *Ph. argentipes* (0.2 ug/gland of protein) was further analyzed by SDS-PAGE. The selected coating buffer was 0.01 M carbonate-bicarbonate, pH 9.6 & 1 µg of crude salivary antigen per well was used for optimized ELISA protocol. The blocking buffer contained 4% bovine serum albumin in 0.01M PBS with 0.05 % Tween 20 & 1/200 serum as the primary antibody. Goat Anti-Human IgG at 1/1000 was the secondary antibody dilution. Estimated cut-off was 0.162 at 90.0 % test sensitivity & 100 % test specificity. In SDS-PAGE, 12 protein bands were observed with molecular weights ranging from 14 kDa to 48 kDa. Detected protein bands size of ~14 kDa and ~33 kDa were highly expressed in SDS-PAGE & similar to the size of PagSP07 & PagSP09 proteins respectively. Other protein bands were common to the reference protein profile of *Ph. argentipes* except for three bands of ~36 kDa to 39 kDa are likely to be salivary apyrase. The applicability of the ELISA assay as a tool to assess vector exposure should be validated in a larger population in different endemic settings. Identification of the most immunodominant proteins associated with the human serological response by western blot would expand the further characterization of salivary proteins.

1122

UPTAKE AND DETERMINANTS OF RABIES PRE-EXPOSURE PROPHYLAXIS AMONG AT-RISK TRAVELERS

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Rabies pre-exposure prophylaxis (PrEP) can be given before travel and simplifies post-exposure prophylaxis (PEP). We studied the knowledge about rabies, the uptake of PrEP, and reasons for deciding for or against PrEP in at-risk travelers. We also examined how healthcare professionals (HCPs) counsel on rabies prevention. On behalf of Bavarian Nordic, Ipsos MORI conducted two online surveys in the USA. Fieldwork from February 24th to April 23rd 2021:•689 participants aged 18-85 years, visited one of 91 rabies endemic countries in the past 3 years for at least 1 week, involved in at least 1 of 7 at-risk activities, heard of rabies, positive towards vaccination and chose to take part (surveyed travelers). 76 HCPs, with responsibility for advising/ making decisions about vaccination requirements for their patients, personally recommend or prescribe vaccines for rabies, positive towards vaccination and chose to take part (surveyed HCPs). A minority (36%) of surveyed travelers classified rabies as a life-threatening disease. A third of surveyed HCPs (37%) did not discuss rabies vaccination with at-risk travelers, 18% discussed only PEP, 23% only PrEP and 22% both.A minority (21%) of surveyed travelers reported to have received rabies vaccination since they were 18. Among those participants (n=145), the most common reasons for deciding to get PrEP were for their own peace of mind (35%) and following an HCP recommendation (32%).Of those who decided not to receive the rabies vaccine (n=319), the most common reasons were that they did not think their risk of rabies was sufficient (23%) and that the HCP did not suggest it (23%). The survey demonstrated knowledge gaps around rabies and low PrEP coverage among surveyed travelers. It also highlighted the role of HCP recommendation and showed that most HCPs did not discuss PrEP with at-risk travelers.

1123

MODELLING MODIFIABLE FACTORS ASSOCIATED WITH THE PROBABILITY OF HUMAN RABIES DEATHS IN NIGERIA IN THE CONTEXT OF SPARSE DOG BITE SURVEILLANCE DATA

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Rabies is a vaccine-preventable zoonotic disease with a substantial global burden. In Abuja, Nigeria there have been multiple rabies outbreaks, with associated human deaths. However, the lack of quality data on human rabies hinders advocacy and resource allocation for effective prevention and control. We obtained 20 years of dog bite surveillance data across 19 major hospitals in Abuja, incorporating epidemiological and ecological covariates. To overcome the challenge of missing data, we used a novel Bayesian approach with expert-solicited prior information to guide multiple imputations for missing data to model the additive effects of the covariates on the predictive probability of death after rabies virus exposure (RABV) exposure. Of 1,155 dog bite victims reported, 4.2% (n=49/1155) died of rabies. The odds for risk of death were predicted to decrease among individuals who were bitten by owned dogs (OR= 0.230,95% CrI: 0.075- 0.683) compared to those bitten by free-roaming dogs. Similarly, there was a predicted decrease in the probability of death among victims bitten by owned vaccinated dogs (OR= 0.111 (95% CrI: 0.021-0.447) compared to those bitten by unvaccinated dogs. The odds for the risk of death after bitten individuals received at least one human rabies vaccine were predicted to decrease (OR=0.001, 95% CrI: 0.0001-0.008) compared to zero doses. This study highlights the importance of human post-exposure prophylaxis (PEP), canine vaccination, and responsible dog ownership in preventing human rabies deaths. It underscores the need for more innovative strategies to manage free-roaming dogs and the urgency to advocate for responsible dog ownership to avert rabies fatalities. Our analytic pipeline demonstrated the practical application of a Bayesian approach to model sparse dog bite surveillance data to uncover risk factors for human rabies with broader applications in other endemic rabies settings.

1124

SNAKEBITE ENVENOMATION IN BURKINA FASO, PROSPECTIVE STUDY ON THE DESCRIPTION AND ECOLOGICAL PARAMETERS OF SNAKES IN THE HAUTS BASSINS REGION FROM 2019 TO 2020

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Snakes are very common in the world. In Burkina Faso, some ophidian species are incriminated in envenomation accidents with sometimes fatal outcomes during inappropriate encounters with humans. Despite the existence of old data on Burkina, there are still very few updated herpetological data. A community-based surveillance of snake species involved in envenomation was conducted in 10 health areas of the Hauts-Bassins region. A cross-sectional collection of snake specimens was conducted from January 2019 to December 2020in ten health areas of the Hauts-Bassins region. The collection was done on specimens of snakes killed and brought to the primary health centers. Collected specimens were identified morphologically to determine the species composition of ophidian species circulating in the region. We recorded 124 individuals of 28 species in 18 genera from the Hauts-Bassins area of Burkina Faso and the most common species were *Echis ocellatus* and *Naja Kakiensis.*Of the124 specimens, we collected 48.38% (60/124) during field work, 39.51% (49/124) in homes, 6.45% (8/124) during travel and 5.64% (7/124) during road traffic. The venomous species collected were 45.97% (57/124) with a predominance of those of the family *Viperidae* which represented 59.64% (34/57) of specimens. Of the 124 individuals collected, 17 were responsible for biting accidents. The other 107 were killed either by fear of being bitten in inappropriate encounters with humans, or by road traffic accidents. Considering the nychthemeral moment of collection, the species were abundantly obtained during the day,83.06% (103/124) between 06h-18h against 16.93% (21/124) at night between 19h-05h in the morning. The present study characterized the species of ophids circulating in the 10 health areas of the Hauts-Bassins, revealing an exceptional herpetological richness of the region with28 species recorded.

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HIGHLY-MULTIPLEXED SEROLOGY FOR NON-HUMAN MAMMALS

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Emerging and re-emerging infectious diseases represent a serious and ongoing threat to the human population. However, we do not know which viruses pose the greatest future risk, which complicates efforts aimed at prevention and mitigation. One thing we do know is that the vast majority of (re-)emerging viruses are maintained in stable relationships with other species of animals, and emergence within the human population results from cross-species transmission facilitated by close contact between humans and animals. Therefore, if we want to be prepared for the next emerging virus, we need to broadly characterize the diversity and ecology of the viruses currently infecting other animals (i.e., the animal virosphere). High-throughput metagenomic sequencing has accelerated the pace of virus discovery by facilitating deep, agnostic characterization of nucleic acids. However, molecular assays can only detect active viral infections and only if virus is present within the sampled fluid or tissue at the time of collection. In contrast, serological assays measure long-lived antibody responses to infections, which can be detected within the

blood, regardless of the infected tissues. Therefore, serological assays can provide a complementary approach to understanding the circulation of viruses within captive and wild animal populations, and while serological assays have historically been limited in scope, recent advancements now allow 1000s to 100,000s of antigens to be assessed simultaneously using <1 µl of blood (i.e., highly-multiplexed serology). Application of highly-multiplexed serology for characterization of the animal virosphere is dependent on the availability of reagents that can be used to capture or label antibodies of interest. Here, we demonstrate the potential for commercial immunoglobulin-binding proteins to facilitate highly-multiplexed serology in various species of mammals and we describe a competitive FLISA assay that can be used as an initial screen for choosing the most appropriate capture protein for a given host species.

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HUMAN-ANIMAL CONTACT NETWORKS: A NOVEL AND POWERFUL TOOL FOR ZOONOTIC DISEASE PREPAREDNESS AND RESPONSE

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The rapid emergence of SARS-CoV-2 from a presumed animal origin has demonstrated once more the importance of emerging zoonotic diseases, and key knowledge gaps surrounding zoonotic disease emergence. As demonstrated by SARS-CoV-2, as well as ebolavirus, SARS-CoV, and MERS-CoV, and others before it, zoonotic diseases spillover into human populations along complex network involving animal and human hosts. Originating in sociology, the utility of network analysis for infectious disease transmission modeling has been repeatedly demonstrated. Network centrality is an important predictor of disease burden for both human and animal diseases, including zoonotic diseases, however to date these analyses have been limited to human-only or animal-only disease networks. Elucidating the structure of human-animal zoonotic disease networks is a potentially powerful addition to refining both surveillance and intervention deployment for early detection of and rapid response to zoonotic disease outbreaks. We will present methods to model animal-only and human-only networks, and insights arising from these methods. We will conclude by presenting an approach to measuring human-animal networks, along which zoonoses are transmitted, using a combination of wearable technologies (GPS loggers and proximity sensors), modeling, and self-report, among pastoralist communities in Mongolia and Kenya.

1127

IMPLEMENTATION OF THE ONE HEALTH APPROACH AND PLASTIC WASTE MANAGEMENT IN AFRICA: ISSUES, CHALLENGES AND PERSPECTIVES

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In Africa, as in developing regions, the issue of plastic waste is poorly known: volume and effects on the human-animal-environment interface for quality of life. The objective is to provide information to decision makers, researchers and partners on plastic waste management capacities and practices. The methodology consists of combined approaches: literature review, interviews and cross-sectional analysis of information. The theoretical framework demonstrates the links between policy, plastic waste management practices and public health actions. In Africa, in addition to recurrent epidemics and conflicts, causing systemic disruptions beyond predictions, the situation of plastic waste remains a major problem. It clogs dams, gutters, roads, provides spaces for wastewater to stagnate, and is a source of pollution to nature by affecting the harmony of the ecosystem. Multiple plastic wastes are harmful. A cross-section of health issues reveals: recurrent health emergencies, low resilience of health systems, and a context of poor plastic waste management. This situation underscores the need to build human, technical, and financial capacity to manage waste for public health. One Health is an appropriate innovation. The challenges and stakes are enormous to guarantee the future. This requires a coherent, pragmatic and participatory approach that is One Health to change the paradigm through policy review, education and information programs, collaboration, training, research and resources. The lessons learned highlighted gaps in approaches and the need to improve waste management through evidence-based problem-solving strategies adapted to the One Health context. The impact of the misuse of plastic waste on the environment, biodiversity, and health is clear. To reverse the trend, strong political will translated into strategic directions, cost sharing and responsibility in promoting good waste management practices and community engagement in the perspective of a culture of change.

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EVALUATION OF THE KNOWLEDGE AND LEVEL OF CONCERN OF RABIES AMONG SOUTH CAROLINA RESIDENTS FOR APPROPRIATE PUBLIC HEALTH EDUCATION PROGRAMS

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Animal rabies cases have recently increased in South Carolina. Since the last human rabies case in 2011, the state population's awareness about rabies has not been evaluated, potentially underestimating the rabies transmission risk to humans. An understanding of community disease perceptions is needed to tailor public health interventions. Using a marketing list-serv of South Carolina residents' email addresses, we recruited anonymous respondents to answer a Knowledge, Attitudes and Practices 31-question electronic survey. A total of 516 South Carolina residents completed the electronic survey. The survey evaluated knowledge on topics of rabies biology, state prevalence, and rabies pet-related laws; concern was evaluated at the community and personal level; and finally, there was an assessment on rabies-related practices for pet owners. Quantile regression and Pearson's correlation evaluated the potential associations between respondent's rabies knowledge and their attitudes and practices. Level of concern and level of knowledge showed to be positively correlated. Geographical Information Systems (GIS) approaches were used to perform state-wide hotspot analysis and a bivariate representation of rabies cases in animals, revealing areas warranting targeted public health interventions in the upstate region; counties with low public concern were juxtapositioned with areas of higher animal rabies prevalence. Rabies remains a potential risk for certain rural and urban areas upstate such as Greenville and Spartanburg counties and should not be neglected in the minds of health professionals and public health leaders. The results of this study demonstrate the utility of state-wide KAPs to gauge population's rabies perception and related preventive actions to tailor appropriate educational programs to limit human-animal rabies exposures. Awareness and quality education are pertinent to rabies control and public health efforts should not be neglected.

1129

EXPLORING THE DETERMINANTS AND INDICATORS OF POULTRY FECES MANAGEMENT BEHAVIORS IN RURAL WESTERN UGANDA

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Animal ownership has reported financial and nutritional benefits but has also been associated with enteric and respiratory infections in humans, and inadequate sanitation and hygiene can lead to children touching and ingesting animal fecal matter. We identified key indicators for poultry feces management and investigated their social determinants using data from a baseline survey of a randomized-controlled trial of a poultry management training program in rural Western Uganda. The baseline survey was conducted in September 2019, and data from all participating households who owned poultry (N=609) were used in our analysis. We

evaluated indicators for poultry feces management behaviors using scale development methods, including descriptive statistics, bivariate correlation analyses, and Factor Analysis of Mixed Data. We also investigated social determinants of key poultry feces management behaviors using logistic and multinomial logistic regression models. We found a significant increase in the odds of having free-roaming poultry for each additional poultry owned (OR = 1.18, P < 0.001). The odds of a household having an observed enclosure for poultry was 5% higher with each incremental poultry owned (OR = 1.05, P < 0.001), and 4% higher with each additional point on the wealth index score (OR = 1.04, P < 0.001). We also found that enclosures were intermittently used. Therefore, constructing them without further intervention likely will not effectively manage animal fecal contamination, and intermittent exposure to pathogens can still present significant health risks. We recommend that future studies on animal feces management measure indicators for corralling and feces disposal practices and evaluate their relationship to enteric pathogen exposure and health outcomes. Insights from this work can inform the development of indicators of poultry feces management behaviors that can be used for monitoring and evaluation purposes.

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ESTABLISHING A DEMOGRAPHIC SURVEILLANCE PLATFORM AS A TOOL FOR IMPLEMENTING THE BOHEMIA CLINICAL TRIAL IN MOPEIA, MOZAMBIQUE

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Many geographical areas of sub-Saharan Africa, especially rural settings, lack complete and up-to-date demographic data, posing a challenge for implementing public health interventions and carrying out large scale health research. A demographic survey has been completed in Mopeia district, located in the Zambezia province in Mozambique and with a surface area of 7,671 km^2, as the foundation to establish a demographic surveillance system in the area. This survey was designed to inform the BOHEMIA (Broad One Health Endectocide-based Malaria Intervention in Africa) cluster randomized trial which will test ivermectin mass drug administration to humans only and to humans and livestock as a novel strategy to decrease malaria transmission. The data collected was used to determine cluster boundaries, as well as to plan and implement the clinical trial activities. The demographic survey was a prospective descriptive study in which data on households, population and livestock ownership was collected. Households were mapped through geolocation and identified with a unique number. The district population was enumerated and assigned a permanent identification number per person, while data on housing, animal ownership, deaths in the last 12 months, proximity to mosquito breeding sites, and malaria prevention tools were collected at the household level. Approximately 25700 households were enumerated and over 132000 people were registered. A description of basic demographic data and socio-economic characteristics of households and population in the Mopeia district is presented along with data from the first year of enhanced malaria surveillance at health facility level.

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TRANSFORMATION OF IVERMECTIN AND 3-O-DEMETHYL IVERMECTIN IN SOILS: IMPLICATIONS FOR ENVIRONMENTAL IMPACT OF IVERMECTIN MASS DRUG ADMINISTRATION

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The use of ivermectin (IVM) mass drug administration in human and livestock populations is under investigation for its potential use as a novel vector control tool for malaria. Recognizing that IVM administrated to human and livestock and its subsequent biological metabolites enter into the environment via excretion, we must consider the environmental fate and impact of these compounds. Studies on environmental fate and impact of ivermectin have been conducted in the temperate regions. However, regional differences such as soil types and climate can individually and collectively influence the fate and impact of ivermectin. Photodegradation experiments were conducted for IVM and 3-O-demethyl ivermectin, a common IVM biological metabolite found in cattle manure. Both compounds were spiked at 1 µg/g into a North America soil and East Africa soil and exposed to natural sunlight for up to 3 days at 3 different temperatures and 10, 15, and 20% soil water contents. Top 5 mm soil and the soil below 5 mm were collected at 6 different time points during each photodegradation experiment, quantified for IVM and 3-O-demethyl ivermectin, and identified for their transformation products using liquid chromatographic instrument coupled with mass spectrometry. The transformation kinetics and pathways of both compounds in both soils under different conditions were characterized and compared. Both compounds in the top 5 mm surface soil rapidly photodegraded following the 1st order kinetics with half-lives ≤ 5 h and had faster degradation rates in the East Africa soil compared to the North America soil. Because sunlight does not penetrate beyond 5 mm soil depth, the degradation rates of both compounds were significantly slower, with < 40% degraded at 40 h and ceased to further degrade thereafter. The relative short half-lives found for the thin layer of surface soil exposed to sunlight suggest that mass usage of ivermectin in the field is of limited concern regarding non-target organisms if these compounds do not move to deeper soil profiles. Ongoing studies in the context of mass drug administration for malaria will provide additional data in this regard.

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MEASUREMENT IN THE STUDY OF HUMAN EXPOSURE TO ANIMAL FECES: A SYSTEMATIC REVIEW AND AUDIT

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Exposure to animal feces and associated zoonotic pathogens are important threats to human health; yet significant challenges remain in estimating the burden of disease from such exposures. Challenges are in part due to lack of clarity around and inconsistencies in measurement of human exposure to animal feces, a construct that is multidimensional or has many attributes. The objective of this study is to understand and identify gaps in approaches taken to assess human exposure to animal feces in low-and-middle-income countries, where animals are vital and ownership is promoted through development and nutrition intervention programs. We conducted a systematic review to identify, categorize, and synthesize properties of measures of human exposure to animal feces. We searched peer-reviewed and gray literature databases in April 2021 for articles that included a quantitative measure of exposure. We used a 'best-fit framework' to categorize measures into three components of exposure defined *a priori* (animals, environment, human behavior) and one component that inductively emerged (evidence of exposure). We

synthesized properties of tools by mapping where they fell along the exposure science conceptual framework. Across 162 included articles, we identified 1,305 measures; 83% of studies reported more than one measure (median=5). All but seven measures were single items capturing one attribute of exposure. Microbiology approaches were most common (47%) followed by surveys (37%) and observation (15%). Most (79%) captured information about source (animals) and contaminants (animal feces, animal-sourced pathogens) in the environment, which are most distal from exposure. Our review revealed considerable diversity in measurement approaches that limits cross-study and -setting comparisons, and a lack of validated tools that account for the fact that no one causal condition may sufficiently predict human exposure to animal feces. We offer guidelines for the development of a comprehensive, validated, multidimensional measure that would support improved estimates of the burden of disease associated with human exposure to animal feces.

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OPPORTUNITIES TO INTERRUPT TRANSMISSION OF ENTEROPATHOGENS OF POULTRY ORIGIN IN MAPUTO, MOZAMBIQUE: A TRANSMISSION MODEL ANALYSIS

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The burden of diarrheal diseases remains a critical issue among children in low-income countries, but WASH intervention trials have had limited impacts on diarrhea and child growth. One explanation is that these interventions focus on interrupting one or more transmission pathways (e.g., water and/or environment), while neglecting other critical routes of exposure (e.g., food and/or animals). Therefore, we developed an infectious disease transmission model to compare the contribution of a comprehensive set of transmission pathways related to enteropathogens of poultry origin (direct person-to-person transmission and environmental transmission via food, water, soil, live chickens, and all other sources) and to evaluate the potential impact of interrupting these pathways on human infection. We developed models for *Campylobacter* spp. and non-typhoidal *Salmonella* spp. and employed a sampling-importance resampling approach to estimate pathway contribution based on data from Maputo, Mozambique and WHO estimates of attributable risk by pathway. To identify effective mitigation opportunities, we simulated the prevalence of human infection after reducing each transmission rate. The simulation analysis showed that a reduction in foodborne transmission by 50% and 90% yielded declines in the prevalence of *Campylobacter* infection from 8% (baseline) to 5.8% (95% CI: 4.5-7.5%) and 3.5% (2.6-5.2%), respectively. Similarly, a reduction in foodborne transmission by 50% and 90% yielded declines in the prevalence of *Salmonella* infection from 21% (baseline) to 14.2% (13.0-19.8%) and 9.8% (7.5-14.1%), respectively. Interruption of the remaining pathways did not have a substantial impact. To understand how we can interrupt each pathway, we interpreted these simulation results based on locally collected survey and microbiology data along the poultry value chain in Maputo. Our models capture a comprehensive set of transmission pathways and highlighted the importance of controlling foodborne transmission. Our model can serve as a tool to generate hypotheses on effective mitigation opportunities to control zoonotic enteropathogens.

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STRENGTHENING NATIONAL AND CROSS-BOUNDARY OUTBREAK RESPONSE TO ZOONOSES IN LIBYA USING A ONE HEALTH SYSTEMS ASSESSMENT APPROACH

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Timely response to emerging infectious diseases is dependent on coordination and communication to prevent national and possible cross-boundary spread. In Libya, rapid detection, surveillance, and response efforts are challenged due to the weakened public and animal health systems from recurrent political instability and social conflicts. Through a systems assessment of Libya's public health and veterinary response capabilities, this project aims to determine whether current, vertical disease frameworks can be leveraged to build sustainable national and cross-boundary One Health strategies. In partnership with the Libyan National Centre for Disease Control (NCDC) and the National Centre for Animal Health (NCAH), we deployed our established One Health Systems Assessment for Priority Zoonoses (OHSAPZ) methodology and tool to map existing laboratory and surveillance networks for detecting and reporting priority zoonotic diseases. We then assessed prevention and outbreak management capacities, from index case to notification, at subnational, regional, and national levels. Systems maps were created to identify the intersections between health, veterinary and environmental sectors for communication, coordination, and decision-making, as well as priorities and gaps that limit information-sharing for action. A Memorandum of Cooperation has been established between NCDC and NCAH to support multi-sectoral coordination for zoonoses detection and response, however, execution has been limited due to ongoing national security crises and economic and resource shortages. Assessing current coordination and communication can therefore assist in identifying key areas for capacity building and target actions. We anticipate this project will influence both national and cross-boundary strategies for zoonotic disease response and result in the formal creation of intersectoral One Health rapid response teams to manage zoonotic disease outbreaks in Libya.

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TUBERCULOSIS SEPSIS, CLINICAL FEATURES, TREATMENT OUTCOMES AND MORTALITY RISK: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CASE REPORTS

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Tuberculosis sepsis (TBS) is sepsis due to *Mycobacterium* species causing tuberculosis (TB). It seems to be rare in HIV-negative patients and mainly individual case reports have been reported. We performed a systematic review and meta-analysis of summarises the epidemiology, clinical features, and treatment outcomes of TBS in HIV-negative patients. An electronic search of PubMed, Google Scholar, Embase, and Web of Science was performed to identify published case reports of TBS between 1991 up to February 2022. Of 119 articles screened, twenty-two articles were eligible and reported 25 cases of TBS, among which 56% (14/25) were women; with 48% (12/25) of patients not having reported predisposing factors. A total of 64% (16/25) of patients died, and the diagnosis was obtained for many of them only post mortem. Only 1/25 reports mentioned the BCG vaccination status. A higher proportion of deaths occurred in patients with delayed diagnosis of sepsis. Our review showed TBS occurred in HIV-negative patients and some of them have no known immunocompromised

underlying co-morbidity. TBS might not be rare as clinicians thought but might be prone to be missed. In endemic settings, *M. tuberculosis* etiology of sepsis should be accounted for early irrespective of HIV infection status.

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CLINICAL OUTCOMES AMONG INDIVIDUALS INFECTED WITH SARS-COV-2 IN RURAL ZAMBIA - A LONGITUDINAL STUDY

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The long-term clinical effects of SARS-CoV-2 infection are not fully known and relatively understudied in sub-Saharan Africa. A cohort study of individuals with laboratory-confirmed SARS-CoV-2 infection was initiated in rural Zambia at Macha Hospital in December 2020 after the first case was detected. The goal of this analysis was to describe clinical outcomes up to 12 months after acute infection among participants enrolled between December 2020 and February 2022. Individuals testing positive for SARS-CoV-2 through clinical testing or contact tracing were recruited within two weeks of testing, enrolled in the study, and followed for up to 12 months. Questionnaires were administered and chart reviews were performed at enrollment and on Day 30, 90, 180, and 365 to collect information on demographics, current symptoms and medical history. Overall, 131 participants were enrolled (median age: 33 years [range: 3 months to 79 years]; 44.3% female; 16.7% had received ≥1 dose of a COVID-19 vaccine). At enrollment, 120 participants (91.6%) reported having experienced at least one symptom, with the most common being cough (72.5%), headache (63.4%), fever (57.3%), rhinorrhea (48.9%), and body aches (46.9%). 72 participants (55.0%) had sought care, including five participants (3.8%) who were hospitalized. The proportion of participants reporting at least one symptom was 17.9% at Day 30 (n=112), 16.0% at Day 90 (n=75), 11.1% at Day 180 (n=63), and 18.9% at Day 365 (n=37). One participant (0.8%) was hospitalized after enrollment and died. The proportion of participants returning to normal activities was 77.7% at Day 30, 87% at Day 90, 88.7% at Day 180, and 97.3% at Day 365. In summary, most participants in this cohort of individuals with relatively mild SARS-CoV-2 infections returned to their normal activities within one month of acute infection. However, 10-20% of participants reported persistent symptoms up to one year after infection, which is generally consistent with other studies and demonstrates COVID-19's long-term impact on individual health.

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COVID OPERATIONS CENTER (OPS CENTER) - AN INNOVATIVE ACADEMIC-PUBLIC HEALTH PARTNERSHIP FOR PANDEMIC MITIGATION

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COVID has strained U.S. public health and medical systems, and state and local health departments struggle to contain the pandemic. In Brazos County, Texas, a small county with one of the largest University campuses in the nation, a unique interagency partnership between the county Health District and Texas A&M University (TAMU) had 3 main objectives: (1) augment case investigation capacity, (2) absorb the contact tracing responsibility, and (3) create secure electronic data systems for real-time epidemiologic awareness and analysis and efficient, adaptive mitigation efforts. The COVID Operations Center (Ops Center) leveraged TAMU infrastructure, technology, and students (largely public health undergraduate & graduate students), who received rigorous training by faculty for case investigation and contact tracing. Data collection and management were established in REDCap, with essential data transferred to county and state reporting systems and additional data collected to inform community and campus response. COVID cases were referred by clinical & testing sites through traditional disease reporting or directly to the Ops Center by campus testing sites or the voluntary campus reporting system - a secure REDCap web form to report if sick, exposed, or test-positive. Cases were contacted for phone interviews; close contacts traced via interview or portal entry were managed over a 2-week period for wellness checks and routing contacts-turned-cases back to case investigators. During Jun 2020-Jan 2022 the Ops Center managed >55,000 cases and >22,000 contacts, monitored trends and clusters, and informed prevention, intervention, compliance, and resource needs in the community and on campus. The trained and diverse surge workforce provided testing & vaccination recommendations, isolation and quarantine guidance, and provided reliable COVID information & resources (e.g., food or financial assistance). The portal facilitated data collection, provided public health messages, and automated reporting, enhancing campus operations for safe return to activities on an accelerated timeline compared to other universities nationwide.

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COMPARISON OF THREE PRESENTATIONS OF READY-TO-USE POWDERED 7H9-OADC MEDIUM FOR THE DETECTION OF GROWTH AND SUSCEPTIBILITY TO ISONIAZID, RIFAMPIN, AND PYRAZINAMIDE OF M. TUBERCULOSIS BY THE MODS CULTURE METHOD FROM SPUTUM SAMPLES

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First-line antituberculous treatment is based on the administration of the drugs: rifampicin (RIF), isoniazid (INH), ethambutol (EMB), and pyrazinamide (PZA). The MODS assay (Microscopic Observation Drug Susceptibility Assay) consists of a liquid medium culture that detects the growth of *M. tuberculosis* and evaluates susceptibility to INH RIF from sputum samples. An adaptation of the MODS assay combined with the Wayne test, MODS-Wayne is a phenotypic test that indirectly assesses *pncA* mutations by detecting POA, the enzyme product of PZAse. Currently there are two tests responsible for detecting susceptibility to PZA, which are BACTEC MGIT 960 and the Wayne test. The problem with these tests is their low reliability, difficulty in use and high cost. In order to create a rapid and economical diagnostic kit, through the MODS test in this study, the evaluation of susceptibility to INH and RIF and the evaluation of growth in 3 dehydrated presentations of culture media were carried out: lyophilized, mixed without sterilization and mixed irradiated with gamma radiation. Additionally, to determine resistance to PZA, the MODS-Wayne test was performed using a PZA concentration of 8 mg/ml, the results were compared using a reference standard (MGIT-PZA, pncA sequencing and the Wayne assay). A total of 282 sputum remnant samples from tuberculosis patients with minimal Bk1+ smear microscopy were used. The growth of the cords of *M. tuberculosis* was reported from day 4 and growth was recorded until the second week from the first day of observation. 83 resistant samples were obtained, of which 47 were MDR, 34 resistant to INH and 3 resistant to RIF. It was observed that the growth is not affected by the type differences in the growth of the evaluated media ($p > 0.05$). The preliminary PZA resistance study showed good agreement between PZA resistance and the reference standard (kappa > 0.6). In conclusion, these results show the potential of the MODS-Wayne technique in the evaluation of PZA resistance and also show that both lyophilized, mixed non-sterile and mixed media irradiated with radiation are good candidates for the generation of a diagnostic kit. fast and low cost.

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BACTERIAL PNEUMONIA ASSOCIATED WITH HEALTH CARE IN A HOSPITAL IN NORTHWESTERN OF COLOMBIA, 2017-2019

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Healthcare-associated bacterial pneumonia (HCABP) is pneumonia that develops outside the hospital among patients who have had a recent substantial exposure to the healthcare environment. It is considered as the main cause of death among hospital infections.Considering that the microorganisms involved in this pathology may differ in each care center, it was decided to investigate the prevalence of HCABP and the bacterial agents involved in the Intensive Care Unit (ICU) of the Hospital San Jerónimo de Montería-Córdoba-Colombia, through the carrying out a prospective study, which included patients undergoing mechanical ventilation and staying in the ICU and with mechanical ventilation (MV) for a period greater than 48 hours, who met according to the American Thoracic Society/American Society of Infectious Diseases (ATS/IDSA) the criteria for HCABP and to whom cultures of bronchial secretions or tracheal aspirate had been performed during the years 2017-2019.A total of 70 patients were diagnosed with HCABP according to these criteria. The bacteria isolated and identified by the microbiology area of the clinical laboratory of the E.S.E Hospital San Jerónimo with greater frequency in cultures of bronchial secretions and tracheal aspirates in patients admitted to the adult ICU were: *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, with equivalent percentages at 39.34% and 27.87% respectively, followed in order of frequency by *Acinetobacter baumannii* (16.39%), *Escherichia coli* (4.92%) and *Staphylococcus aureus* (4.92%) of the isolates. The least frequent bacteria found correspond to *Enterobacter aerogenes* (3.28%) and *Burkholderia cepacia* (1.64%) and *Serratia marcescens* (1.64%).Although HCABP has recently been proposed as a new category of respiratory infection, there are limited data to substantiate this assumption. Furthermore, the definition of HCABP varies between studies and includes mixed patient populations. Therefore, it is necessary to carry out more surveillance studies that allow us to know the true magnitude of the problem and design more appropriate intervention strategies to face it.

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ELEVATED PERIPHERAL BLOOD VIRAL LOADS ON ADMISSION TO HOSPITAL PREDICT SEVERE COVID-19 AND MORTALITY IN KENYAN ADULTS

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Novel SARS-CoV-2 virus rapidly disseminated around the globe with efficient human-to-human transmission after first being identified in Wuhan, China in November 2019. SARS-CoV-2 was first identified in Kenya on 11 March 2020 and has since spread to all regions of the country. Factors that influence whether an infection with SARS-CoV-2 will result in severe COVID-19 and mortality are largely undefined in sub-Saharan Africa. As such, we are conducting a prospective observational study in hospitalized patients who reside in a high-burden infectious disease region for HIV-1, tuberculosis, and malaria at Siaya County Referral Hospital, in western Kenya. Complete hematological, laboratory, and clinical values are obtained daily, whereas SARS-CoV-2 viral load dynamics are captured for the upper respiratory tract (URT) and peripheral blood (PB) on days 0, 3, 6, and 9. SARS-CoV-2 viral loads (log_{10} copies/1,000 cells) are quantified using RT-qPCR with N1 and RNase P primers and probes (CDC 2019-nCoV Real-Time RT-PCR diagnostic panel). In the first 192 patients enrolled from 17 June 2020 to date, we found that PB viral loads upon admission are higher in patients who received external oxygen during the course of hospitalization (SpO_2<95%, P=2.16x10^{-6}), those with SpO_2 ≤90% (P=1.28x10^{-8}), and in patients who died (P=9.00x10^{-6}). However, URT viral loads did not significantly differ in the three clinical categories. Logistic regression analyses with age, sex, BMI, steroid treatment, and admission viral load measures in the model revealed that PB viral load levels were a predictor of patients with SpO_2<95% [OR=1.34 (1.01-1.05), P=0.002], SpO_2 ≤90% [OR=1.51 (1.22-1.86), P=1.39x10^{-4}], and mortality [OR=1.37 (1.08-1.68), P=0.008]. Collectively, the results presented here demonstrate that elevated peripheral blood viral load levels on admission are associated with severe COVID-19 and in-hospital mortality.

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PROFILING AUTOANTIBODY SIGNATURES AFTER SARS-COV-2 INFECTION OR COVID-19 VACCINATION UTILIZING HIGH-DENSITY PEPTIDE MICROARRAYS

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Antibodies play an important role in combating a wide range of infectious diseases. However, there is considerable evidence indicating that dysregulated humoral immunity might contribute to immunopathology in various viral infections. Intriguingly, autoimmune diseases and COVID-19 show common immunological features. Molecular mimicry is one mechanism described for viral-induced autoimmunity. It has been suggested that the immune response induced to fight against SARS-CoV-2 may cross-react with human proteins sharing epitope sequences with viral antigens. The goal of the present study was a comprehensive analysis of the epitope-specific autoantibody responses in COVID-19 patients. Moreover, considering the epitope sharing between SARS-CoV-2 and human proteins, epitope recognition in infected or vaccinated individuals was investigated. High-density peptide microarrays are the method of choice to screen large libraries of peptides against serum antibodies. In this study, we examined antibody profiles in patients with a mild versus severe COVID-19 disease progression. For this, we screened sera from COVID-19 patients on peptide microarrays covering 3,723 human B-cell-epitopes associated with autoimmune diseases. Furthermore, sera from infected or vaccinated subjects were analyzed on peptide microarrays displaying described potential cross-reactive epitopes present in SARS-CoV-2 and human proteins. Profiling epitope-specific autoantibody responses of COVID-19 patients with mild versus life-threatening disease progression revealed heterogenous epitope reactivity patterns between the study groups with far stronger autoantibody responses in severely ill subjects. Indeed, we discovered several IgG and/or IgA specific autoantibody reactivities, which were associated with severe COVID-19 disease. Analyzing antibody responses to shared epitopes demonstrated more frequent cross-reactivities in infected than in vaccinated individuals. A detailed understanding of the autoantibody specificities that are induced in response to infection is mandatory for successful clinical management.

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PREVALENCE OF SARS-COV-2 VARIANTS IN VACCINATED AND UNVACCINATED POPULATION IN THE AMAZONAS REGION, PERU

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Several SARS-CoV-2 variants have been reported and classified by the WHO as variants of concern and variants of interests. In this context, genomic surveillance is necessary to monitor how the virus changes over time, to understand how these changes affect the characteristics of the virus and use this information to assess the impact on public health. Peru has reporting to date (March 2022) 3544862 cases with a lethality of 5.98%. Amazonas was severely affected, reporting over 43979 cases with a fatality rate of 3.03%. Here, we aimed to determine changes in prevalence of SARS-CoV-2 variants in samples from vaccinated and unvaccinated patients from the region of Amazonas, one with the highest rate of unvaccinated people. A total of 343 nasopharyngeal swab samples collected between August 28 and February 4 2022 by the Regional Health Directorate were included in the study. Samples reported Ct values lower than 30. Variants were determined using the Ilumina COVIDSeq RUO kits in a NextSeq500 Sequencing System and analyzed using the Illumina DRAGEN COVID workflow. According to the results, the variants detected were Delta (53%), Omicron (28.4%), Gamma (16.3%), Mu (1.5%) and Lambda (0.8%). Of the total patients, 56.6% did not have any vaccine against SARS-CoV-2, of which 4.1% were hospitalized, being Gamma the most predominant variant. Meanwhile, from the vaccinated patients, 4.9% were hospitalized, having a statistically significant relationship with the Gamma variant. It is worth noting that the prevalence of variants has been very changing throughout the pandemic in this region. In August, the predominant variant was Lambda; then Delta increased between September to December, and finally Omicron was present in most of the samples between January and February. Our results agree with the propagation dynamics of the variants that have been reported worldwide. The data obtained was presented in a timely manner to the health authorities so they could take appropriate health policies, including vaccination coverage, to prevent an increase and propagation of particular variants considered to be more virulent and contagious in the Amazonas region.

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FACILITY-LEVEL UPTAKE OF THE NATIONAL POLICY GOVERNING COVID-19 TESTING, QUARANTINE AND ISOLATION IN THE HEALTHCARE WORKFORCE: LESSONS FROM THE NIGERIAN MILITARY HEALTH SYSTEM

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National IPC policies are crucial for protecting health care systems, workers, and clients during the COVID-19 pandemic. It is unclear how well these policies work at facility level. We explore staff exposure, testing, & quarantine patterns to understand national policy implementation in the Nigerian military health system. Four Nigeria Ministry of Defense facilities from Lagos, FCT, & Kaduna, in partnership with the U.S Military HIV Research Program, implemented a staff daily self-screening checklist from January to April 2021. All facilities adopted the national policy on COVID-19 & IPC for healthcare staff that emphasizes Screen, Isolate, and Notify approach. The checklist consisted of yes/no questions about possible COVID-19 symptoms, recent exposures, testing & current isolation or quarantine. We calculated frequencies & proportions for each question by the facility for staff who responded at least once per 5-day week. A "new" episode of symptoms defined as having symptoms after no report in the previous week. Overall, 254 staff self-screened one or more times (51 FCT; 84 Kaduna; 72 & 47 Lagos, respectively). Report of new, symptomatic episodes varied by facility from 18% to 45%. Most episodes occurred in January, coinciding with the peak of Nigeria's second, and largest, COVID-19 wave. Facilities in Lagos reported high recent exposures including suspected or confirmed COVID-19 cases (26 of 47, 55%), but low current isolation or quarantine (6, 13%) & testing (11, 23%). Self-report of current isolation or quarantine was low overall for each facility ranging from 2-13%, with notably fewer staff reporting testing in FCT (2, 4%) & Kaduna (3, 4%). In conclusion, staff isolation or quarantine and testing were infrequent compared to symptoms and potential exposures. Needs to improve IPC operationalization at the facility level by identifying and addressing facilitators and barriers to policy uptake. Safeguarding the military and national health workforce in Nigeria is crucial for protecting clients from hospital-acquired COVID-19 and ensuring continuity of healthcare services during the pandemic.

1144

BACTERIAL AND VIRAL ETIOLOGY OF ACUTE RESPIRATORY INFECTION AMONG THE FORCIBLY DISPLACED MYANMAR NATIONALS (FDMNS) IN FRAGILE SETTINGS IN COX'S BAZAR- A PROSPECTIVE CASE-CONTROL STUDY

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We enrolled a total of 538 acute respiratory infections (ARI) cases according to WHO criteria and age-sex matched 514 controls in the Forcibly Displaced Myanmar National (FDMN) refugee camps in Cox's Bazar, Bangladesh between June 2018 and March 2020 to investigate the role of bacteria, viruses and their co-infection patterns and *S. pneumoniae* serotype distribution. Males were in a higher proportion of 54% and children <5 years were 59.5% of total ARI cases. Collected blood specimens were cultured and AMR was determined where nasopharyngeal swab samples (NPS) were tested for three major bacterial and eight viruses using qRT-PCR, further positive *S. pneumoniae* were serotyped via RT-PCR for 40 serotypes. From the NPS samples, bacteria were detected in 85% cases and 88% control where viruses were more predominant in cases (31%) than control (16%). Children <5 years of age group were the highest risk group than those who were older in s both cases and controls. *S. pneumoniae* was the most often detected in 81% cases followed by *S. aureus* 21.5% and *H. influenza b* 16% where no significant difference was observed between case and control. Adenovirus (7%), influenza viruses (6%), and respiratory syncytial virus (5%) were the most predominant and significantly higher in cases suggesting ARI cases were mostly virus-mediated. Only 3% were found to be positive from blood culture. Serotype distribution showed 30% for PCV10 serotypes, 41% for PCV13, and 59% for other serotypes. Moreover, a negative interaction was seen between viruses and positive interaction between bacteria and viruses. This was common and higher in cases than controls, particularly for those <5 years of age. Additionally, bacterial and viral load was found to be higher in cases than control group considering Ct value <30 as the threshold for high positivity. Logistic regression analysis data showed the prevalence of each pathogen distribution frequency between cases and controls.

Region-specific etiological data particularly for crisis settings is crucial for disease management and disease prevention control as well as vaccination immunization strategies.

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SARS-COV-2 DETECTION AND SEROLOGICAL RESPONSE IN THE FORCIBLY DISPLACED ROHINGYA MYANMAR NATIONALS (FDMN) IN COX'S BAZAR

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SARS-CoV-2 infection causes severe respiratory virus infection with a death rate of 2%-4% and creates a substantial public health issue globally. Since August 2017, over 7,00,000 Forcibly Displaced Myanmar Nationals (FDMNs) entered in Cox's Bazar, Bangladesh. Among the newly arrived, 60% are women and children living in conditions deprived of public health facilities. Refugee camps are highly crowded, have poor health facilities, lack access to water, and poor sanitation and hygiene. ARIs contribute the most mortality and morbidity in FDMNs. The prevailing conditions puts FDMNs at high risk for COVID-19. The aim of this study is to observe the SARS-CoV-2 circulation and the serological response against SARS-CoV-2 in the camps. In this study 194 confirmed SARS-Cov-2 positive primary cases were enrolled along with their household members (n=150) with respective follow-up day points in compliance with the approved protocol and blood and nasopharyngeal swab (NPS) samples were collected on the day of enrollment (Day 0). Blood and NPS samples were collected on day-30 from 114 primary cases and 99 household members and on day-180 and 360 from 100 primary cases only. Real-time PCR was used to confirm the positivity, followed by in-house ELISA to investigate the serological responses against SARS-CoV-2. Till now, 14 primary cases were tested positive again on day-30 and 3 at day-180 follow up. In addition, 17 of the household members were tested RT-PCR positive at the time of enrollment, and 5 at 30-day follow-up. According to the serological testing of 300 specimens (185 confirmed cases and 115 household members), almost 57% of confirmed primary cases and 49% of household members developed IgG antibody response against SARS-CoV-2 at that time. The seropositivity of cases and household contacts are both high at the first time point of testing, suggesting exposure to Covid-19 is high. Further testing will show if this level of antibody persists. Upon completion, this study will show a community-specific scenario of SARS-CoV-2 circulation and seroprevalence status, which would help in better disease management in such humanitarian settings.

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ROLE OF BACTERIA AND THEIR ANTIMICROBIAL RESISTANCE PATTERN IN COMMUNITY ACQUIRED PNEUMONIA IN BANGLADESH

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Community acquired pneumonia (CAP) is a leading cause of death in children and the elderly globally and may be caused by bacteria or viruses. Amongst bacterial pathogens, *Streptococcus pneumoniae, Haemophilus influenzae*, and *Staphylococcus aureus* are predominant causes of pneumonia. In a resource setting like Bangladesh, identifying the aetiology of CAP is challenging, which increases antibiotic misuse and contributes to antimicrobial resistance (AMR). Additionally, *S. pneumoniae* serotypes have changed over time in response to available vaccines and emerging serotypes that are not covered by the vaccine. We are conducting a case-control study to improve our understanding of the bacterial etiology of CAP in hospitalized patients in Bangladesh and the current AMR patterns of isolates. Enrollment of participants began on March 14, 2022 at a tertiary level hospital in Bangladesh. The goal is to enroll 1200 participants from <5 and >18 years (400 patients and 800 control) by 30th October, 2022. The methods used: blood, nasopharyngeal swab (NP), sputum and urine collected from cases and controls. Bloods from cases are cultured using the automated Bact/ALERT system. In addition to culture, level of blood biomarkers (procalcitonin and C-reactive-protein) is estimated to determine the co-relation with the bacterial etiology. NP swabs and sputum samples are cultured. Urine samples are tested to detect recent consumption of antibiotics prior to hospitalization. To date (April 4, 2022), 11 controls and seven cases have been enrolled; all the blood cultures were concluded as growth negative. Among the seven cases, three *S. pneumoniae*, two *H. influenzae* and one *S. aureus* were detected in significant numbers (>10^4 CFU/ml) from NP samples. From NP swabs of controls, *S. aureus, Moraxella catarrhalis* and *coagulase negative Staphylococci, and nonpneumococcal Streptococci were* detected. Ongoing analyses include phenotypic and genotypic AMR characterization of the isolates. Our findings will increase the understanding of the cause of CAP in Bangladesh, the epidemiology of pneumococcus and the AMR patterns of common respiratory bacterial pathogens.

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INTEGRATION OF POINT OF CARE TESTING FOR DIABETES AND HYPERTENSION IN COVID-19 RAPID ANTIGEN SCREENING IN JOHANNESBURG, SOUTH AFRICA

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The COVID-19 pandemic has resulted in the establishment of point-of-care testing(POCT) sites. These sites presented an opportunity to integrate POCT for non-communicable chronic diseases(NCD) in communities that have high rates of undiagnosed NCDs. The objective of our study was to evaluate the yield and linkage to care of POCT for type 2 diabetes mellitus(DM) and hypertension(HTN) alongside a study assessing the use of rapid antigen tests for COVID-19 in taxi ranks in Johannesburg. For all participants, we recorded results of a POC blood glucose(BG), blood pressure(BP), waist circumference, smoking status, height, and weight. Clients who had elevated BG(fasting>7.0 or random>11.1mmol/L) and/or BP(diastolic>90 and systolic>140mmHg) were referred to their local clinic and phoned to confirm linkage. Modified Poisson regression was used to assess predictors of outcomes. A total of 1169 clients were enrolled and screened for DM and HTN. The majority were employed, male and between 30-40 years old, with a body mass index (BMI) >25kg/m^2. The prevalence of DM and HTN was 7%(n=79) and 26%(n=298), respectively, of which, 23(2%) and 124(11%) had a previous diagnosis of DM and HTN, respectively, at enrollment. 56(5%) participants with no known DM diagnosis had elevated BG and 174(17%) clients with no known HTN had elevated BP at study enrollment. 32%(n=19) of those with elevated BG and 23%(n=45) of those with HTN were linked to care. Regression models showed that those older in age, males, those with a BMI >25kg/m^2, smokers and individuals with elevated BP were at increased risk of DM. Older age and high BMI were also associated with HTN along with having an elevated BG, while males and smokers were at decreased risk. Those >40 years and clients with BMI >25kg/m^2 were more likely to link to care. Our study provides evidence that it is feasible to integrate POCT for NCDs into screening for COVID-19. We identified 70% of DM cases and 40% of HTN cases in our cohort that would have otherwise gone undiagnosed. Further research is needed to improve linkage to care and assess the feasibility and costs of integrating POCT NCD screening into other health screening efforts.

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CLINICAL OUTCOMES IN A COHORT OF NEWBORNS WITH CONFIRMED COVID-19 IN A REFERENCE HOSPITAL IN SALVADOR, BAHIA, BRAZIL

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SARS-CoV-2 infection in the pediatric population may result from transmission during close contact with caregivers over the course of their first days of life. Studies to evaluate the impact of SARS-CoV-2 infection in newborns are lacking. To identify factors associated with poor outcomes in a cohort of newborns with confirmed COVID-19 infection, a prospective observational study was conducted from May 2020 to March 2022 in a reference hospital for maternal and neonatal care in Salvador, Brazil. Data was obtained from the electronic medical records. 58 newborns with suspected COVID-19 were recruited and 11 newborns with confirmed COVID-19 were enrolled. Of these, 63.6% were diagnosed within 24h of birth, with maternal diagnosis confirmed in 54.4% up to 7 days prior to delivery while 81.9% were born less than 37 weeks. Delivery was slightly more common vaginally (54.5%). Most newborns (81.8%) presented with respiratory manifestations and 54.5% had oxygen saturation less than 95%. Resuscitation maneuvers at time of delivery included aspiration of upper airways in 71.4%, chest compressions in 28.6%, 57.1% required central venous catheterization, 28.6% required epinephrine and 36.4% needed oxygen therapy primarily via CPAP (75%). Over the course of hospitalization, ventilatory support was required with invasive support (33.3%) and non-invasive CPAP support (66.7%). 36.4% of infected newborns required admission to the intensive care unit and 90.9% with admission to the semi-ICU. Overall hospital length of stay was prolonged with a mean of 31 days. All infected newborns were alive at time of discharge. Given that most infections were diagnosed within 24 hours of birth, our study highlights the possibility of perinatal transmission and need for rigorous precautions to prevent COVID-19 infection in a vulnerable population. Infected newborns required interventions at time of birth and over the hospital course resulting in prolonged length of stay and significant resource investment. In this setting, it is critical for the healthcare team to develop expertise in reduction of COVID-19 transmission and need for lifesaving interventions.

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SENTINEL SURVEILLANCE OF SEVERE ACUTE RESPIRATORY ILLNESS SARI IN THE KINGDOM OF JORDAN DURING THE SARS-COV-2 PANDEMIC FROM 2020 AND 2021

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Surveillance of respiratory pathogens is an early warning system for any pandemic. In Jordan, sentinel SARI surveillance has been conducted since 2010. The 2014 World Health Organization case definition for SARI was used to identify cases. During the period from January 2020 through December 2021, the Central Public Health Laboratory in Jordan, supported by the US Naval Medical Research Unit No. 3 (NAMRU-3), enrolled and collected nasopharyngeal (NP) and oropharyngeal (OP) samples from 5741 cases from four sentinel hospitals distributed at the north, middle, south, and east of Jordan. Demographic and epidemiologic data were collected from each case in addition NP/OP swabs. Swabs were sent to the CPHL, where they were tested using a RT-PCR multiplex panel for detection of 33 respiratory viruses and bacteria, including SARS-CoV-2. Male gender constituted 53.3% of SARI cases. The majority of cases were ≥ 50 years old (42.9%), whereas children ≤ 16 years constituted only 22.8% of cases. All samples were tested for Influenza A and B viruses, 5153 samples were tested to SARS-CoV2 (testing started in March 2020), and 4686 samples were tested for other respiratory pathogens. The etiology of SARI was identified in 38% (2181/5741) of the cases, with 9.5% (548/5741) being positive for more one pathogen. SARS-CoV2 was detected in 18% (924/5153) of cases. Of those 11.6% (107/924) had SARS-CoV-2 coinfection with other respiratory pathogen(s). Influenza A was detected in only 1.5 % (85/5741) of the tested samples and Influenza B was detected in only 0.3% (16/5741) of samples. Cases of influenza A were enrolled only during January through March 2020, and November through December 2021; influenza B cases were enrolled only during 2020. 41.7% of samples (1954/4686) were positive for other respiratory pathogens; the most frequently detected pathogens were Staphylococcus aureus (19.9%) followed streptococcus pneumonia (16.5%) and rhinovirus (11.1%). Understanding the epidemiology of SARI in Jordan provides critical data for developing force health protection measures for U.S. Forces stationed and deployed in the CENTCOM area of responsibility.

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XPERT MTB/RIF ULTRA ASSAY FOR THE DIAGNOSIS OF TUBERCULOUS MENINGITIS USING CEREBROSPINAL FLUID OF CHILDREN IN BANGLADESH

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While there are tests in place, a rapid, sensitive, and reliable diagnostic technique for the detection of tuberculous meningitis (TBM) using cerebrospinal fluid (CSF) is still lacking. In this study, we assessed the performance of Xpert MTB/RIF Ultra assay (Xpert Ultra) for the diagnosis of TBM in children. Presumptive TBM children (aged 2 months to 15 years) were recruited prospectively from three large tertiary hospitals in Dhaka, Bangladesh. CSF collected from patients were tested by Xpert Ultra, conventional Xpert MTB/RIF assay (Xpert), Lowenstein Jensen (L-J) culture, and acid-fast bacilli (AFB) microscopy. Each test's diagnostic performance was evaluated against the uniform case definition of probable or definite TBM and a composite microbiological reference standard. Between December 2019 and January 2022, a total of 186 presumptive TBM children were enrolled. Based on the uniform clinical case definition, 49 patients were categorized as having probable or definite TBM. Against this uniform case definition, Xpert Ultra had 89.8% sensitivity (95% CI, 77.7-96.6; 44/49), and a negative predictive value (NPV) of 96.5% (92.3-98.4; 137/142), compared with 32.7% sensitivity (20.0-47.5; 16/49), and NPV of 80.6% (77.4-83.5; 137/170) for Xpert, 20.4% sensitivity (10.2-34.3; 10/49) and NPV of 77.8% (75.3-80.2; 137/176) for L-J culture, and 2.0% sensitivity (0.05-10.9; 1/49) and NPV of 74.1% (67.3-80.3; 137/185) for AFB microscopy. Against the composite microbiological reference standard, Xpert Ultra had a sensitivity of 100% (92.0-100; 44/44) that was higher compared with Xpert at 36.4% (22.4-52.2; 16/44), L-J culture at 22.7% (11.5-37.8; 10/44), and microscopy at 2.3% (0.06-12.0; 1/44). Xpert Ultra detected 28 TBM cases which were missed by other tests, and 75% (21/28) of them were trace detected. In conclusion, Xpert Ultra identified TBM cases with higher sensitivity than Xpert, L-J culture, and AFB microscopy, and thus can be used for rapid diagnosis of TBM among children in clinical settings of Bangladesh.

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SARS-COV-2 VIRAL LOAD DYNAMICS IN THE UPPER RESPIRATORY TRACT AND PERIPHERAL BLOOD IN A DIVERSE COHORT OF HOSPITALIZED PATIENTS IN NEW MEXICO: PRE- AND POST-DELTA VARIANT

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The impact of SARS-CoV-2 viral load dynamics on severe disease and mortality remains largely unreported for certain minority groups. Here, we report the relationship between SARS-CoV-2 viral load dynamics [pre- (n=219) and post-transmission (n=115) of the Delta variant] and clinical outcomes in hospitalized patients: American Indian/Alaska Native (AI/AN) n=98; Hispanic/Latino n=162; Non-Hispanic White n=58; and Other n=16. Viral loads in the upper respiratory tract (URT) and peripheral blood (PB) were quantified on days 0-3, 6, 9, and 14. SARS-CoV-2 was sequenced using a novel chip-based technology and phylogenetically defined using Nextclade. Severe COVID-19 (n=107) was defined as admission to the ICU and/or death, while non-severe patients (n=227) did not require ICU support. Patients presenting with Delta were younger (P=0.025), particularly in the 18-44 age group (P=0.032). Time symptomatic prior to hospital admission in this group of patients was longer (P=1.823x10^{-4}). Patients with Delta also had significantly increased URT and PB viral loads during the initial infection and cumulatively across the time course. Severe disease and mortality did not differ in univariate analyses. However, multivariate modeling revealed that severe COVID-19 was associated with older age [OR=1.042 (1.020-1.063), P=1.023x10^{-4}], being male [OR=3.943 (2.218-7.009), P=2.938x10^{-6}], higher BMI [OR=1.065 (1.028-1.202), P=4.177x10^{-4}], remdesivir treatment [OR=0.346 (0.171-0.700), P=0.003], AI/AN ancestry [OR=3.702 (1.515-9.048), P=0.004], and Delta infections [OR=2.038 (1.089-3.816), P=0.026]. Similarly, in-hospital mortality was associated with older age [OR=1.045 (1.018-1.073), P=0.001], being male [OR=2.766 (1.365-5.610), P=0.005], higher BMI [OR=1.064 (1.023-1.107), P=0.020], remdesivir treatment [OR=0.439 (0.190-1.014), P=0.054], AI/AN ancestry [OR=2.673 (0.897-7.969), P=0.078], and Delta infections [OR=2.462 (1.159-5.230), P=0.019]. Findings here show that Delta infections result in increased COVID-19 severity and mortality and that certain ancestral groups have an increased risk of adverse outcomes.

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THE SEVERITY OF COVID-19 PATIENTS IS ASSOCIATED WITH ZINC AND INTERLEUKIN 6 LEVELS

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Presentation of COVID-19 range from mild respiratory disease to severe illness with acute respiratory failure. Severe disease is characterized by a dysregulated immune response with a greater expression of pro-inflammatory cytokines, particularly IL-6. On the other hand, regulator molecules such as zinc may be downregulated. This study aimed to determine the serum concentrations of zinc and IL-6 as biomarkers of severity in COVID-19 patients from Lima, Peru. An observational, cross-sectional study was performed, the levels of IL-6 /Zinc were measured by ELISA. ICU and non-ICU hospitalized patients and non-hospitalized patients were included. Data regarding age, gender, symptoms, and comorbidities was collected. A descriptive statistical analysis was performed with the data provided, the measures of central tendency and frequency distribution were calculated. The Kruskal-Wallis test was performed to determine if there was a difference in the levels of IL-6 and Zinc between the ICU, non-ICU, outpatient, and control groups. A total of 52 hospitalized patients were included, of which 26 were in the ICU and 26 were not in the ICU. Also 36 non-hospitalized patients were included, of which 24 belonged to the outpatient group and 12 to the control group. Most of the patients corresponded to the 30-59 age group and 64.8% of the patients were male. The descriptive statistics of IL-6 showed the lowest values among outpatient subjects (2.00 pg/mL) and the highest values among ICU patients (168.5 pg/mL). The lowest zinc levels were identified among outpatient and control groups (0.001 nmol/ul) and the highest levels in ICU patients (0.100 nmol/ul). Male patients had significantly higher levels of IL-6. The bivariate analysis using the Kruskall-Wallis test showed a statistically significant association ($p<0.01$) between both independent variables. In conclusion, hospitalized patients with COVID-19 who presented higher plasma concentrations of IL-6 had lower levels of zinc. Likewise, high levels of this inflammatory cytokine were associated with the male gender.

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ASSESSING THE SUSTAINED EFFECTS OF A WATER FILTER INTERVENTION IN RWAMAGANA, RWANDA: A 30-MONTH LONGITUDINAL STUDY

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An estimated 2 billion people use drinking water contaminated with indicators of fecal bacteria, with the majority residing in sub-Saharan Africa, Central America, and South Asia. Household water treatment and safe storage interventions have been shown to improve microbial water quality and reduce diarrheal disease in areas lacking access to safe water, at least in the short term. However, little is known about their sustainability, with few studies evaluating their effectiveness for over a year. We aimed to assess the longer-term uptake and effects of a household-based filter with safe storage delivered and promoted through Community Health Clubs in Rwanda's national environmental health program. We undertook a 30-month longitudinal study in Rwamagana District, following 608 households across 30 villages receiving the intervention. We conducted four unannounced follow-up visits and

measured filter coverage, condition, and use, drinking water quality, and child diarrhea prevalence at ~6, 15, 24, and 30 months since the delivery of the intervention. Coverage of the water filter remained high throughout the follow-up period, with 94% of households observed to have the filter by the 30-month visit. Compared to the 6-month visit, the households with filters in good condition declined by 12% at the 30 month-visit, adjusting for seasonal and household characteristics. Filter use was comparable between the 6- and 15-month visits but fell by the 24- and 30-month visits. About 84% of households reported using the filter, and 59% had filters with observed water in the storage container by the end of the follow-up. Water quality did not deteriorate over the duration of the study visits, and child diarrhea prevalence did not increase after the 6-month visit. These findings suggest coverage, condition, and use of a household water filter delivered using Community Health Clubs in Rwanda declined only modestly over time. The effects on drinking water quality and child diarrhea were sustained even 30 months post-implementation.

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DEVELOPMENT AND EVALUATION OF RT-QPCR ASSAYS FOR SAR-COV-2 VARIANT OF CONCERN (VOCS) DETECTION IN CLINICAL AND ENVIRONMENTAL SPECIMENS

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The global public health systems were severely impacted by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) outbreak and were further challenged by the emergence of SARS-CoV-2 variants carrying mutations that are of concern (VOCs). Next generation sequencing (NGS), the gold standard for monitoring the emergence and spread of VOCs, is limited by its relatively slow turnaround time, the relatively high cost, and the technical expertise required for bioinformatics. To identify the VOCs in settings with limited sequencing capabilities, we developed real-time RT-qPCR assays to detect VOCs. The assays were designed to detect mutation of the spike (S) protein-encoding gene based on mutation prevalence, which is unique for each variant. The mutation maker included the deletion amino acid position 69-70, mutation A570D and T716I for the Alpha variant. Mutation D80A and D215G for Beta, T19R and T478K for Delta, R190S and K417T for Gamma, L452Q and F490S for Lambda, and G339D, SSS371-3-5LPF, and T547K for Omicron. The assays were tested in duplex, yielding a seven-panel testing scheme. The analytical performance of assays was evaluated using the synthetic positive control. The PCR efficiency was ≥98% except for 490S (78%) and 371-3-5LPF (71%) and the limit of detection ranged between 40 – 400 copies per reaction. The assays were first validated against Sanger sequencing on 152 SAR-CoV-2 positive clinical samples and yielded 100% concordance. We then evaluated the performance of the assays on 134 wastewater samples, a subset of the SAR-CoV-2 surveillance study in Dhaka, Bangladesh. The sensitivity of the assays ranged between 83 – 99 % and specificity was 98 -100% compared to Illumina COVIDSeq sequencing. The assays were further used to test our wastewater surveillance samples from April 2021 through February 2022. The most prevalent circulating variant was Beta from April to May 2021, followed by Delta from June to December 2021, and Omicron from January 2022 to the present. The relatively low-cost VOCs RT-qPCR assays are well suited for rapid testing of clinical and wastewater samples in resource-limited setting.

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ASSOCIATIONS BETWEEN MATERNAL NUTRITIONAL STATUS, INFLAMMATION, STRESS, AND ESTRIOL DURING PREGNANCY AND CHILD STRESS RESPONSE

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Maternal prenatal well-being, which can be measured through stress, immune status, nutrition, and estriol biomarkers, affects child health in the short and long term. Within a cluster-randomized controlled trial in rural Bangladesh, we assessed the following maternal blood biomarkers during the first two trimesters of pregnancy at baseline: cortisol, C-reactive protein (CRP), alpha-1-acid glycoprotein, 13 cytokines (including IFN-γ), vitamin D (25-hydroxy-D [25(OH)D]), ferritin, soluble transferrin receptor, retinol binding protein, and estriol. In children, we measured salivary alpha-amylase (sAA) and cortisol reactivity to a venipuncture stressor, methylation of the glucocorticoid receptor gene (including the nerve growth factor-inducible protein A (NGFI-A) binding site), resting heart rate, and mean arterial pressure. We adjusted for prescreened covariates and used generalized additive models. We reported the mean difference and 95% confidence intervals at the 25th and 75th percentiles of exposure distribution. The study measured outcomes in 542 children at age 28 months. Maternal cortisol, estriol, IFN-γ, and the cytokine sum score during pregnancy were negatively associated with child resting heart rate. Maternal cortisol was negatively associated with post-stressor salivary cortisol [-0.26 log μg/dl (95% CI -0.47, -0.05)] in children. Maternal CRP was positively associated with child mean arterial pressure, and maternal IFN-γ was negatively associated with sAA reactivity and methylation of NGFI-A in children. Maternal vitamin D was negatively associated with child mean arterial pressure [-1.26 mmHg (95% CI -1.98, -0.53)], and maternal ferritin was negatively associated with mean change in sAA [-1.23 log U/ml (95% CI -2.33, -0.13)] in children. The neuroendocrine-immune profile and nutritional status during pregnancy affect child stress physiology, which may have implications for development.

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HYGIENE ASSESSMENT, PARASITOLOGICAL AND MICROBIOLOGICAL ANALYSIS OF WATER USED BY RESTAURANTS AND STREET VENDORS IN OWERRI METROPOLIS, IMO STATE NIGERIA

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The hygienic aspects of food vending operations are a vital source of a public health concern as they factor in the use of pathogen-contaminated water by vendors. Hygiene assessment, parasitological and microbiological analysis of water used by restaurants and street food vendors in Owerri metropolis, Imo State Nigeria was carried out between January to October 2020. A structured questionnaire was administered to 384 food vendors. A total of 330 water samples from 55 vending sites across 3 vending types

were screened for enteric parasites, bacterial and fungal contamination using standard procedures. The data generated were statistically analyzed. The respondents have significantly good knowledge (52.50%) and attitude (66.34%) towards food safety and hygiene, which improved with training and had a positive impact on practice irrespective of age, gender of the vendor, and the types of the vending business. The result showed that 24.62% of water samples from 36.36.% of the vending sites were contaminated with pathogenic parasites (*Giardia* spp, *Entamoeba* spp*, Cryptosporidium,* and *Entamoeba* spp), while 63.85% of the water samples collected from 81.81% of the vending sites were contaminated with bacteria genera such as species of *Serratia*, *Proteus*, *Enterobacter*, *Shigella* spp, *Salmonella*, *Yersinia*, *Bacillus*, *Staphylococcus*, *Micrococcus,* and *Klebsiella*. The fungal genera isolated were *Penicillium, Aspergillus, Paecilomyces*, *Candida, Drechslera, Coccidiodes,* and *Aspergillus*. The microbial quality of a good number of the water samples exceeded the World Health Organization (WHO) allowable limit of $1.0x10^2$CFU/ml for potable water. However, based on WHO guidelines, 89.23% of the water samples pose no foreseeable risk to the populace due to the absence of fecal coliform bacteria. The knowledge in food safety recorded is instructive and should factor in education tailored to improve some aspects of the attitude of the vendors. The identification of pathogenic parasites and microbes in usable domestic water presents a grave epidemiological threat to public health which requires behavioural change and public infrastructural improvement.

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CAN THE INTRODUCTION OF THE "PERSONAL DOMAIN" HELP US IMPROVE WASH INTERVENTIONS?

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Until recently, we assumed to have a good understanding of the transmission routes in the F-diagram and how relatively simple interventions, such as clean drinking water, hygiene education, handwashing, and toilets, in the public (outside the household) and domestic (in-house) domains can break these routes and, with this, prevent diarrheal diseases. However, lately larger projects (Wash Benefit and Shine from Kenya, Zimbabwe, and Bangladesh) reported back with results that still did not show a clear effect of these interventions, particularly water quality on linear growth/diarrhea among children. Over a 2 years period, every second month we measured the *E.coli* contamination on 5 different contamination hotspots (toilet doorknob, washed dishes, glasses, etc) in 32 households in a low-income area in Dhaka, Bangladesh. The results showed considerable in-house contamination in the kitchen environment. The toilet door knob showed the lowest contamination, while the washed food plates and the interior of the drinking glasses were the most contaminated with 0-2436 and 0-2280 *E. coli* (cfu/10 cm^2) respectively. Combined with other results from the same project, including the extensive E.coli contamination by flies, and of raw fish in the kitchens, indicates an almost lack of connection between the contamination in the traditional measuring locations in the domestic domain i.e. drinking water containers and food, and the actual personal intake of bacteria. To understand the effect of different pathogen flows, we introduce "the personal domain," a third domain to the Cairncross two domain model, representing the pathogens that are actually consumed by the person: via water from a dirty glass, food from a contaminated plate, or fingers inserted in the mouth. Monitoring the personal domain is essential because it represents the sum of the transmission routes in the domestic domain, and only by evaluating and comparing the individual pathogen flows inside the complex domestic domain can we have an indication of which interventions might have a measurable effect on the health outcomes.

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IMPACT OF SAMPLE COLLECTION AND PROCESSING ON THE DETECTION OF PATHOGENS FOR WASTEWATER SURVEILLANCE

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Wastewater-based epidemiology (WBE) has gained wide recognition throughout the COVID-19 pandemic as a method to monitor trends of SARS-CoV-2. WBE has been particularly crucial in low and middle-income countries (LMICs), where case data is often incomplete or delayed. While the current focus of WBE has primarily been on a single pathogen, the future should look toward expanding to a multi-pathogen approach. However, determining the proper concentration and capture methods for specific pathogens or a broad spectrum of pathogens is difficult due to differences in sample collection methods and processing. To determine the optimal method of specific pathogen detection, two different sample collection and processing methods, Bag-Mediated Filtration System (BMFS) and Ceres Nanotrap® Virus Capture, were compared to capture SARS-CoV-2 on 272 wastewater samples from an ongoing wastewater surveillance system in Dhaka, Bangladesh. The Nanotrap method showed higher detection of SAR-CoV-2 (N1; 62.1%) than the BMFS method (38.2%). The Ct value was significantly lower ($p<0.05$) in Nanotrap processed samples (32.7 ± 1.5) compared to BMFS (33.5 ± 1.2). Additionally, a subset of samples (n=32) processed by BMFS and Nanotrap were compared to detect other enteric pathogens using TaqMan Array Card, which can detect more than 50 enteric pathogens in a single run. The pathogen detection rate was mostly higher in BMFS processed samples compared to Nanotrap, especially for enterovirus (41% vs. 9%), Shigella spp. (100% vs. 53%), Salmonella Typhi (53% vs. 13%), norovirus (100% vs. 80%), rotavirus (100% vs. 38%), and Sabin1 poliovirus (6% vs. 0%). Overall, BMFS outperformed Nanotrap in its ability to capture multiple pathogens from wastewater. However, compared to Nanotrap, BMFS is expensive (USD 100 vs. USD 15), requires a high-volume intake (6L vs. 40ml), and a time-consuming process (4 hours vs. 30 mins). Cost is a large determining factor for many LMICs; therefore, a simple and low-cost method like Nanotrap would be ideal. However, a modification to capture more pathogens is required to provide an affordable solution for WBE in both high and low-income settings.

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ASSOCIATION BETWEEN WATER, SANITATION, AND HYGIENE ACCESS AND THE PREVALENCE OF SOIL-TRANSMITTED HELMINTH AND SCHISTOSOME INFECTIONS IN WOLAYITA ZONE, ETHIOPIA

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The Geshiyaro project is a five-year intervention to assess the impact of community and school-based water, hygiene, and sanitation (WaSH) interventions on reducing infection with soil-transmitted helminths (STH) and schistosome parasites, in combination with deworming. This

paper summarises baseline infection levels of STH and schistosomiasis infection and the association with WaSH in 136 communities from 15 districts in the Wolayita zone, Ethiopia. Data on STH and schistosome parasite prevalence with information on household and community access to improved drinking water, latrines, and handwashing facilities were obtained during a population based, cross-sectional (by age and gender) survey conducted between 2018 and 2019. Prevalence of STH was found to be 15.6% for any STH species, 9.5% for *Ascaris lumbricoide*s, 1.8% for *Trichuris trichiura*, and 7.2% for hookworm. Intestinal schistosomiasis (*Schistosoma mansoni*) infection prevalence was 0.85% by Kato Katz, 21.4% by POC-CCA when trace was considered positive and 13.1% when negative. Microhaematuria, used as a proxy for urinary schistosomiasis (*Schistosoma haematobium*), was 2.71%. Increased risk of Hookworm infection was significantly associated with unimproved latrine usage at the household level, lack of handwashing facilities, and no shoe wearing. Not disposing of infant stool was significantly associated with *A. lumbricoides*, *T. trichiura*, and hookworm infection. Aggregating WaSH data at the community level, increased sanitation and access to improved drinking water coverage was associated with both reduced *A. lumbricoides* and hookworm infection. These findings demonstrate some improvements in infection levels due to the impact of household and community-based WaSH infrastructure for both STH and SCH infections, but these were not always significant when considering the degree of heterogeneity of infection between and within communities.

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THE IMPACT OF WATER, SANITATION, AND HYGIENE INTERVENTIONS BY SEASON: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Severe weather, increasingly driven by climate change, can drive infectious disease transmission. Diarrheal diseases are particularly sensitive to environmental drivers- including ambient temperature and precipitation-meteorological conditions that are expected to be affected by climate change. Additionally, many studies have found that seasonal diarrhea peaks typically occur during rainy seasons. Water, sanitation, and hygiene (WASH) interventions that aim to disrupt transmission of diarrheal diseases have shown minimal impact on health outcomes in several recent large trials. It is possible that WASH interventions may have an effect in some seasons but not others. We conducted a systematic review of the available literature on the impact of WASH interventions on diarrheal diseases spanning from 1970 to 2021 to explore whether the impact of WASH interventions on diarrheal diseases varies by season, or periods of higher meteorological exposures. We found 126 published WASH studies that met our inclusion criteria and created data-driven seasons using proximate land weather station data for the study time period from the NOAA Global Surface Summary of the Day catalogue of datasets. We paired each raw weather dataset with its corresponding study and created weather clusters as a proxy for seasons using principal component analysis and k-means clustering on precipitation, temperature, and humidity values. Of the 126 studies, 29 studies contained disaggregated diarrheal results that occurred across our data-driven seasons and 20 were contained entirely in one season. We will present the results of the meta-analyses on these 49 studies, examining whether WASH interventions in these studies interrupted seasonal transmission of diarrhea. This type of result would suggest that WASH interventions may provide resilience to weather-related exposures and future climatic changes.

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PREVENTIVE CHEMOTHERAPY AND WATER CHLORINATION: QUASI-EXPERIMENTAL IMPACT ANALYSIS OF COMBINED PROGRAMS ON HELMINTH RISK IN KENYA

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Soil-transmitted helminths (STH) and schistosomiasis (SCH) are the most widespread NTDs globally. Control of both is via preventative chemotherapy (PC). WASH interventions, such as safe water, likely have a synergistic effect with PC in controlling helminths, however, research outcomes often focus on general child health as opposed to helminth infection. We exploit a natural experiment where PC has been conducted in areas of operation and non-operation of a water chlorination program in Kenya to measure combined impact on risk of helminth infection. Kenya's National School-Based Deworming Program (NSBDP) and Dispensers for Safe Water program have operated in Kenya since 2013. NSBDP is active in 27 counties, Dispensers for Safe Water in 8, all which implement NSBDP. Counties to implement both programs were selected via health and socio-demographic indicators. We analyse this overlap with; data from NSBDPs helminth prevalence surveys among school-aged children before and during operation of both programs; census socio-demographic data; NSBDP coverage data; and operational data from Dispensers for Safe Water. Outcomes are estimated using doubly robust difference-in-difference models, incorporating baseline control for key variables, pre-balanced inverse selection probability weights, and random intercepts at multiple levels. Dispensers for Safe Water/NSDBP when compared to NSBDP alone is estimated to statistically significantly reduce odds of STH infection by 21% ($p<0.001$), and of combined STH/SCH infection by 21% ($p<0.001$). A non-statistically significant reduction of SCH risk is also estimated. Prior evidence suggests PC as highly cost-effective against helminths. The large and statistically significant effect demonstrated in this study shows the additional benefit which may be gained by adding safe water programs to areas already receiving PC. Water chlorination, already cost-effective for child mortality, has additional positive outcomes when considering reductions in helminth risk. In addition, long term economic benefits previously estimated for PC may be more sustainable when combined with water chlorination.

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REGIONAL SCALE PATHOGEN CONCENTRATIONS AND ASSOCIATED HUMAN HEALTH RISKS DUE TO WASTEWATER REUSE IN THE MEZQUITAL VALLEY, MEXICO

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Urban wastewater reuse for agriculture is an important climate change adaptation strategy that provides reliable nutrient-rich water, reduces water stress, and strengthens food systems. Wastewater exposure also presents health risks to farmers and their communities. These risks can be mitigated by treating the wastewater, however, communities downstream of treatment plants could recontaminate treated wastewater, negating the benefits of treatment. In 2019, we collected water samples at various points along irrigation canals carrying treated and untreated wastewater in the Mezquital Valley and quantified the concentration of a range of bacterial, protozoal, and viral pathogens. Pathogen concentration data was used to conduct multi-pathogen comparative risk analyses to assess the impact of water treatment and community recontamination. We found decreases in bacterial pathogen and protozoal gene counts following water treatment but increases in bacterial pathogen and protozoal gene

counts after the treated water passed through communities. Decreases in viral pathogen gene counts were not as pronounced following water treatment. In untreated wastewater, bacterial pathogen and protozoal gene counts decreased after transit through communities, while viral pathogen gene counts increased. Pathogen specific relative risk comparisons between treated and untreated canals showed that prior to transit through communities, relative risks ranged from 1.09 for norovirus GII to 9.09 for atypical EPEC. After transit through communities, relative risks diminished, ranging from 1.02 for norovirus GII to 2.15 for *Giardia lamblia*. The equalization of risks likely results from local community recontamination of the treated water stream. Understanding the entire wastewater reuse chain provides valuable information for the development of comprehensive mitigation strategies.

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CAPTURING WATER QUALITY VARIABILITY USING A REPEATED MEASURES DESIGN: IMPLICATIONS FOR THE SELECTION OF SAMPLING STRATEGIES IN ENVIRONMENTAL STUDIES

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In settings with inadequate drinking water treatment, water quality can vary rapidly over short time scales. This variation in water contamination can be challenging to capture when a source is measured only once. In addition, highly contaminated water samples can be sporadic and hard to capture but may greatly contribute to disease risk. The collection of repeated measures of water samples to assess household water contamination can be used to decrease intra-household variability when estimating exposure; which increases statistical power to identify households that are exposed to highly contaminated water. We collected water samples from drinking water sources and maternal and infant hand rinses at 3 different visits over a 7-day period from 286 households in northern Ecuador. Household water quality was assessed by combining Colilert and Petrifilm results to obtain 5 categories: non detected, low, medium, high and very high contamination. We used Fleiss and Cohen Kappa agreement indexes to assess variability within households, and extreme value theory to model high-risk events with a Generalized Pareto Distribution. We found that although there was a substantial agreement in the source of drinking water collected during the 7-day period (Fleiss's Kappa=0.76), there was only fair agreement in drinking water (0.3), maternal (0.19) and infant (0.17) hand rinse water quality. After randomly dropping one of the three samples from each household, agreement indexes showed decreased variability. Also, the number of very highly contaminated water samples tend to disappear. Based on our Pareto distribution, at least 100 water samples are needed to identify a single highly contaminated event in this setting. We present a framework for identifying the number of water samples needed in a given population to capture variability and extreme values.

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ASSOCIATIONS BETWEEN WATER, SANITATION, AND HYGIENE AND CHILDREN'S MALNUTRITION AND MENTAL HEALTH IN METRO MANILA, PHILIPPINES: PRELIMINARY RESULTS OF A CROSS-SECTIONAL STUDY

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Urban poor adolescents experience health consequences due to inadequate water, sanitation, and hygiene (WaSH) and social determinants. Our study aimed to measure associations between these determinants and adolescents' malnutrition and mental health in order to find risk factors. We conducted a cross-sectional survey of four public secondary schools in Manila, Philippines. We measured children's demographic information, food insecurity, and social determinants via questionnaire. We used anthropometry to measure stunting, thinness, overweight, and obesity according to the World Health Organization's standards. We measured mental health (anxiety, depression, suicidal thoughts, self-harm, panic attacks) via self-report. We measured the adequacy of WaSH via questionnaire. We surveyed 1,767 adolescents in grades 7-12. While 21% of adolescents were stunted, 14% were overweight and 8% were thin. Self-reported mental illnesses were prevalent: suicidal thoughts (15%), practice of self-harm (18%), anxiety (21%), panic attacks (27%), and depression (64%). Over 7% of adolescents' families relied on social assistance, while 37% experienced not being able to afford food and 5% experienced hunger "often". Almost 70% lived in homes where the main source of drinking water was a home water connection. Over 27% obtained drinking water from bottled sources. Over 72% and 24% had a flush and composting toilet, respectively. About 2% had no toilet facility and 2% used a bucket. About 76% of adolescents washed their hands after using the toilet. Data analysis is in progress. Preliminary findings indicate severe WaSH inadequacies. During our presentation, we will report logistic regression results describing associations between home WaSH and children's malnutrition and mental health, as well as identify social determinants of disease.

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IMPROVING AND SUSTAINING HAND HYGIENE BEHAVIOR IN RURAL LIBERIAN HOSPITALS

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In rural Liberian hospitals, hand hygiene supply shortages and inadequate hand hygiene behavior among staff increases risk of hospital-acquired infections. Past hand hygiene interventions in these settings have lacked sustainability, undermining the ability to perform hand hygiene consistently. Following a design and piloting process, we implemented interventions to improve and sustain hospital hand hygiene. Hand hygiene interventions consisted of hospital-based production of alcohol-based hand sanitizer and distribution of novel hand hygiene holster devices to clinical staff. We randomized 6 hospitals to receive one of two intervention packages or a control. Data collection included structured observations of staff hand hygiene behavior using the WHO Five Moments framework and spot checks of hand hygiene supply availability. Implementation and data collection took place over a 6-month period in October 2021-March 2022. We did not observe a sustained change in overall hand hygiene compliance at intervention hospitals. At facilities receiving both holster and hand sanitizer production interventions, we observed an increase in usage of hand sanitizer for hand hygiene; we did not observe a similar increase at hospitals receiving only the hand sanitizer production intervention or controls. At hospitals receiving the holster intervention, usage of a holster was associated with higher hand hygiene compliance, but causality cannot be determined. While hospital staff consistently expressed satisfaction with interventions, uptake was low, with under 50% of nurses and no doctors using hand hygiene holsters after month 4. These results indicate that obstacles to hand hygiene may extend beyond availability of supplies and infrastructure at Liberian hospitals. Findings suggest that hand hygiene holsters may contribute to behavior change, but more work is needed to promote uptake of this intervention. We propose a follow-on project

that will overcome these obstacles and establish causality of intervention efficacy, but may not measure sustainability of long-term hand hygiene performance.

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THE RELATIONSHIP BETWEEN SYSTEMIC INFLAMMATION AND GROWTH FALTERING IN BANGLADESHI CHILDREN IS MODIFIED BY IMPROVED NUTRITION AND WASH

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Systemic inflammation resulting from infection may contribute to growth deficits in children. We assessed the relationship between inflammation and growth in children, and whether it was modified by a WaSH and nutrition intervention. We analyzed the control and intervention arms of a cluster-randomized trial that provided a combined intervention of upgraded sanitation, chlorinated drinking water, handwashing stations with soap and nutrition counseling with lipid-based nutrient supplementation in Bangladesh. Blood was collected at 14 months and C-reactive protein (CRP) and alpha-1-acid glycoprotein (AGP) were assessed. Child growth was measured at 14 and 28 months and length-for-age (LAZ), weight-for-age (WAZ) and weight-for-length (WLZ) Z-scores were calculated, as well as Z-score change between timepoints and absolute velocity. We accounted for non-linear relationships using generalized additive models and obtained mean differences in growth between children in the 25th and 75th percentile for each marker of inflammation. We adjusted for prescreened covariates and included an interaction term for treatment. Blood was collected from 609 children, of which 50% and 14% had AGP and CRP above reference values (1 g/L and 5 mg/mL respectively). The median CRP value was 1.02 mg/ml (IQR: 0.34, 3.08) and AGP value was 1.00 g/L (0.75, 1.38). There was no significant difference in mean LAZ, WAZ or WLZ at 28 months, however above 1.75 g/L (89th percentile), predicted LAZ and WAZ sharply declined. Those in the control arm had a more negative effect of AGP inflammation on LAZ change (int. p = 0.07) and length velocity (0.009) than treatment. CRP was associated with WAZ at 14 months (-0.27; 95% CI: -0.51, -0.031) and LAZ (-0.16 SD; -0.28, -0.036) and WLZ (-0.13 SD; -0.25, -0.012) at 28 months but not with change or velocity. There was no consistent interaction with CRP and treatment. In this cohort low-grade CRP inflammation and high AGP inflammation were negatively associated with growth. Early supplementation and improved WaSH may help children overcome deleterious effects of elevated AGP, common in this population, on later growth faltering.

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PRECLINICAL DEVELOPMENT OF A NANOPARTICLE MALARIA TRANSMISSION BLOCKING VACCINE PFS230D1-EPA WITH MATRIX-M™ ADJUVANT

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Conjugated Pfs230D1-EPA transmission-blocking vaccine (TBV) is produced by chemically cross-linking recombinant Pfs230D1M, a recombinant protein corresponding to domain 1 of the *Plasmodium falciparum* sexual stage antigen Pfs230, to a recombinant nontoxic carrier protein ExoProtein A (EPA). Pfs230D1-EPA has been assessed in Phase 1 and 2 trials with different adjuvants. A phase 1 human trial is ongoing in Mali (clinicaltrials.gov ID NCT05135273) to evaluate Pfs230D1-EPA formulated in saponin-based Matrix-M™ adjuvant (Novavax). Here, we report improved manufacturability of Pfs230D1-EPA vaccine with comparability to Drug Substance and Drug Product previously evaluated in mice, rhesus monkeys and humans. In a non-human primate study, we are evaluating immunogenicity of Pfs230D1-EPA with Matrix-M™ adjuvant by ELISA and serum activity by the standard *ex vivo* membrane feeding assay in a group of 8 rhesus monkeys following a 0-, 28- and 56-day immunization regimen. RNA sequencing was performed on fine needle aspirates collected from draining nodes proximal to the intramuscular injection site, prior to and at days 1, 7, 49 and 77 after vaccination. Differential gene expression coupled with immune cell transcriptome deconvolution illustrated a rapid and transient increase in the neutrophil signature in draining lymph nodes at day 1, followed by increases in myeloid and plasmacytoid dendritic cells and monocytes at later timepoints after vaccination. The TBV comprised of conjugated Pfs230D1-EPA formulated with Matrix-M™ adjuvant merits continued investigation.

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PFRIPR5, A NOVEL BLOOD-STAGE MALARIA VACCINE CANDIDATE, FORMULATED WITH ADJUVANTS FOR HUMAN USE, INDUCED POTENT GROWTH INHIBITORY ANTIBODIES

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The PfRipr antigen is a highly conserved asexual-blood stage malaria vaccine candidate against *Plasmodium falciparum*. We previously identified PfRipr5, the most potent inhibitory fragment of PfRipr. This antigen demonstrates the desired profile and is a promising candidate for the development of next-generation malaria vaccines. Recently, we established the method to produce PfRipr5 with a GMP-compliant scalable expression system. In this study, we examined the antigenicity of vaccine formulations with PfRipr5 and adjuvants for human use, i.e., Alhydrogel, GLA-SE, or CAF01. Purified PfRipr5 (50 or 200 µg) produced by GMP-compliant

expression system was adjuvanted with Alhydrogel, GLA-SE or CAF01. Six female Japanese White rabbits per group were immunized twice at three-week intervals subcutaneously with formulated PfRipr5. Antisera were collected two weeks after the last immunization. Antibody titers were measured by ELISA using purified PfRipr5 as an antigen. Functional activity of the rabbit antibodies was assessed in in vitro growth inhibition assay (GIA) with P. falciparum 3D7.Formulations with Alhydrogel, GLA-SE, and CAF01 induced significantly higher levels of anti-PfRipr5 antibodies than a group immunized with PfRipr5 alone. Average GIA activity of PfRipr5 (200 µg) formulated with CAF01 adjuvant was the highest among all groups. Based on the promising GIA results obtained with the antibodies elicited in rabbits after immunization, PfRipr5/CAF01 formulation is most suitable for subsequent pre-clinical development.

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WELL-MAINTAINED EFFICACY OF THE MALARIA VACCINE CANDIDATE R21 WITH MATRIX-M™ ADJUVANT (R21/MM) IN BURKINA FASO CHILDREN OVER 30 MONTHS WITH A SINGLE BOOSTER DOSE

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Progress in reducing malaria morbidity and mortality has stalled, with significantly increased incidence during the Covid-19 pandemic. A safe, low-cost, high-efficacy vaccine, suitable for large-scale production, is needed urgently. We recently reported efficacy over 24 months of 75% with 5µg R21 and 50µg Matrix-M™ adjuvant in a seasonal setting: this is the only malaria vaccine to date to reach the WHO-specified goal of ≥75% efficacy in African children. In June 2021, one year following a first booster (or fourth) dose, and two years following the primary series of three vaccinations (4 weeks apart), approximately 67% of the participants who previously received R21/MM, received a further (fifth) R21/MM vaccine dose, using again 50µg of MM, prior to the malaria season. A well-tolerated safety profile was observed with no vaccine-related SAEs. NANP-specific IgG levels were boosted significantly in those receiving a fifth dose. At 24 months following the primary series of vaccinations and 12 months after a fourth (booster) dose, vaccine efficacy (VE) in participants administered R21/MM with an adjuvant dose of 50µg, was 80% (95% CI, 72-85) measured as reduced incidence, and 78% (71-83) as reduced episodes. The VE (on incidence reduction) over the subsequent six months was 66% (95 CI%, 53-75) for the 67% of vaccinees receiving a further booster dose at 24 months, and this was similar to VE in those not administered this further booster dose, 73% (59-83). VE over 30 months after the primary series of vaccinations was 73% (59-82) and 69% (57-77) in those receiving four and five doses, respectively. VE data to 36 months will also be presented. These data support further development of the R21/MM vaccine and a 4800 participant phase III trial across four countries is now fully enrolled. Critically, there would be capacity to manufacture R21/MM at the likely required scale of 200-300 million doses annually for the target population after approval. Furthermore, these new data suggest that a four-dose regime of R21/MM may be sufficient to achieve a substantive impact over at least three years in endemic African settings.

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SOLUBLE PFCSP (FMP013) ADJUVANTED IN ALFQ INDUCES STERILE PROTECTION IN PHASE I TRIAL WITH CONTROLLED HUMAN MALARIA INFECTION CHALLENGE IN MALARIA-NAÏVE ADULTS

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Malaria vaccine candidate FMP013/ALFQ combines a soluble, nearly full-length, recombinant *Plasmodium falciparum* Circumsporozoite Protein (CSP) construct (FMP013) with Army Liposomal Formulation containing QS-21 (ALFQ) adjuvant. We present data from a single center, open-label Phase I clinical trial of intramuscularly administered FMP013/ALFQ with controlled human malaria infection (CHMI) challenge. Twenty-nine volunteers were enrolled to three groups. Ten volunteers (standard group) were administered 20 µg FMP013 in 0.5 mL ALFQ at each vaccination on a 0, 1, and 2 month schedule. Ten participants (delayed group) received the same dosing on a 0, 1, and 6 month schedule. The final nine volunteers (delayed fractional group) were vaccinated on a 0, 1, and 6 month schedule, and received a fractional third dose (4 µg FMP013 in 0.1 mL ALFQ). Doses were well tolerated with an acceptable safety profile. CHMI was conducted three weeks after third vaccination. We observed significant protection against parasitemia among delayed group volunteers through day 28 post-CHMI, with limited protection among delayed fractional and standard group volunteers. Further, significant delays in time to parasitemia were observed in delayed group volunteers who developed parasitemia. Preliminary serological profiling has revealed that FMP013/ALFQ recipients develop robust CSP antibody responses that are biased toward the C-terminal region of CSP, and achieve protection despite lower concentrations of CSP repeat region binding antibodies. Overall, intramuscularly administered FMP013/ALFQ is safe and immunogenic, making it an ideal resource for further study. The protective efficacy against CHMI elicited demonstrates that a particulate antigen is not an essential feature of efficacious CSP-based vaccine candidates. We continue to explore dose optimization and the immunologic basis for the difference in protective efficacy elicited in the delayed group versus delayed fractional and standard group vaccination regimens.

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GENERATION AND CLINICAL DEVELOPMENT OF A *PLASMODIUM FALCIPARUM* GENETICALLY ATTENUATED PARASITE VACCINE WITH COMPLETE LATE LIVER STAGE ARREST (PFSPZ-LARC2)

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Vaccination with-live-attenuated pre-erythrocytic *Plasmodium* parasites confers durable, sterilizing immunity against infection. Studies using rodent malaria models conclusively showed that genetically attenuated parasites

(GAP), which arrest late in liver stage development engender superior protective immunity compared to early liver stage-arresting RAS or GAPs. Such replication-competent attenuated parasites however have been difficult to establish in *P. falciparum* (Pf). In recent years, we have identified two gene knockouts in *P. yoelii* (Py) and Pf, which create similar late liver stage arresting replication-competent GAP (LARC GAP) phenotypes. These are, *Plasmei2*, a cytoplasm-localized RNA-binding protein and an uncharacterized protein expressed in liver stage nuclei called LINUP. To optimize attenuation, we generated *plasmei2*$^{-}$*/linup*$^{-}$ double knockout parasites (LARC2) in both Py and Pf. Infection of highly susceptible BALB/cByJ mice with a high dose of 250,000 Py LARC2 sporozoites (SPZ) did not result in any breakthrough infections, demonstrating that we have successfully generated a fully attenuated LARC GAP. Immunization with PySPZ-LARC2 conferred sterilizing immunity against sporozoite challenge. The Pf LARC2 strain was used to generate cryopreserved PfSPZ-LARC2 and was tested for full attenuation in a liver-humanized mouse model. PfSPZ-LARC2 has entered GMP manufacturing and is currently slated to be assessed for safety, tolerability, immunogenicity and efficacy in a clinical trial in 2022 using an injectable formulation. Vaccine efficacy of PfSPZ-LARC2 will be evaluated using controlled human malaria infection (CHMI) with heterologous Pf parasites, Pf7G8.

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INTRADERMALLY DELIVERED GLYCOLIPID-ADJUVANTED RADIATION-ATTENUATED SPOROZOITES ARE PROTECTIVE IN PRIME-AND-TRAP MALARIA VACCINATION

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Malaria is caused by *Plasmodium* parasites and was responsible for ~240 million infections and 600,000 deaths in 2021. Radiation-attenuated sporozoite (RAS) vaccines can completely prevent blood stage infection by inducing protective liver-resident memory CD8+ T (Trm) cells. Trm cells can be induced by 'Prime-and-Trap' vaccination, which combines nucleic acid-encoded antigen priming with a single intravenous (IV) dose of liver-homing RAS to direct and "trap" activated and expanding T cells in the liver. Prime-and-Trap confers durable protection in mice and efforts are underway to advance this vaccine strategy into non-human primates and possibly humans. It is unclear whether the RAS dose must be strictly administered by the IV route. In this study, intradermal (ID) dosing of RAS was evaluated for Prime-and-Trap vaccination. ID inoculation is an attractive route for vaccination since the skin is easily accessible, patrolled by antigen presenting cells, and possibly dose-sparing. Previous attempts at ID RAS delivery were ineffective - there was higher RAS vaccine efficacy following repeated IV administrations than after ID. Here, ultra-low volume (2.5µL) ID delivered *Plasmodium yoelii* RAS (irrPySPZ, Sanaria, Inc.) dosing in Prime-and-Trap vaccination resulted in increased vaccine efficacy compared to standard volumes (10-50µL). Co-administration of irrPySPZ with the glycolipid adjuvant 7DW8-5 in the ultra-low ID volume completely protected against *P. yoelii* wild-type sporozoite challenge in mice and was dose sparing. *P. yoelii* circumsporozoite protein-specific liver Trm cells and parasite liver burden following irrPySPZ administration were also evaluated to better assess the mechanism of vaccine efficacy. The finding that adjuvanted ultra-low volume ID RAS delivery is protective may explain why prior reports about higher volume ID RAS proved less effective. In summary, our findings demonstrate that Prime-and-ID-delivered adjuvanted RAS Trap is highly efficacious as a pre-clinical malaria vaccine. The ID route offers significant translational potential and may help advance the prime-and-trap vaccine toward the clinic.

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UNDERSTANDING PATTERNS OF ANTIGEN DIVERSITY AND IMMUNE SELECTION PRESSURE AMONGST LEADING *PLASMODIUM VIVAX* VACCINE ANTIGEN CANDIDATES AND SEROSURVEILLANCE MARKERS

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The recent WHO recommendation on the use of RTS,S vaccine against *Plasmodium falciparum* was a significant step towards global malaria control and elimination. Despite this, vaccine studies for the other major human malaria parasite, *Plasmodium vivax* (*Pv*) lag far behind with only two antigen-based candidates currently in clinical trials. A major gap in *Pv* vaccine research is the lack of information on the genetic diversity of antigens, which could provide critical data for designing a broadly-effective vaccine against *Pv*. We have completed a comprehensive meta-population genetic analysis of the diversity and immune selection of potential *Pv* vaccine candidate antigens. We measured patterns of genetic diversity and selection pressure based on comparisons of combined data from MalariaGEN *Pv* genomes and published gene sequences and we estimated the global distribution using traditional population genetics, Tajima's D test for neutrality, network analysis, and three-dimensional protein structures. Overall, our findings showed extensive allelic diversity in the merozoite surface protein genes *msp1, msp3α, msp5,* and *p41* and microneme antigen genes *dbp* and *ama-1*; low to moderate variability in majority of rhoptry encoding genes *rbp1α, rbp2α, rbp2b, ripr, s12*; and high gene conservation in gametocyte (*s16, s25,* and *s28*) and pre-erythrocytic (*csp*) genes. Haplotype network analyses showed geographic clustering in antigens with medium to high gene diversity, whereas low diversity antigens lack population structure. Furthermore, evidence of immune selection was observed across the length of antigen genes *rbp1α, rbp2α, cyrpa, ama-1, msp1* C-terminal, *msp3α* Block 1-B, *p41*, and *ripr*. Lastly, protein structural information showed immune selection hotspots clustered predominantly around important binding domains of *ama-1*, *dbp* RII, *cyrpa*, *rbp1α*, and $msp1_{33}$ consistently in all populations, suggesting that these residues are being targeted by protective antibodies. Information gathered from our study will guide researchers on the rational selection of antigen gene constructs to be included in designing a widely effective vaccine against *Pv.*

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A NOVEL VERSATILE BIO-PESTICIDE FOR INSECT-BORN DISEASE CONTROL

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Two-thirds of the world's population live in areas that are at risk for some of the world's most dangerous mosquito -borne diseases. The

wide-spread emergence of mosquito resistance against chemical insecticides and their negative environmental impact has created the need for a novel class of biological "bio-pesticides" as safer mosquito control agents. Propagated by climate change, the United States is also experiencing a surge in mosquito borne diseases such as various types of encephalitis-causing viruses, dengue and chikungunya. We have identified a natural soil bacterium, *Chromobacterium sp* Panama (*Csp_P*), that produce insecticidal factors and thereby provides an opportunity for the development of a novel bio-pesticide. The versatility of targeting both larval and adult mosquito stages with the same non-live and highly stable *Csp_P* preparation, that has been validated through both laboratory and semi-filed testing, is unique compared to other mosquitocides. Mosquito exposure to *Csp_P* for over 10 generations did not detect any emergence of resistance. We have developed an approach for cost-effective production of the *Csp_P* mosquitocidal that can be formulated to target and kill a variety of adult and larval stages of mosquitoes, as well as *Leishmania*-transmitting sand-flies (*Phlebotomus* and *Lutzomyia*) and major agricultural pests. Our innovation enables low-cost and highly efficacious control of both larvae and adult mosquitos with a highly stable biological insecticide powder that is soluble and can be combined with existing delivery methods such as bait stations and granules along with other formulations suitable for specific target pests.

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YEAST RNAI ATTRACTIVE TARGETED SUGAR BAITS (ATSBS) FOR ECO-FRIENDLY MOSQUITO CONTROL

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Attractive targeted sugar bait (ATSB) stations exploit mosquito sugar-feeding behavior by luring mosquitoes to feed on a sugar source containing an insecticide. This novel mosquito control intervention may help to combat pesticide resistance and reduce the burden of mosquito-borne illnesses. We have identified hundreds of interfering RNA-based pesticides, several of which kill both adults and juveniles and have target sites that are conserved among mosquitoes but not in non-target organisms. *Saccharomyces cerevisiae* strains that express the interfering RNAs were generated, permitting scaled RNA production in yeast, which was heat-inactivated, dried, and incorporated into sugar baits. Top-performing yeast RNAi ATSBs targeting *Shaker, Irx, Rbfox1,* and *GPCRs* were down-selected and evaluated in bait station trials conducted on *Aedes, Anopheles,* and *Culex spp.* mosquitoes. Adult mosquitoes of each species actively fed on the ATSBs in simulated field trials in which the yeast enhanced the attractiveness of the sugar bait and resulted in >90% morbidity (LD_{50} = ~0.16 µg yeast/µl bait) secondary to neural deficits. No evidence of resistance to RNAi yeast has yet been detected in laboratory studies to date, and no toxicity has been detected in non-target arthropod species. Preliminary studies predict that the costs of scaled propagation and drying of the RNAi yeast strains is expected to be comparable to that of industrial yeasts, suggesting that this system will facilitate cost-effective insecticide production. These studies indicate that mosquito-specific yeast interfering RNA pesticides will enhance existing mosquito control technology as second generation ATSB active ingredients. Current efforts, which include the pursuit of outdoor semi-field trials at multiple field sites, development of commercially-suitable yeast strains and formulations with extended residual activity, and scaling yeast production for future incorporation of this new control intervention into mosquito control programs worldwide will be presented.

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COMMUNITY-LED DEPLOYMENT OF SPATIAL REPELLENTS OFFERS PROTECTION AGAINST *AEDES AEGYPTI* IN MEXICO

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We have previously demonstrated that the deployment of a 10% w/w metofluthrin spatial repellent prototype, that requires no power or heat, can be deployed at 3 week intervals to reduce human landings (80-90% decreases) and the abundance of blood-fed mosquitoes (50-60% decreases). In a follow-up trial using a three-arm entomological cRCT (households= 588) in Uman (Yucatan State, Mexico) we now show that householders and communities can deploy the same product as effectively as an experienced vector control team. "Community-led deployment" (CD) and "Managed deployment" (MD) of the metofluthrin device were compared with an untreated control. The former (CD) consisted of the delivery of devices, a verbal "briefing", materials offering guidance on positioning and replacement, and an SMS reminder of the replacement cycle. The latter (MD) consisted of installation by an experienced research team. Treatment arms were switched at the trial midpoint to increase statistical power and determine whether a period spent observing the professional teams' deployment procedures had an impact on the efficacy of the community-led installation. A comparison of Incidence Risk Ratios across the trial arms demonstrated that the managed (MD) arm had higher efficacy (x = 82.5%) in reducing human landing activity in comparison to the community-led (CD) arm (x = 62%). The protection afforded by both arms was highly significant in comparison to untreated households. The trial was conducted against a mosquito population that displayed high frequencies of pyrethroid-resistance mutations (F1534C, V1016I, V410L). In the CD arm, most devices (80.6%) were installed as recommended by the promotional materials. After having participated in both treatment arms, participants preferred the community-led deployment (67%) over managed deployment (32%). The majority (92%) were satisfied with the trial outcomes. For urban, Aedes-borne diseases, community "ownership" and deployment of control tools may increase their effectiveness. Our results suggest safe, portable spatial repellents are suited to deployment by householders as a rapid response to local outbreaks.

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EFFECTIVENESS OF RELEASING MALE MOSQUITOES WITH *WOLBACHIA AS A* POPULATION SUPPRESSION METHOD FOR *AEDES AEGYPTI* MOSQUITOES IN PONCE, PUERTO RICO

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Arboviruses transmitted by *Aedes* mosquitoes, such as dengue, pose a public health challenge in tropical regions. Assessment of vector control methods is needed to determine effectiveness and scalability. In the *Wolbachia*-mediated population suppression method (*Wolbachia* suppression), releasing male mosquitoes infected with *Wolbachia pipientis* (strain wAlbB) reduces the mosquito population after mating with wild females because the resulting eggs do not hatch. Previous trials of this method have achieved *Aedes aegypti* population suppression up to 95%. Communities Organized to Prevent Arboviruses (COPA) is a cohort study in 38 clusters in Ponce, Puerto Rico (PR) to determine the incidence of arboviral diseases and evaluate vector control methods. The PR Vector

Control Unit implemented *Wolbachia* suppression in COPA in September 2020 after a widespread educational campaign. *Wolbachia* male mosquitoes were reared in San Francisco and shipped 5 days per week to PR using commercial flights. A total 604 Autocidal Gravid Ovitraps (AGO) were installed to monitor female *Aedes* mosquitoes. Preliminary results from releases in 19 clusters showed low suppression levels (~20%) and in January 2021, a phased-expansion strategy was adopted, concentrating releases in 4 clusters. A total of 96 million mosquitoes were released between September 2020 and December 2021. Overall, 30% of mosquito shipments were delayed. From April to December 2021, after a 3-month rollout period, the unadjusted highest weekly aggregated suppression level was 56% (95% CI 48-63%). Analyses are under way to determine cluster-specific and overall population suppression in intervention clusters after adjusting for rainfall, humidity, and temperature. Given the low number of incident infections in participants of the intervention and control clusters, epidemiological outcomes were not analyzed. A combination of logistical challenges, mosquito viability after transport, and local conditions may explain the suboptimal suppression levels and underscore the need to conduct integrated vector management, especially in tropical areas with robust mosquito populations.

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A CHLORFENAPYR-BASED NET INTERCEPTOR® G2 SHOWS HIGH EFFICACY AGAINST RESISTANT MALARIA VECTORS IN CAMEROON

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The increasing reports of resistance to current insecticides associated with reduced efficacy of control interventions highlight the urgency of introducing new non-pyrethroid control tools. Here, we investigated the performance of PBO-based (Permanet 3.0) and the dual active ingredients (AI) Long Lasting Insecticidal Nets (Interceptor G2 (IG2)) and Royal Guard (RG)) against pyrethroid-resistant mosquitoes in Cameroon. The efficacy of these tools was firstly evaluated on major malaria vectors *Anopheles gambiae* and *Anopheles funestus* sensu lato (s.l.) using cone assay in five sites across the country. In addition, a tunnel test assay followed by experimental hut trials (EHT) was carried out to evaluate the performance of these nets in semi-field conditions with unwashed and 20times washed nets. Furthermore, pyrethroid-resistant markers were genotyped using PCR-based technics in dead vs alive, blood-fed vs unfed mosquitoes after exposure to these nets for potential cross-resistance assessment. Our findings revealed that the chlorfenapyr-based net IG2 was the most efficient bednet followed by the PBO-based Permanet 3.0. In EHT, pyrethroid-only net (Royal sentry) killed just 18% (95% CI 13-23%) of host-seeking *An. funestus* whilst unwashed IG2 induced up to 87.8% (95% CI 83- 92%) mortality and 55.6% (95% CI 48- 63%) after 20 washes. The unwashed P3.0 killed up to 54% (95% CI 44-63%) of field-resistant mosquitoes and 47% (95% CI 38- 57%) when washed 20 times. IG2 and P3.0 provided also better personal protection (66.2% and 92.8%) and blood-feeding inhibition (17.7% and 24.9%) compared to pyrethroid-only net (8.4% personal protection and 2.3% blood-feeding inhibition). Interestingly, genotyping of the L1014F-kdrw in *An gambiae* and the L119F-GSTe2 mutation in *An funestus* revealed no impact of these markers on the efficacy of IG2. This demonstrates that the combination of chlorfenapyr/PBO and pyrethroids on bed nets (IG2 and P3.0) could be a suitable insecticide resistance management tool for preventing malaria transmission in areas compromised by the spread of pyrethroid resistance.

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MOLECULAR DRIVERS OF INSECTICIDE RESISTANCE IN THE SAHELO-SUDANIAN POPULATIONS OF A MAJOR MALARIA VECTOR

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Information on common markers of metabolic resistance in malaria vectors from countries/regions sharing similar eco-climatic characteristics can facilitate coordination of malaria control. Here, we characterized populations of the malaria vector *Anopheles coluzzii* from Sahelo-Sudanian region, spanning four sub-Saharan African countries, Nigeria, Niger, Chad and Cameroon. Genome-wide transcriptional analysis identified major genes previously implicated in insecticide resistance, overexpressed across the Sahel. These include CYP450s, glutathione S-transferases, carboxylesterases, and cuticular proteins. Several, well-known markers of resistance were found in high frequencies-including in the voltage-gated sodium channel (V402L, I940T, L995F, I1527T and N1570Y), the *acetylcholinesterase*-1 gene (G280S) and *CYP4J5*-L43F. High frequencies of 2La (2La arrangement is fixed), 2Rb and 2Rc chromosomal inversions were observed across the Sahel, with some of the commonly overexpressed metabolic resistance genes sitting in these inversions. Two most commonly overexpressed genes, *GSTe2* and *CYP6Z2* were functionally validated. Transgenic *Drosophila melanogaster* expressing *GSTe2* exhibited extremely high DDT and permethrin resistance (mortalities<10% in 24h). Serial deletion of the 5′ intergenic region, revealed that simultaneous insertion of adenine nucleotide and a transition (T->C), between Fork-head box L1 and c-EST putative binding sites are responsible for the high overexpression of *GSTe2* in the resistant mosquitoes. Transgenic flies expressing *CYP6Z2* exhibited marginal resistance towards 3-phenoxybenzylalcohol (a primary product of pyrethroid hydrolysis by carboxylesterases) and α-cypermethrin. These findings will facilitate regional collaborations within the Sahel region, and refine implementation strategies through refocussing interventions, improving evidence-based, cross-border policy towards local and regional malaria pre-elimination.

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RESTORING PYRETHROID SUSCEPTIBILITY IN *AEDES AEGYPTI*: A LONGITUDINAL STUDY IN TAPACHULA, MEXICO

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Pyrethroid resistance in the mosquito *Aedes aegypti* has become widespread after almost two decades of frequent applications to reduce the transmission of *Ae. aegypti* borne viruses. There are few available insecticide classes for public health; consequently, resistance management is required to retain their use. A key hypothesis of resistance management assumes that there is a negative fitness associated with resistance so that when insecticides are removed resistance will decline, and susceptibility will be restored. To assess if pyrethroid susceptibility is restored in the field, we conducted a longitudinal study in Tapachula, Mexico from 2018 to 2021, after the local authorities partially replaced pyrethroids by organophosphates for vector control. In this period, we determined the permethrin and deltamethrin lethal concentration required to kill 50% of *Ae. aegypti* populations (LC_{50}) and we screened two knockdown-resistance (*kdr*) mutations (V1016I and F1534C) in the voltage-gated sodium channel. Large spatial heterogeneity in pyrethroid LC_{50}'s was not explained by geographical distance, but possibly driven by focal selection at a smaller spatial scale. Despite this, significant decreasing rates of permethrin and deltamethrin resistance were observed in a multivariate logistic regression model that tested the relationship between the odds of dying (dead/batch) and three independent variables: concentration of insecticide, time,

and collection site. Holding concentration and site constant, for each month after discontinuing pyrethroids (2014), there was an increase of the odds of dying by 3.4% and 10.7% for permethrin and deltamethrin, respectively; this result supports the hypothesis of resistance decline after pausing the selective pressure. The rate of permethrin resistance decline appears to be associated with the fixation of F1534C and non-significant reduction of V1016I alleles. Continuing these long-term studies is critical to generate models that predict the restoration of pyrethroid susceptibility in field conditions as well to translate their significance in operational control.

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MICRORNAS ALTER PARASITE GROWTH, INFLAMMATION AND CELL ADHESION IN *LEISHMANIA* INFECTION

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Leishmaniases are diseases caused by parasites of the genus *Leishmania* that manifest as visceral, cutaneous and mucosal diseases. In Brazil the cutaneous form (CL) is mostly caused by *Leishmania (Viannia) braziliensis* and visceral (VL), by *L. (Leishmania) infantum*. Infection development is related to host immune and inflammatory responses and the *Leishmania* modulates host gene expression including miRNA. In previous studies, we evaluated the expression of miRNAs in *L. (L.) infantum* and *L. (V.) braziliensis* promastigote-infected human monocytic THP-1 cells in vitro and in plasma from patients with VL and CL. We identified some differentially expressed miRNAs, and some both in vitro and in patient samples, including miR-548d-3p that was upregulated in all approaches. Transfection of *L. (L.) infantum* and *L. (V.) braziliensis* infected- THP-1 cells with miR-548d-3p inhibitor, modulated the parasite growth, and altered certain chemokine levels such as MCP1/CCL2, RANTES/CCL5, and IP10/CXCL10, IL-8/CXCL8, MIG/CXCL9 (Souza et al. 2021, doi: 10.3389/fcimb.2021.687647; Ramos-Sanchez et al., 2022 doi: 10.3389/fcimb.2022.826039). In the present study, plasma samples from CL patients were analysed, five having active and other five self-healed lesions and five controls. We identified 14 differentially expressed miRNAs in self-healed individuals, eight up-regulated and six down-regulated in relation to the control. When comparing self-healed with the active disease group, we found 23 significantly different miRNAs, 14 of these up-regulated and nine down-regulated. Considering all differentially expressed miRNAs, we searched for target genes and metabolic pathways to predict miRNA/mRNA interactions. Two of these miRNAs found in plasma and in vitro approach were related to the pathway of adherens junction with 28 possible target genes. Our data suggest the involvement of miRNAs in the development of the lesion in leishmaniasis patients affecting parasite growth and inflammation as suggested by miR-548d-3p data and epithelial adherens junction leading to ulcer formation or healing.

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NEW INSIGHTS ON THE IMMUNOMODULATORY PROPERTIES OF THE *LEISHMANIA INFANTUM* EUKARYOTIC INITIATION FACTOR

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Leishmaniases are a complex group of neglected diseases, caused by intracellular *Leishmania* parasites. Neutrophils play an important role in the early recognition and elimination of *Leishmania* parasites and thus seems to influence the outcome of the infection. The exposure of neutrophils to immunomodulatory molecules, such as the LieIF protein (*Leishmania* eukaryotic Initiation Factor), could influence the functional activity of neutrophils. In this context, we aimed to evaluate the effect of the recombinant LieIF antigen on the modulation of neutrophils activity, and to assess its effect on neutrophils signaling pathway activation. For this purpose, human neutrophils isolated from healthy volunteers were stimulated with LieIF, and neutrophil activation was assessed through reactive oxygen species (ROS) quantification, degranulation, apoptosis and cytokines release. The activation of phosphatidyl-3-phosphate kinase (PI3K)/AKT and Mitogen-*activated* protein kinases (MAPKs)ERK1/2, *p38* and *JNK* were also determined from un-stimulated and stimulated neutrophils by western blotting. We demonstrated that LieIF-stimulated neutrophils induced ROS production, the release of elastase and myeloperoxidase. Interestingly, LieIF induced high level of IL-8 secretion along with increased TNF-α, IL-1β and IL-6 cytokines production and reduced level of the anti-inflammatory TGF-β1 cytokine. The life span of LieIF stimulated neutrophils was prolonged. Furthermore, LieIF induced the activation of p38 kinase with no effect on AKT, ERK1/2 and JNK pathways. The significance and the link between the functional activity of neutrophils and the activation of p38-MAPK pathway are under investigation. In conclusion, our results demonstrate that LieIF modulates *in vitro* functional activity of human neutrophils, thus providing additional insights on the immunomodulatory properties of the recombinant LieIF antigen.

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IMMUNE RESPONSE TO SAND FLY SALIVARY PROTEIN, LINB-13, IS ASSOCIATED WITH DISEASE SEVERITY AND TREATMENT OUTCOME IN TEGUMENTARY LEISHMANIASIS PATIENTS

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Sand flies inject saliva while feeding in the vertebrate host and anti-saliva antibodies can be used as biomarkers of exposure to Leishmania vectors. We have previously shown that seropositivity to LinB-13, a salivary protein from *Lutzomyia intermedia*, predicted sand fly exposure and was associated with increased risk of developing cutaneous leishmaniasis (CL). Herein, we investigated the cellular immune response to saliva from *Lu. intermedia*, using LinB-13 as a surrogate antigen in naturally exposed individuals presenting positive serology to LinB-13, but without disease. We also investigated the response to LinB-13 in tegumentary leishmaniasis (TL) patients including CL (n=28), mucosal leishmaniasis (ML) (n=17), disseminated leishmaniasis (DL) (n=46) and 33 subjects with subclinical *Leishmania braziliensis* infection (SC). Peripheral blood mononuclear cells (PBMCs) from exposed individuals stimulated in vitro with LinB-13 secreted elevated levels of IL-10, IL-4, IL-1β, IL-1α, and IL-6 compared to unexposed controls. CL, and DL patients displayed a significantly higher IgG response

to LinB-13, compared to healthy subjects and SC individuals. Anti-LinB-13 IgG was positively correlated with the number of lesions in DL patients and positive serology to LinB-13 was also associated with treatment failure in DL. PBMCs from DL patients stimulated with LinB-13 secreted significantly higher levels IL-10 and IL-1β compared to CL individuals. In this study, we observed an association between humoral and cellular immune response to the sand fly salivary protein LinB-13 and disease severity in TL. This study brings evidence that immunity to LinB-13 may influences disease outcome in *L. braziliensis* infection and results indicate that antibody response to LinB-13 can be employed in the field for identification of patients at high risk of failing antimonial therapy in DL, an emerging and severe form of disease caused by *L. braziliensis*.

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SUNDRY LITTLE PAWS: INVESTIGATING THE IMMUNOLOGY OF *GIARDIA INTESTINALIS* INFECTION IN INDIVIDUALS WITH AND WITHOUT TUBERCULOSIS

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Giardia intestinalis is a protozoal parasite causing intestinal infections, especially in areas with poor sanitation and limited access to clean drinking water. The host response to tuberculosis (TB) disease is complex and multi-faceted and may cause individuals to be more susceptible or have altered immune responses to parasite infections, such as *G. intestinalis*. Little is known about the immunology of co-infection and information to date is mainly limited to murine models. In a cohort of individuals diagnosed with pulmonary tuberculosis and their household contacts who were TB-exposed, we performed a nested cross-sectional study to describe the prevalence of *G. intestinalis* infection and identify immunologic profiles associated with TB disease and *G. intestinalis* co-infection. Subsets of these patients underwent analysis of immune markers including TNF-alpha, interferon gamma (IFNγ), CXCL9 and IL-18 levels. Individuals with TB disease and *G. intestinalis* infection had increased basal (non-stimulated) expression of TNF-alpha level than those without *G. intestinalis* (p-value 0.035). In addition, patients with TB disease and *G. lintestinalis* infection had higher basal (non-stimulated) CXCL9 levels than those without *G. lamblia* (p-value 0.015). TB patients with *G. intestinalis* infection had decreased IFNγ immune responsiveness when stimulated with a mitogen than those without *G. intestinalis* infection (p-value 0.047). In those with TB disease, basal IL-18 levels were not significantly different between those with and without *G. intestinalis* infection (p-value 0.34). In conclusion, patients with TB disease who are co-infected with *G. intestinalis* demonstrate increased inflammation (increased basal expression of TNF alpha and CXCL9) but have decreased mitogen-induced IFNγ immune responsiveness. Inflammation with decreased immune responsiveness is a common immune phenotype of chronically infected individuals, potentially suggesting that *G. intestinalis* infection is exacerbating immune suppression in TB.

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TRANSCRIPTOME LANDSCAPE OF PLACENTAL TROPHOBLASTS REVEALS SIGNALING PATHWAYS ASSOCIATED WITH RESISTANCE TO *TRYPANOSOMA CRUZI* INFECTION

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Vertical transmission of *Trypanosoma cruzi* (*T. cruzi*) has become a global health problem accounting for 22% of new cases of Chagas disease (CD). Congenital infection is considered the main route of CD spread in non-endemic countries where no routine disease testing of pregnant women is implemented. Congenitally infected infants have the risk of developing chronic CD with severe cardiomyopathy or gastrointestinal disease later in life. The mechanisms that lead to fetal infection by *T. cruzi*, despite the presence of a placental barrier, remain unclear. Mother-to-child transmission most likely occurs when bloodstream trypomastigotes reach the placental intervillous space and interact with the large cellular surface provided by the syncytioptrophoblasts (SYNs). These highly specialized cells not only function as a physical barrier, but also modulate immune responses against pathogens. To recreate the human placenta environment, we previously established a three-dimensional (3D) cell culture system of SYNs that exhibits differentiation characteristics comparable to placental trophoblasts. Further, we have shown that 3D-grown SYNs are highly resistant to *T. cruzi* infection. In this work, we performed whole transcriptome analysis of 3D-grown SYNs exposed to *T. cruzi* using RNA sequencing. The largest category of differentially expressed genes (DEGs) control inflammation and immune response functions. Other DEGs are involved in the regulation of apoptosis and cytoskeleton remodeling. Quantitative RT-PCR evaluation of selected DEGs, together with detection of cytokines (IL-6, IL-8, TNF-a) and chemokines (MCP-1, GM-CSF) in 3D-grown SYNs culture supernatants, confirmed the transcriptome data. Specific pathways affected in SYNs exposed to *T. cruzi* were predicted by Ingenuity Pathway Analysis (IPA). The top canonical pathways included phagosome formation, pathogen-influenced signaling, cytokines signaling and production of nitric oxide and reactive oxygen species. Our findings indicate that SYNs may limit parasite infection by upregulating multiple defense mechanisms associated with the host innate immune response.

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CHARACTERIZATION OF THE ENZYMATIC ACTIVITY OF AN UNUSUAL DED1/DDX3 LIKE PROTEIN FROM THE PROTOZOAN PARASITE *LEISHMANIA INFANTUM*

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Leishmania DExD/H-box proteins, particularly the DEAD-box proteins, are highly divergent from their eukaryote counterparts in other organisms, and thus they provide a rich source of potential, protein-specific, drug targets. In general, they present an RNA-dependent ATPase activity in which the divalent cation Mg^{2+} is needed to catalyse the hydrolysis reaction. We previously identified two potential homologs and one paralog of the Ded1/DDX3 subfamily of proteins in *L. infantum* by an *in-silico* analysis of the conserved sequence elements based on sequence alignments of a large collection of Ded1/DDX3 proteins from various organisms. In this study, we particularly characterized the *L. infantum* paralog, encoded by *LINF_080005700*, "LINF08", of the Ded1/DDX3 subfamily because it showed several differences that would be expected to affect its enzymatic activity. Thus, we cloned and expressed this protein using *E. coli* cloning and expression vectors and IPTG induction, and purified the recombinant LINF08 protein on nickel nitrilotriacetic acid agarose columns. Then, we optimized the ATPase assay based on previously published conditions for yeast Ded1, by testing different reaction conditions. We used Ca^{2+} as a negative divalent cation control and monitored the catalysis of the hydrolysis reaction. LINF08 showed an original observation for a DEAD box protein, exhibiting a very high intrinsic ATPase activity in absence of RNA, and a higher enzymatic efficiency than Ded1 in presence of RNA and Mg^{2+}. Interestingly, we demonstrated that LINF08 preferentially uses Ca^{2+} over Mg^{2+} as a cation, showing more than 2-fold higher reaction velocity with Ca^{2+} than with Mg^{2+}. In fact, LINF08 present particular characteristics, such as the Ca^{2+} dependence, which are also found in ectonucleoside triphosphate diphosphohydrolases. The ecto-NTPDases are extracellular enzymes that hydrolyse ATP to modulate levels of NTPs. It is likely that LINF08 diverged from a role as an RNA helicase to have other functions in the parasite. Thus, further studies are conducted to investigate expression, localization and functions of LINF08 protein in *Leishmania* parasites.

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REGULATION OF INFLAMMATORY RESPONSE IN CUTANEOUS LEISHMANIASIS PATIENTS THROUGH PPAR-GAMMA SIGNALING

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Cutaneous leishmaniasis (CL) due to *Leishmania braziliensis* infection can lead to skin ulcers development, characterized by intense inflammatory infiltrate, composed mainly by mononuclear phagocytes, lymphocytes and NK cells. Macrophage-derived TNF and IL-1β is a hallmark of the disease and low number of *Leishmania* parasite is observed at lesion site. Pentavalent antimonial is the drug of choice to treat leishmaniasis in Brazil, however, since high therapeutic failure rates to this drug has been documented, adjuvant therapies to decrease inflammation may benefit CL patients. The aim of this work was to identify mechanisms of regulation of inflammatory response in CL patients. Blood and skin lesion fragments were obtained from CL patients and cultured in the presence of soluble *Leishmania* antigen (SLA) and recombinant IL-10 or ligands of PPAR-gamma, a nuclear lipid receptor expressed by macrophages. Levels of IL-1β, IL-6 and TNF were determined in supernatant cultures, by ELISA. We observed that lesion cells from CL patients produce high levels of proinflammatory mediators early and late after infection. Addition of exogenous IL-10 failed to decrease the production of granzyme B, IL-1β, CXCL9 and CXCL10 in CL individuals, independently of the time since lesion appearance (early or late CL). Signaling through PPAR-gamma has been shown to decrease inflammatory response. Addition of PPAR-gamma ligands, Omega 3 fatty acids (EPA and DHA) or Pioglitazone, to lesion cells decreased the levels of IL-6, TNF and IL-1β without affecting parasites counts. Our results suggest that adjuvant topical treatment with Omega 3 fatty acids or Pioglitazone may be beneficial for CL patients.

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ABAMETAPIR - A PROMISING SINGLE DOSE SCABICIDE CANDIDATE WITH MULTIPLE TARGETS

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Scabies, a contagious skin disease in humans, is caused by the obligatory parasitic mite, *Sarcoptes scabiei* var *hominis*. There are no vaccines and only few therapeutics with sub-optimal efficacies available to treat scabies. The commonly used oral ivermectin and topical permethrin are single target neuro-inhibitors and ineffective on the egg which is the "amplification" stage in the *S. scabiei* life cycle. Therefore, repeat treatments are required for the complete elimination of the parasite. Patient incompliance to repeat treatments and prolonged use of current drugs have led to emerging parasite resistance. Abametapir is a FDA-approved ovicidal lousicide with metal chelating properties. It has the ability to target multiple proteins and pathways that require metal ions as co-factors and are essential for parasite survival. We aim to evaluate the potential of abametapir as a single dose topical treatment against *S. scabiei*. *In vitro* drug exposure assays were conducted using *S. scabiei* var *suis*. Mites and early /late egg stages were exposed to the FDA approved dose of pure abametapir at different exposure times. Mite mortality and egg hatchability were recorded compared to untreated control samples. Lethal exposure times (LT) were determined by probit analysis at 95% confidence interval. Proteomes of treated vs untreated mites and eggs were generated and analysed for abametapir target elucidation. Abametapir effects in metalloproteases were investigated by zymography assays combined with mass spectrometry. LT_{50} and LT_{95} were 15.30 (14.00–16.75) h and 49.50 (41.20–63.00) h for mites, 1.23 (0.98–1.52) h, 9.32 (6.75–14.65) h for early stage eggs and 8.27 (6.78 – 9.95) h and 23.49 (17.97 – 36.25) h for late stage eggs. The data indicates that abametapir affects all developmental stages of *S. scabiei*. Proteomic and zymography analyses indicated that abametapir interferes with several *S. scabiei* proteins and proteases, including multiple metalloproteases involved in a range of biological processes. Our results indicate abametapir as a promising single dose scabicide candidate with multiple targets and novel modes of action.

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B-TRIKETONES, A NOVEL NEXT GENERATION SCABICIDE?

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Scabies is a contagious skin disease caused by the obligate parasitic mite *Sarcoptes scabiei*. It affects approximately 300 million people per year globally and is linked to secondary bacterial infections with life-threatening sequelae. Scabies is a major public health problem in Australian Aboriginal communities. Available drugs for scabies are suboptimal as they mainly target the motile parasite stages and fail to kill eggs. We tested six commercial Mānuka oils for scabicidal efficacy *in* vitro and among these, the best one showed ovicidal and miticidal activities of >95% and 100% respectively. The active constituents of this Mānuka oil were determined through a bioactivity-guided fractionation together with compositional analysis of the crude oil and fractions via 1H NMR and gas chromatography. β-triketones were revealed as active chemicals using Spearman's Correlations analysis. Three β-triketones were tested on mites and eggs at different concentrations and different time points *in vitro*. The LC50 and LT50 values were generated using Probit analysis. Possible synergistic effects in combinations of β-triketones were tested on mites and eggs and the data were analysed using Compusyn Software. The β-triketones did not show significant differences in LC50 and LT50 values. The lowest LC50 values measured at 4h exposure of mites were 57.8 mM (95% CI 54-61.7) and 33.6 mM (95% CI 29.2-38.0) when eggs were continuously exposed and hatching was recorded after three days post-exposure. The lowest LT50 values for mites and eggs at a concentration of 150 mM were 1.3 (1.2-1.4) h and 8.0 (6.3-9.7) h, respectively. No synergism was observed between the three β-triketones. Our findings suggest that β-triketones in Mānuka oil have strong scabicidal activities, which could be exploited further to develop a novel scabicide.

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ONGOING TRANSMISSION OF ONCHOCERCIASIS IN THE ENDEMIC CAMEROON-CHAD CROSS-BORDER AREA AFTER MORE THAN TWENTY YEARS OF MASS IVERMECTIN DISTRIBUTION

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In Africa, human onchocerciasis caused by *Onchocerca volvulus* is transmitted mainly by members of the *Simulium damnosum* complex.

The disease prevalence and intensity is related to vector biting rates. Onchocerciasis transmission is targeted for elimination mainly through mass distribution of ivermectin (MDA). This started in 1987 in the Vina Valley, Cameroon, an endemic cross-border area between Cameroon and Chad, known for its high vector biting rates and pre-control endemicity. This area has had between 24 to over 30 years of MDA. Evaluations in some border communities in 2008-2010 showed ongoing transmission, while the endemic area on the Chad side is close to transmission interruption. Any ongoing transmission in the Cameroon side of the border poses a challenge to Chad's onchocerciasis elimination goal. This study aimed at investigating onchocerciasis transmission status in the border communities in Cameroon. Blackflies were collected and dissected from seven border communities (Mbere-Tchad, Babidan, Mafare, Touboro, Gor, Djeing, Koinderi) within Cameroon by Human Landing Collection method from August 2021 to February 2022. Dissected flies were examined for parity and presence of filarial parasites indistinguishable from *O. volvulus*. The transmission potential for the duration of the study was calculated by adding individual monthly transmission potentials. A total of 13,331 female flies were collected, 6,522 (49 %) dissected of which 3,862 were parous (59%). Thirty-two (32) parous flies were infective carrying a total of 71 infective larvae (L3H). The biting rates (bites/man/ study period) and transmission potentials (infective larvae/man/study period) were respectively 16,407 and 344 (Mbere-Tchad), 15,805 and 146 (Babidan), 1,554 and 51 (Mafare), 9,720 and 20 (Gor), 1,245 and 0 (Touboro), 2,148 and 0 (Djeing) and 186 and 0 (Koinderi). These values exceed the WHO Annual Transmission Potential threshold of <20 infective larvae/man/year. Thus, 24 to more than 30 years of MDA has not eliminated onchocerciasis in the study area, posing a risk to neighbouring endemic areas in Chad that may attain transmission elimination.

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EVALUATION OF THE ESPERANZA WINDOW TRAP FOR CATCHING ONCHOCERCIASIS VECTORS IN DIFFERENT ECOLOGICAL AREAS OF ETHIOPIA

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Entomological surveillance on *Simulium* black flies is an indispensable component of onchocerciasis elimination. However, collecting black flies by human landing collection (HLC) has many issues although it is the gold standard as recommended by the World Health Organization (WHO). Issues of exposing fly collectors to onchocerciasis and stationing them in one place for long periods triggered the search for an alternative catching method. The Esperanza Window Trap (EWT) was evaluated in different ecological areas of Ethiopia between 2014 and 2018. Materials were sourced both locally and from the US for EWTs. The trap was designed as a one-meter square polyester sheet with black and blue vertical stripes. Carbon dioxide was generated by combining white sugar and baking powder (yeast). The trap was painted with a tanglefoot (insect adhesive) to capture all landing black flies. The trap was erected at a 90° angle to the river and at least 10 cm above the ground. The BG lure® (human sweat) was attached at the middle of the trap. Worn clothes were also used as a lure to enhance fly attraction. HLC was done by volunteer catchers based on WHO guidelines from 7:00 AM to 6:00 PM in conjunction with the traps. *S. damnosum* complex and *S. neavei* group were caught by both HLC and EWT. In West Gondar zone in northwestern Ethiopia, vectors caught by EWT ranged from negligible to 150% as many flies as HLC. In southwestern Ethiopia on the Dembi River, an area known for its high fly density (annual biting rate [ABR]=304,302 bites/person/year), and the Gojeb River (ABR=90,045), EWTs produced 41% of the overall yield compared to 59% from HLC. In hot areas, flies caught by EWT became desiccated which impaired O150 PCR analysis. Use of worn clothes incurred economic concerns despite their efficiency of olfactory attraction. The study indicated that HLC is still a better method of fly collection due to inefficiencies and drawbacks of the trap. We recommend optimizing the trap with more concentration of BG lure® and experimenting with different sizes and color patterns to eventually replace HLC.

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INFLUENCE OF DERMAL IMMUNITY FOLLOWING EXPOSURE TO SAND FLY BITES ON LEISHMANIA INFECTION

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Leishmaniasis is a significant public health problem in many regions of the world. During acquisition of a blood meal, sand fly introduce an array of pharmacologically active salivary proteins and microbiota into the skin that influence hemostasis and inflammation. While it is known that these responses can influence the outcome of *Leishmania* infection, the immunological mechanisms underpinning this phenomenon and the immune response elicited by blood feeding are poorly understood. In the present study we investigated the immune response elicited by exposure to the bites of *Lutzomyia longipalpis* sand flies. As previously shown, short-term exposure to insect blood feeding activated salivary antigen-specific interferon (IFN)-gamma producing dermal-derived $CD4^+$ Th1 cells. However, upon repeated exposure, the immune response underwent diversification at the population level to include multiple salivary antigen-specific $CD4^+$ subsets (Th1, Th2, Th17 and T_{REG}), at both the dermal site of exposure and systemically. Analysis of the development of delayed type hypersensitivity (DTH) at the bite site during ongoing chronic exposure to sand fly bites revealed four phases of bite-induced DTH, the last of which correlated with a high-degree of immunoregulation. Chronic exposure was associated with enhanced cellular recruitment to the skin, an alteration in the maturation of inflammatory monocytes towards an alternatively activated macrophage phenotype, and enhanced disease upon subsequent challenge with *Leishmania* plus salivary gland homogenates. These observations demonstrate how exposure to sand fly blood feeding can alter the dermal environment and how the 'host-vector-pathogen' relationship may impact the success of prophylactic and therapeutic intervention strategies against leishmaniasis.

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NATURAL SUGAR FEEDING RATES OF *ANOPHELES* MOSQUITOES COLLECTED BY DIFFERENT METHODS IN WESTERN KENYA

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Attractive targeted sugar baits (ATSBs) are a potential vector control tool that exploits the sugar-feeding behavior of mosquitoes. This study evaluated the sugar feeding behavior of *Anopheles* mosquitoes in western Kenya as part of baseline studies in advance of a cluster-randomized trial to evaluate the impact of ATSBs on malaria transmission. *Anopheles* mosquitoes were collected from two villages in Siaya County in western Kenya. Three trapping methods were compared, including UV light traps placed indoors, outdoors within 10 meters from the structure, outdoors

10 meters from the compound, prokopack aspirations (conducted indoors and outdoors), and malaise traps (set outside the compound). Individual mosquitoes were subjected to cold anthrone test to assess the presence of sugar. Overall, 17% of collected mosquitoes had fed on natural sugar sources. *Anopheles funestus* had the highest rate of sugar feeding with 38.2% of males and 27.3% of females. followed by *An. arabiensis* with 26.4% of males and 12.7% of females. For *An. coustani*, 9.7% of males and 8.2% of females had fed on sugar. Male mosquitoes collected by aspiration had the highest levels of sugar feeding both indoors and outdoors compared to the other collection methods. Female mosquitoes showed no significant difference in sugar feeding rates by collection method. Sugar feeding among the unfed female and male mosquitoes was significantly higher compared to blood-fed and gravid mosquitoes across all the species. The highest sugar feeding rates were observed between 03:00 and 07:00 hours for *An. coustani* (14%), between 17:00 and 21:00 hours for *An. gambiae* s.l. (16%), and between 00:00 and 03:00 for *An. funestus* (52%). Indoor resting *An. funestus* have the highest sugar feeding rate suggesting the potential for ATSB to impact on the principal malaria vector in this region. Both indoor and outdoor resting mosquitoes are shown to sugar feed suggesting the potential of outdoor placed ATSBs to control both indoor and outdoor resting mosquitoes.

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FIELD EVALUATIONS OF NOVEL SPATIAL REPELLENT TOOLS FOR VECTOR-BORNE DISEASES IN CONFLICT AFFECTED COMMUNITIES LIVING IN TEMPORARY SHELTERS - STUDIES ON MOSQUITOES AND SANDFLIES

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From March 2021 to March 2022 The Mentor Initiative conducted a randomized controlled trial (RCT) in North-East Syria to evaluate the effectiveness of the novel spatial repellent "Envelope" on the reduction of cutaneous leishmaniasis (CL) transmitted by the sandfly vector. This comprises of a plastic sheet which releases transfluthrin over the period of 1 month which repels insects and builds a protective "bubble" inside the shelter. The tool is very lightweight, easily transportable, safely storable, stable over long time periods and also low cost. . A total of nine camps were randomly allocated to either intervention arm (Envelope and medical service), positive control arm (IRS and medical service) or negative control arm (medical service only). The study is monitored on epidemiological (CL incidence rates) and entomologic level (sand fly collection in households). In the intervention arm, the Envelopes were distributed to 10`000 individuals on a monthly bases and the uptake, understanding and acceptance was assessed among the conflict-affected community. Preliminary results indicate lower numbers of monthly collected sand flies in the intervention arm (between 4 and 38) compared to the negative control arm (between 26 and 209) throughout the study period. Similarly, first epidemiological results show a reduction of the number of newly diagnosed patients in the intervention arm (27/10`000 persons) compared to the negative control arm (48/10`000 persons) over the months from March to December. An Envelope uptake rate of 101% was achieved and the majority (88%) of the households correctly understood how to use the Envelopes according to pictogram instructions, 72% of the families retained the spatial repellent until the end of the month, 58% appreciated it and 79% wished to access it also in future. In conclusion, the novel spatial repellent "Envelope" appears to be highly effective as a VC tool and thus in reducing CL transmission within a camp setting hosting mobile and hard to reach populations. The vector control tool was largely up taken, well understood, and highly appreciated amongst the beneficiaries.

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RNA SEQ REVEALS DIFFERENTIAL TRANSCRIPTOME PROFILES IN KENYAN CHILDREN WITH SEVERE MALARIA ANEMIA AND PREDICTS BIOLOGICAL PATHWAYS MEDIATING IMMUNITY

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Severe malarial anemia (SMA: Hb<5.0 g/dL, with any density parasitemia) is a common clinical manifestation of severe malaria in infants and young children in holoendemic *Plasmodium falciparum* transmission areas. For example, SMA is the leading cause of malaria-related morbidity and mortality in the lake-region Siaya community of western Kenya. To understand the changing dynamics in gene expression and identify biological pathways involved in malarial immunity, we determined host transcriptome profiles in children with non-SMA (Hb≥5.0g/dl, n=41) and SMA (n=25) presenting at Siaya County Referral Hospital. Total RNA was isolated from whole blood and triplicate libraries were generated for samples collected upon presentation at hospital for acute malaria (pretreatment). RNA sequencing was performed to a coverage of >20 million high-quality mappable reads using the Illumina platforms. Sequence reads were mapped to the human genome (GR Ch38) using the STAR software. Differential gene expression analysis between the two clinical groups was performed using the EdgeR package, while functional enrichment analysis was performed using clusterProfiler software. Results revealed that 992 genes were uniquely expressed in children with non-SMA and 328 genes SMA, while 15,596 genes were co-expressed in both the clinical groups. Inference of the overall distribution of differentially expressed genes revealed that 3,420 were up-regulated and 3,442 were down-regulated. Gene ontology enrichment analysis identified neutrophil activation ($p$adj=1.0411^{-20}), immunity ($p$adj=1.0412^{-20}), and degranulation ($p$adj=1.5275^{-20}) as the top 3 pathways. KEGG enrichment analysis revealed protein processing in the endoplasmic reticulum ($p$adj=7.8818^{-09}) and endocytosis ($p$adj=3.3826^{-05}) as top-ranked pathways. Collectively, these results identified differentially expressed genes in children with SMA that identified central biological pathways that appear to be involved in modulating the immune response against severe disease.

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MALARIA PARASITE SERINE/ARGININE-RICH PROTEIN KINASE 1 REGULATES ASEXUAL BLOOD STAGE SCHIZOGONY AND IS ESSENTIAL FOR MALE GAMETE FORMATION

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Serine/arginine-rich protein kinases are cell cycle-regulated serine/threonine protein kinases and are important regulators of splicing factors. The genome of *Plasmodium* species encodes two distinct SRPKs. In this

study, we functionally characterize SRPK1 of the human malaria parasite *Plasmodium falciparum* (*Pf*). *PfSRPK1* was expressed in asexual blood stages and sexual stage gametocytes. *Pfsrpk1*¯ parasites formed asexual schizonts that generated far fewer merozoites when compared to wildtype parasites, causing reduced replication rates. *Pfsrpk1*¯ parasites also showed a severe defect in the differentiation of male gametes, causing a complete block in parasite transmission to the mosquito. RNA-seq analysis of wildtype *Pf*NF54 and *Pfsrpk1*¯ stage V gametocytes suggested a role for *Pf*SRPK1 in regulating transcript splicing and transcript abundance of genes coding for (i) microtubule/cilium morphogenesis related proteins, (ii) proteins involved in cyclic nucleotide metabolic processes, (iii) proteins involved in signaling such as *Pf*MAP2, (iv) lipid metabolism enzymes, (v) osmophilic bodies and (vi) crystalloids. Our study reveals an essential role for *Pf*SRPK1 in parasite cell morphogenesis and suggests a potential therapeutic avenue in the design of developing transmission-blocking drugs against *Pf*SRPK1 to prevent malaria transmission from man to mosquito.

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RNA SEQUENCING WITH *DE NOVO* ASSEMBLY INDICATES EXPRESSION OF DUAL-BINDING PFEMP1S IN MALIAN CHILDREN WITH SEVERE MALARIA

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Severe malaria disproportionately affects children under the age of five in sub-Saharan Africa. *Plasmodium falciparum* is the cause of most severe malaria in children, and this parasite species has the unique ability to sequester in the host's vasculature by attaching to cells in the endothelium. Cytoadhesion is mediated by parasite variant surface antigens including *P. falciparum* erythrocyte membrane protein-1 (PfEMP1) antigens that are displayed on the surface of the infected erythrocyte. To identify PfEMP1 variants associated with cerebral malaria and severe malarial anemia, we conducted a case-control study of severe malaria cases matched to uncomplicated malaria controls in Mali, West Africa, from 2014-2018, that included children aged six months to five years. Using RNA sequencing data, we assembled *de novo* reads from *var* transcripts encoding PfEMP1s for cases of severe malaria and matched uncomplicated malaria controls. We classified expressed PfEMP1s, including identifying domain subtypes to predict binding targets in the host, such as endothelial protein C receptor (EPCR) and intercellular adhesion molecule-1 (ICAM-1). We identified *var* transcripts in cases of cerebral malaria (n = 14), severe malaria anemia (n = 8), cerebral malaria and severe malarial anemia (n = 8), and matched uncomplicated malaria controls with or without a history of severe malaria (n = 39). Cases had significantly more unique *var* transcripts compared to matched controls without a history of severe malaria ($p = 0.0014$) and compared to matched controls with a history of severe malaria ($p = 0.045$). We did not find increased expression of EPCR-binding PfEMP1s in cases of severe malaria compared to uncomplicated malaria controls. However, transcripts for PfEMP1s containing both an EPCR-binding domain and an ICAM-1-binding motif were significantly more expressed in cases of severe malaria compared to matched controls without a history of severe malaria ($p = 0.014$). These "dual-binding" PfEMP1s may be a promising target for development of vaccines or severe malaria treatments.

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CD47 REGULATES PARASITE BURDEN AND PROMOTES PATHOGENESIS IN MURINE MALARIA MODELS

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CD47 is an anti-phagocytic ("don't eat me") signal that inhibits programmed cell self–removal; loss of this molecule by aging erythrocytes is associated with increased likelihood of macrophage phagocytosis. We have investigated the role of CD47 in malaria immunity and pathogenesis in murine malaria models. Previously, we demonstrated that absence of CD47 confers resistance to infection with *Plasmodium yoelii* 17XNL, a murine malaria that exhibits an aged-based preference for young erythrocytes. Next, we established that CD47 blockade with an anti-CD47 monoclonal antibody promotes survival and reduces the pathologic features of experimental cerebral malaria (ECM) during *Plasmodium berghei* ANKA (*Pb–A*) infection in C57BL/6 mice, a murine model of ECM. To delineate the immunological mechanism of CD47 regulation of ECM pathogenesis, we present studies comparing *Pb–A* infection in wildtype (WT) versus CD47 KO C57BL/6 mice. In CD47 KO mice, absence of CD47 resulted in partial but highly significant ($p<0.001$, log-rank) resistance to ECM; following infection with *Pb–A* parasites, 22/23 (95.6%) WT mice developed ECM by day 10 post-infection. In contrast, only 13/23 (56.5%) of CD47 KO mice succumbed to malaria during the cerebral phase of infection. Through flow cytometric analysis of brain sequestered and splenic immune cell subsets and cytokine profiling of serum, we show that absence of CD47 during *Pb–A* malaria is associated with a significant reduction in brain sequestered $CD8^+$ T cells which are pathogenic during ECM, an increase in splenic $CD107a^+$ NK cells, and alteration of a small subset of cytokines. In addition, comparative analysis of WT versus CD47 KO brain tissue by immunohistology demarcates clear differences in pathologic features such as hypertrophied endothelial cells, presence of parasite hemozoin, macrophage infiltration, vasculopathy, and ring hemorrhages. A further understanding of the mechanism of anti-CD47 antibody-mediated protection from ECM may open avenues for novel immunologic-based treatment options against cerebral malaria in African children.

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EXPRESSION OF SYNDECAN-1, A RECEPTOR FOR *PLASMODIUM FALCIPARUM* INFECTED RED BLOOD CELLS, MAY BE DETERMINED BY SEX OF THE PLACENTAL SYNCYTIOTROPHOBLAST

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Placental malaria occurs when *Plasmodium falciparum* infected erythrocytes sequester in the placenta, leading to adverse health outcomes for the mother and fetus. This is mediated by the binding of parasite antigens on the surface of the RBC to chondroitin sulfate A (CSA) glycosylated syndecan-1 (SDC-1) proteoglycan on the placental syncytiotrophoblast. SDC-1 can also be unglycosylated. Past studies suggest that female placentas may be at higher risk of placental malaria infection, but the mechanism behind this is unknown. We hypothesized that female placentas express higher levels of SDC-1 on the syncytiotrophoblast, leading to increased infected RBC adherence. Placental biopsies taken from full-term, uncomplicated pregnancies delivered by caesarean section were collected and fresh-frozen. Fetal sex was blinded until analysis was completed. We evaluated SDC-1 mRNA and protein levels from whole placental lysates by RT-PCR and western blot (n=23 male, 30 female). Both glycosylated and unglycosylated SDC-1

were detected by western blot. We performed immunofluorescence assays to quantify SDC-1 expression in the syncytiotrophoblast, defined using placental alkaline phosphatase (PLAP) (n=7 male, 9 female). Student's t-tests were used to assess significance at p<0.05. There were no significant sex differences in SDC-1 mRNA (p=0.76). Immunofluorescent staining of SDC-1 showed significantly higher expression in female syncytiotrophoblast (p=0.038) with noticeable variability within and between placental samples. To capture this variability, we tested three biopsies from each placenta by western blot. There were no significant sex differences in expression of glycosylated SDC-1 (p=0.69), unglycosylated SDC-1 (p=0.98), or total SDC-1 (p=0.49). Although SDC-1 staining showed significant sex differences, these findings were not supported by other methodologies that examined whole placental biopsies. This may be due to the variability in SDC-1 expression we observed. Further investigation of this variability is needed to determine whether there are sex-dependent differences in SDC-1 expression.

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EAST AFRICAN *PLASMODIUM VIVAX* TRANSCRIPTOMES REVEAL DIFFERENCES IN THE EXPRESSION PROFILES OF GENES RELATED TO ERYTHROCYTE INVASION FROM OTHER GEOGRAPHICAL ISOLATES

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Plasmodium vivax malaria has been increasing at alarming rates in Africa and a portion of these cases were detected in Duffy-negative individuals. Members of the *P. vivax* reticulocyte binding protein (RBP) and tryptophan-rich antigen (TRAg) families have been shown to play a role in erythrocyte invasion. While the transcriptomes of the Southeast Asian and South American *P. vivax* are well documented, the gene expression profile of *P. vivax* in Africa is unclear. For this study, we obtained transcriptomes via RNA-seq from 10 clinical *P. vivax* isolates in southwestern Ethiopia. Parasite samples were cultured to majority schizont stage prior to RNA extraction and library constructions. The expression levels of candidate erythrocyte binding protein genes were examined and compared to published transcriptomes from the Cambodian and Brazilian *P. vivax*. Sequences were deconvoluted to differentiate reads belonging to trophozoites and schizonts, respectively. For trophozoites, the top 30 genes that are exclusively expressed with 90% confidence are similar among the three continental isolates. However, for schizonts, the gene expression profiles vary among isolates. For instance, *PvDBP*1, *PvEBP*/*DBP*2, and MSP1 was highly expressed in the Cambodian but not the Brazilian and Ethiopian isolates. *PvRBP*2a and *PvRBP*3 showed higher expression in the Ethiopian than the Cambodian and Brazilian isolates. In the Ethiopian schizonts, *PvRBP*2a and *PvRBP*3 expressed six-fold higher than *PvDBP*1and 60-fold higher than *PvEBP*/*DBP*2. Other genes including *PvRBP1a, PvMSP3.8*, *PvMSP3.9*, *PvTRAG2, PvTRAG14, and PvTRAG22* also showed higher expression than *PvDBP*1 and *PvEBP*/*DBP*2. The contrasting difference in gene expression profiles provides critical insight into parasite invasion ligands involved in the Duffy-independent pathway in the African *P. vivax*. Ongoing study further examines the transcriptomic profiles of *P. vivax* between *in vitro* culture and *in vivo* samples.

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HARBORING OF MULTIPLE *PLASMODIUM* SPECIES TRIGGERS SYMPTOMATIC MALARIA IN ENDEMIC POPULATION

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The predominant malaria species in Kenya is *Plasmodium falciparum (Pf)* which can occur sympatrically with *P. ovale curtisi (Poc), P. ovale wallikeri (Pow), and P. malariae (Pm).* Detection and counting of these species has been conducted by semi-conveniently sampling symptomatic malaria during case management. When developing strategies to interrupt malaria transmission it's important to consider both symptomatic and asymptomatic transmission. This study compared the composition *of Plasmodium species* among symptomatic versus asymptomatic individuals in the Kombewa Kisumu West sub-county in western Kenya. Blood samples from 437 individuals presenting at Kombewa Sub-county hospital with symptoms of malaria and 304 individuals recruited from their households within the same catchment without symptoms of malaria between 2015 and 2016 were tested for *Plasmodium species* composition using the genus-specific small subunit ribosomal RNA gene (ssrRNA). *P. falciparum/P. malariae/P. ovale curtisi* mixed-species infections were more frequent among the asymptomatic than symptomatic individuals (OR of 0.08, 95% CI ranged [0.02 – 0.36, P = 0.0008). *P. malariae* 18 (2.43) and *P. o. curtisi* 13 (1.75%) single-species infections occurred among the asymptomatic yet none were detected among the symptomatic individuals, suggesting that these single-species infections, are often benign. The significantly higher multiple species infections containing *P. ovale* (OR of 15.3, 95% CI range [6.1 – 38.3 and P = 0.0001) among the symptomatic as compared to asymptomatic individuals appear to suggest the role of species-species interactions in modulating disease progression. *P. falciparum, P. malariae, and P. ovale* single-species infections were mostly detected among asymptomatic individuals. Broadly, this finding at one of the major malaria endemic sites of Kenya suggests that intervention strategies need to consider the diverse species in asymptomatic cases to progress the region to elimination phase.

1202

PROMOTING SUSTAINABLE ACCESS TO QUALITY-ASSURED NTD PRODUCTS IN LOW- AND MIDDLE-INCOME COUNTRIES

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NTDs are a diverse group of approximately 20 chronic, disabling, and disfiguring conditions that disproportionately affect the world's poorest people. Few local pharmaceutical manufacturers of priority medicines in low- and middle-income countries (LMICs) produce a volume of NTD medicines sufficient to meet local demand. This scarcity of quality-assured medical products is a threat to the sustainability of NTD control and elimination programs. For many years, international partnerships have enabled donations of billions of treatments to help control these infections in patients in LMICs. Global stakeholders have raised questions about how to prepare for possible declines in donation programs in the near future. To address these concerns, the Promoting the Quality of Medicines Plus (PQM+) program, funded by the U.S. Agency for International Development (USAID), conducted a study in sub-Saharan Africa and select Asian countries to assess local production of albendazole, mebendazole, azithromycin, diethylcarbamazine, ivermectin, tetracycline eye ointment, and praziquantel. Researchers submitted questionnaires to known NTD product manufacturers in sub-Saharan Africa (n=82) and Asia (n=159) to spotlight market dynamics, supply bottlenecks, and procurement mechanisms of NTD products. Findings suggest that the supply of NTD drugs available for procurement is inadequate due to multiple factors, including limited local production of the finished products, complete dependence on a few active pharmaceutical ingredient (API) manufacturers, and low volume demand due to reliance on donation programs. Some current manufacturers may exit the market due to the likely introduction of new national regulatory authority requirements necessary to guarantee drug quality, safety, and efficacy according to international standards. The study identified several technical interventions to address these challenges and to ensure sustainable access to quality-

assured NTD products. The primary interventions include strengthening the quality and supply of APIs, strengthening regulatory systems, and improving regional collaborations.

1203

THE IMPACT OF ONE VS. TWO DOSES OF IVERMECTIN MASS DRUG ADMINISTRATION ON THE PREVALENCE AND INTENSITY OF SOIL-TRANSMITTED HELMINTH (STH) INFECTIONS

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Soil-transmitted helminth (STH) infections affect 900 million people globally. Although WHO guidelines recommend albendazole preventive chemotherapy targeted to school-aged children for STH control, albendazole has limited efficacy against two major species, *T. trichiura* and *S. stercoralis*. Ivermectin may play an important role in improving the control of these two species especially in the context of ivermectin-based mass drug administration (MDA) programmes for the control of other neglected tropical diseases. We aimed to evaluate the effectiveness of one vs two doses of ivermectin MDA, delivered in the context of a scabies trial, on the prevalence and intensity of STH.Cross-sectional surveys were conducted in the Western Province of Solomon Islands, where 20 villages were randomised to receive ivermectin in single- or double-dose form, at baseline and 20-months following MDA. Stool samples were collected from 830 village residents across 18 villages at baseline for STH diagnosis, compared to1179 stool samples across 20 villages at follow-up. Quantitative PCR was used to detect and quantify infection intensity of 6 STH species. Generalised linear models were built to estimate the relative differences in STH prevalence between timepoints and treatment arms, accounting for household- and village-level clustering. Preliminary analyses show that at baseline overall prevalence of *T. trichiura* was 20.7%, 5.9% for *S. stercoralis*, 55.4% for *N. americanus*, and 16.9% for *A. ceylanicum*. At 20-months follow-up, the overall prevalence was 11.6% for *T. trichiura*, 1.4% for *S. stercoralis*, 57.4% for *N. americanus*, and 19.3% for *A. ceylanicum*. Statistical analyses to investigate whether there are significant differences in prevalence and intensity of infection between timepoints and treatment arms are underway. This study will contribute to our understanding of the role of ivermectin preventive chemotherapy in the control of STH and may be used to optimise integrated neglected tropical disease control strategies locally in Solomons Islands and in other endemic settings, particularly in the context of scabies MDA programmes.

1204

MASS DRUG ADMINISTRATION (MDA) COVERAGE SURVEY RESULTS FROM CARTER CENTER-ASSISTED AREAS OF ETHIOPIA

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Mass drug administration (MDA) is the single most important strategy for the elimination of onchocerciasis and lymphatic filariasis (LF) in many countries, including Ethiopia. Community Directed Treatment with Ivermectin/Albendazole (CDTI/A) using community drug distributors (CDDs) is the main platform for drug distribution. Since 2001, annual MDA with ivermectin was conducted for onchocerciasis control, shifting to twice-per-year treatments beginning in 2013 following the elimination policy. LF intervention started in 2009 through integration with the onchocerciasis program, adding albendazole to ivermectin once per year. Most districts have reported coverage above World Health Organization minimum levels (i.e., ≥80% for onchocerciasis and ≥65% for LF) for at least 10 rounds. The program conducted post-MDA coverage surveys between 2014 and 2021 to validate the administrative reports, investigate areas with poor coverage, and improve the quality of the program. Ninety-two districts and 1060 villages were assessed using paper-based (2014-2018) and electronic (2019 to date) survey tools. Community-based cross-sectional surveys with multistage random sampling were used to select villages, households, and individuals. Overall, 79,983 individuals were interviewed, and 62,470 (78%) received ivermectin. Out of 247 kebeles (the smallest administrative unit) surveyed, 132 (53%) had therapeutic/epidemiological coverage between 80-100%, 108 (44%) between 60-80%, and 7 (3%) were below 60%. One-hundred eighty-one (73%) of the surveyed kebeles had >75% coverage. Very low coverage was found in areas new to the program and was associated with lack of awareness, absenteeism due to farming, inaccessibility/insecurity to some areas and overburdened CDDs. Such surveys are useful to identify areas of low coverage in order to intensify efforts towards elimination. Strengthening health education, advocacy, and community mobilization during campaigns, and CDTI capacity-building would help to improve MDA coverage.

1205

SYSTEMATIC REVIEW AND META-ANALYSIS OF QUALITATIVE ASSESSMENTS OF PERSISTENT TRANSMISSION OF NTDS IN 5 COUNTRIES

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Remaining endemic implementation units (IUs) that fail to meet prevalence thresholds often pose challenging situations for disease elimination. In these IUs, qualitative data provides insights into factors facilitating ongoing disease transmission. While these data were collected to assess IU-specific hypotheses, we assess the degree to which underlying themes overlap across diseases and geographic areas. We conducted a systematic review and meta-analysis of qualitative data collected during outcome investigations for IUs that failed to reach threshold prevalence during disease specific assessments for trachoma, lymphatic filariasis, and onchocerciasis. Outcome investigations conducted between 2019-2022 from USAID's Act to End NTDs | East portfolio were reviewed for the addition of qualitative data collection. Of the 61 outcome investigations, 28 across five countries (Ethiopia, Mozambique, Nigeria, Tanzania, and Uganda) met the criteria for inclusion. These studies successfully used individual interviews, focus group discussions, participatory mapping, and social network analysis to generate programmatic recommendations. Thematic coding was applied across all available data sources and reports. Commonly identified challenges included barriers to program implementation, geographic isolation, timing and length of mass drug administration campaigns, and degree of supportive supervision for implementers at the lowest level. Other factors commonly identified included a lack of WASH infrastructure, uneven degree of social mobilization and exposure to NTD behavior change communication campaigns, and generalized misinformation and fear of side effects relating to the drug distribution. Population mobility was also a common theme, though the type of mobility varied widely by occupation, gender, and ethnicity. Despite the overlap in themes, however, proposed solutions

to many of these factors were highly context specific, emphasizing the need to engage in locally led programming for IUs with persistent transmission.

1206

CHARACTERISTICS OF NON-TREATED POPULATIONS AMONG SELECT NEGLECTED TROPICAL DISEASE MASS DRUG ADMINISTRATION CAMPAIGNS IN WEST AFRICA

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Effective mass drug administration (MDA) is the cornerstone of preventive chemotherapy (PC) neglected tropical disease (NTD) programs. USAID's Act to End NTDs | West program supports Ministries of Health to eliminate or control five PC NTDs across 11 West African countries by assisting with (among other interventions) MDA and monitoring and evaluation, such as coverage evaluation surveys (CES) to validate coverage shortly after MDA. Non-treated populations (MDA eligible people at risk in endemic districts who do not participate in the treatment campaign) are of concern as they may enable ongoing transmission of infection. If these populations can be better characterized, programs can take more precise actions to identify and target them. Using CES data from six surveys (45,315 respondents) conducted in Ghana, Niger, Senegal, and Sierra Leone, we conducted a meta-analysis to describe demographic characteristics among non-treated and a geospatial analysis to map clusters of non-treated populations. The results showed minimal refusals to take the drugs (7.1%). Instead, the chief reason for not participating in MDA was due to absence during MDA (43.8%), followed by not being visited by community drug distributor (CDD) (28.3%) and unawareness of the MDA (13.8%). Age distributions indicated youth and young adults (ages 15-34) were disproportionately not treated relative to other age groups. Additionally, a significant relationship between age groups and sex among the non-treated was observed ($X^2(3,N=9,039)=14.0$, p &lt .003) - more female than male youth and young adults were among the non-treated. We also identified spatial clusters of non-treatment areas and found villages that were not visited by the CDD. Our findings indicate the most influential programmatic response could include implementing age and sex specific MDA mop-up, reviewing CDD catchment areas, or improving CDD motivation to visit or re-visit households to reach non-treated populations. In the future, we plan to investigate the movement of targeted populations and the timing of MDA to determine if there is a more suitable time for MDA activities.

1207

PROMISING PRACTICES IN COLLABORATIVE PLANNING FOR INTEGRATED HEALTH CAMPAIGNS: SYNTHESIS OF CASE STUDIES IN NEGLECTED TROPICAL DISEASES, MALARIA, VITAMIN A SUPPLEMENTATION, AND IMMUNIZATIONS

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Health campaigns are time-bound, intermittent activities deployed to address specific epidemiologic challenges, expediently fill delivery gaps, or provide surge for coverage of health interventions. The increasingly sought efficiencies in implementing campaigns, COVID-19-related disruptions and the recognition that successive health campaigns often reach the same communities have led global programs to explore cross-program collaboration. The Health Campaign Effectiveness Coalition funded implementation research. Eight case studies documented approaches to integrate health campaigns in neglected tropical disease (NTD) programs, immunizations, malaria, and vitamin A supplementation in six countries -- Colombia, India, Nepal, Guinea, Nigeria, and Ghana. By design, two case studies were retrospective, and others were pilots or about planned integrated campaigns. A total of 65 themes related to the promising practices for campaigns integration were identified, and consolidated into ten overarching practices. Relating to coordination and macroplanning are the practices of establishing national, regional, and local coordination bodies, responding to community health needs, regularly assessing readiness, embracing learnings from prior integrated campaigns, and considering subnational-level decision making. Engaging stakeholders at all levels early on, including at the community level, leads to innovative strategies to address often missed populations. Harmonizing campaign tools and guidance early in the campaign process strengthens microplanning and data collection. Providing real-time data to manage and monitor the supply chain and logistics is facilitated through an array of digital tools and technologies. Additional practices were related to social mobilization and training, recognition and supervision of campaign workers. The synthesis across the portfolio of investments led to the creation of a framework that can be expanded to embrace additional practices across the campaign lifecycle. Examples from the countries on the promising practices will also highlight practical tools used.

1208

KEY INFLUENCERS OF MASS DRUG ADMINISTRATION IMPLEMENTATION AND SCALE-UP: A NETWORK ANALYSIS OF SOIL-TRANSMITTED HELMINTH PROGRAMS IN BENIN, INDIA, AND MALAWI

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Large community-based programs, such as mass drug administration (MDA), require coordination across numerous stakeholders. We used social network analysis (SNA) to systematically identify networks of stakeholders involved in school-based & community-wide MDA for soil-transmitted helminths (STH) and determine how network dynamics may impact implementation at scale. This study was embedded within the DeWorm3 Project, a hybrid clinical trial in Benin, India, & Malawi testing the feasibility of STH transmission interruption via community-wide MDA compared to school-based MDA. Each site developed an index of stakeholders engaged in both MDA programs, indicating their attitudes towards the intervention & influence over intervention delivery. We developed digital sociograms for both MDA networks by site, comparing baseline vs. endline. We descriptively compared changes over time in stakeholder attitudes and influence and compared key SNA measures, including centrality, centralization, & density over time. We identified nearly 700 stakeholders involved in delivery of school-based (139, 162, 63) and community-wide MDA programs (65, 136, 60) at endline in Benin, India, and Malawi, respectively. At both timepoints, a majority (>70%) of stakeholders held positive attitudes towards both programs. For both programs, the most connected stakeholders (i.e., with highest degree centrality scores) were those responsible for program implementation, while stakeholders who controlled resource flow (i.e., highest betweenness centrality) were responsible for policy-making & program leadership. Low network density scores indicated networks had poor overall connectedness due to minimal connectivity across administrative levels. Low centralizations scores reflected stable networks where no single individual exhibited high control over resource flow. Identifying stakeholders who serve as key

connectors, resource brokers, or intervention champions and quantifying their collective influence over successful intervention delivery is critical for policymakers and implementers launching and scaling MDA programs.

1209

THREE YEAR EFFICACY RESULTS FROM AN INDIVIDUALLY RANDOMIZED CONTROLLED DOUBLE-BLINDED TRIAL OF A TYPHOID CONJUGATE VACCINE IN MALAWI

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Typhoid fever is a high-burden, vaccine-preventable, multidrug resistant systemic disease which remains a major health threat in sub-Saharan Africa (sSA), including Malawi. The World Health Organization recommended the use of Typhoid Conjugate Vaccines (TCV) in countries with a high burden of disease, and/or high rates of antimicrobial resistance. We present here the longest-term efficacy data available globally to date, from the ongoing randomized, blinded, controlled clinical trial in Malawi. 28,130 healthy children aged 9 months through 12 years were randomised 1:1 and received TCV (Typbar, Bharat Biotech) or meningococcal A conjugate vaccine (MenA). Enhanced passive surveillance at secondary and tertiary health facilities identified febrile presentations and serious adverse events (SAEs). Children presenting with axillary temperature of ≥38°C, or subjective fever for ≥72 hours, or hospitalization with history of fever of any duration had blood culture collected (5-10ml) to confirm *S.* Typhi-positive typhoid fever. As of 30 September 2021 (minimum 36-month follow-up), intention-to-treat (ITT) analysis showed that 92,862 person-years of surveillance yielded 100 culture-confirmed typhoid cases; 18 cases in the TCV group (38.69 per 100,000 person-years) and 82 cases in the MenA group (176.97 per 100,000). Vaccine efficacy through 9/2021 was 78.2% (95% confidence interval (CI): 63.7%- 86.9%) in an ITT analysis, and 80.4% (95% CI: 66.4%- 88.5%) in a per protocol analysis. Subgroup analysis showed a consistent efficacy across all age-groups. We detected 499 serious adverse events, mostly hospitalizations for common childhood illnesses, and 20 deaths. No SAEs or deaths were related to the vaccine, and there was no excess of either in the vaccine group. Long term efficacy data are crucial to inform decision making and accelerating the introduction of TCVs globally and especially in sSA. The results of the trial have demonstrated durable protection in African children up to 36 months, which is consistent across a range of age-groups, and an excellent safety profile.

1210

FIELD EVALUATION OF TYPHOID CONJUGATE VACCINE IN A CATCH-UP CAMPAIGN AMONG CHILDREN AGED 9 MONTHS TO 15 YEARS IN SINDH, PAKISTAN

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Typhoid conjugate vaccine (TCV) has recently been introduced in the expanded program for immunization (EPI) in Pakistan. Before its introduction in routine immunization, a onetime catchup campaign among children 9 months to 15 years old was conducted in November 2019. We performed field evaluation of TCV against culture confirmed *Salmonella* Typhi (*S. Typhi*) among 9 months to 15 years old children during the catch up campaign in Karachi and Hyderabad. A rapid assessment of blood culture confirmed *S. Typhi* was performed. Age eligible cases of culture confirmed *S.* Typhi were identified from the laboratory networks of Aga Khan University Hospital Karachi and Hyderabad, Kharadar General Hospital Karachi, and Liaqat University of Medical & Health Sciences (LUMHS) Hyderabad. Information on sociodemographic, typhoid vaccination history and antimicrobial resistance was collected using a structured questionnaire. Patient medical records and lab reports were also reviewed to collect information on diagnosis and antimicrobial susceptibility information. Information about the population vaccination coverage during catch-up campaign was obtained from the provincial EPI office. Field performance of TCV in catchup campaign was measured by calculating the effectiveness using rapid screening method. Overall, 968 culture confirmed typhoid cases were enrolled. Among them, 82% (793/968) were from Karachi and 18% (175/968) from Hyderabad. The average age of the participants was 5.68 years, and 54% (523/968) were male. 6% (62/968) of the culture confirmed *S.* Typhi cases were multidrug resistant (MDR), and 61% (586/968) were extensively drug resistant (XDR). The VE using the TCV coverage data provided by EPI was 98%. TCV is effective against culture confirmed *S.* Typhi among children aged 9 months to 15 years in the catch-up campaign setting. While typhoid vaccination can significantly decrease the burden of typhoid disease, improvements in sanitation and hygiene are necessary for the prevention of spread of enteric fever. Longer term follow up will be needed to assess the duration of protection and requirement for booster doses of TCV.

1211

CASE-CONTROL INVESTIGATION OF INVASIVE SALMONELLA DISEASE IN AFRICA REVEALS NO EVIDENCE OF ENVIRONMENTAL OR ANIMAL RESERVOIRS OF INVASIVE STRAINS

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Invasive *Salmonella* infections are a major cause of morbidity and mortality in Sub-Saharan Africa (SSA). However, the sources and modes of transmission are uncertain. To shed light on potential transmission routes of invasive Salmonellosis, we obtained *Salmonella* isolates from healthy people, animals, and the environment of index-cases and geographically-matched control households. Sixty index cases of human invasive *Salmonella* infection were recruited. Twenty eight invasive Non-Typhoidal *Salmonella* (iNTS) disease and 32 typhoid patients consented to household sampling. Each index-case household was geographically matched to a control household. Extensive microbiological sampling included stool sampling from healthy household members, stool or rectal swabs from household-associated animals and boot-sock sampling of the household environment. 1203 samples were taken from 120 households, yielding 43 non-Typhoidal *Salmonella* (NTS) isolates from 25 households (overall sample positivity 3.6%). In the 28 iNTS patients, disease was caused by 3 STs of Salmonella Typhimurium, mainly ST313. In contrast, the isolates from households spanned 15 sequence types (STs). Two *S.* Typhimurium isolates from index cases closely matched isolates from their respective asymptomatic household members (2 and 3 SNP differences respectively). Despite the recovery of a diverse range of NTS, there was no overlap between the STs causing iNTS disease and any environmental or animal isolates.In conclusion, the finding of NTS strains from index cases that matched household members, coupled with lack of related animal or environmental isolates, supports a hypothesis that healthy humans were the source of iNTS infections in the household. The breadth of NTS

strains found in the household environment across all sites demonstrated the robustness of NTS sampling methodology, and suggests a diverse ecology of *Salmonella* in this setting. The lack of *S.* Typhi isolates from the household environment suggests that further methodological development may be needed to culture *S*. Typhi from the environment.

1212

CHARACTERIZING THE NATURAL HISTORY OF SHIGELLA DIARRHEA AND SUB-CLINICAL INFECTIONS AMONG CHILDREN IN A LONGITUDINAL BIRTH COHORT

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Shigella is a leading cause of diarrhea morbidity and mortality among children in low-resource settings. The detection of Shigella in the absence of diarrhea (subclinical infection) has been associated with linear growth faltering, but it is unknown how often subclinical infections can be attributed to post-diarrheal shedding and the relative importance of different infection types on long-term morbidity. We characterized the natural history of Shigella infections among children in the Malnutrition and Enteric Disease (MAL-ED) Study, a multisite birth-cohort, during which stool samples were collected monthly and during diarrhea from birth to 2 years. Consecutive non-diarrheal specimens with a Shigella detection (PCR cycle threshold <35) were defined as post-diarrheal shedding if they followed a Shigella-attributable diarrhea episode, or as a subclinical infection otherwise. Of 1,715 children, 1,407 (82.0%) experienced at least one Shigella infection, and the average number of infections was 2.19 (IQR: 1-3). The majority (900/1,407, 64.0%) only experienced subclinical infection(s), 131 (9.3%) only experienced diarrheal infection(s), and the rest experienced at least one of each (214 [15.2%] subclinical first, 162 [11.5%] diarrhea first). The average age of first diarrhea infection was 15.5 months (IQR: 11.9-19.2) and of first subclinical infection was 13.3 months (IQR: 9.0-18.0). About 26% (614/2,361) of subclinical and 38% (237/632) of diarrheal infections lasted >1 month, with 7.2% (223/3,078) of all infections lasting ≥3 months. Most subclinical infections were distinct from post-diarrheal shedding and occurred before a child had Shigella diarrhea (79.2%). These results counter the assumption that children generally experience Shigella diarrhea first, acquire natural immunity, and subsequently experience subclinical infections. Further analyses will characterize the impact of subclinical infections on child growth and development, as well as the potential impact of a Shigella vaccine that may not protect against subclinical infections.

1213

GASTROENTERITIS-ASSOCIATED DEATHS AMONG CHILDREN AGED 1-59 MONTHS IN RURAL AND URBAN WESTERN KENYA, 2017-2021: FINDINGS FROM THE CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS)

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Gastroenteritis (GE) remains a significant cause of morbidity and mortality especially in low-middle-income countries where precise data on mortality among children <5years is limited. The Child Health and Mortality Prevention Surveillance (CHAMPS) is a multisite program which enrolls hospital and community-based deaths among children <5 years to ascertain cause of death (COD). A panel of experts decides COD using data from minimally invasive tissue sampling, verbal autopsy, maternal/child clinical and laboratory procedures. We assessed characteristics of gastroenteritis associated deaths (GEAD) in CHAMPS Kenya cases. A GEAD was defined as a decedent child aged 1-59 months whose death had vomiting and/or diarrhea in the causal pathway. Characteristics of GEAD vs. non- GEAD were compared using unconditional logistic regression. From May 28, 2017, to December 31, 2021, a total of 402 deaths among children aged 1-59 months had cause of death determined; GEAD accounted for 31/402 (7.7%) of all deaths; 24/31(77.4%) as immediate COD (n=17) or a comorbid condition (n=7), and 7/31 (22.6%) as underlying COD. The leading underlying COD among the seventeen cases whose immediate COD was GEAD included: GE (35%), malnutrition (35%) and HIV (18%). The median age of GEAD vs. non- GEAD was 10.1 vs. 1.8 months (p<0.001). Compared to non-GEAD, GEAD were 9 times more likely to be a cause of death in children aged 6-11 months (95%CI 3.45-23.45, p<0.001), 4.8 times more likely to be aged 12-23 months (95%CI 1.60-14.29, p=0.006), and 2.6 times more likely to be urban residents (95%CI 1.10-6.25, p=0.033). The leading etiologies among 11 GEAD whose laboratory results were available included: rotavirus (27%), adenovirus (27%), norovirus genogroup I (18%), *Campylobacter jejuni* (18%) and *Salmonella spp*. (9%). Despite the existing diarrhea interventions including rotavirus vaccines, children <2years bear the greatest burden of GEAD mainly caused by viral etiologies, suggesting modest impact of such interventions on GEAD in this setting. Programs targeted at reducing GEAD may need to pay attention to breastfeeding practices, malnutrition, and HIV in these settings.

1214

META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES OF DIARRHEA IN THE FIRST YEAR OF LIFE AMONG BANGLADESHI INFANTS IDENTIFIES GENOME-WIDE SIGNIFICANT LOCUS ON CHROMOSOME 21

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Diarrhea causes significant illness and death among children < 5 years, including greater than 500,000 deaths/year globally. In poor areas with limited sanitation or access to clean water, the rates of infectious diarrhea are high. However, despite similar environmental risk, not all children in these areas report diarrheal infections. We hypothesized that host genetics may contribute to the heterogeneity in observed diarrhea. We evaluated genotypes from 3 well-characterized birth cohorts from Dhaka, Bangladesh (Dhaka Birth cohort (DBC), PROVIDE, and Cryptosporidiosis Birth Cohort (CBC)). In each study, infants were followed from birth with multiple home visits per week, well-child checks, and data collection for illness. Diarrhea was defined as ≥ 3 abnormally loose stools in a 24-hour period and an episode of diarrhea was a string of days during which an infant had diarrhea. We compared infants who reported no diarrhea to those with ≥ 6 episodes of diarrhea in the first year of life. We included 123 infants from DBC (26 no diarrhea:97 diarrhea), 157 infants from PROVIDE (31 no diarrhea:126 diarrhea) and 111 from CBC (32 no diarrhea:79 diarrhea). Each cohort was analyzed separately adjusting for sex and population differences using the first principal component. In a fixed effects meta-analysis across the three studies we identified a locus on chromosome 21 in the non-coding RNA, *AP000959.2*. The top variant was rs2827548 (G/C) in the intron of *AP000959.2*, (ORmeta = 0.30, minor allele frequency = 0.26, p=2.05x10^{-8}). Infants with the G allele were 3.2 times as likely to have ≥ 6 episodes of diarrhea when compared to those with the C allele. This region is independent of host loci previously identified for *Entamoeba histolytica*, *Cryptosporidium*, *Shigella*, and *Campylobacter* in these same birth cohorts (Wojcik 2018, Wojcik 2020,

Duchen 2021, Munday 2022), and suggests that this is a diarrhea and not pathogen-specific locus. In sum, we report a novel host genetic finding on chromosome 21 located in a non-coding region that is associated with susceptibility to diarrhea among infants. Future studies should explore this region as a target for therapeutics.

1215

AKKERMANSIA MUCINIPHILA IS ASSOCIATED WITH IMPROVEMENTS IN LINEAR GROWTH AMONG YOUNG CHILDREN IN THE DEMOCRATIC REPUBLIC OF THE CONGO (REDUCE PROGRAM)

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Globally there are estimated to be 500,000 deaths each year among young children under 5 years of age attributed to diarrheal diseases. Enteric pathogens inhabit the intestinal tract and can cause diarrhea, which reduces the child's ability to absorb nutrients resulting in malnutrition and impaired growth. In 2020, 144 million children under 5 years of age were estimated to be stunted globally. To investigate the association between enteric infections, fecal microbes, and child growth. A prospective cohort study of 236 children under 5 years of age was conducted in rural eastern Democratic Republic of the Congo (DRC). Baseline stool specimens were analyzed by quantitative PCR. Child growth was measured at baseline and at a 6-month follow-up visit. At baseline, sixty six percent (156/236) of children had three or more pathogens in their stool. Larger increases in height-for-age-z-scores from baseline to the 6-month follow-up were observed for children with *A. muciniphila* in their stool (coefficient: 0.02 (95% CI: 0.0001, 0.04, p=0.04)). Children with *Cryptosporidium* in their stool had larger declines in weight-for-height/length-z-scores from baseline to the 6-month follow-up (-0.03 (95% CI: -0.05, -0.005, p=0.02)). Our study showed a high burden of enteric infections among this pediatric cohort in DRC, and suggests *A. muciniphila* can potentially serve as a probiotic to improve child growth.

1216

FOOD SAFETY AND ECONOMIC IMPLICATIONS OF IVERMECTIN MASS DRUG ADMINISTRATION IN SWINE - A ONE HEALTH PERSPECTIVE ON THE FUTURE OF MALARIA VECTOR CONTROL

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A body of evidence is being generated from completed, ongoing and planned field trials for the use of insecticide-treated livestock (ITL) strategies for malaria vector control. Although the global health community's primary interest in the use of ITL is for its potential effect against zoophillic mosquitoes, the use of endectocides on a mass scale offers to enhance livestock health and productivity to support household economic security, while also raising issues of food safety and resistance in parasites of veterinary importance. Therefore, as we seek to determine efficacy of endectocides in livestock for malaria control, we must also quantify the additional risks and benefits of such an approach. The BOHEMIA clinical trial, which delivers the endectocide ivermectin as a mass drug administration for three consecutive months to humans and to both humans and pigs, is ongoing in Mopeia, Mozambique. The following data are being collected: i) longitudinal survey data from 280 pig-owning households on pig management and health; ii) information on the number of treated pigs and follow-up slaughter data; and iii) biometric and fecal sample data collected from 140 treated and untreated pigs. Using these data streams, we will present results that summarize the risk of treated pigs entering the food chain before the recommended withdrawal time; the development, or lack of development of phenotypic resistance in intestinal helminths to ivermectin during the study period; and a summary of the impact of ivermectin on pig health and productivity. Results will provide an important One Health perspective on the future of using ITL for malaria vector control. Implications for future research, implementation of malaria strategies involving endectocide-treated livestock, and cost-effectiveness studies will be discussed.

1217

EXPLORING SARS-COV-2 DYNAMICS AT THE ANIMAL-HUMAN INTERFACE: WHITE-TAILED DEER AND WHITE-FOOTED MICE AS SECONDARY RESERVOIRS IN CONNECTICUT

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The COVID-19 pandemic began with an initial zoonotic spillover from an unknown animal into humans. Since then, research has necessarily focused on human-to-human SARS-CoV-2 transmission. However, research into the risk posed by viral spillback (human-to-animal) and secondary spillover (human-to-animal, followed by animal-to-human) is increasingly vital for two reasons. Firstly, as the pandemic gradually moves toward endemicity and human-to-human transmission lessens, animals will become an increasingly important source of new outbreaks. Secondly, adaptive evolution within new non-human host species increases the emergence risk of new viral variants, which may be better able to compete in a reduced transmission environment. Such variants may have properties such as increased virulence or enhanced immune escape. Given the ubiquity among vertebrate species of the angiotensin-converting enzyme 2 receptor used by SARS-CoV-2 to enter host cells coupled with the increasing detection of the virus in animal species, we aimed to fill key animal reservoir surveillance gaps in Connecticut. To date, very limited animal testing has been performed in the state. We first screened white-tailed deer (*Odocoileus virginianus*) and white-footed mice (*Peromyscus leucopus*) serum samples from 2020 and 2021 for neutralizing antibodies. Both species are important potential reservoirs due to their ability to contract and transmit SARS-CoV-2 and their contact with human populations. We then collected additional samples and sample types (nasal, oropharyngeal, and rectal) in 2022 to screen for active SARS-CoV-2 infection. Lastly, we performed targeted sequencing of positive samples and conducted a phylogenetic analysis. Using the generated data, we characterized patterns of SARS-CoV-2 transmission at the animal-human interface and discussed the implications for long-term risk mitigation.

1218

CRIMEAN-CONGO HEMORRHAGIC FEVER VIRUS IN CENTRAL, EASTERN, AND SOUTH-EASTERN ASIA

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Crimean-Congo hemorrhagic fever (CCHF) is endemic in Africa and in areas below the 50th parallel of north (latitude 50°0′ N) in Asia and Europe, but the epidemiology of CCHF needs to be better characterized in most regions. In this study, we aimed to describe CCHF endemicity in Central, Eastern, and South-eastern Asia. We comprehensively searched scientific databases for studies on CCHF epidemiology in these regions. We used a One Health approach to describe disease burden through human cases, animal and human serology studies, and Crimean-Congo hemorrhagic fever virus (CCHFV) isolation from ticks. In addition, we leveraged a classification scheme to sort countries into five categories based on the level of evidence and the maturity of their CCHF surveillance systems. We identified 2,253 CCHF cases that occurred in the region during the period 1944-2021. Central Asian countries reported most cases (1,966). China is the only country in Eastern and South-eastern Asia that reported CCHF cases (287). Six countries (China, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan) have been regularly or intermittently reporting CCHF cases and were assigned to level 1 or level 2, based on maturity of their surveillance systems. Two countries (Mongolia and Myanmar) were assigned to level 3, due to conclusive evidence of CCHFV circulation in the absence of reported CCHF cases. Subsequently, 13 countries in Eastern and South-eastern Asia were categorized in levels 4 and 5, based on CCHFV vector prevalence. Furthermore, we described the species of *Hyalomma* dominant in each region (if available) and discussed the reason for their absence in some areas, even though published literature indicates that they are present there. This study describes the past and present status of the CCHF epidemiology and reporting systems to inform international and local public-health agencies to strengthen or establish CCHF surveillance systems and address shortcomings in the discussed regions.

1219

RISK FACTORS AND SPATIOTEMPORAL PATTERNS OF CEPHALOSPORIN-RESISTANT AND EXTENDED-SPECTRUM BETA-LACTAMASE PRODUCING *ESCHERICHIA COLI* CARRIAGE IN CHILDREN AND DOMESTIC ANIMALS IN A FOOD-ANIMAL PRODUCING REGION OF QUITO, ECUADOR

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The spread of antimicrobial-resistant bacteria may be driven by human-animal-environment interactions, especially in regions with limited restrictions on antimicrobial use, widespread food-animal production, and free-roaming domestic animals. We conducted a repeated-measures study from 2018-2021 in 7 semi-rural parishes in Quito, Ecuador to identify determinants and spatiotemporal patterns of third-generation cephalosporin-resistant *E. coli* (3GCR-EC) and extended-spectrum beta-lactamase *E. coli* (ESBL-EC) in children and domestic animals. We used multivariable log-binomial regression models to estimate relative risks (RR) of 3GCR-EC and ESBL-EC carriage associated with risk factors related to domestic animals, backyard food-animals, and commercial food-animal production in the community. We collected 1,699 child fecal samples from 600 households with a child under 5 years old and 2,731 animal fecal samples from 376 of the same households. 3GCR-EC was detected in 38.2% of child samples and 54% of animal samples; ESBL-EC was detected in 9.0% of child samples and 12.2% of animal samples. Risk factors for 3GCR-EC included living within 5 km of 6 or more commercial food-animal operations (RR: 1.30; 95% Confidence Interval: 1.10, 1.53), backyard food-animal ownership (1.25; 0.97, 1.61), child pet contact (1.24; 1.08, 1.42), and rarely/never washing hands after contact with animals (1.21; 1.01, 1.44). Risk factors for ESBL-EC were dog ownership (1.43; 1.00, 2.04), animal feces with ESBL-EC in yard (1.37; 0.90, 2.09), and child pet contact (1.52; 1.04, 2.24). Community interventions that improve hygiene and regional policies that restrict the use of critically important antimicrobials in domestic animals and food-animals may be necessary to curb the spread of resistant bacteria within and between communities.

1220

GENETIC EVOLUTION AND TRANSMISSION DYNAMICS OF H5N1 AND H5N6 VIRUSES IN HOUSE CROW (*CORVUS SPLENDENS*) AND POULTRY IN BANGLADESH

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The highly pathogenic avian influenza virus (HPAIV) H5N1 caused >550 reported outbreaks in poultry and wild birds in Bangladesh since 2007. We investigated multiple crow mortality events that occurred during the winter season (Nov-March) between 2016 and 2018 within the same areas of Dhaka and Rajshahi in Bangladesh to understand the transmission dynamics and genetic evolution of HPAIV in house crows and poultry from nearby live bird markets (LBMs). We collected cloacal and oropharyngeal swabs from moribund and dead crows (N=375) and offal and environmental samples from nearby live bird markets (LBMs; N=430). We tested all samples using specific q-PCR for influenza A (M gene) H5/H7/H9/N1/N6. We observed crows feeding on poultry offal and waste in neighboring LBMs. Of the total, 61% (n=228) of crows and 22.6% (n=97) of LBM samples tested positive for H5N1. 20.5% (n=77) of crows and 15% (n=64) of LBM samples tested positive for H5Nx. The Bayesian phylogenetic analysis of HA and NA genes of H5N1 and H5N6 suggests that the virus belongs to clade 2.3.2.1a and 2.3.4.4b respectively. The HA genes of A/H5 clade 2.3.2.1a diverged into at least nine genetic subgroups (R1-R9), and subcategories (R1-R8) were not detected after 2016, and the R9 subgroup currently circulating in Bangladesh. The H5N6 is a genetically alike virus detected in wild birds in China and Mongolia, signifying migration-linked transmission of this emerging zoonotic virus. This investigation detected and characterized the novel reassortant multiple subtypes of H5Nx in wild birds and highlighted the potential for the exchange of HPAI between poultry and wild birds. The virus may have been transmitted to crows while they were feeding on poultry waste in the LBMs. Continued surveillance of both poultry and wild birds is needed for early detection of novel viral introductions, to trace the transmission route, and to reduce public health risks.

1221

BURDEN AND RISK FACTORS OF SNAKEBITE IN MOPEIA, MOZAMBIQUE: A DESCRIPTIVE ANALYSIS

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Snakebite is a severe condition that disproportionally affects the rural poor and was named a priority Neglected Tropical Disease by the World Health Organization in 2017. There is a dearth of evidence regarding incidence

and risk factors in snakebite endemic countries. Without this basic data, it will be impossible to achieve the target of a 50% reduction of snakebite morbidity and mortality by 2030 as set by the World Health Organization, in alignment with the Sustainable Development Goals. To our knowledge, this is the first study to describe snakebite burden and risk factors in a rural population in Mozambique. We analysed data collected from over 60,000 individuals in a 2021 census conducted in Mopeia, Mozambique, undertaken in preparation for a malaria cluster randomized trial. We describe the incidence, demographics, socioeconomic indicators and outcomes of snakebite in this population. Emerging data from household surveys globally is suggesting much higher incidence of snakebite than was previously estimated, our findings concur that these previous figures grossly underestimate the burden of snakebite. We found the incidence of self-reported snakebite in Mopeia to be 475 bites per 100,000 person-years at risk, with 2% of households being affected by snakebite in the preceding 12 months. Whilst no fatalities were recorded, over 3,000 days of work or school were lost and nearly 20% of those affected had not made a full recovery at the time of census. The results of a logistic regression showing the association between snakebite and relevant socioeconomic variables are also presented. This study exposes higher than expected incidence and burden of snakebite in rural Mozambique. Whilst snakebite elimination seems unattainable, it remains a preventable disease with manageable sequelae. This study aims to help local policy makers to make informed decisions regarding prevention of snakebite and to highlight topics in which further research can shed light on this problem, both in Mozambique and globally.

1222

DETECTION OF *PLASMODIUM* SP. IN NEOTROPICAL PRIMATES RESCUED FROM WILDLIFE TRAFFICKING IN PERU

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Malaria is a tropical parasitic disease endemic to Peru that annually affects over 200 million people around the globe. Evidence of natural infection with *Plasmodium* sp. has been reported in wild Neotropical primates (NP) across Central and South America, including Peru. Wildlife trafficking translocate primates from malaria-endemic areas to densely populated cities, representing a risk for the introduction of the parasite to malaria-free urban areas where the vector is present. We evaluated the presence of *Plasmodium* spp. in 184 NP recovered from trafficking using a qPCR assay, through the detection of the mitochondrial *cox-3* gene. Blood samples were obtained from animals rescued in Peruvian departments: Lima (N=43), Loreto (N=14), Piura (N=30), and Madre de Dios (N=97) between 2017 and 2022. *Plasmodium* spp. parasite DNA were detected in 4.4% (8/184) of individuals evaluated, and all cases corresponded to juvenile spider monkeys (*Ateles chamek*, n=7) and one red howler monkey (*Alouatta* sp.) housed at rescue centers in Madre de Dios. Estimations of malaria parasite density ranged from < 4 parasites/µL to 103.9 parasites/µL. Our findings highlight the need to further investigate the involvement of Peruvian NP in malaria transmission and the consequences that wildlife trafficking poses to Public Health for the translocation of parasitic agents across different geographic regions. In Madre de Dios, human malaria is caused mainly by *P. vivax* and *P. falciparum*; and *P. malariae/brasilianum* have been reported in wild tamarins. The molecular identification of the *Plasmodium* species found in this study is under evaluation and will provide valuable insights into the zoonotic potential, transmissibility, and diversity that could be found occurring in a human-NP interface.

1223

LONGITUDINAL TRACKING OF T FOLLICULAR HELPER CELLS IN CHILDREN DURING MALARIA TRANSMISSION DISRUPTION

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Naturally acquired immunity against malaria develops gradually with age and repeated infection, but it is thought to wane in the absence of exposure leaving previous immune populations at risk of disease in case of transmission rebounds. Immunity is mediated by antibodies induced by T follicular helper cells (Tfh) which activate B cells. However, factors that modulate the development and longevity of Tfh responses during malaria transmission disruption are still unknown. We assessed circulating Tfh (cTfh) responses in a longitudinal cohort of children 0-10 years (n=12) and adults(n=7) in a high malaria endemic setting in Uganda that experienced malaria transmission disruption with the introduction of mass indoor residual spraying (IRS). We measured parasite-specific cTfh responses using the Activation Induced Marker assays before IRS and at three time points post-IRS. Malaria specific CD4-cTfh cells were analysed by 20 colour spectral flow cytometry. We observed that children had lower frequencies of memory parasite-specific cTfh than adults. Further, the parasite-specific cTfh were predominantly Th1-cTfh subset in children and declined rapidly during malaria transmission disruption. In contrast, adults had higher Th2-cTfh subset levels and were maintained post-IRS. Results suggest age-related differences in the subset distribution and longevity of malaria-specific cTfh responses. Understanding the factors and mechanisms underpinning the maintenance of cTfh responses will be vital in directing the vaccine design and improving efficacy.

1224

IL-10 DERIVED FROM MAST CELLS PROTECTS INTESTINAL BARRIER INTEGRITY DURING MALARIA AND CONTROLS PARASITE TRANSMISSION TO *ANOPHELES STEPHENSI*

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Malaria strongly predisposes to bacteremia, which is associated with sequestration of parasitized red blood cells, increased gastrointestinal permeability and poor clinical prognosis. We have implicated mast cells (MCs) as early functional mediators of intestinal permeability in malaria and have described multiple cytokines that increase with rising parasitemia, including IL-10, that could contribute to the control of intestinal permeability. Activated MCs produce IL-10 in a variety of immunological settings, but the possible roles of MC-derived IL-10 in malarial immunity and bacteremia have not been identified. Herein, we studied the role of mouse MC-derived IL-10 in malaria-induced bacteremia using mice deficient for MC IL-10 (-) [Cpa3-Cre (+) IL-$10^{flox/flox}$ mice], matched genotype controls MC IL-10 (+) [Cpa3-Cre (-) IL-$10^{flox/flox}$ mice] and the non-lethal mouse malaria parasite *Plasmodium yoelii yoelii* 17XNL. We monitored intestinal permeability (FITC-dextran translocation into blood post-gavage), bacteremia (bacterial 16S copy numbers in blood) through 10 days post-infection (PI) and transmission of *P. yoelii* from infected MC IL-10 (-) and MC IL-10 (+) mice to the mosquito host *Anopheles stephensi*. Although, bacterial 16S DNA levels in blood were not different between genotypes, blood FITC-dextran levels were significantly increased by days 4 and 6 PI in MC IL-10 (-) mice relative to MC IL-10 (+) mice. This phenotype was associated with increased

levels of interleukin-1β (IL-1β), and important intestinal tight junction barrier-modulator and contributor to intestinal inflammation. In addition, transmission success of *P. yoelii* to *A. stephensi* was significantly higher from MC IL-10 (-) mice, a pattern that was associated with increased MC IL-10 (-) blood levels of gametocytes, myeloperoxidase (MPO) and KC, markers of neutrophil activation and recruitment, respectively, as well as RANTES and IL-6, important mediators of inflammation. These data suggest that MC-derived IL-10 protects intestinal barrier integrity and controls the host immune response to infection and parasite transmission during malaria.

1225

PLASMODIUM FALCIPARUM GAMETES AND SPOROZOITES ACQUIRE PLASMINOGEN TO EVADE HUMAN COMPLEMENT

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Malaria is a devastating disease caused by parasites of the genus *Plasmodium*. Successful completion of the parasite's life cycle, that is infection of the vertebrate host and transmission to a mosquito vector is contingent upon the ability of the parasite to overcome the host's antipathogenic responses. It has been shown that the extracellular stages of the parasite, including the gametes and the sporozoites, are targeted by the complement system. However, the parasite is still able to evade complement attack to infect both, the mammalian host and the mosquito vector. Our data suggest that *Plasmodium falciparum* gametes and sporozoites acquire plasminogen (a mammalian serine protease of the fibrinolytic system) on their surface to evade complement attack. Upon acquisition, plasminogen is activated to active plasmin and degrades parasite bound C3b thus halting the complement cascade. Importantly, we show that gamete and sporozoite permeabilization are increased when incubated in plasminogen-depleted plasma, suggesting that plasminogen is important for parasite survival against complement. Depletion of plasminogen in plasma also led to lower gamete exflagellation suggesting a critical role of plasminogen during microgamete exflagellation. Additionally, we find that sporozoites incubated in plasminogen-depleted plasma had reduced motility compared to their normal plasma counterpart. The reduced motility is reverted to normal levels upon plasminogen supplementation. Taken together, our data suggest that *Plasmodium* gametes and sporozoites hijack host plasminogen to evade complement. Thorough understanding of the mechanisms of complement evasion by the parasite is key to the development of novel effective therapeutics.

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IMPACT OF IMMUNITY AGAINST *PLASMODIUM VIVAX* GAMETOCYTES IN MODULATING THE HUMAN-TO-MOSQUITO TRANSMISSION OF PARASITES IN ETHIOPIA AND CAMBODIA

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Immunity against gametocyte antigens of *Plasmodium* parasites may reduce transmission of parasites from humans to mosquitoes. This paves possibilities for the development of transmission blocking vaccines and is important for understanding natural transmission dynamics. However, information on the prevalence and relevance of naturally acquired transmission reducing activity (TRA) is scarce, in particular for *P. vivax.* In this study, we investigated mosquito infectivity and TRA in 358 symptomatic *P. vivax* patients from Ethiopia (n=136) and Cambodia (n=222). Direct membrane feeding assays (DMFA) using serum replacement was performed, for a selection replacing autologous plasma with heterologous plasma of individuals with potent TRA. Antibody responses against a panel of *P. vivax* sexual stage antigens, being Pvs230, Pvs48/45, Pvs47, PvCelTOS and PvHAP2, are being evaluated by ELISA. Overall, 358 paired DMFA with autologous and replaced malaria-naïve control sera were performed, and 30 to 50 mosquitoes were dissected per feed to detect parasite transmission. A number of feeds in Ethiopia (n=100) and Cambodia (n=177) resulted in mosquito infection. The average percent infected mosquitoes during autologous and control sera feeds were 47.2% and 68.2% in Ethiopia, and 51.6% and 73.3% in Cambodia respectively. High TRA, >80%, was observed in 16% (16/100) and 22% (39/177) of Ethiopian and Cambodian sera respectively. In Ethiopia, sera with high TRA in autologous feeds were further tested against parasites from other gametocyte donors in heterologous feeds. 77.8% (7/9) of these sera blocked transmission of heterologous parasites. Serological analysis is ongoing with 80% and 66% of a first batch of tested sera showing reactivity to Pvs230 and PvCelTOS respectively. Antibody responses will be related to the proportion of infected mosquitoes and level of TRA. These results provide insightful information on the impact of immunity against *P. vivax* sexual stages in limiting parasite transmission to mosquitoes, and potential candidacy of selected antigens.

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LEVELS OF NEUTROPHIL EXTRACELLULAR TRAPS ARE ELEVATED IN CLINICAL CASES OF *PLASMODIUM KNOWLESI* MALARIA

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Invasion of red blood cells (RBCs) by *Plasmodium* parasites results in neutrophil activation and subsequent formation of neutrophil extracellular traps (NETs). Previous findings reported NETs inhibit growth of *P. falciparum* parasites, and are positively correlated with both parasite biomass and the release of activation products which mediate host organ damage and are associated with severe disease. The relationship between NETs and mechanisms of disease severity has not been evaluated in *P. knowlesi* infections. Venous blood samples were collected from patients enrolled with symptomatic *P. knowlesi* infections and malaria-negative healthy controls in Sabah, Malaysia. Quantification of NETs was done on Giemsa-stained blood slides using conventional microscopy. Knowlesi malaria cases were defined as severe or uncomplicated disease according to WHO criteria. NET counts were compared between disease states and healthy controls. Markers of neutrophil activation, i.e., neutrophil elastase (NE) and citrullinated histone H3 (CitH3) were examined by ELISA from plasma samples, then correlated with parasite biomass and other indicators of disease severity. Study participants consisted of 68 *P. knowlesi* microscopy-positive patients and 20 healthy controls, with median age of groups being 45 years (range 10 - 85) and 32 years (range 18 - 67) respectively. Malaria-positive cases had a geometric mean parasitaemia of 14,687/μL (95% CI 10,549 - 20,447). Increased NET counts (p=0.04) were observed in severe malaria patients (median 120 [IQR 62 - 296] per μL blood) compared to healthy controls (median 60 [IQR 40 - 102] per μL blood), but not when compared to non-severe group (median 71 [IQR 30 - 209] per μL blood). ELISA quantification of plasma NE showed increase only in severe knowlesi cases against healthy controls (p=0.002); whereas CitH3 levels were found elevated in both severe (p<0.001) and non-severe (p=0.0014) cases compared to the controls. Complete analyses will be presented at the ASTMH meeting. Preliminary findings indicate that enhanced neutrophil activation and high NET counts play a role in the pathogenesis of severe knowlesi malaria.

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TEMPORALLY PERSISTENT HEMOSTASIS DYSFUNCTION IN KENYAN CHILDREN RECOVERING FROM CEREBRAL MALARIA

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Pediatric cerebral malaria is manifest clinically by fever, seizures, coma, and a high Plasmodium falciparum biomass. Despite administration of artemether that rapidly reduces the parasite biomass, CM survivors can have long-lasting neurocognitive problems. We collected plasma and peripheral blood mononuclear cells (PBMC) at presentation and 6 weeks after recovery from 37 Kenyan children with CM, 20 with uncomplicated malaria (UM), and 13 with acute febrile non-malaria (AFNM) illness, e.g. pneumonia. Several plasma cytokines, chemokines, and biomarkers of endothelial dysfunction were higher in both CM and UM relative to AFNM, e.g. TNF, IL-6, syndecan-1 and -4, Vascular Endothelium Growth Factor Receptor 1. Those higher in CM than UM included Angiopoietin 2, Tyrosine Kinase Receptor-2, Tissue Factor Protein Inhibitor, Plasminogen Activation Inhibitor-1 (PAI-1), Myeloperoxidase, von Willebrand Factor (vWF), and cell-free dsDNA. Unlike 6-week recovery plasma from UM cases that showed no difference from 6-week plasma from AFNM, 6-week plasma from CM cases had persistent elevation of PAI-1, vWF, dsDNA, IL-21, and IL-27. DESeq analysis of PBMC RNA-Seq data from 9 children in each of the 3 comparator groups showed that only 4 genes (*LAG3*, *CCR5*, *PDGFRB*, *ICMT*) were significantly upregulated in acute CM vs. acute UM among the many more compared to AFNM. Whereas 6-week recovery PBMC from UM and AFNM cases showed no transcriptomic differences, 6-week recovery PBMC from CM cases showed highly significant ($P=2.9 \times 10^{-6}$) downregulation of the Hemostasis Reactome Pathway (R-HAS-109582) with no additional pathway differences relative to AFNM cases. These data suggest that temporally persistent lack of fibrinolytic activity and related hemostatic functions required to clear vascular endothelium thrombosis and fibrin deposition distinguishes CM survivors from UM. Additional network analyses that include clinical and parasitological metadata will be presented.

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PROTEOME-WIDE PROFILING OF ANTIBODY TARGETS WITH PHIP-SEQ IN UGANDAN COHORTS IDENTIFIES ASSOCIATIONS BETWEEN AGE, EXPOSURE INTENSITY, AND RESPONSES TO REPEAT-CONTAINING ANTIGENS IN *PLASMODIUM FALCIPARUM* MALARIA

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Factors contributing to the inefficient acquisition and maintenance of immunity to malaria remain incompletely understood, but certain properties of parasite antigens may contribute. We deployed a customized *Plasmodium falciparum* PhIP-seq T7 phage display library composed of 238,068 62-amino acid long peptides tiled with 25-aa step size, covering all known coding regions of the parasite, including antigenic variants, to systematically profile the targets of antibodies in response to natural malaria infection at near-epitope resolution. Proteome-wide profiles for 198 Ugandans from high and moderate transmission settings identified 9927 seroreactive peptides from 1648 proteins, mapping at high resolution many previously well-characterized as well as novel parasite antigenic regions. Our dataset characterized seroreactivity to repeat elements and potential cross-reactive epitopes among antigens in detail, and the results suggest a possible role for them in inefficient acquisition of immunity. Repeat elements, which are short amino acid stretches repeated multiple times within a protein, were found to be immunodominant, being significantly enriched in peptides with high seroprevalence. Furthermore, significant exposure-setting dependent differences were observed in the enrichment of repeat-containing peptides in children, more than non-repeat peptides. Additionally, we also identified an extensive presence of shared motifs among seroreactive peptides from large numbers of antigens, including many proteins highly targeted by the immune system. These motifs were significantly associated with seroreactivity, and potentially represent cross-reactive epitopes. Particularly, numerous shared motifs was observed between PfEMP1 and other antigens, partly driven by the large number of PfEMP1 sequences included in the analysis. The mechanism of evolving PfEMP1 variants within a network of shared sequences with other antigens could be another ploy used by the parasite for immune evasion.. These observations have implications for future vaccine candidate selections as well as our fundamental understanding of malaria.

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PREVALENCE OF *PLASMODIUM FALCIPARUM* INFECTIONS IN PREGNANT WOMEN DURING THE FIRST ANTENATAL CLINIC VISIT AND ASSESSMENT OF MATERNAL AND PLACENTAL *P. FALCIPARUM* INFECTIONS AT DELIVERY IN TANZANIA, KENYA AND MALAWI

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Malaria in pregnancy (MIP) leads to adverse pregnancy outcomes; therefore, early detection and prompt treatment are crucial in sub-Saharan Africa. However, as asymptomatic and sub-microscopic infections are common, the WHO recommends intermittent preventive treatment (IPTp) using sulfadoxine-pyrimethamine (SP) from the second trimester of pregnancy and onwards to avert the impact of MIP. We explored the prevalence of *P. falciparum* malaria at enrolment and at delivery in a cohort of 4755 women in Tanzania, Kenya, and Malawi using a highly sensitive qPCR. The study was part of a three-country randomized trial comparing monthly IPTp with SP, dihydroartemisinin-piperaquine (DP) and DP plus a single-course of azithromycin at enrolment conducted from June 2018 to Dec 2019. The prevalence of *P. falciparum* infections at enrolment was determined among women between 16-28 weeks pregnant by microscopy, RDT and qPCR. Malaria at delivery was assessed by qPCR of parasite DNA extracted from maternal peripheral blood (MPB) and placental blood (PLB) samples. The prevalence of positive *P. falciparum* infections in pregnant women from Tanzania, Kenya and Malawi, respectively were 5.0%, 14.7% and 11.6% by microscopy; 12.6%, 22.9% and 30.9% by RDT, and 10.8%, 14.4% and 19.1% by qPCR. At delivery, the qPCR prevalence in MPB were 6.6%, 4.6% and 8.4% in the IPTp-SP arm vs. 2.9%, 2.3% and 6.5% in the pooled IPTp-DP arms (P=.001, .028 and .258) in Tanzania, Kenya and Malawi respectively. The corresponding

qPCR prevalence in PLB were: 6.1%, 6.1% and 6.5% vs. 3.8%, 3.9% and 4.5% (P=0.074, .113 and .162). When data from the three countries were pooled, the prevalence for MPB was 6.9% vs 3.9% in the SP vs. DP arms (P=0.0002), and it was 6.6% vs 4.2% for PLB (P=0.006). Prevalence of *P. falciparum* infections by qPCR at enrolment was higher than 10% in all three countries emphasizing the need for IPTp. Pooled prevalence of *P. falciparum* infections at delivery for both MPB and PLB samples was higher in the IPTp-SP than in the IPTp-DP arm suggesting a superiority of DP at this stage of pregnancy.

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ENHANCING THE CAPACITY AND USABILITY OF VIETNAM'S ELECTRONIC SURVEILLANCE SYSTEM (ECDS-MMS) TO ENSURE COMPREHENSIVE MALARIA DATA AND SURVEILLANCE FOR ELIMINATION

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Malaria in Vietnam has decreased from 9,331 confirmed cases in 2015 to 467 cases in 2021. As Vietnam moves closer to its goal of malaria elimination, a sustainable system to track malaria cases and responses is needed to identify and clear the last reservoirs. The General Department of Preventive Medicine, Institutes of Malariology, Parasitology, and Entomology[JCD1] [JG2] , and CHAI collaborated to integrate the Malaria Management System (MMS) into the Ministry of Health's Electronic Communicable Disease System (eCDS). After the completion of a pilot, the system was scaled up in July 2020 including trainings of staff nationwide. Performance metrics were evaluated to assess quality, accessibility and use of data to best target responses and supervision. For prompt case reporting, all commune health staff were provided accounts and required to report malaria to the system. Malaria reporting completeness increased from 41% in July 2020 to 97% in October 2020 and has been above 90% in the central and southern regions since then. From July 2020 to December 2020, 91% (418) of confirmed cases were reported into the eCDS-MMS compared to the paper forms. Of those, 62% (260) were reported within the required timeframe of 48 hours. Over 2021, 100% (467) of confirmed cases were reported into the eCDS-MMS and 69.2% (323) within 48 hours. The eCDS-MMS also supports entry and visualization of demographic data for malaria cases. The system showed that 75.4% of the cases (352 cases) are of working age (from 15-49). Of these, 79% are male and 84% are forest-goers or agricultural workers. Through monthly data reviews at central level, provinces and districts with low reporting completeness and timeliness have been identified and notified, ensuring high data quality. Intervention and epidemiological data for all administrative levels can now be used to assess and target responses in the remaining malaria hotspots in Vietnam. The lessons learned from the speed and scale at which Vietnam was able to fully scale up the system provides important lessons for countries who are seeking to rapidly integrate malaria information into national systems as they approach elimination.

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IDENTIFYING STRENGTHS AND GAPS IN DATA MANAGEMENT AND REPORTING THROUGH MALARIA ROUTINE DATA QUALITY ASSESSMENT: RESULTS FROM TWO HEALTH REGIONS IN MADAGASCAR

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In 2021, The U.S. President's Malaria Initiative Measure Malaria project supported the National Malaria Control Program to conduct Malaria Routine Data Quality Assessment (mRDQA) in Madagascar. This assessment was conducted in 30 health centers (HCs) that had &gt 10% data showing errors from two regions: Atsinanana (14 HCs; analyzed data from May to July) and Atsimo Andrefana (16 HCs; analyzed data from July to September). The objective was to support targeted HCs to improve malaria data reporting, quality, and use using the mRDQA new tool. The team reviewed data from outpatient disease registers (OPD), monthly reports (MR), and District Health Information Software, version 2 (DHIS2) to assess reporting timeliness, data completeness, and availability of reporting tools at each facility. The team also performed data consistency checks for the number of fever cases tested in children 6-13 years old, comparing figures between OPD registers, MR, and DHIS2 data using a verification factor (VF). While overall completeness of monthly report submission for the 3- month period was inadequate in Atsinanana region HCs (43%) and Atsimo Andrefana region HCs (68%), the reporting timeliness among submitted reports was acceptable, respectively 95% and 85% (MOH target:100%). The availability of data source documents was 59% in Atsimo Andrefana and 48% in Atsinanana. The use of standard reporting forms (MR, OPD register, antimalarial stock forms) was 44% for Atsinanana and 54% for Atsimo Andrefana, however MR forms and OPD registers were available in 100% of HCs. Data discrepancies were found between the OPD registers and both the MR and DHIS2 data. Overall, the VF was 120% in Atsinanana and &gt 110% in Atsimo Andrefana for both MR and DHIS2, indicating overreporting. Reasons for data discrepancies were arithmetic errors (25%), transcription errors (13%), and additional discrepancies arising from incomplete forms and confusion about variable definitions. Although acceptable reporting timeliness, data reporting accuracy, use of standard reporting forms, guidelines availability, and staff data management capacity are gaps requiring improvement.

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DIGITALIZED LONG LASTING INSECTICIDAL NET (LLIN) DISTRIBUTION FOR TARGETED REPLACEMENT CAMPAIGN IN THE CONTEXT OF COVID-19 PANDEMIC: A CASE STUDY FOR KATAVI REGION, WESTERN TANZANIA

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Katavi region in western Tanzania saw an increase in malaria incidence in 2020, shifting the region from moderate transmission to high transmission status. This coincided with low population access of ITNs (<50%). To increase LLIN access and protect communities against malaria, Tanzania National Malaria Control Programme (NMCP) in collaboration with partners distributed LLINs in a Targeted Replacement Campaign (TRC) in Katavi region late 2021. The TRC used a digitalized approach called Electronic Targeted Mass Replacement Campaign using Management Information System (eTMRC-MIS). Campaign staff used smartphones to record household registration information, manage logistics, and issue LLINs to beneficiaries. The system generated a unique identifier that enabled each household to receive its allotted number of nets during issuing. Data were visualized in dashboards with online and offline modes. Household registration data showed that 11% more households were registered than the initial estimate of 151,636 households. A total of 611,717 PBO nets were issued at 633 distribution stations in Katavi. The campaign increased population LLIN access to at least 80%; consequently, as part of other interventions within Katavi, eTMRC-MIS may significantly contribute to reduction of malarial morbidity and mortality. The deployment of eTMRC-MIS provided five key benefits for LLIN distribution compared to the traditional paper-based approach. First, real time monitoring of results reduced the total implementation period. Second, the programme got more accurate and timely registration information. Third, fewer human resources were needed to conduct the monitoring and follow up of different activities. Fourth, it increased accountability as verification of household net need was simplified and easy to follow. Lastly, analysis of results for reporting was faster and less burdensome as there was no need for manual data entry or aggregation. Given the success of the digitalized approach in the Katavi TRC, the eTMRC-MIS model is highly recommended for use in similar targeted replacement campaigns that aim to scale up population access to LLINs.

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SEROLOGICAL SIGNATURES OF RECENT DECLINES IN MALARIA TRANSMISSION IN PREGNANT WOMEN

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In areas approaching malaria elimination, transmission becomes increasingly sparse and heterogenous. In these settings, women are less likely to be infected during pregnancy, and consequently less likely to acquire pregnancy-specific immunity. We hypothesized that serological data from pregnant women attending antenatal care clinics can be utilized as sensitive and stable metrics of malaria burden. In addition, we wanted to better understand how different transmission intensities affect the acquisition and maintenance of pregnancy-specific immunity. We analyzed a set of 11,798 dried blood spot samples from pregnant women in three areas of southern Mozambique. Plasmodium falciparum infection was determined with quantitative polymerase chain reaction (PCR). Antibody levels were measured using quantitative suspension array technology with a panel of 21 malaria antigens, including seven pregnancy-specific ones. In all three areas, temporal trends in seroprevalence of one pregnancy-specific antibody in primigravid women reflected temporal trends in PCR positivity rates in the same cohort, as well as in clinical cases among children below 5 years of age from health facilities. The seroprevalence had a larger amplitude, and lagged behind the clinical cases, similar to PCR positivity rates. Some short-lived general malaria antibodies were also correlated with PCR positivity rates and clinical cases, across all gravidities. Women with more than two previous pregnancies showed a stronger and broader antibody profile, in particular in high-transmission settings. When transmission decreased, secundigravid women developed weaker pregnancy-specific immune responses, indicating less exposure in their first pregnancy. These findings show that recent declines in transmission are reflected in antibodies that can be measured from pregnant women attending antenatal care. Particularly useful for surveillance efforts in low-transmission settings, seroprevalence of one pregnancy-specific antibody showed an amplified and smoothed trend of burden in the community, and informed about a recent decline.

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ASSESSMENT OF BASELINE MOLECULAR MARKERS OF SULFADOXINE-PYRIMETHAMINE RESISTANCE IN OSUN AND EBONYI STATE NIGERIA TOWARD IMPLEMENTATION OF INTERMITTENT PREVENTION TREATMENTS IN INFANTS (IPTI)

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The global malaria death in children under five (U5) reduced from 87% in 2000 to 77% in 2020. Nigeria reported higher malaria-related deaths in 2020 compared with 2019. Although the overall U5 mortality rate reduced by 15.9 percent from 157 to 132 per 1000 live births between 2008 and 2018, the reduction in infant mortality rate (IMR) during the same period was less marked: 10.7 percent, from 75 to 67 per 1000 live births. Nigeria intends to explore IPTi implementation to reduce IMR. IPTi is recommended for areas with prevalence of the dhps K540E mutation less than 50%. Pre-intervention assessment of the prevalence of molecular markers of SP resistance was conducted in Ebonyi and Osun states Nigeria to determine eligibility for IPTi implementation. A stratified cluster sampling method was used to select 12 LGAs, six in each state. Blood sample (Dry Blood Spot (DBS)) were collected from patients aged six months old and above with fever or history of fever in 24-48 hours preceding presentation at the HF. Next-generation sequencing (NGS) amplicon deep sequencing was used for the DBS analysis. A total of 1,248 DBS samples collected from Ebonyi and Osun state were initially analyzed while 1,161 samples were successfully sequenced using NGS amplicon deep sequencing. 969 samples with high sequence quality were analyzed for dhps540 mutation. No sample has dhps-540**E** as a single clone and 180 samples (18.58%) carried the mutant variant mixed with the wildtype (dhps-**K**540**E**). The prevalence of dhps-**K**540**E** was slightly higher in Ebonyi compared to Osun (Ebonyi, 21.11%; Osun, 16.54%; p=0.069, 95% CI 0.52-1.04). The highest prevalence of the *dhps*-**K**540**E** variant in Ebonyi and Osun was observed in Izzi (33.33%) and Orolu (23.26%) respectively. While lowest prevalence was observed in Ezza-North (6.78%) and Ede

South (6.25%) LGAs respectively. The estimated low prevalence of the resistant variant dhps **K**540**E** mutation confirmed both states eligible for IPTI implementation.

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DISENTANGLING CO-ENDEMIC *PLASMODIUM FALCIPARUM* AND *P. VIVAX* TRANSMISSION DYNAMICS USING SYNCHRONOUS GENOMIC SEQUENCING AND MODELING

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The malaria parasites *Plasmodium falciparum* and *P. vivax* exhibit distinct modes of human infection and pathogenesis. Unlike *P. falciparum*, *P. vivax* forms dormant liver-stage hypnozoites that relapse into blood-stage infections featuring rapid gametocytogenesis and little to no host cell cytoadherence to endothelial tissue. This study examines the consequences of distinct *P. falciparum* vs. *P. vivax* infection biology on malaria transmission dynamics and control strategies in Guyana, where both species contribute strongly to the national case count (34% and 65%, respectively) but distribute heterogeneously across a metapopulation structure shaped significantly by gold mining activity in remote rainforest regions. We use large spatiotemporally matched genomic datasets (737 *P. falciparum* genomes and 908 *P. vivax* genomes sequenced from human blood spot samples collected continuously between January 2020 and June 2021) to map malaria species dispersal networks among mining and non-mining communities within Guyana and adjacent states. We observe strong contrasts in complexity of infection (>3x higher mixed-strain infection frequency in *P. vivax*) and parasite relatedness within and between infections (>4x higher median population-level identity-by-descent in *P. falciparum*), describing how these metrics relate uniquely to host ethnicity (Amerindian, Indian, Afro-American, and mixed backgrounds), gender, and age as a function of local transmission intensity and population connectivity levels over time. We further explore distinct epidemiological patterns in *P. falciparum* vs. *P. vivax* malaria using an agent-based transmission model unique to each species. We show how species-specific determinants such as the proportion of asymptomatic cases, presence/absence of relapse, and infectivity to mosquitos affect spatiotemporal patterns of transmission. The results from the molecular and transmission modeling studies demonstrate how individual infection variables affect regional malaria epidemiology and provide species-specific guidance for surveillance and control.

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DEVELOPMENT OF A DOSE-RESPONSE MODEL FOR PORCINE CYSTICERCOSIS

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Taenia solium is an important cause of acquired epilepsy worldwide and remains endemic in Asia, Africa, and Latin America. Transmission of this parasite is still poorly understood despite the design of infection experiments to improve our knowledge of the disease, with estimates for critical epidemiological parameters, such as the probability of human-to-pig infection after exposure to eggs, still lacking. In this research, a systematic review was carried out and eight pig infection experiments were analyzed to describe the probability of developing cysts. These experiments included different pathways of inoculation: with ingestion of proglottids, eggs, and beetles that ingested eggs, and direct injection of activated oncospheres into the carotid artery. In these experiments, different infective doses were used, and the numbers of viable and degenerated cysts in the body and brain of each pig were registered. In order to analyze these data, five alternative dose-response models (exponential, logistic, log-logistic, and exact and approximate beta-Poisson) were assessed for their accuracy in describing the observed probabilities of cyst development as a function of the inoculation dose. Dose-response models were developed separately for the presence of three types of cysts (any, viable only, and cysts in the brain) and considered for each of the four inoculation methods ("Proglottids", "Eggs", "Beetles" and "Carotid"). The exact beta-Poisson model best fit the data for the three types of cysts and all relevant exposure pathways. Estimated parameter values from this model suggest that a low infective dose is sufficient to result in a 50% probability for the development of any cyst or for viable cyst infections. Although this is a preliminary model reliant on a limited dataset, the parameters described in this research should contribute to the design of future experimental infections related to *T. solium* transmission, as well as the parameterization of simulation models of transmission aimed at informing control.

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CLINICAL, RADIOLOGICAL AND SEROLOGIC CHARACTERISTICS OF PATIENTS WITH SUBARACHNOID NEUROCYSTICERCOSIS: A LARGE SERIES OF A NON-ENDEMIC REGION

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Subarachnoid neurocysticercosis (SANCC) is the most severe and difficult to treat form of neurocysticercosis (NCC). We describe the clinical, radiologic, and serologic characteristics of the largest series of patients with SANCC in a non-endemic area by reviewing the medical records of patients seen at Jacobi Medical Center in New York. From 302 cases of NCC, 98 patients (32.5%) had subarachnoid involvement. Most individuals were male (65.3%) and born in Mexico (37.8%); the mean age was 41.8 years. Thirty-six patients had only subarachnoid involvement, 47 patients had both parenchymal and SANCC, 5 patients (5.1%) had both intraventricular and SANCC and 10 patients (10.2%) had all three spaces involved. Sixty-eight patients (69.4%) presented with headaches. Of these, 36 patients had intracranial hypertension and 27 required shunt placement. Twenty-eight patients (28.6%) presented with seizures, most of whom had concomitant parenchymal disease. Fourteen patients (14.3%) presented as an ischemic event, 12 patients (12.4%) had symptoms due to spinal disease and 8 patients (8.2%) had aseptic meningitis. Screening for spinal disease was performed on 63 patients. Of these, 13 patients (21.7%) had asymptomatic spinal involvement. Delay in diagnosis was found in 48 patients (49.0%) with a median of 12 months; chronic headache was the most common missed symptom (48.2%). Calcified SANCC was found in 33 patients (33.7%). Of these, 18 patients (18.4%) did not receive previous antiparasitic. Based on both CT scan and MRI, 14 of these patients were categorized as completely

calcified and 19 patients were partially calcified with a cystic component seen on MR T2 images. The cysticercosis antigen in serum and CSF were negative in all cases of completely calcified and only in one case of partially calcified SANCC. This is the largest series of SANCC reported in the US and highlights its clinical spectrum. Our data also shows that there is an important under-recognition of this severe form by the clinician, and reports a newly described observation. Calcified SANCC is common and can occur before and after treatment.

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MASS DRUG ADMINISTRATION IS COST-EFFECTIVE COMPARED TO SCHOOL-BASED PREVENTIVE CHEMOTHERAPY FOR HOOKWORM CONTROL IN DAK LAK PROVINCE, VIETNAM

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School-based preventive chemotherapy (PC), where school children are administered anthelmintic drugs, is the main strategy recommended by WHO for control of soil-transmitted helminths (STH) including hookworms. This strategy leaves out adults and preschool children who are important STH infection reservoirs. Mass drug administration (MDA), where everyone in endemic areas is given anthelmintic drugs, provides an alternative that could more effectively reach current STH control targets and potentially lead to elimination of transmission. This study aimed to examine the cost-effectiveness of MDA compared with school-based PC in Dak Lak province, Vietnam from a government payer perspective. Resource use and costs were obtained through interviews with health and education staff. Costs were converted to 2020 USD and a one-year time horizon was used. Hookworm cases and DALYs averted were derived from the CoDe-STH trial, a cluster randomised controlled trial comparing the impact of MDA versus school-based PC on hookworm infections in school children. Preliminary results indicate the total cost for MDA compared to school-based PC was USD 591,722 (range: USD 322,143 - USD 953,810) and USD 153,117 (range: USD 73,811- USD 276,993) respectively. The cost per person treated for MDA was USD 0.32 (range: USD 0.17-USD 0.51), while for school-based PC it was USD 0.54 (range: USD 0.26- USD 0.98) per person treated. Implementing MDA in Dak Lak province would avert 35,515 hookworm infections and 1,217 DALYs annually, while school-based PC averts 14,176 hookworm infections and 151 DALYs. Sensitivity analysis is being conducted to assess the robustness of results over a range of parameter values. The incremental cost-effectiveness ratio (ICER) of MDA compared to school-based PC was USD 20.55 per hookworm case averted and USD 412 per DALY averted. Our study indicates that a higher investment in MDA is cost-effective as the ICER is below the estimated cost-effectiveness threshold in Vietnam (USD 2,777 per DALY averted). This supports the value of MDA in averting hookworm infections and contributing to efforts towards eliminating STH as a public health problem.

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COSTS OF COMMUNITY-WIDE MASS DRUG ADMINISTRATION AND SCHOOL-BASED DEWORMING FOR SOIL-TRANSMITTED HELMINTHS: EVIDENCE FROM BENIN, INDIA, AND MALAWI

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Current guidelines for the control of soil-transmitted helminths (STH) recommend deworming children and other high-risk groups, primarily using school-based deworming (SBD) programs. However, targeting individuals of all ages through community-wide mass drug administration (cMDA) may interrupt STH transmission in some settings. This study compares the costs of cMDA to SBD to inform decision making about future updates to STH policy. We conducted activity-based micro-costing of cMDA and SBD for two years in Benin, India, and Malawi within an ongoing cMDA trial. We calculated total financial and opportunity costs and costs per treatment administered (unit costs) from the service provider perspective, including costs related to community drug distributors and other volunteers. Sensitivity analyses explored uncertainties around input prices, opportunity costs, and MDA treatment coverage. On average, we found cMDA unit costs were more expensive than SBD in India ($1.17 vs. $0.72) and Malawi ($2.26 vs. $1.69), and comparable in Benin ($2.45 vs. $2.47). cMDA was more expensive than SBD in part because most costs (~60%) were "supportive costs" needed to deliver treatment with high coverage, such as additional supervision and electronic data capture. A smaller fraction of cMDA costs (~30%) were routine expenditures (e.g. drug distributor allowances). The remaining cMDA costs (~10%) were opportunity costs of staff and volunteer time. A larger percentage of SBD costs were opportunity costs for teachers and other government staff (between ~25%-75%). Unit costs varied over time and were sensitive to the number of treatments administered. Our results suggest that cMDA is generally more expensive than SBD but relative differences depend on supportive activities used to increase coverage across delivery settings. Accounting for local staff time (volunteers, teachers, health workers) in community programs is important and drives higher cost estimates than commonly recognized in the literature. Costs may be lower outside of a trial setting, given a reduction in supportive costs used to drive higher treatment coverage and economies of scale.

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AN INTEGRATED RESEARCH APPROACH FOR SOIL-TRANSMITTED HELMINTH CONTROL

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Soil-transmitted helminths or intestinal parasitic nematodes (IPN) are the most common of the neglected tropical diseases inflicting significant morbidity on impoverished populations with largest impacts on children and pregnant women. No vaccines exist. The very few drugs available for treatment are prone to parasite's resistance in veterinary medicine and are showing signs of insufficiency in human medicine. Because of the impoverishment of those infected, there are few concerted efforts to develop new drugs and vaccines. Because we maintain whipworms, *Strongyloides*, and two species of human hookworms and whipworms in our laboratory, we are taking a multi-pronged, integrated approach to researching new anthelmintics and vaccines. We are using nature and small molecules as inspiration for anthelmintics. Crystal proteins made by the soil bacterium *Bacillus thuringiensis* are the most successful biologically produced insecticides in the world and non-toxic to vertebrates. We have shown that oral Cry5B given to animals infected with IPNs cures a wide variety of IPNs. Current work is focused on optimizing Cry5B protein sequence to prevent premature proteolysis and increase bioactivity as well as testing new Cry proteins for additional anthelmintic activities. We

have also developed a novel anthelmintic discovery pipeline using a wide range of nematode parasites to screen >30,000 compounds for activity *in vitro* using hookworm larvae, followed by screening against adult hookworms and whipworms.. Prioritized compounds were then tested for mammalian cell tox, and then *in vivo*. To date, we have identified four new small molecules that significantly impact hookworm infections in small rodents. Finally, we are using transcriptomics, proteomics, bioinformatics, and immunoinformatics to prioritize hookworm antigens for vaccine development. Our goal is to test a relatively large number of vaccine antigens *in vivo* for protection of rodents against hookworm infection.

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MONITORING PATTERNS OF SYSTEMATIC NON-TREATMENT IN A MASS DRUG ADMINISTRATION PROGRAM THROUGH BIOMETRICALLY VERIFIED POPULATIONS: THE CONTROL OF SOIL TRANSMITTED HELMINTH AND SCHISTOSOME INFECTIONS IN SOUTHERN ETHIOPIA BY THE GESHIYARO PROJECT

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Control of soil-transmitted helminths (STH) and schistosomiasis (SCH) centres around repeated mass drug administration (MDA) in communities with endemic infection. Attaining consistent, individual compliance over subsequent rounds of MDA is critical for removing infectious egg or larvae reservoirs created from untreated cohorts, who currently prevent transmission break. The Geshiyaro project is a five-year longitudinal study, designed to define the endgame for STH and SCH transmission break.To date, Bolosso Sore woreda, Wolaita zone, has received three rounds of community-wide MDA. During MDA distribution, participants' identity was verified using biometric fingerprint capture. The eligible population were offered one dose of 400mg albendazole (ALB) (1< years old, non-pregnant women) and 600mg praziquantel (PZQ) (4< years old, non-pregnant women) at a height-dependent dose. Individual-level data was analysed for trends in systematic non-treatment at each MDA round using multinomial logistic regression and conditional probabilities.A total of 192,082 participants were identified across the three years, constituting the longitudinal cohort for analysis. The adjusted odds of urban participants of being contacted at MDA was less than that of rural counterparts, yet once contacted, urban participants were more likely to swallow the offered drug. The conditional probability of an individual swallowing drugs increased over the three years, and with incrementing age groups, when compared to school-aged children (SAC).The monitoring of individual compliance is rarely conducted in longitudinal MDA programmes. The lack of commonality is disproportionate to the importance the epidemiological parameters hold. By highlighting key demographics of the non-treated population, programmes can use this information two-fold; to brief drug distributors with these target populations to increase the spread of the offered anthelmintics, and to improve sensitisation methods for targeted populations to reduce the refusal rate once a participant has been contacted.

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CHROMOSOME LEVEL ASSEMBLY OF THE *STRONGYLOIDES STERCORALIS* GENOME IMPROVES CHARACTERIZATION OF NON-CODING DNA

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Strongyloides stercoralis (Ss) is a globally distributed pathogenic nematode that, when disseminated, can cause significant morbidity and mortality. Although the current draft genome has been available since 2014, its fragmentation (833 contigs) has made understanding the physical organization of non-coding DNA difficult. Because genomic satellite repeats have been shown to be useful as sensitive molecular diagnostic targets, we sought to better characterize the organization of these and other non-coding Ss DNAs, by improving the contiguity of the previously constructed draft genome. Using Oxford nanopore sequencing on high molecular weight DNA extracted from infective L3 Ss larvae followed by assembly using long-read assembly programs (Flye, SmartDenovo, Necat, and Canu) coupled with haplotig removal and polishing, we were able to condense the Ss genome into 8 contigs. Using synteny with other nematodes including *S. ratti*, 2 of these contigs could be assigned as the full-length assemblies of chromosome 1 and 2 with the remaining 6 fragments composing the remaining X chromosome. The resulting genome identified an additional 299 genes and expanded the genome from 43Mb to 44Mb. Satellite repeated elements, predicted to account for about 0.5% of the genome, were found to be symmetrically arranged at the distal ends of both autosomes. Canonical telomeric repeats (TAAGCC, TAGGCT), as found in other helminths, could not be identified in Ss. Rather a repeated 106bp and 111bp sequence flanked the 5' and 3' region of chromosome 2, respectively, suggesting the possibility that Ss may be under a novel telomeric regulatory schema. Centromere analyses suggest that, like *C. elegans*, the centromere is organized in a dispersed point manner. Thus, the chromosome level assembly of Ss has improved the understanding of the unique genomic organization of Ss.

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NOVEL SALIVARY ANTI-HEMOSTATIC ACTIVITIES FROM *ANOPHELES GAMBIAE* FACILITATE BLOOD FEEDING

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Salivary secretions of blood feeding mosquitoes contain bioactive molecules to counteract the host's natural hemostatic and inflammatory responses. The D7 proteins are some of the most abundantly expressed proteins in female mosquito salivary glands and have been implicated in inhibiting platelet aggregation, coagulation, and inflammation. *Anopheles gambiae* has three D7 long-form and five D7 short-form proteins. Previous studies have characterized the AngaD7 short-forms. Here, we characterized the *An. gambiae* D7 long-forms by a combination of biochemical, biophysical, and *ex vivo* assays. We found that AngaD7L1 binds leukotriene C4 and the thromboxane A2 analog, U-46619; AngaD7L2 weakly binds leukotrienes B4 and D4; and AngaD7L3 binds serotonin. AngaD7L3 is the first member of an anopheline D7-long protein to bind serotonin. Functional assays confirmed AngaD7L1 inhibits U-46619-induced platelet aggregation and vasoconstriction and AngaD7L3 inhibits serotonin-induced platelet aggregation and vasoconstriction. Finally, AngaD7L2 has a dose-dependent anticoagulant effect via the intrinsic pathway by interacting with factors XII, XIIa, and XI. This is the first member of the D7-long form to display anticoagulant activity. This work highlights the complex yet highly specific biological activities of mosquito salivary proteins and serves as another example of the sophisticated biology underlying arthropod blood feeding.

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CRISPR-CAS9-MEDIATED GENE KNOCKOUT OF *CTL4* REVEALS TEP1-INDEPENDENT MELANIZATION OF HUMAN MALARIA PARASITES

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Melanization is one of the most effective innate defense mechanisms in mosquito vectors. Numerous studies have shown that the *Anopheles* TEP1-controlled complement-like system is essential for melanization of the rodent model malaria parasite *Plasmodium berghei*, which evades this defense by recruiting C-type lectins. But the role of TEP1 has not been sufficiently addressed in the context of malaria infection with the clinically relevant human malaria parasite, *P. falciparum*. Using CRISPR/Cas9-based C-type lectin 4 knockout, we show that *A. gambiae* can mount melanization-based refractoriness to the human malaria parasite in a TEP1-independent manner, and a small proportion of *P. falciparum* ookinetes are capable of evading this defense mechanism in the midgut tissue of CTL4^{null} mosquitoes, in contrast to the complete melanization of rodent *P. berghei*. Our study proves CTL4 as an essential host factor for *P. falciparum* transmission and one of the most potent mosquito-encoded malaria transmission-blocking targets, and highlights discrepancies in the *Anopheles* innate immunity response to *P. falciparum* versus *P. berghei*, while stressing the importance of conducting malaria laboratory-based transmission studies using clinically relevant parasites.

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THE HUMORAL PROTEOME OF *ANOPHELES GAMBIAE* REVEALS NEW HOST-PARASITE-VECTOR INTERACTIONS SHAPING MALARIA TRANSMISSION

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Most of *Plasmodium* development in mosquitoes takes place in the hemocoel in the presence of hemolymph, which homes not only anti-parasitic molecules and immune cells, but also nutrients and immune regulators that enable parasite survival. How the parasite impacts the hemolymph protein composition is currently unknow. We characterized the hemolymph proteome from uninfected and *P. berghei*-infected mosquitos at three different points after infection (AI): 30 hours, when ookinetes reach the hemocoel; 10 days, during oocysts growth; and 19 days, when sporozoites are released. We observed significant changes in protein expression induced by parasite infection. Interestingly, at 30 hours AI, we found a significant enrichment of mouse blood proteins involved in iron transport and metabolism, including hemoglobin and the heme neutralizing protein, hemopexin. Ookinete invasion induced hemopexin uptake by the midgut epithelium, suggesting active transport of hemopexin rather than mere diffusion. We observed a strong increase in oocyst formation when mosquitos fed on infected hemopexin-ko mice that were intravenously injected with hemopexin. Moreover, intrathoracic injection of hemopexin into infected mosquitoes also increased oocyst formation, suggesting that hemopexin potentially protects the parasite from the noxious effects of free heme. Our proteomic data unveils new host-parasite-vector interactions that could be targeted in malaria transmission-blocking interventions.

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EXPLORING *WOLBACHIA*-DERIVED *CIF* GENES AS POTENTIAL VECTOR CONTROL TOOLS FOR MALARIA

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Wolbachia bacteria can be powerful tools for control of vector-borne disease due to their combined ability to block replication of certain pathogens, and their capacity to induce Cytoplasmic Incompatibility (CI) which allows them to spread rapidly through insect populations. In CI, males that are infected with *Wolbachia* cannot produce viable progeny unless they mate with females infected with the same *Wolbachia* strain. Currently, there are no suitable *Wolbachia* infections in *Anopheles* mosquitoes that are utilized for malaria control, in part due to a dearth of CI-inducing *Wolbachia* infections in these vectors. The *Wolbachia* genes underlying CI have been elucidated, and we have recently shown that in the dominant malaria vector *Anopheles gambiae,* expression of *cifB* from the *w*Pip *Wolbachia* strain in male mosquitoes is sufficient to cause infertility associated with CI in females. This infertility was completely rescued by expression of *cifA*^{wPip} in females. Further, we showed that *cifB* expression alone in females impairs reproduction, demonstrating toxicity associated with *Wolbachia*-derived factors in *An. gambiae* that has not been observed in other insects to date, suggesting a possible reason for the lack of CI-inducing *Wolbachia* strains in this species. We continue to investigate whether these strains can be used in novel vector control strategies against *Anopheles* mosquitoes. These transgenic lines show promise in population invasion experiments where wild-type cages are seeded with males and females expressing *cifA* and *cifB.* Transgenes can reach high frequencies, highlighting the possibility of linking antimalarial genes with the *cif* genes to drive antimalarial effectors into mosquito populations. Further, we investigated whether expression of the *cif* genes alters infection by *Plasmodium falciparum*. Preliminary studies have shown no effect of *cif* expression on oocyst development, demonstrating that these genes may be safe to use in control strategies. Together, these data provide valuable insight toward the future of *Wolbachia* in malaria control.

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DE NOVO FATTY ACID SYNTHESIS MEDIATES *ANOPHELES* REPRODUCTION AND *PLASMODIUM* TRANSMISSION

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Female *Anopheles* mosquitoes require several blood meals during their life span to initiate multiple cycles of egg development, and these obligatory steps are exploited by *Plasmodium* parasites for their own transmission. Blood feeding is therefore a critical step for both mosquito reproduction and parasite transmission that could be exploited to impact malaria dynamics in endemic areas. Here we elucidated the specific role of lipogenesis in *Anopheles gambiae* reproduction and *Plasmodium falciparum* development in mosquito stages. Targeted lipidomic analyses revealed a coordinated accumulation and depletion of major lipid classes across key mosquito tissues during blood meal digestion, suggestive of an active engagement of lipogenic and lipolytic pathways. RNA interference against key mosquito lipogenic enzymes, acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), the rate limiting enzyme in *de novo* fatty acid synthesis, significantly reduced lipid accumulation in key mosquito tissues, completely abrogated egg development and impaired *P. falciparum* infection. Interestingly, supplementation with lipids partially rescued *P. falciparum* infection prevalence in FAS-silenced females. Altogether, this study identifies mosquito lipogenic pathway as a critical metabolic

checkpoint for mosquito reproduction and the establishment of *Plasmodium* infection, providing new targets for the control of malaria transmission.

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PLASMODIUM A-TUBULIN-1 IS AN *ANOPHELES* FREP1 LIGAND AND PROMOTES PARASITE INFECTION OF THE MOSQUITO

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Invasion of the mosquito midgut by *Plasmodium* parasites is essential for infection of the vector and subsequent pathogen transmission. Fibrinogen-related protein 1 (FREP1), a mosquito midgut peritrophic matrix protein, binds to the parasite ookinete stage and mediates *Plasmodium* infection of *Anopheles* mosquitoes. This FREP1-mediated *Plasmodium* invasion pathway is conserved highly across multiple species of *Plasmodium* and *Anopheles*. During mosquito infection, ookinetes must orient their apical invasion apparatus toward the midgut epithelium. We conducted biochemical and cell biological studies to identify *Plasmodium* ookinete proteins that bind mosquito FREP1. Among the newly identified FREP1-binding partners (FBPs), we show that *Plasmodium* α-tubulin-1 at the ookinete apical complex is critical for invasion. Cell biological studies revealed that anti-α-tubulin antibodies bound to the apical polar ring of the living *P. falciparum* ookinetes. Functional analyses showed that polyclonal serum directed against *P. falciparum* α-tubulin-1 significantly reduced the number of *P. falciparum* oocysts in *An. gambiae* midguts. Our data support the conclusion that interactions between *Anopheles* FREP1 protein and *Plasmodium* α-tubulin-1 anchors and directs the ookinete invasive apparatus towards the midgut peritrophic matrix, which promotes the efficient infection of the mosquito by the parasite. Thus, *Anopheles* FREP1 and *Plasmodium* α-tubulin-1 are potential targets for blocking parasite development and subsequent transmission.

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EXPOSURE OF COMPOUNDS THAT BLOCK MALARIA TRANSMISSION TO MOSQUITOES BY SPRAYING INHIBITS *PLASMODIUM FALCIPARUM* INFECTION

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Malaria transmission can be controlled by exposing mosquitoes to drugs that block transmission. We have determined that pre-exposure of the ethyl acetate extract of the fungus *Purpureocillium lilacinum* inhibits the transmission of *Plasmodium falciparum* to mosquitoes. We further developed a spray-exposure method to study its transmission-blocking activity. The results showed that the fungal extract at 40 mg/m^2 significantly prevented the transmission of parasites to mosquitoes after 1 or 8 hours of exposure. In addition, we evaluated the activity of 11 compounds known to inhibit the development of the sexual stages or mosquito stage of *Plasmodium* parasites by spraying. Notably, only methylene blue and primaquine at 0.1 mmol/m2, respectively, significantly reduced *P. falciparum* oocyst density in mosquitoes, while the other nine compounds did not show any transmission-blocking activity. This spray-exposure method using compounds that block malaria transmission is a new strategy for malaria control.

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LEVERAGING DIGITAL HUMAN RESOURCE INFORMATION SYSTEMS AND GEOSPATIAL ANALYSIS TO PROMOTE SUSTAINABLE CHW CONTRIBUTIONS TO COMMUNITY CASE MANAGEMENT IN BURKINA FASO

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In Burkina Faso, current community health worker (CHW) coverage policy (2 per village) does not account for heterogeneous subnational needs, such as high malaria incidence in the Central East and insecurity and essential service disruption in the North and East. As of February 2022, 127 health facilities have shut down in the four regions most affected by internal displacement due to recurring levels of violence, representing 79% of the total number of health facilities closed at the national level. As a result, CHWs have been expected to fill service gaps normally covered by health facility personnel, including malaria case management. To better quantify, as well as understand, the contribution of CHWs to malaria case management across the 13 different regions, we carried out a series of analyses using routinely collected testing and treatment data, geolocated health facility information, and CHW master lists. National level, aggregated results depict minimal CHW contributions (~1% of cases were detected by CHWs in 2021); however, wide variation exists across subnational geographies. We found that the greatest number of malaria cases was in the Central East region, which is also the region with the least amount of CHWs, and greatest CHW contributions to malaria case management were in the North, where essential service disruption is most prevalent. To understand the drivers of CHW contributions, as well as heterogenous community health trends, a comprehensive resource mapping exercise will be carried out by July 2022, with MoH partners, for the 70 health districts of Burkina Faso, highlighting how variation in human, material, media, and financial resources can impact coverage and access to essential community health services. Our work underscores the need for a government-owned and geolocated CHW master list in order to monitor the overall performance of CHWs based on a changing political and epidemiological landscape.

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REVIEW OF THE USE OF BEHAVIORAL DATA IN PHYLOGEOGRAPHIC ANALYSES OF INFECTIOUS DISEASES

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Recent years have seen both an increasing availability of pathogen genomes and of human mobility data. Genomic data can inform phylogeographic analyses combining the isolation location and time with the divergence times between sequences, to understand disease spread. Human mobility data, which can include social media, smartphone, and air traffic, can convey correlations between disease prevalence and human mobility. Combining these data sources can shed light on the ways in which individuals' interactions with others and with their environment inform pathogen spread. However, it remains unclear how best to conduct such analyses. Here, we performed a systematic literature review to understand the approaches being used in the combination of phylogeography with mobility data.. We searched publications on PubMed and Web of Science with a set of focused search terms, which yielded 2137 initial unique references. Conducting successive title, abstract, and

content reviews, we excluded publications that did not address infectious diseases or that did not analyze human/vector/host behavior. This led to a final set of 28 papers, published between 2010 and 2021. The most common pathogens were SARS-CoV-2 (7 papers) and dengue (5 papers), with 7 different studied pathogens in total. 9 (32%) papers relied on post hoc correlations between the output of the phylogeographic models and the behavioral data, and 11 (39%) integrated the behavioral data into the phylogeographic model itself (ie using Generalized Linear Models to explore potential predictors of spread within phylogenies). Only 4 (14%) papers used a mechanistic model that attempted to incorporate the transmission process into the phylogenetic model. This review has highlighted that despite the substantial interest and wide availability of sequence and behavioral datasets, appropriate models to appropriately analyze them remain small and relatively simplistic Further incorporation of mobility data and phylogeography to mechanistically describe pathogen spread is a notably important area for future methodological development.

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PHAROS: A NEXT-GENERATION MOBILE HEALTH SURVEYING TOOL

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Mobile health (mHealth) has rapidly gained popularity as an important tool for infectious disease surveillance and control in the past decade. Previous work has shown that, despite skepticism from some stakeholders in the global health sphere, mobile phone-based tools are viable options for inexpensive, accurate, point-of-care work. However, it has also been demonstrated that the ability to survey a site prior to launching a large-scale mHealth can be critical for increasing the likelihood of long-term intervention success. In this work, we present the results of a mobile network survey in and around a proposed schistosomiasis study site in western Kenya, near Lake Victoria. To perform this study, we developed a mobile application that is capable of automatically collecting descriptive data related to the strength of the surrounding network landscape. A previous iteration of this application was used to measure the mobile network characteristics surrounding a study site in Southern Province, Zambia. This application— Pharos – assesses upload and download speed for a given data packet while also collecting GPS locations and time points for each specific measurement. In addition, Pharos incorporates a mapping component, in which a user can elect to manually annotate GPS coordinates of interest, and tag them with a specific label relevant to schistosomiasis transmission: landmark, plant life, snail colony, or water source. These location tags are recorded separately and can be analyzed alongside the mobile network data to create a clearer understanding of both the mobile and physical landscape. Thus, using Pharos, trends in data transfer were investigated over a multi-week period in 2022. The app was able to detect time periods in which data transfer was slowed, areas in which network signal was unavailable, and correlation of network metrics to landmarks of interest for schistosomiasis. The analysis of this data will be valuable for the implementation of a larger-scale mHealth intervention in the region.

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ACCEPTABILITY, FEASIBILITY, AND ADOPTION OF A FAMILY MID-UPPER ARM CIRCUMFERENCE (MUAC) MHEALTH INTERVENTION FOR EARLY DETECTION OF CHILDHOOD MALNUTRITION IN KENYA

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Only 38% of malnourished children are reached by nutrition treatment programs and these children are often identified late. Providing tools to screen children at home may facilitate early identification and timelier malnutrition treatment. The Maternally Administered Malnutrition Monitoring System (MAMMS) provides mothers with weekly child health SMS messages and reminders to measure and text their child's mid-upper arm circumference (MUAC) for malnutrition screening in Kenya. To expand the scope of MAMMS, evidence is needed on the acceptability, feasibility, adoption, and drivers of engagement. Mixed methods were used to evaluate acceptability and feasibility of MAMMS and factors influencing adoption of targeted behaviors using the Theoretical Domains Framework. Targeted behaviors are 1) weekly measurement of child MUAC and 2) sending MUAC measurements by SMS in response to MAMMS prompts. We conducted 4 focus group discussions with MAMMS users, interviewed 7 highly engaged and 7 less engaged users, and administered a survey among all MAMMS users. Mothers suggested that MAMMS was acceptable and feasible with evidence of sustained adoption. Many mothers measured their child multiple times a week with some measuring daily, and 92% stated that it required little or no effort. Mothers were motivated to send their child's MUAC measurements as they observed their child gain weight. Mothers felt empowered that they could monitor their child's nutrition status at home with 96% responding that household members were supportive. Most (91%) mothers responded to at least one text message. Enablers to high engagement with MAMMS were knowledge of malnutrition severity, belief about capabilities, social support, optimism, skills, developing a routine, and intrinsic motivation. Barriers to sending and receiving messages were shared or lack of regular phone access, forgetting, and inability to use SMS. Our findings suggest that home monitoring of MUAC with mHealth support has high acceptability, feasibility, and adoption, further supporting strategies to empower mothers to monitor their child's nutrition status in Kenya.

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GRAPHICAL USER INTERFACE FOR A DASHBOARD TOOL WITH SIMULTANEOUS VISUALIZATION OF ENVIRONMENTAL SURVEILLANCE AND CLINICAL CASE DATA

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Dashboard visualization has become a popular tool for public health and government officials to convey COVID-19 metrics to the public. However,

most dashboards only report clinical case data. Environmental surveillance (ES) of SARS-CoV-2 has been shown to be a valuable and complementary data source, as it predates case data by nearly one week. Therefore, public health officials could benefit from a dashboard that integrates both ES and clinical case data. However, the development of a dashboard is often code-intensive and requires dedicated personnel, which many research teams may not have the resources for, especially in low- and middle-income countries. To increase the accessibility of this tool, we developed a graphical user interface (GUI) for researchers to create a dashboard tool by simply importing their data sources. The GUI consists of three sections: 1) customized Excel framework for user input of clinical case and ES data; 2) user uploads their data sources; and 3) user selects aesthetic preferences for the dashboard, including maps, data tables, and longitudinal plots. The GUI then outputs an R file consisting of an RShiny dashboard, and the user is prompted to confirm the accuracy of the data upload. The final dashboard provides color-coded visualization of the geospatial distribution and trends over time. The dashboard can easily be published to the web via the free shinyapps.io server. The instructions for the GUI are outlined in a user manual and read.me file and all code has been uploaded to an open-source GitHub repository. With a dashboard tool in their possession, researchers can convey their findings in real-time and provide public health stakeholders with multiple data sources that will allow them to make informed decisions about mitigation efforts. Reporting ES results allows public health officials to track the prevalence of the virus and rapidly detect hot spots at the community level, where clinical-based data is incomplete or lacking. In the future, the GUI could be modified to create dashboard tools for tracking other infectious diseases (e.g. polio) and catch the emergence of new infectious diseases in real-time.

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PROMOTING ACCESS TO DIAGNOSTICS FOR NEGLECTED AND EPIDEMIC DISEASES THROUGH SUSTAINABLE MANUFACTURING IN AFRICA

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The prevention and control of infectious diseases is a major driver of social and economic development. Achieving such goals requires broad availability of, and easy access to, reliable diagnostic tools. In high-income economies, the problems of availability and access are solved mostly by submitting the development, manufacturing and distribution of diagnostic tests to market rules. As a consequence, high quality diagnostic tests have been developed for most of the diseases combining an existing market pull, and a purchasing entity recognizing the value-for-money proposal. Unfortunately, this system fails to operate in low- and middle-income economies where local circumstances completely disrupt the rules of "for-profit" market economy. Africa homes a population of 1.3 billion people which will double by 2050. The continent remains extremely vulnerable to natural disasters, including epidemics and the burden of human and animal diseases. It faces major hurdles such as the circulation of dozens of endemic and epidemic pathogens, a health system under financial stress and the lack of universal healthcare insurance coverage. To fix these fragilities, Africa needs to build new infrastructure, aiming to facilitate the preparation, management and response to infectious diseases. With regard to diagnostics, it is clear that tests produced and priced according to high-income country specifications will be inadequate to serve the African environment, specifications, pricing & demand. In that respect, a new access/business model has been developed through DIA*TROPIX* in order to produce high quality tests locally, adapted to African needs, and at an affordable price. DIA*TROPIX* is a social venture, headquartered in Dakar (Senegal) and striving to promote access to diagnostics in Africa for epidemic and neglected tropical diseases through local manufacturing.

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IMPROVING AND REDESIGNING CLINEPIDB TO ENABLE EXPLORATORY DATA ANALYSIS OF GLOBAL HEALTH STUDIES

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Data sharing from epidemiology studies, clinical trials, and implementation research provides opportunities for innovation and collaboration among global health researchers. ClinEpiDB (https://clinepidb.org) is an open-access, online resource that enables investigators to maximize the utility and reach of their work and expedite the use of data from others. During dataset integration, variables are harmonized with other integrated studies using ontologies. A newly rebuilt intuitive web interface overlays SQL queries, providing insight into frequency distributions and variable associations. Classic features like creating a subset of data remain and are enhanced by new innovations like "Featured variables" and the ability to star favorite variables, which make it easy to identify variables that are key to understanding the study data and keep track of variables of interest. New data visualization tools offer additional ways to explore study data online and contain powerful controls, allowing stratification by other variables, zooming within plots, adding best fit lines or calculating basic statistics, and more. Users can choose whether to download a subset or all of the data, or request access directly within the browser, if required by the original study team. Over 87% of data access requests are approved. ClinEpiDB, first released in 2018, contains data on >1 million participants from >30 studies, and includes datasets from the MAL-ED, GEMS, and WASH Benefits enteric disease projects, SCORE schistosomiasis project, and ICEMR malaria studies, among others. Additional studies and new tools are released every two months. The ClinEpiDB resource provides an intuitive interface to access epidemiological data and will continue to grow with integration of new datasets, tool development, and user outreach and education.

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REPEATABILITY OF PULSE OXIMETRY MEASUREMENTS IN CHILDREN

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Pulse oximetry is a low-cost, non-invasive method of measuring blood oxygen saturation (SpO_2) that depends on red and infrared light. It is commonly used to monitor the oxygenation status of critically ill patients. When combined with clinical signs, a low SpO_2 has been shown to be a strong predictor of poor outcomes in critically ill patients. Pulse oximetry can also ensure efficient use of oxygen, especially in low- and middle-income countries (LMICs), where the demand for oxygen outstrips supply. In these settings, health workers typically use pulse oximeters for spot measurements of SpO_2, rather than continuously measurement. However, the repeatability of spot measurements, or the ideal length of time of measurement, is unknown. We assessed the repeatability of SpO_2 measurements from 6,153 children presenting with suspected or proven severe sepsis to Jinja Regional Referral and Gulu Regional Referral hospitals in Uganda. Two sequential one-minute recordings were done on each patient at the time of triage using a Masimo, iSpO_2® pulse oximeter. A signal quality index (SQI) was calculated, as a percentage, using the Masimo status flags (excess light, artifacts, etc.), the perfusion index and

variability of SpO_2 and heart rate (HR) trends. SQI, SpO_2, and HR were measured at 1Hz and the median HR and SpO_2 for only those seconds with SQI >= 90% was calculated for each recording. The repeatability was assessed using an intraclass correlation coefficient. Using the entire data set, the repeatability between the two measurements was 0.725 (95% confidence interval (CI) = 0.710, 0.740). When measurements with a mean signal quality index below 70% were eliminated, the repeatability was 0.905 (95% CI = 0.898, 0.911). Using the first 5 seconds of each measurement, using the entire data set, reduced the repeatability to 0.320 (95% CI = 0.292, 0.348). These results suggest that measuring oxygen saturation over a longer period is more accurate than instantaneous readings. The findings may improve training of pulse oximetry use in LMICs and provide developers with key insights into designing new devices that will support more accurate pulse oximetry measurement.

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APPLYING EFFECTIVE APPROACHES CONTRIBUTING TO THE REDUCTION OF WASTAGE AND BETTER AVAILABILITY OF ESSENTIAL MEDICINES IN ETHIOPIA

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Since 2012, with support from USAID's Global Health Supply Chain Program, the Ethiopian Federal Ministry of Health (FMOH) has implemented Auditable Pharmaceutical Transaction and Services (APTS) interventions in 224 hospitals (63% of Ethiopian hospitals) to address wastage, improve availability, transparency and accountability of medicine's transactions. APTS interventions include developing pharmaceutical legislation, creating a better system for physical inventory (PI), stock transfer (ST) based on stock status analysis (SSA), conducting pharmaceutical cost analysis (Pareto analysis), prioritizing medicines, and auditing. In APTS, PI includes preparation, actual count, and analysis stages that ensure effective utilization of pharmacy workforce. A cross-sectional study was conducted in 26 hospitals in September 2020 to assess the status of APTS implementation. 62 percent of hospitals that conducted PI activities as per APTS principles took 1 to 4 days to complete whereas those hospitals that did not follow APTS principles took 5 to 15 days. 24 hospitals (92%) undertook ST by using the APTS directive for improving availability and reducing wastage. This is especially important for diseases like malaria which are seasonal and have variable epidemiology. The average wastage rate of medicines was 0.9% (national target, 2%). This is a steep reduction from the 2014 baseline assessment (4.7%). Assigning bin ownership was implemented in 80.8% of hospitals contributing to better tracking of expiry dates, ST, and improved availability. Availability of essential medicines in 12 hospitals (46%) that implemented ST based on SSA was between 75% and 100%. However, availability in other hospitals that did not implement both SSA and ST ranged from 61% to 73%. APTS implementation at hospitals improved the regular practice of more efficient PI. The results also showed that conducting ST based on SSA contributed to improved pharmaceutical availability and reduction of wastage. The FMOH is working to scale up APTS to improve the pharmaceutical supply chain and pharmacy service practices at health facilities.

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COVID-19 IN SOUTH AFRICA: ADAPTIVE MODELLING FOR A NOVEL VIRUS

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The South African COVID-19 Modelling Consortium (SACMC) was established in March 2020 to support planning and budgeting for COVID-19 related healthcare in South Africa. We developed several tools in response to the most pressing needs of decision makers in the different stages of the epidemic, allowing the government to plan several months ahead of time. Our tools included epidemic projection models, cost and budget models, and dashboards to help government and the public visualise our projections and track case development. Information on new variants, including Delta and Omicron, were incorporated in real time to allow the shifting of scarce resources when necessary. Given the rapidly changing nature of the outbreak globally and in South Africa, the model projections were updated regularly. The updates reflected 1) the changing policy priorities over the course of the epidemic; 2) the availability of new data local systems; and 3) the evolving response to COVID-19 in South Africa such as changes in lockdown levels and ensuing mobility and contact rates, testing policy, contact tracing strategy, and hospitalisation criteria. Insights into population behaviour required updates by incorporating notions of behavioural heterogeneity. To aid the effective communication and dissemination of our work, we developed two online applications to visualise the most important model outputs for policymakers and the public, and to enable case tracking and visualisation of case resurgence driven by new variants of concern. We incorporated these aspects into developing scenarios for the third and fourth wave with real-time analyses of the most important characteristics of the Omicron variant. The SACMC's models, developed rapidly in an emergency setting and regularly updated with local data, supported national and provincial government to plan several months ahead of time, expand hospital capacity when needed, allocate budgets, and procure additional resources where possible. Across four waves of cases, the SACMC continued to serve the planning needs of the government, tracking waves and developing models to support the national vaccine rollout.

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A WEB-BASED HISTOLOGY QUALITY ASSURANCE PLATFORM AS A REMOTE TRAINING TOOL FOR GLOBAL USE IN LOW RESOURCE SETTINGS

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Pathology-based mortality surveillance using minimally invasive tissue sampling (MITS) improves the accuracy of ascertaining the cause of death determination (CoD). A web-based quality assurance (QA) platform was collaboratively designed and developed to support remote assessment and ongoing quality improvement of MITS collection and processing for histopathology in low resource environments. The QA platform was coded using .NET Core, JavaScript, and Microsoft SQL Server. The QA platform was part of a larger portal designed to share resources with a community of researchers interested in MITS. The platform was built as a training resource to provide remote feedback and improve histopathology, rather than to support full scale telepathology. This allowed adequate image quality for assessment without creating a bandwidth burden on the participants with limited internet connectivity. All sites were able to upload images and evaluation information without issue. Participating sites uploaded slides and images of each tissue type for a case and conducted a self-evaluation. The evaluation consisted of a series of assessments around adequacy of sampling, tissue preparation and staining, and was simple for the users to make slide level self-assessments of up to several images per slide at varying magnifications. Following the self-evaluation, an expert pathologist then conducted a parallel evaluation and provided image-specific feedback. The expert evaluation identified areas where the trainees and expert reviewers differed in the assessment of their cases. Additionally, the expert reviewers were able to provide an evaluation of the overall adequacy at the case level, as well as tissue and image level comments.

The goal was to see measurable improvement in the quality of sample preparation over time. As of April 1, 2022, over 150 cases have been reviewed. These cases constitute over 600 tissue samples, 1050 slides and 3000 images from 17 sites across 8 countries. This platform has proven to be an effective tool to enhance remote training and improve quality by linking experts with global trainees.

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STRENGTHENING LAST MILE PANDEMIC RESPONSE USING ARTIFICIAL INTELLIGENCE AIDED CHEST X-RAY BASED COVID-19 SCREENING AND TRIAGE IN RURAL AND SEMI-URBAN INDIA

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COVID-19 pandemic had a devastating impact on the resource constrained healthcare systems in rural and semi-urban India, that had to handle about half of the COVID-19 burden of the entire country. Most of these hospitals had minimal/no access to RT-PCR testing, delaying the diagnosis by days, and exposing the limited hospital staff to the risk of infection. Given that these hospitals were equipped with chest X-Ray facilities, but had no radiologists, an AI-based automated chest X-ray interpretation tool was deployed to support clinicians handling the crisis at 20 charitable hospitals across 15 states in India from August 2020. Between January to June 2021, a total of 17,500 individuals were screened and triaged for COVID-19 using the AI tool, of which 40% were flagged as COVID-19 presumptive with a low/medium or high risk. The analysis of data available for 1,681 patients revealed that 50% of presumptives identified were admitted within the hospital, referred to another COVID treatment facility or advised for home isolation. 62% of the presumptives were referred for a COVID-19 confirmatory test such as RT-PCR or Rapid Antigen test, or a supportive test like CT Chest. A 27% median RT-PCR positivity rate was observed for those flagged as COVID-19 presumptives by the AI screening tool across hospitals. The RT-PCR positivity was double when the x-ray was flagged as high risk compared to low risk. Overall, out of 1,523 COVID presumptives flagged by AI for which a final COVID-19 diagnosis result was available, it was observed that 24% patients were managed as COVID patients by the hospital. Further, 27% of patients who were isolated, tested or referred were incidentally detected as COVID-19 presumptives as a result of chest X-Ray based screening, and might have been missed otherwise. A total of 109 clinicians out of which close to one third were junior doctors/non-specialists, were empowered with the AI tool serving as clinical decision support to direct COVID-19 suspects immediately for next step in the patient management process. We conclude that AI tools can aid as clinical decision support especially for non specialist physicians in resource limited settings.

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OPEN SOURCE APPROACHES TO PEDIATRIC GLOBAL HEALTH TECHNOLOGY DEVELOPMENT AND IMPLEMENTATION

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Access to medical technologies is a critical component of universal access to care; however, the advancement of pediatric technologies has historically lagged behind that of adults. The small market size, anatomic and physiologic variability, and legal and ethical implications are unique barriers to developing and commercializing biomedical innovations for children. These challenges are magnified in low-resource settings (LRS), which often lack appropriate regulatory oversight, support for service contracts, and supply chain capacity. We propose that open source pathways - where products are freely licensed to be distributed and modified - represent a viable framework to improve access to pediatric technologies in LRS. Unlike the traditional medical device industry, the open source approach can be tailored to clinical needs independent of market factors and adjusts for local manufacturing capabilities. Furthermore, diverse stakeholders, including families, local engineers, and medical providers, are empowered to participate in collaborative open source platforms and communities. Low-cost bubble continuous positive airway pressure (CPAP) devices are a compelling example of open source projects that have demonstrated comparative performance to commercial products and have been widely used in LRS. Importantly, governing the manufacture and use of open source technologies in LRS remains an area of critical need. For example, rigorous standards are necessary to ensure quality and patient safety. This can be achieved, in part, through close coordination between national regulatory bodies and decentralized open source networks through which designs can be collectively reviewed. By highlighting success stories, advantages, and ongoing challenges, we aim to illustrate the potential for open source models to expand access to innovative pediatric technologies and facilitate more sustainable and equitable healthcare in LRS.

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ALL CREATURES DEADLY AND DEBILITATING: BRITISH MISSIONARY ENCOUNTERS IN AFRICA, 1850-1914

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Missionary life remains, and has long been, a potentially risky business for missionaries who visit sub-Saharan Africa. Hazards such as venomous reptiles, voracious felines, and enraged rhinoceroses could inflict serious injuries or death to the uninitiated newcomer. The noted missionary David Livingstone himself managed to escape a vicious lion attack with only a fractured arm. Drawing on published and archival accounts, this presentation will examine British missionaries' encounters with potentially dangerous African fauna during the latter half of the 19th up to the outbreak of the Great War.

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"INHERIT THE KINGDOM PREPARED FOR YOU": MORTALITY AMONG 19TH-CENTURY BRITISH EVANGELICAL MISSIONARIES IN SUB-SAHARAN AFRICA

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"Inherit the Kingdom Prepared for You": Mortality among 19th-Cetury British Evangelical Missionaries in Sub-Saharan Africa. Nineteenth-century British missionaries to Africa often faced lethal risks from ferocious animals, deadly infections, and angry indigenous populations. This was especially true of those who went there with little more than quinine and opium in their medical kit. Many counted their survival in days or weeks. The role of insects and microscopic pathogens did not emerge until around the turn of the 20th century. So, what motivated them to face such risks? Certainly, British imperialism was an important factor by the late 1800s. For evangelicals with organisations such as the (Anglican) Church Missionary Society, however, a deeply felt mandate to convert what they viewed as the "heathen" to Christianity also spurred them on. Death in a foreign mission field, the "white man's grave," they held, was something to be welcomed rather than feared. Their earthly end represented not an end but a glorious, new beginning, which they believed was their patiently faithfully anticipated opportunity to "inherit the kingdom" that awaited

them in heaven. Relying on archival and published contemporary accounts, this presentation will historically examine evangelical missionary attitudes toward death in 19th-centuryAfrica.

1266

PARENT USE OF PHYSICAL PUNISHMENT OF CHILDREN BY RELIGIOUS AFFILIATION IN THE DOMINICAN REPUBLIC

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Eliminating children's exposure to violence is a United Nations' Sustainable Development Goal. Child rights inform this goal and violence includes the use of physical punishment in the home. Identifying factors associated with physical punishment is important in informing intervention efforts to reduce its use. There is some evidence from high-income English-speaking countries that physical punishment of children may be more prevalent among Conversative Protestant (CP) households compared with Catholic and non-religious households. The current study examined this relationship in a middle-income, Spanish-speaking, country with a large Catholic and CP population. Data from the 2019 Dominican Republic Multiple Indicator Cluster Survey were used and included responses to standardized questions about six types of physical punishment asked of a caregiver in households with children 1-14 years of age. Of the sample of 12,760 households, 52.2% were Catholic, 24.3% non-religious, and 23.5% CPs. Spanking and hitting with an object (e.g., a belt) were the two most common physical punishments across groups. The final logistic regression models adjusted for socioeconomic and demographic differences, as well as a variable on caregiver's belief in the need for physical punishment in child rearing. Consistent with a priori hypotheses, children in CP households had a higher odds of being (i) hit with an object compared to the other two groups, and (ii) spanked compared to those in Catholic households. However, children in CP households did not have a higher odds of being spanked than non-religious households. Also inconsistent with hypotheses, children in Catholic households did not have higher odds of exposure to these two common physical punishments than non-religious households. Further examination of the relationship between Conservative Protestantism and physical punishment is warranted to inform potential interventions. However, as any physical punishment was reported in >40% of households for each group, there is also a need to identify other factors contributing to this substantial reliance on physical punishment.

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MITIGATING INFODEMIC THROUGH MHEALTH, SOCIAL MEDIA AND ELECTRONIC MEDIA ON COVID-19 AND ITS VACCINATION AMONG PARENTS AND HEALTH CARE PROVIDERS - A QUALITATIVE EXPLORATORY STUDY

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COVID-19 had a massive impact with digital technology playing a crucial role with considerable challenges, including misinformation creating infodemics. Thus, we aimed to understand the role of mHealth, social media and electronic media related to COVID pandemic acceptance and vaccine uptake among caregivers (n=60) and healthcare providers (51). This study employed a qualitative exploratory study design, with purposive sampling technique. All together seven FGDs with HCPs and 60 IDIs with caregiver/parents were conducted by using semi-structured interview guides at peri-urban, urban and rural sites of Sindh, Pakistan using virtual platforms. The data were analyzed using standard qualitative data analysis guidelines by using content and thematic approaches. The key findings of this study were usage of electronic media and mhealth for dissemination and communication during COVID-19 pandemic however the misinformation majorly spread through social media which led to vaccine related infodemics. HCPs got vaccination and pandemic-related information through WhatsApp, Facebook and government dashboards. Misinformation on social media, they claim, led to caregivers' vaccine hesitancy. Moreover, both urban and rural participants perceived electronic media (television) as the reliable source of information than mhealth and social media however, study revealed the phenomena of digital divide among rural population. Social politic narrative and digital divide had a significant impact on COVID-19 acceptance and uptake of vaccine which needs to be monitored. Furthermore, public health measures such as SMS, caller tone messaging and SMS-based vaccine registration were shown to be effective in addressing COVID-19 vaccine reluctance. This study concluded that the electronic and social media has great impact on information and communication during COVID pandemic that can be used for other health related promotion platforms in LMICs. Lastly, healthcare providers should be trained on order to tailor credible health information among general population via digital and social media.

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TRENDS IN NEGLECTED TROPICAL DISEASES BURDEN ASSOCIATED WITH DEVELOPMENT LEVEL: A MODELLING ANALYSIS FOR THE GLOBAL BURDEN OF DISEASE STUDY 2020

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While the global burden of Neglected Tropical Diseases (NTDs) has been declining, progress has varied across different levels of development. We aim to describe the association of trends in NTDs burden with development level. We used estimates of the burden of NTDs from the Global Burden of Disease (GBD) Study 2020. We separately modeled the burden of 22 NTDs. Disability Adjusted Life Years (DALYs) were calculated as the sum of Years of Life Lost and Years Lived with Disability. We compared the trends in age-standardized DALYs rates due to NTDs and the sociodemographic development, using the Socio-Demographic Index (SDI). SDI is a composite measure based on age-distributed income per capita, total fertility rate in women younger than 25 years, and mean education for those 15 years or older, varying from 0 to 100. We used a constrained mixed-effects meta-regression to quantify the global relationship between NTDs burden and SDI. Then, we compared the estimated NTD burden in each country from 1990 to 2020 in relation to expected burden based on SDI value alone. We present here preliminary results from GBD 2020. In 2020, the age-standardized DALYs rate due to NTDs was 219.4 (95% UI: 168.7- 379.6) DALYs per 100,000, a decrease of 58.5% (95% UI 52.3% - 66.9%) compared to 1990. We found that lower age-standardized DALYs rates due to NTDs were associated with higher SDI values, but this relationship was not linear. The average expected reduction in NTDs burden was more pronounced in lower levels of SDI than in higher levels. Comparing progress in the burden of NTDs across countries, some countries, like Mali, showed a lower burden than expected according to SDI level alone. On the other hand, some countries, like Cameroon, presented a higher NTDs burden compared to countries with a similar level of SDI. NTDs burden decreased over time, and part of this decrease was associated with the level of development of the countries. These results help to recognize countries that have achieved greater reductions than expected for their SDI level, as well as identify locations that are lagging behind changes in development.

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RETROSPECTIVE MOLECULAR ANALYSIS OF SEXUALLY TRANSMITTED INFECTIONS (STI) FOR THE DETECTION OF *MYCOPLASMA GENITALIUM* IN GHANA

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Mycoplasma genitalium (MG) is a fastidious non-gonococcal sexually transmitted pathogen primarily found in the human urogenital tract. It has emerged as one of the common causes of non-gonococcal urethritis and cervicitis worldwide and is becoming less susceptible to doxycycline and azithromycin, macrolides of choice for treatment. Reports of dysuria and/ or discharge normally associated with urinary tract infections (UTIs) are frequently reported among some MG-infected patients; however, data in Ghana regarding the prevalence and burden of MG is relatively limited. Therefore, we conducted a retrospective molecular analysis to investigate MG presence and macrolide resistance among patients who previously reported to selected hospitals in Ghana for STI symptoms. Stored samples from STI patients with consent for future use, who reported at the selected hospitals, were screened for MG using the ResistancePlus™ MG kit from SpeeDx, Australia. Detection of MG and five mutations in the 23S rRNA gene, associated with azithromycin resistance, occurred on the Roche LightCycler 480 II Instrument. Interpretation of results was done with the ResistancePlus™ MG FastFinder™ Analysis Software. A total of 1038 samples were processed in this retrospective study, out of which 34 (3%) tested positive for *M. genitalium* with only one mutation. Also, 32 (3%) of 983 (95%) patients with dysuria and/ or discharge tested positive for MG. Patients presenting with other urethritis symptoms were more likely to test positive for MG than those presenting with dysuria and/ or discharge (OR=1.12; 95% CI: 0.26-4.85; p=0.877). *M. genitalium* coinfection rates with gonorrhea and chlamydia were 3% each in dysuria and/ or discharge positive samples. A low occurrence of *M. genitalium* and subsequently low rate of macrolide-resistance was recorded in this study, comparable to earlier work conducted in Ghana. This retrospective study design had significant limitations that could be improved upon by conducting prospective sexually transmitted infection surveillance to better estimate the incidence and prevalence of MG in Ghana.

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HISTO-BLOOD GROUP ANTIGENS AND LINEAR GROWTH IN A NICARAGUAN BIRTH COHORT

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Secretor and Lewis phenotypes are determined by fucosyltransferase-2 (FUT2) and FUT3 gene expression, respectively. These histo-blood group antigen (HBGA) phenotypes, which are expressed on epithelial tissue surfaces, can modulate the risk of infection with certain diarrheagenic enteropathogens. However, it is uncertain whether child and/or maternal HBGAs, which are transferred to children via breastmilk, can predispose children to chronic malnutrition. We evaluated the associations between HBGAs and linear growth in a Nicaraguan birth cohort. We examined cross-sections of 444 children enrolled in a birth cohort at 6, 12, 24, and 36 months of age. Child and maternal HBGA phenotypes were determined by enzyme immunoassay of saliva samples of mother-child dyads at enrollment. Mother and child phenotypes were described individually as either secretor or nonsecretor and either Lewis positive or Lewis negative. Anthropometric measurements were performed at regular intervals. Change in length-for-age z-scores (LAZ) was analyzed with two-sample t tests for each secretor and Lewis phenotype of mothers and children. Stunting, or LAZ less than -2 standard deviations (SD) below the mean, was analyzed by Fisher's exact test for each secretor and Lewis phenotype of mothers and children. Of the 444 child participants, 396 (89.4%) were secretors, and 374 (84.2%) were Lewis positive. Of the 314 mothers with determined HBGA phenotypes, 244 (78.5%) were secretors, and 225 (72.4%) were Lewis positive. No significant associations were found between secretor status or Lewis status and change in LAZ or stunting at any time points on univariate analyses. This cross-sectional study with univariate analyses does not provide evidence that secretor or Lewis status affects a child's risk of linear growth faltering or stunting in the first three years of life. Future analyses are pending to model interactions with breastfeeding and diarrheal episodes. Further data are being collected to assess for a causal role of human milk oligosaccharides in the association between HBGAs and child growth in this cohort.

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FACTORS ASSOCIATED WITH HEMOGLOBIN LEVEL IN CHILDREN LIVING AT HIGH ALTITUDES IN CUSCO-PERU

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Anemia is a complex health problem associated to multiple factors. The WHO estimates that 42% of children less than 5 years of age and 40% of pregnant women worldwide are anemic. Living with anemia may lead to impaired neurocognitive development and overall growth problems which contribute to perpetuating the financial and potential development gap between high and low-middle income countries. Children living at high altitudes have higher hemoglobin levels due to relative hypoxemia. However, they are also exposed to repeated and chronic infections and often lack iron in the diet. We conducted a cross-sectional study among children in Cusco- Peru to identify potential factors affecting the hemoglobin concentration at high altitude. Children 3 -16 years of age from rural agricultural communities were enrolled. We collected demographic, socioeconomic, medical, anthropometric, and environmental data. Children provided one blood sample and three stool samples. Blood samples were tested for complete blood count with differential, TIBC, iron, and *Fasciola hepatica* serology. Stool samples were tested to detect parasites. 2000 participants were enrolled with a median age of 10 years, 50.2% were female, and the median house altitude was 3398 m. The median hemoglobin level was 15 mg/dl. Overall mean HAZ was -1.4 SD. Children with anemia were younger and had higher iron levels. On linear regression using hemoglobin as the dependent variable: *Giardia lamblia* and *Blastocystis hominis* infection were associated with lower levels of hemoglobin and age, Anta district, SES and *Fasciola hepatica* or Uncinariasis infection were associated with higher levels of hemoglobin. In the multivariate analysis age, Anta district, and Uncinariasis infection were associated with higher hemoglobin levels. The final model goodness of fit showed a p>0.05 and an adjusted r2 of 0.25. In conclusion, demographic and socioeconomic variables were significant in our regression model, but explained a small percentage of the variation. Prospective studies are needed to evaluate anemia in low and middle-income children living at high altitudes.

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EVOLUTION OF GLOBAL HEALTH EDUCATION AND TRAINING IN A MASTER OF PUBLIC HEALTH PROGRAM

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Case Western Reserve University's Master of Public Health (MPH) Program was founded over twenty years ago within an institution with rich global health research, service, and collaboration legacy. The training program fosters diverse training skillsets and perspectives with five concentrations and 11 dual degrees. Though based in the School of Medicine, the program's global health training is supported by University-wide faculty across five schools and nine departments. The program has designed approaches to overcome the complexities of global health training, including program partner and international mentoring, language, cost, time, travel, safety, and new barriers experienced as a result of the ongoing pandemic. COVID-19 travel and course delivery restrictions have produced innovations to our global health training. Examples of student experiences made possible through new online training opportunities during social distancing and travel restrictions associated with the pandemic will be highlighted. In addition, many students discovered local community partners working on diseases of global importance and global populations. During COVID-19, our courses shifted learning methodologies, objectives, and examples to focus on the pandemic and infectious disease concepts. New courses were also designed including 1) a course to quantify the intersection of political science and public health at a global scale, 2) a course to evaluate health equity and racism and as public health crisis, and 3) a course to examine the historical development of public health structures and responses to better understand current responses to the pandemic and underlying health barriers. This presentation highlights these approaches to establishing and supporting global health training within the context of our students, partners, and communities.

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IDENTIFYING AND ADDRESSING EXCESS BURDEN OF NEURAL TUBE DEFECTS FROM CHAMPS ETHIOPIA: TRANSFORMING DATA TO ACTION

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Neural tube defects (NTDs) are birth defects resulting in severe morbidity and mortality; they can be largely prevented with preconception maternal intake of folic acid. Understanding the occurrence of NTDs and their contribution to mortality in settings where their burden is highest would aid prevention efforts and inform health policy. The Child Health and Mortality Prevention Surveillance (CHAMPS) network aimed to determine causes of death (CoD) among stillbirths and deaths in children aged below five years capturing facility and community deaths using advanced diagnostic methods. CHAMPS and Demographic Surveillance System (DSS) data from South Africa, Mozambique, Bangladesh, Kenya, Mali, Ethiopia and Sierra Leone were used to describe the frequency and characteristics of detected NTDs among eligible deaths, identify child and maternal factors, and estimate the mortality fraction and mortality rate (per 10 000 births) by CHAMPS site. CoD were determined for 3232 deaths occurring from January 2017 through December 2021. Of these, 69 (2.1%, 90% CrI:1.7, 2.6) died due to a NTD. The majority of NTD deaths were stillbirths (73.9%) followed by neonatal deaths (23.2%); most (67%) were NTDs incompatible with life such as anencephaly, craniorachischisis, or iniencephaly, and 32% were spina bifida. More than half occurred in Ethiopia (n=44, 64%), followed by Mozambique (n=9, 13%) and South Africa (n=7, 10%). Ethiopia had the highest adjusted mortality fraction of deaths due to NTDs among all sites (7.5%, 6.7, 8.4) and the highest adjusted mortality rate attributed to NTDs (104.0 per 10 000 births, 92.9, 116.4), which was 4-23 times greater than in any other site. CHAMPS identified that NTDs, a preventable condition, were a common CoD among stillbirths and child deaths, especially in Ethiopia. Interventions including folic acid fortification should be urgently implemented in countries such as Ethiopia to prevent mortality due to NTDs.

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ACUTE ORAL PEDIATRIC CHAGAS DISEASE CASE SERIES IN LATIN AMERICA: BROAD IMPLICATIONS OF AN EMERGING TRANSMISSION

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In the 1990's and early 2000s, the W.H.O. invested efforts for a multi-country vector control campaign to eradicate the principal domestic vectors of Chagas disease in Latin America. Unfortunately, this has resulted in the establishment of new emerging vector species with undefined vector ecologies. We present a case series of pediatric oral acute Chagas disease that happened in Brazil and Colombia, and we will discuss the broader implications of this important emerging transmission route in low-middle income Latinx countries. The 2-year old case from Brazil highlights the cultural practices associated with breast-feeding weaning in babies. Taking them off of breast milk by substituting their ingestion with açai fruit juice, is associated with ingestion of *Trypanosoma cruzi* contaminated juice. Specific *Rhodnius* species live in açai palm trees and get crushed in the juice making process. Nonetheless, this case highlights the fatality of the orally acquired acute disease in infants. On the other hand, the two case reports from Colombia highlight the lack of timely diagnosis likely influenced by unusual clinical presenting illness, in an emerging area where acute transmission was never registered before. Despite historically elevated Chagas disease case burdens in the Andean region, there is still unawareness among physicians. Additionally, here the access to healthcare is uneven for areas where transmission risk is greater. This case series brings attention to important sylvatic vector species newly established in domestic environments of vector-free geographic areas. Given the 'low risk' dogma, these areas are at particularly high-risk for clinician misdiagnosis.

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USE OF MICROBIOLOGICAL LABORATORY DATA ANALYSIS FOR ANTIBIOTIC STEWARDSHIP IN A HOSPITAL BASED SETTING: A TWO YEARS DATA REVIEW TO GUIDE PRESCRIPTIONS AND ANTIBIOTIC SUSCEPTIBILITY TESTING PRACTICES

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Antimicrobial resistance is a major health concern with a particularly high burden in low income countries. Weak regulations, inappropriate prescription and consumption of antibiotics are some of the factors contributing to worsen the phenomenon. Our study conducted in a low income Hospital based setting, aimed to assess how data collected from the laboratory could guide and improve practices. Monthly data collected from January 2020 until December 2021 through the laboratory WHONET software were compiled and analyzed. Out of 2247 specimen received, 660 were cultured positive (29.3%). Gram negative bacteria and specifically *Escherichia coli* and *Klebsiella pneumonia* were most frequently isolated (28.8 and 20.8% respectively). Antibiotic susceptibility results analysis showed high resistance rates of gram negative bacteria to B lactamins, which were in contrary the most prescribed class of antibiotics for empiric treatment; 38% were classified as EBSLs whereas low resistance was observed to carbapenems. As inappropriate prescription of antibiotics could result in increased morbidity and prolonged hospitalizations, our interventions included new recommendations based on our data , for empiric antibiotic treatments upon availability of susceptibility testing results as well as update of testing guidelines at the laboratory. Antibiotic susceptibility testing results may not only be used for prospective guidance of treatment, but rather data analysis can contribute to antibiotic stewardship. However, good record keeping, standardization of practices at the lab and communication between clinicians and laboratory scientists are mandatory.

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THE DEMOCRATIC REPUBLIC OF THE CONGO AS A REGIONAL TRAINING CENTER TO CREATE SUSTAINABLE MONKEYPOX SURVEILLANCE SYSTEMS IN PRIORITY COUNTRIES: YEAR ONE ACTIVITIES OF A MULTI-YEAR PROJECT

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Monkeypox (MPX) is an orthopoxvirus related to smallpox with global concern for bioterrorism. The Democratic Republic of the Congo (DRC) has developed regional expertise in MPX disease surveillance, detection, and diagnostics as it is considered endemic in multiple regions. In 2021, 3,074 suspected MPX cases were reported in the DRC, more than any country globally. We hypothesized that DRC and other nearby countries with internationally mobile populations (e.g., Uganda, Gabon, and Cameroon) likely underreport MPX cases, especially transmission chains across national borders. Building regional capacity for MPX outbreak response can benefit from a high-quality training environment and a location where consistent community cases consistently occur such as in the DRC. This 5-year project aims to create sustainable MPX surveillance programs in the region by reinforcing the MPX surveillance system in collaboration with the DRC National Program against Monkeypox and Viral Hemorrhagic Fevers (PNLMPX-VHF) in select regions to improve MPX incidence reporting and establishing a training center in DRC for countries in East and Central Africa. Three major activities will occur in Year 1: 1) a training site established in DRC, 2) a high-level kick-off meeting in Kinshasa with partner stakeholders, and 3) an in-depth training in Kinshasa and field sites with technical partners. The initial training site is in Tshopo province of DRC, the region with the highest reported case mortality and potentially high MPX underreporting. Before the end of the year, the study team will meet with selected local partners to evaluate the site, build surveillance capacity, and host a training event which includes in-depth knowledge transfer on case identification and conducting investigations. The high-level meeting will precede the in-depth training and establish country partnerships, current surveillance capacity, and training priorities. Building capacity for MPX surveillance will improve incidence estimation and understanding of MPX transmission for more effective outbreak control.

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CHANGES IN PERCEPTIONS AND IMPACT OF COVID-19 ON RESIDENTS IN A RURAL COMMUNITY IN BANGLADESH: A LONGITUDINAL QUALITATIVE RAPID ASSESSMENT

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After COVID-19 second wave (August-September 2021), we revisited residents in rural Baliakandi, Bangladesh to explore changes in their perceptions of COVID-19 transmission and prevention, and the impact of pandemic response on their food consumption, health-seeking and livelihood. We interviewed 13 key informants, including residents who had COVID-19 infection, local leaders, healthcare providers and staff with a child health project. Respondents perceived that COVID-19 has become a seasonal disease and they are no longer afraid of being infected. They believed that residents crossing the Indian border brought the deadly 'delta' variant into the country. Local spread continued due to people hiding symptoms when in public places and low rates of COVID-19 testing. Respondents noted that movement restrictions and social distancing were not practiced, and cases were not isolated. They explained that people had become exhausted from being restricted due to lockdowns and their livelihoods were in jeopardy, so they were reluctant to comply with public health guidance. Yet, respondents reported washing hands, wearing masks and infected persons staying home to prevent spread. In this wave, infected families disclosed their infection status and requested neighbors not to visit their home. During the peak of this wave, some residents received support from an online group created in social media to provide treatment (e.g. oxygen) and food support to local communities. In the changing context, many residents were visited local health facilities for antenatal care, child delivery and routine immunization. Middle-income families were suffered more than others as they lost their jobs and faced financial hardship in managing minimum daily food and necessities. Day laborers were able to change their work and managed livelihood a bit better than the first wave. As the long-term pandemic impact, school drop-out and girls' marriage also increased. The findings indicate the importance of identifying control measures that safeguard livelihoods and also addressing school dropout to prevent child marriage and thus adverse health outcomes of the pandemic.

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EVALUATION OF INFECTION PREVENTION AND CONTROL PREPAREDNESS DURING COVID-19 IN SELECTED HEALTH FACILITIES IN KISUMU AND SIAYA COUNTIES OF WESTERN KENYA

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The novel Coronavirus, SARS-CoV-2, created a new global focus on IPC to reduce virus transmission, many of which require additional procurement and distribution of commodities, conducted a baseline survey in 100 health facilities in Kisumu and Siaya Counties, western Kenya, from January-March 2021. Health facilities selected based on patient volume of > 20 first ANC visits per month and >20 fever cases per day. Aimed at understanding health facility preparedness and response to the pandemic by evaluating facility infrastructure, patient volume, readiness to support safe service delivery, implementation of IPC practices. Then designed a strategy to bridge gaps identified in IPC by providing interventions such as a screening kiosks, hand washing stations, proper waste management, supply of PPE and commodities. Conducted 100 provider interviews, including 79 with facility in-charges. Most (81%) healthcare workers from Kisumu County and 18% from Siaya County reported lack of adequate PPE to keep them and their patients safe. Only 56% of facilities had written guidelines on IPC and waste management, 64% had dedicated staff trained for triage, and 59% conducted temperature screening at the facility entrance. Half (52%) of facilities lacked provisions for social distancing, 55% isolated patients presenting with cough, and half of the facilities had healthcare workers trained on IPC guidelines. Following provision of supplies, training, and monthly supervision to address the gaps, at follow up in February 2022, 84% of facilities had updated written guidelines on IPC and waste management, 97% had dedicated staff trained for triaging, 96% were conducting routine temperature screening at the entrance, 78% routinely separated patients presenting with cough, and 94% practiced social distancing. Robust interventions to enable and ensure adherence to IPC measures among healthcare workers is critical to protect the community during a pandemic.

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FACTORS ASSOCIATED WITH COVID19 VACCINE UPTAKE IN A COMMUNITY BASED COHORT IN PONCE, PUERTO RICO

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COVID-19 vaccine distribution and uptake are critical to reducing SARS-CoV-2-associated morbidity and mortality. In Puerto Rico (PR), the COVID-19 vaccine primary series became widely available in April 2021 and the booster dose in November 2022 for all residents vaccine-eligible by age. As of March 31, 2022, 86.7% of vaccine-eligible residents of PR completed their primary series, and 59.8% received a booster dose. In June 2020, a COVID-19 cohort study (COCOVID) was implemented within the Communities Organized to Prevent Arboviruses (COPA) platform among residents of 15 communities in Ponce, PR; COCOVID participants (N=1,030) complete in-person interviews every 6 months. We calculated unweighted frequencies and univariate risk ratios to identify factors associated with COVID-19 vaccine uptake after widespread availability. Among 816 vaccine-eligible participants interviewed during June 2021-February 2022, 747 (92%) had ≥1 COVID-19 vaccine dose. Participants ages 12-20 years were more likely to be vaccinated (95%) than those age >60 years for which vaccine uptake was lowest (86%) (RR: 1.10; 95% CI: 1.02-1.20). Participants who previously reported intention to get the COVID-19 vaccine (in interviews conducted November 2020-February 2021) were more likely to be vaccinated (92%) than those who were unsure or did not intend to get the vaccine (67%) (RR: 1.37; 95% CI: 1.13-1.67). Among adult participants (n = 625), those who were employed were more likely to be vaccinated (94%) than those who were not (88%) (RR: 1.08; 95% CI: 1.01-1.14); adult vaccination status did not differ significantly by chronic disease history, education, or income. Preliminary data (January-February 2022) showed high COVID-19 booster uptake in eligible participants (106, 88%) with no significant differences by demographics or other response variables. Consistent with regional data, COVID-19 vaccine uptake was high in the COCOVID cohort, particularly among minors ages 12-20 years, working adults, and participants that previously reported vaccine intention. Educational campaigns and targeted interventions will increase vaccine confidence and uptake.

1280

BUILDING THE CASE FOR ENHANCED SAMPLE REGISTRATION SYSTEMS FOR PUBLIC HEALTH: SIMULATING POTENTIAL LIVES SAVED IN ETHIOPIA, BANGLADESH, AND MOZAMBIQUE

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Civil registration and vital statistics (CRVS) systems are the gold-standard source for mortality data, capturing all vital events, including births and age-and-sex-specific deaths. Yet many resource-limited countries do not have CRVS systems. Lack of population vital statistics limits policymakers' ability to establish infrastructure, prioritize health needs, and mitigate mortality and morbidity. We propose *Enhanced Sample Registration Systems* (E-SRS) as an interim step towards establishing comprehensive CRVS in resource-limited countries. E-SRS would institute nationally representative sample registration systems in combination with methods for determining causes of death (e.g., verbal autopsy (VA) or minimally invasive tissue sampling (MITS)). Child Health and Mortality Prevention Surveillance (CHAMPS), a network of Health and Demographic Surveillance Systems that employ VA and MITS, could serve as a pilot platform for establishing E-SRS. We estimate the value of establishing E-SRS in three countries where CHAMPS operates (i.e., Ethiopia, Bangladesh, and Mozambique) and discuss how data from these E-SRS could be used to save lives. To simulate the number of lives saved from establishing E-SRS in these countries, we used the Lives Saved Tool (LiST), which simulates estimates of the lives saved by scaling up child and maternal health interventions in low- and middle-income countries after accounting for secular improvement in survival. Nine interventions related to top causes of child mortality (birth asphyxia, diarrhea, HIV/AIDS, lower respiratory infections, malaria, neonatal infections, and/or prematurity/low birth weight) were selected for simulation. Using baseline increases in intervention coverage as anticipated by Program Strategy Teams from the Bill and Melinda Gates Foundation from establishing E-SRS in these countries, we estimated 47,263 lives (children under age five) saved over a 15-year modeling period from all interventions modeled. Upper and lower bounds related to five percent scale-up or reduction in intervention coverage from baseline yield a range between 32,390 and 55,001 lives saved.

1281

PERFORMANCE EVALUATIONS OF SARS-COV-2 DIAGNOSTICS DURING THE PANDEMIC: CHALLENGES AND LESSONS

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Since March 2020, FIND has conducted performance evaluations of diagnostic tests for SARS-CoV-2 to provide independent data to the global health community so that countries have objective evidence on assay performance.

FIND opened several expressions of interest for test suppliers to participate in evaluations of molecular and immunoassays for SARS-CoV-2 in collaboration with independent study sites around the globe. Test submissions were selected through a scoring system including multiple criteria: supplier-reported analytical and clinical performance, test ease of use, manufacturing and distribution capacity and regulatory status.

By April 2022, sensitivity and specificity results were available on the FIND website for 26 antigen rapid tests, 24 molecular and 51 antibody assays. Results reveal high variability in performance among test types and across evaluation sites, highlighting the need for evaluations in various settings. Conducting retrospective and prospective evaluations during the pandemic has been extremely challenging due to continuous changes in COVID-19 incidence, logistical constraints, delays in building partnerships and obtaining ethical and regulatory approvals. A ready network for diagnostic test evaluation is essential for pandemic preparedness. FIND intends to build on this experience to establish study site networks, generic clinical trial protocols and partnership accords that can be rapidly activated and implemented.

1282

UNDERSTANDING DATA MANAGEMENT PRACTICES IN LIBERIA: A CONVERGENT PARALLEL MIXED METHOD

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Transitioning from paper to electronic data collection has been a step taken by Liberia's health sector over the years. Ranging from the District Health Information System to the Liberia Open data kit, different platforms are now being utilized at national and subnational levels. However, the scale of data collection is not being matched by efforts for effective data management. As a result, despite a significant investment in data collection, the quality of data may not be good enough to conduct rigorous analyses. Understanding data management practices at the Ministry of Health (MoH) and specific data management needs of graduate-level student researchers in Liberia is a major step to assessing the current situation and ultimately addressing gaps. A convergent parallel mixed method study was undertaken. Convenient sampling was used to recruit 200 students to complete a self-administered survey and 6 of them from the health sciences discipline were invited to key informant interviews with 6 data managers from MoH. Analysis for quantitative and qualitative used R Statistical Software and Dedoose. Findings from the interviews with data managers suggest that MoH does not have data management protocols for handling data collected during an outbreak; a major challenge preventing the development and implementation of such protocols is the availability of funding. Student represented a total of 9 disciplines with Health Sciences accounting for (n=74, 37%). More than half the health sciences graduate-level student researchers did research in the area of tropical medicine or hygiene (63, 85.1%). Capacity building around data collection, storage and presentations are concerns of students researchers. Only 14, 18.9% of them indicated using a data management plan for their research. Better case management and policy development are possible when data management systems are in place to ensure high quality data collection. Allocation of funding by the MoH could lead to an improved data management unit. And adding data management to the curriculum at local graduate programs, particularly ahead of thesis proposal development, may address capacity gaps.

1283

ACUTE FEBRILE ILLNESS IN REMOTE RIVERINE COMMUNITIES OF THE PERUVIAN AMAZON: AN OUTBREAK PREPAREDNESS PILOT STUDY

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Acute febrile illness is an endemic public health problem in the Peruvian Amazon and other tropical regions of South America. Malaria is considered the most frequent AFI associated pathogen due to diagnostic capacity available in remote regions. As a result, emerging infectious diseases with outbreak potential are seldomly detected by traditional diagnostic techniques. This limitation is also associated with delays in epidemic response and geographical coverage gaps in surveillance in remote riverine communities of the Amazon. As part of a larger AFI surveillance study in the city of Iquitos, Loreto, we piloted an outbreak preparedness response in remote communities living in the Peruvian, Colombian and Brazilian border in coordination with regional and national health authorities. The team was composed of local professionals was trained and deployed for a 15-day trip between March 14 and April 04, 2022. Patients documenting a fever of 38ºC and an age matched control were enrolled in the study. Blood and mid-turbinate samples were collected and stored in liquid nitrogen tanks. Upon arrival to the laboratory in the city of Iquitos, samples were processed using a TaqMan Array Card to diagnose the following pathogens*: Bartonella sp., Brucella sp., Coxiella burnetti, Campylobacter spp., Leptospira sp., Mycobacterium tuberculosis, Orientia tsutsugamushi, Rickettsia sp. Salmonella spp*., *Salmonella* Typhi, *Yersinia pestis, Streptococcus pneumoniae*, CMV, Dengue virus (including Dengue-1, Dengue-2, Dengue-3 and Dengue-4), Mayaro virus, Oropuche virus, SARS-CoV-2, West Nile virus, Zika virus, Yellow fever, Hepatitis E, EBV, Histoplasma, Leishmania, *Plasmodium sp. P. vivax, P. falciparum* and *Trypanosoma cruzi*. Additionally, mid turbinate samples were processed using for SARS-CoV-2 using standard qPCR diagnostics. A total of 28 cases and 28 controls were enrolled. Blood and saliva samples arrived to our laboratory facilities April 04, 2022 and are currently being processed. Results are pending and will be presented at the ASTMH 2022 meeting.

1284

ADOLESCENT CHILDBIRTH IN SOUTHERN RURAL MOZAMBIQUE: AN ANALYSIS OF LEVELS, TRENDS, AND DETERMINANTS USING A 22-YEARS HEALTH AND DEMOGRAPHIC SURVEILLANCE SYSTEM IN MANHICA DISTRICT, 1998-2019

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Adolescent childbirth is amongst the major problems of public health in low- and middle-income countries like Mozambique. However, it is in these countries where reliable data for guiding the design and monitoring of public health interventions are scarce. This study contributes with data on levels, trends, and the determinants of early childbearing that can inform the design of public health interventions in rural areas

of Mozambique. The data come from the Health and Demographic Surveillance System that is running in Manhica district since 1996. The study presents annual proportions of live births produced by adolescent girls, and age-specific fertility rates. Two logistic regression models were developed to estimate the risk of giving a live birth during adolescence, and to estimate the risk of having two or more live births during adolescence. Between 1998 and 2019, 118,805 women 10-49 years were followed, of which 83,923 (70.6%) were seen at least once when they were adolescents. Thirty three per cent of adolescents had at least one live birth before age 18 years (of which 35.9% had two or more live births), and these adolescents contributed to 53.9% of total live births in the study period. Total fertility rate has decreased in Manhiça, from 4.9 in 1998 to 3.2 in 2019, a trend that was captured also by other nation-wide studies. Fertility has decreased faster in adult women while slowly in adolescents. Early childbirth is higher in adolescents not living with their parents (particularly where they are wives or daughters-in-law of heads of household or heads by themselves), and those living in larger households or in households headed by adolescents. The fact that fertility has decreased faster in adult women but slowly in adolescents calls for more research to inform policy makers on how to better improve the efforts towards empowering adolescents in terms of their sexual and reproductive health, and education, in general.

1285

ORPHANHOOD IN SOUTHERN RURAL MOZAMBIQUE: AN ANALYSIS OF CAUSES, PREVALENCE, INCIDENCE, AND IMPACT ON CHILD MIGRATION USING A 22 YEARS HEALTH AND DEMOGRAPHIC SURVEILLANCE SYSTEM IN MANHICA DISTRICT

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In sub-Saharan Africa orphanhood is amongst the major socio-economic challenges, but little is known about the burden and consequences of orphanhood. This paper contributes with data on causes and trends of prevalence and incidence of orphanhood, and on the impacts on the living arrangements and migration of children, using a 22-years data from the Heath and Demographic Surveillance System (DSS) in Manhica district, Mozambique. The study presents annual prevalence and incidence of orphans; and rates of cause-specific orphans calculated using verbal autopsies conducted routinely by the DSS; and it compares the living arrangements and rates of migration by orphan status. Orphanhood in Manhica increased from 1.8% in 1998 to 7.2% in 2019, after a peak of 9.3% in 2010. There are more orphans who lost their fathers (3.1%) than those who lost their mothers (2.1%) - in line with the observed higher adult mortality in males than in females. The causes of orphanhood are HIV/AIDS, tuberculosis, digestive neoplasms, and stroke, with 30.3%, 10.8%, 8.8% and 8.1% of orphans, respectively. Orphanhood increases with age of children, such that 72.0% of orphans are aged 10-17 years. There are more orphans living in female-head household (67.4%) than non-orphans (19.7%), and more orphans living in households headed by children <18 years (7.8%) than non-orphans (4.2%) and by elders (13.4%) than non-orphans (6.3%). About 32.6% of orphans live with their grand-parents or uncles/unties compared to 14.3% in non-orphans. Orphans have higher rates of migration than non-orphans (internal migration rate of 108.5 per 1000 person-years in orphans vs 76.0 in non-orphans). Maternal orphans migration more than paternal orphans, particularly at younger ages. By age, orphans have higher risk of migration even at ages 6-17 years (where in general migration is lower), compared to non-orphans. Orphanhood in Mozambique is high and it has been increasing over the past two decades; and it is highest in the southern region where adult mortality is high.

1286

RETHINKING THE ELECTRONIC DISEASE SURVEILLANCE LANDSCAPE IN LIGHT OF THE SARS-COV-2 PANDEMIC

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For over 20 years, the Johns Hopkins Applied Physics Lab (JHU/APL) has been considered one of the foremost thought leaders in the space of global health surveillance technology development and implementation. In that time, teams at the laboratory have developed and operationalized instances of the Electronic Surveillance for the Early Notification of Community-based Epidemics (ESSENCE) for the US Centers for Disease Control and Prevention, the US Department of Defense, and numerous state and local entities. Additionally, building upon this success, JHU/APL developed the Suite for Automated Global Electronic bioSurveillance (SAGES), and open-source tool for health surveillance for use by international partners. These technologies have served the public health communities well for over two decades, but as the SARS-CoV-2 pandemic has illuminated, the health surveillance landscape is dynamic. Improving surveillance capability going forward will require the integration of novel data sources, analytic methods, and knowledge from the response community. We discuss our work incorporating publicly available information into a comprehensive data set to support analytic efforts as part of the JHU Coronavirus Resource Center, as well as our modeling work on behalf of the United Nations Office for the Coordination for Humanitarian Affairs (UN OCHA) as two exemplars of this expanding surveillance landscape. Leveraging our perspective from supporting US and global pandemic response efforts, we present a construct for considering contributing technologies to comprehensive biosurveillance.

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ASSOCIATION BETWEEN BASIC VACCINATION COMPLETION AND MALNUTRITION AMONG CHILDREN IN MALAWI: MALARIA VACCINE IMPLEMENTATION PROGRAM BASELINE SURVEY

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Basic vaccination among children less than 5 years in low-middle income countries is an important public health intervention that prevents infectious diseases by enhancing the development of the immune system. A competent immune system leads to overall improved health outcomes among vaccinated children, including favorable nutrition outcomes. WHO recommends that by 12-23 months of age that children should receive all basic vaccines; one dose of tuberculosis and measles vaccines respectively, and three doses of pentavalent and polio vaccines respectively. Within a Malaria Vaccine Implementation Program (MVIP) household baseline survey in Malawi, we quantified the impact of complete basic vaccination on malnutrition status among children. We assessed the association between the basic vaccination status and malnutrition, using logistic regression that accounted for the two-stage cluster sample design of the survey and adjusted for the child's sex and socio-economic status(SES). SES was classified as low, middle and high using a wealth index that was constructed based on household characteristics and ownership of durable goods. Malnutrition was defined as mid-upper arm circumference less than 13.5cm. A total of 4856 children were enrolled in the study. Of these,

3929 (80.9%) reported basic vaccination completion and 700 (14.7%) were malnourished. We observed a protective association between basic vaccination completion and malnutrition (OR: 0.57; 95% CI: 0.44, 0.73; p<0.001). Children from households of high SES had lower odds of being malnourished compared to those from the low SES households The odds ratios for children in middle and high SES s compared to those from low SES were (OR: 0.73; 95% CI: 0.57, 0.95) and (OR: 0.73; 95% CI: 0.57, 0.95) respectively**.** This work demonstrates that complete basic vaccination effectively prevents malnutrition. Interventions to prevent malnutrition should be prioritized for children from poor socio-economic status households.

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SOCIAL NETWORK ANALYSIS OF EBOLA VIRUS DISEASE DURING THE 2014-2016 OUTBREAK IN SUKUDU, SIERRA LEONE

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We applied social network analyses to examine decline ofan Ebola (EBOV) outbreakin a rural village in Sierra Leone, We described the EBOV transmission chain within the micro-networks of social contacts to assess for network saturation and transmission risk. We collected two phases of field data: 1) seroepidemiological data of EBOV transmission of all identified Ebola cases in Sukudu (n=48, inclusive of pauci-/asymptomatic and unrecognized EVD (unreported cases)); and 2) name-generator interviews with 148 Sukudu residents, including all survivors from the transmission chain (n=13), to identify social contacts for several key social interactions. Our analyses aggregated the village network into 148 participants and 1522 named contacts (N=1670). We then analyzed which social interactions and relationships shared the most links with the transmission chain. Cumulative incidence of EBOV infection was EBOV-infected people in the network divided by total size of network. We used exponential random graph models (ERGMs) to assess transmission risk. Three of ten identified social networks had strong links (>50% of members included) to the transmission chain and the following cumulative incidence of EBOV infection: 22% (31/143), living in the same household (composition largely kinship); 23% (37/198), spending leisure time; and 40% (32/81), those with whom one talked about important things (composition of latter 2 networks largely non-kin friends). The overall cumulative incidence in these overlapping social networks was 37/311 (12%). Pauci-/asymptomatic and unrecognized cases (unreported) did not have higher network centrality than reported cases and, thus, did not occupy a network position indicative of super-spreader status. In this rural village, three primary social networks played a key role in EBOV transmission, differing primarily by kin- versus non-kin based members. Within these networks, we found neither serological evidence of unreported transmission nor pre-existing herd immunity extinguishing susceptible members. An alternative hypothesis for micro-network transmission burnout is behavioral change.

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ESTABLISHING RT-PCR TESTING CAPACITY FOR COVID-19 AND OTHER DISEASES IN A RURAL DISTRICT IN MADAGASCAR

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The first cases of COVID-19 in Madagascar were identified in the capital on 19 March 2020. As of April 2022, Madagascar has faced three waves of COVID-19 while also confronting a high burden of other infectious diseases (e.g. malaria, diarrhea). Testing is central to disease control, surveillance, and case management. We describe the process and challenges of establishing a rural RT-PCR laboratory to test for COVID-19 infection and discuss the implications for clinical care and research following the immediate pandemic response. Ifanadiana is a rural district in southeastern Madagascar, with a population of 180,000; 36% of the population walks more than 2 hours to a primary health care center. As in other rural districts in sub-Saharan Africa, laboratory capacity is limited; the district hospital tests for common infectious diseases and samples are transferred to central laboratories for advanced testing. Early in the epidemic, testing capacity for COVID-19 was limited with all RT-PCR labs in the capital. To improve COVID-19 diagnostic capacity in Ifanadiana District, the Ministry of Public Health (MoPH), the healthcare organization Pivot, and an international research center, Centre ValBio, partnered to implement an RT-PCR laboratory. Centre ValBio lab infrastructure was adapted to meet safety and performance requirements for RT-PCR testing of COVID-19. The lab was outfitted with equipment for sample processing and storage; staff were trained in accordance with MoPH protocols. The RT-PCR lab in Ifanadiana was launched in May 2021 after overcoming challenges with international procurement. The new laboratory increased testing capacity not only for the district, but also for surrounding regions, extending access to vital diagnostic services for the rural population. This lab significantly reduced the turnaround time for RT-PCR test results, allowing for better management and mitigation of the spread of COVID-19. As the world's response to COVID-19 shifts, the laboratory offers an opportunity for testing linked with health systems strengthening efforts and a means of better understanding overall disease burden in the community.

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IMPORTANCE OF DIRECT NASAL SAMPLE FOR RAPID DIAGNOSIS AND SALIVA AS A NON-INVASIVE SOURCE FOR MOLECULAR DETECTION OF COVID-19

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Accurate diagnosis, a pre-requisite for early detection of diseases, is vital for prompt decision making regarding any treatment. For COVID-19, the burden calls for fast and appropriate actions. Currently the choice of methods includes rapid diagnostics tests and RT-qPCR. The samples used for these detection methods are mostly of respiratory origin and sometimes salivary ones. Purpose of our study was to evaluate a number of rapid diagnostic test devices using nasal or nasopharyngeal (NP) samples from 428 symptomatic prospective patients. We also performed RT-PCR for 316 salivary samples and compared the result with NP VTM. The sensitivity of the Standard Q Covid-19 Ag (SD Biosensor, Inc.) test kit drastically raised from 65.55% (95% CI: 56.282% to 74.016%) to 86.58% (95% CI: 80.033% to 91.604%) for direct nasal samples rather than nasal VTM. For CareStart^{Tm} (Access Bio, Inc.) kit, the sensitivity is almost similar of the result found in SD kit using NP samples; 85.91% (95% CI: 79.266% to 91.059%). The specificity was >95% for both SD and CareStart^{TM}. The RT-PCR result of salivary sample showed high sensitivity and specificity of 96.45% (95% CI: 92.82%-98.56%) and 92.44% (95% CI: 86.13%-96.48%) respectively, with VTM as gold standard. The kits were also able to detect patients with symptoms more than 06 days of onset and the performance can be maximized with Ct ≤ 27.0. The overall result demonstrates high performance of the rapid tests indicating its suitability

for regular surveillance at clinical facilities. Besides, The analysis of salivary sample signifies its ability as a replaceable alternative to nasal specimen rendering ease of sample collection in non-invassive method.

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MICROBIOLOGICAL QUALITY CONTROL OF INTENSIVE CARE UNIT ENVIRONMENT AT THE EPIDEMIC TREATMENT CENTER OF COVID 19 IN ARISTIDE LE DANTEC HOSPITAL IN SENEGAL

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Health care-associated infections (HCAIs) is a serious public health problem in the world. With the COVID 19, pandemic where severe cases are being treated in intensive care units, strict hygiene measures should be taken to prevent bacterial infections of patients with this disease. The objective of this study was to control microbiological quality environment of intensive care unit in Le Dantec hospital. Technical sedimentation was used and air environmental was collected in petri dish about 20 minutes before and after cleaning and antiseptic pulverization. Bacteria such as *Staphylococcus aureus* and *Klebsiella pneumoniae* were isolated before and after cleaning and and antiseptic pulverization. Antibiotic susceptibility testing showed a broad-spectrum beta-lactamase-producing for *K. pneumoniae*, which was resistant to aminoglycosides and fluoroquinolones but susceptible to carbapenem. For *S. aureus* strains, most antibiotics were active excepted penicillin.In conclusion, cleaning and disinfection protocols should be reinforced to limit secondary bacterial infections cases.

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A FLEXIBLE AGE-DEPENDENT, SPATIALLY-STRATIFIED MODEL FOR THE COVID-19 PANDEMIC, ACCOUNTING FOR MULTIPLE VIRAL VARIANTS AND VACCINES

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After COVID-19vaccines received approval, vaccinationcampaigns were launchedworldwide. Initially, these were characterized by ashortage of vaccine supply, and specificrisk groups were prioritized. Once supply was guaranteed and vaccinationcoveragesaturated, the focus shifted from risk groups toanti-vaxxers, the underaged population, andregions of low coverage. At the same time, hopes toreach herd immunity by vaccinationcampaigns were put intoperspective by the emergence and spread of more contagious andaggressive viral variants, and finally the much more contagious but less dangerous Omicronvariant. Ahighly sophisticated and flexible but easy-to-parameterize model for the ongoingCOVID-19pandemic is introduced. The model is age and spatially stratified, incorporatesdifferent viral variants, and vaccine (and booster vaccine)products. The model is particularlyadapted tothe characteristics of the Omicronvariant, i.e., reinfections are possible and theeffectiveness of vaccines is reduced. Inparticular, vaccines candiffer intheir vaccinationschedule, vaccinationrates, and the onset of vaccinationcampaigns. These factors are alsoage and/or locationdependent. Moreover, the effectiveness and the immunizing effect ofvaccines are assumed todepend onthe interactionof agivenvaccine and viral variant.Importantly, vaccines are not assumed toimmunize perfectly. Not all individuals inthepopulationare vaccinable.As anexample, the model was parameterized toreflect the epidemic situationinGermanyuntil summer 2022and predicted the future dynamics of the epidemic under differentinterventions. The model is capable of providing useful predictions for the COVID-19pandemic, and hence provides arelevant tool for epidemic decision-making. Moreover, themodel is flexible enough toaccommodate viral variants that potentially occur inthe future.

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COVID-19 TRANSMISSION POTENTIAL AND POLICY CHANGES IN HAWAII AND GUAM MARCH 2020-APRIL 2022

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We aimed to assess how the SARS-CoV-2 transmission potential changed over time in Hawaii and Guam, given the public health interventions, behavioral changes, vaccination rate, and the impact of the Omicron variant through estimating the time-varying reproductive number (R_t) and analyzing the Google mobility data from March 2020-April 2022. R_t was estimated using the instantaneous reproduction number method utilizing the R *EpiEstim* package. Five categories (retail and recreation, grocery and pharmacy, parks, workplace, and residential) of Google mobility data of Hawaii were analyzed to assess the correlation between population mobility trends in each category with incidence case count and 1-week sliding window R_t. Hawaii had three waves (Summer 2020, Summer 2021, and Winter 2021), and the highest number of daily new cases was recorded in Winter 2021. The median R_t estimates of Hawaii fluctuated around 1 for most of the study period, except the R_t estimate temporarily reached 2 in December 2021 as the Omicron became dominant in the US. Guam had four waves (Spring 2020, Summer and Fall 2020, Summer 2021, and Winter 2021), and the highest number of daily new cases was recorded in Winter 2021. The median R_t estimates fluctuated around 1 most of the time and reached 3 in January 2022. All of the time-lag correlation coefficients between mobility trend and incidence case count were significant ($p<0.0001$), e.g., the retail and recreation category correlated positively ($r=0.237$), and the residential category correlated negatively ($r=-0.144$). All of the time-lag correlation coefficients between mobility trend and 1-week sliding window R_t estimates were significant ($p<0.0001$), e.g., the workplace category correlated positively ($r=0.525$), and the residential category correlated negatively ($r=-0.445$). In conclusion, Hawaii and Guam experienced sustained COVID-19 transmission ($R_t \geq 1$) despite the best efforts of public health interventions. Increased mobility for work and social activities were associated with increased COVID-19 transmission.

1294

BIOCHEMICAL AND MOLECULAR GENETIC ANALYSES OF ORNITHINE DECARBOXYLASE IN *AEDES AEGYPTI* FEMALES

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Aedes aegypti females are the main vectors of dengue, yellow fever, chikungunya, and Zika viruses. We have previously reported that blood-fed *Ae. aegypti* females have evolved to efficiently metabolize and excrete excess nitrogen through multiple metabolic pathways. Although uric acid is the major nitrogen waste that blood-fed mosquitoes synthesize and excrete, mosquitoes have evolutionarily adapted to produce urea through uricolysis and argininolysis. Ornithine - one of the products of argininolysis - can be decarboxylated by ornithine decarboxylase (ODC; EC 4.1.1.17) to form putrescine in the first step of the polyamine biosynthetic pathway. We previously found that ODC mRNA level is up-regulated in the fat body of xanthine dehydrogenase 1 (XDH 1)-deficient *Ae. aegypti* females, suggesting that ODC is involved in nitrogen waste disposal and free-radical detoxification. In the current study, we further investigated a functional role for ODC in sugar- and blood-fed *Ae. aegypti* females by employing modern biochemical, pharmacological, and genetic approaches. We discovered that RNA interference-driven depletion of ODC strongly impairs several physiological processes including nitrogen metabolism, reproduction, and survival in *Ae. aegypti* females. Comparative transcriptional analysis of several genes in fat body, midgut and Malpighian tubules dissected from sugar- and blood-fed females injected with dsRNA against ODC, reveals that a wide variety of crosstalk

mechanisms exists between ODC and genes encoding proteins involved in ammonia, glucose, arginine and free-radical detoxification pathways. Interestingly, most of the transcriptional changes are observed in fat body and midgut of blood-fed *Ae. aegypti* with ODC deficiency. In summary, these findings demostrate that ODC is critical to the regulation of nitrogen metabolism in *Ae. aegypti* mosquitoes.

1295

THE IMPACT OF FEEDING METHOD ON *ANOPHELES* MOSQUITO MIDGUT MICROBIOTA AND *PLASMODIUM FALCIPARUM* INFECTION RATES

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In the mosquito midgut, parasites can encounter an important environmental variation, which determines its infectiousness for the mosquito. The mosquito gut microbiome is considerably altered during blood feeding, which has recently been a hot topic. Current experiments typically use mosquitoes fed on an artificial membrane system to investigate the importance of host microbiome and to measure the success of parasite transmission. Such approach may not adequately represent a natural feeding on human skin. This project was aimed to establish whether or not mosquito feeding mode alters either mosquito gut microbiota and/or parasite infectivity of mosquitoes. We carried out this study in Faladie, a rural village in Kati, 80 kilometers from Bamako in Mali. We used assays to compare parasite infections from skin-fed mosquito -that fully recapitulate the natural infection process- to membrane-fed mosquito. In total, we included 20 volunteers who were carriers of *Plasmodium falciparum* gametocytes to feed 3000 laboratory *Anopheles coluzzii* mosquitoes on skin and on a membrane using blood from the same donor. Both the direct skin feeding and mosquito survival rates were higher than those from the direct membrane feeding assay with a p=0.0198 and 0.0069. Parasite infection rates were similar for both feeding methods. In this study higher feeding rates were observed among DSF mosquitoes as previously shown supported by Diallo et al 2008. DSF mosquitoes also showed a higher survival rate, but no significantly different infection rates were observed between the two feeding methods. However, Diallo et al 2008 have found a higher rate of *Plasmodium falciparum* infection in mosquitoes feed directly on the skin than in those fed on the membrane. This may be due to the fact that the artificial membrane feeding system was more efficient. Therefore, artificial membrane feeding could be a good substitute for a direct skin feeding. The study on the microbiota of mosquito's midguts preserved at 24 hours post-feeding is ongoing and data will be presented.

1296

SUPPRESSION OF THE GENE ENCODING PDZ DOMAIN-CONTAINING PROTEIN DECREASES COLD TOLERANCE AND OVERWINTERING SURVIVAL OF THE MOSQUITO *CULEX PIPIENS*

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In diapausing mosquitoes, cold tolerance and prolonged lifespan are important features of the diapause phenotype that are crucial for overwintering success. In the mosquito *Culex pipiens*, we suggest that PDZ domain-containing protein (PDZ) is involved with these diapause characteristics for overwintering survival. Expression of *pdz* was significantly higher in early stage diapausing female mosquitoes in comparison to their non-diapausing counterparts. Suppression of the gene that encodes PDZ by RNAi significantly decreased actin binding in the midgut of early-stage adult diapausing females. Inhibition of *pdz* also significantly reduced the survivability of diapausing females which indicates that this protein plays a key role in fortifying midgut tissue during cold winter seasons.

1297

NEW FACES OF AN OLD FRIEND: EMERGING NEW ROLES OF *ANOPHELES* SALIVARY APYRASE IN *PLASMODIUM* INFECTION IN THE MOSQUITO MIDGUT

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Plasmodium hijacks mammalian fibrinolytic system to infect both, mosquito vector and vertebrate host. Plasminogen, the key molecule of fibrinolytic system, is activated into plasmin by tissue-type (tPA) and urokinase-type (uPA) plasminogen activator. Mosquito saliva injected in dermis of a human or ingested by mosquito during blood feeding alters hemostatic response. Role of mosquito saliva in immunomodulation and inflammation at the bite site in host skin has been extensively studied but there remains a major gap in understanding the role of saliva in mosquito midgut. We aim to study the role of mosquito saliva in activation of fibrinolytic system and its impact on *Plasmodium* infection in mosquito. Previously, we had identified *Anopheles* apyrase as the saliva tPA activator. Using a colorimetric assay, we showed that apyrase-activated tPA further enhanced plasminogen activation and apyrase also inhibited ADP-mediated platelet aggregation. Mosquitoes fed on *P. berghei* infected mouse treated with recombinant *An. gambiae* apyrase (r*Ag*Apy) showed reduced fibrin polymerization in midgut blood bolus and enhanced *P. berghei* mosquito infection. Immunizing mice with r*Ag*Apy increased fibrin polymerization in mosquito midgut blood meal and significantly inhibited parasite development in midgut. Furthermore, sporozoite transmission to apyrase-immunized mice was highly impaired, suggesting a key role in mosquito to mammal transmission. Together, our data shows a novel role of salivary apyrase in activating fibrinolytic system leading to enhanced fibrinolysis and inhibiting coagulation in the mosquito blood bolus thus, facilitating *Plasmodium* development in mosquito. Our work highlights the importance of mosquito saliva in malaria transmission. Studying the role of arthropod saliva proteins in pathogen transmission will widen our horizons for developing new intervention strategies for treatment of several infectious diseases.

1298

DETECTION OF *PLASMODIUM VIVAX* OOCYSTS AND SPOROZOITES IN *ANOPHELES FARAUTI* MOSQUITOES USING MINOR GROOVE BINDER BASED QPCR

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Transmission blocking interventions such as transmission-blocking vaccine candidates and antimalarial drugs can be assessed by experimental mosquito infection using membrane feeding assays. Light microscopy (LM) is the gold standard for assessing the presence or absence of *Plasmodium* oocysts and sporozoites in mosquito midguts and salivary glands, respectively. However, there are limitations associated with LM as they are labour intensive and require trained personnel, making scale-up for larger studies difficult. In addition, low-level infections can easily be missed or misidentified and differentiation between the *Plasmodium* species in co-endemic settings is impossible. Here we evaluated a minor groove binder (MGB) based qPCR assay for detecting oocysts and sporozoites by targeting the *Plasmodium vivax* 18SrRNA gene. Preliminary results showed that we were able to detect 58.8 % (20/34) *of P. vivax* infections

from midguts containing single oocysts and 60.5 % (72/119) for midguts with oocyst counts of > 1 according to LM. Furthermore, we were able to detect 58.8 % (20/34) of sporozoite-positive salivary gland samples that had been confirmed by LM while 37.5 % (3/8) of LM sporozoite-negative samples were positive by qPCR. We also evaluated the qPCR detection of the parasites from samples which DNA was extracted versus heating the midguts and salivary glands at 95°C for 10 minutes. We observed a significant and moderate correlation between the number of oocysts and the copy numbers (R = 0.6, p=0.019) for the DNA extracted samples. In conclusion, the MGB based qPCR assay can be a useful tool in a high-throughput setting to evaluate the impact of transmission blocking interventions.

1299

WINGLESS-INT-1 (WNT) PATHWAY GENE EXPRESSION IS REDUCED IN RIFT VALLEY FEVER VIRUS-INFECTED *AEDES* AND CULEX MOSQUITOES

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Aedes aegypti and *Culex tarsalis* are vectors of Rift Valley Fever virus (RVFV, *Phenuiviridae: Phlebovirus*). RVFV causes periodic epizootic outbreaks across Africa and the Arabian peninsula. In ruminants, RVF is often characterized by explosive outbreaks marked by fetal death, congenital malformations and adult animal deaths. Though most human cases are typically self-limiting, delayed onset encephalitis, kidney and/or eye damage, severe anemia, hemorrhagic fever and miscarriage can occur. This project seeks to better understand the processes that facilitate vector competence in RVFV-infected mosquitoes by assessment of genes that act in the Wingless-Int-1 (WNT) signaling pathway. Armadillo (*arm*), frizzled2 (*fz2*), and disheveled (*dsh*) are all positive regulators of the WNT pathway. *Domeless* is a positive regulator of the JAK-STAT pathway. *Puckered* is a negative regulator of the JNK pathway and acts as an inhibitor of apoptosis. These five genes of interest were the subject of our investigations. Results were analyzed using the comparative Ct method with actin and RPS7 as internal reference standards. Overall depletion of all five GOIs was observed in RVFV MP-12-exposed mosquitoes, relative to bloodfed controls. Moreover, an association between gene expression level and the presence of RVFV was also observed. Specifically, reduction in GOI expression was more pronounced in individuals with persistent infection compared to those that had cleared the virus. These data are consistent with the importance of WNT signaling in the conditioning vector competence phenotypes and underscore the need for further investigation in this area.

1300

DIMETHYL FUMARATE (DMF) HAS MULTIPLE EFFECTS ON MALARIA INFECTION IN *ANOPHELES GAMBIAE*

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In immunometabolism, glycolysis provides critical metabolic support to immunity. Dimethyl fumarate (DMF) inhibits GAPDH, a key enzyme required for glycolysis. Malaria infection in the mosquito midgut is involved in tripartite interactions of mosquito, *Plasmodium*, and gut microbiota. We found that DMF had multiple effects on the interactions. Prior treatment of DMF via sugar meals caused a significant reduction of *Plasmodium* oocyst load in the gut, and the mosquito survival post-infection was reduced as well. The gut microbiota was changed upon DMF treatment, with a significant decrease in *Asaia*, a *Plasmodium* favoring species, and an increase in *Elizabethkingia* and *Tanticharoenia*. The data suggest DMF may disturb the tripartite relationship by targeting glycolysis in gut microbiota, *Plasmodium*, and host mosquitoes. In addition, DMF treatment suppresses the immunity against bacteria in mosquitoes via inhibiting glycolysis and the Warburg effect. Further study is underway to elucidate metabolic changes upon DMF treatment in the contexts.

1301

CONTRASTING EVOLUTIONARY PATTERNS OF SAP2 AND KDR-MEDIATED RESISTANCE MECHANISMS IN *ANOPHELES COLUZZII* IN CENTRAL BURKINA FASO

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Malaria vector control is primary based on pyrethroid insecticides treated bed nets (LLINs) which are periodically distributed in endemic countries through WHO-recommended mass distribution campaigns. Despite LLINs have contributed to the 68% of the 663 million clinical cases prevented in 15 years in Africa, Burkina Faso is among the sub-Saharan countries continuing to carry a high share of the global malaria burden. One of the major factors accounting for this scenario is the physiological resistance to pyrethroids widespread in the major malaria vectors, either as mutation in the insecticide target site (sodium channel gene) and/or as metabolic and cuticular resistance. L1014F mutation (or kdr-w) is the commonest target site mutation in *A. gambiae* and *A. coluzzii* population of Burkina Faso, although other kdr mutations have been recently described. In addition, in the two species a novel mechanism of insecticide resistance has been described in the country consisting in the overexpression of SAP2 protein which act sequestering pyrethroids in mosquito legs. In *A. coluzzii* population of west Burkina Faso, it was observed a selective sweep upstream the SAP2 locus and a steady increase in a 5 SNPs haplotype potentially mirroring the increasing resistance of mosquitoes to pyrethroids after LLIN introduction occurred in 2010 at country level. We here investigated the allelic frequency of kdr-w and SAP2 associated SNPs in *A. coluzzii* specimens collected from 2011 to 2019 in a village of the Central region of Burkina Faso. We observed an increase in frequency of 4/5 *SAP2*-related SNPs which closely mirrors the insights from western Burkina Faso. Interestingly, a concurrent decrease of the *kdr*-w allele (from 0.72 in 2011 to 0.53 in 2019) has been also observed. Giving the known KDR-w associated fitness cost it can be assumed that, in the study area, the reduction in frequency of this mutation might be counterbalanced by SAP2 resistance thanks to an early sequestration of the insecticide before reaching the target site. Although promising, this hypothesis need to be further tested as well as the involvement of other pyrethroid resistance mechanisms.

1302

LONG-LASTING PERFORMANCE OF PYRETHROID-PBO LLINS AGAINST PYRETHROID RESISTANT MOSQUITOES: A POST MARKET EVALUATION OF PERMANET® 3.0

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With widespread pyrethroid resistance reported throughout Africa, pyrethroid-PBO LLINs are fast becoming the new standard tool for malaria prevention. The updated WHO recommendation indicates mass distribution of pyrethroid-PBO LLINs in areas where pyrethroid resistance has been detected in local malaria vectors. Of the currently WHO prequalified pyrethroid-PBO LLIN products, there are information gaps on their long-term performance, in particular on the biological efficacy of used pyrethroid-PBO LLINs against pyrethroid resistant *Anopheles* strains throughout the three year expected lifetime of a net. Vestergaard

has explored testing PermaNet® 3.0, a deltamethrin-PBO LLIN, after 2-3+ years of use in several countries under its post market monitoring program. In 2021, used PermaNet® 3.0 were collected and evaluated in Tanzania against well characterized pyrethroid resistant *Anopheles* strains. The efficacy of PermaNet® 3.0 roof was assessed against two comparators: a new, unused PermaNet® 3.0 roof and a new, unused deltamethrin-only net, PermaNet® 2.0. Previous testing conducted in Uganda showed PermaNet® 3.0 used for 3.3 years tested against the pyrethroid resistant *Anopheles gambiae s.s* Tiassalé strain knocked down and killed significantly ($p<0.05$) more pyrethroid resistant mosquitoes than the pyrethroid-only PermaNet® 2.0, indicating sustained efficacy through the use period even though efficacy wanes as the product ages. Post market monitoring on PermaNet® 3.0 in Tanzania after three years of use is ongoing and includes evaluation against the pyrethroid resistant *An. gambiae s.l*, Zeneti strain. Findings from this evaluation in Tanzania will be reported.

1303

"GETTING THERE": IMPROVING GENE DRIVE EFFICIENCY IN THE YELLOW FEVER MOSQUITO *AEDES AEGYPTI*

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The yellow fever mosquito, *Aedes aegypti,* is one of the main vectors implicated in the transmission of several arboviruses such as dengue, yellow fever, chikungunya, and Zika virus. Therefore, controlling the mosquito population is crucial for managing these mosquito-borne diseases and reducing their transmission. CRISPR/Cas9 technology has become essential for many research fields, including homing-based gene drive strategies for mosquito control that are under development. However, while studies focused on Anopheles mosquitoes have shown average biased inheritance of >98%, this is not the case in Aedes species which showed lower rates (<81%) in the investigations published to date. In preliminary studies in *Ae. aegypti*, our group had shown a new germline-specific regulatory element (*sds3*) expressing Cas9 that led to biased inheritance of an sgRNAs-expressing cassette inserted into the kmo gene (*kmo*^{sgRNAs}) higher than 90% when Cas9 was inherited from the maternal way. In the present study, we carried out further investigations to assess the performance of the combination of this germline-specific promoter expressing Cas9 and the *kmo*^{sgRNAs} line. Individual crosses were performed to evaluate not only the inheritance of the *kmo*^{sgRNAs} element but also paternal/maternal deposition and cleavage rates. Furthermore, we model the degree of improvement expected from this *sds3*-Cas9 line compared to a previous line (*bgcn*-Cas9) used in a cage trial study that reached up to 89% of carrier frequency of the *kmo*^{sgRNAs} element. Results indicate an average inheritance rate of the *kmo*^{sgRNAs} from the inheritance assay of 97.1%. In addition, an average germline cutting rate of 92.6% was determined. The results obtained with the *sds3*-Cas9 line reveal that the improved ability to bias inheritance translates to an increase in the invasiveness of split drives on *Ae. aegypti* compared to previous studies.

1305

VECTOR BIONOMICS AND INSECTICIDE RESISTANCE IN SIERRA LEONE: OPPORTUNITIES AND CHALLENGES IN DECISION-MAKING FOR MALARIA VECTOR CONTROL

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To support malaria control decisions in Sierra Leone (SL), we monitored 5 districts for monthly entomological indicators of malaria transmission and insecticide susceptibility between 2018-21. *Anopheles coluzzii* (64.5%) and *An. gambiae s.s.* (34.3%) were the predominant species identified. A preference for indoor versus outdoor biting was observed in 2 of 5 districts (Western Area p=0.015, *An. coluzzii* and p<0.001, *An. gambiae*; Bombali District (p < 0.001, *An. coluzzii* and p =0.02, *An. gambiae*). Proportion of blood-fed mosquitoes caught indoors was similarly high in both 2019 (62%) and 2020 (63%) (95% CI 60.8-64.8%). Proportion of gravid females was greater than 30% indicating endophilic mosquito behavior and indoor residual spraying (IRS) could be effective. Mean indoor mosquito resting behavior was higher in Bo and Bombali compared to other districts. Human blood index (HBI) of malaria vectors rose from 79.8% in 2019 to 93.9% (p<0.001) in 2020. These data suggest that targeting indoor biting mosquitoes may provide optimal vector control in Sierra Leone. Vector susceptibility to pyrethroids was very low (4.2-40%), however, the addition of piperonyl-butoxide (PBO) partially restored mosquito susceptibility by 34-40%. Susceptibility tests for non-pyrethroids, clothianidin and chlorfenapyr, showed 100% mortality. Thus, SL distributed insecticide-treated bed nets (ITNs) with PBO for the 2020 mass campaign, becoming the world's first country to achieve universal coverage with PBO ITNs, and are procuring Dual Active Ingredient ITNs containing chlorfenapyr for the 2023 mass campaign. Overall, annual entomological inoculation rate (aEIR) in each district was lower in 2020 (34.4-384.4 infectious bites/person/year (i/b/p/y)) after PBO ITN distribution compared to 2019 (110-634.5 i/b/p/y), results we continue to evaluate. Additionally, in May 2021, National Malaria Control Program introduced IRS with clothianidin in the high malaria burden districts, Bo and Bombali. Entomological monitoring will help determine how deploying different types of PBO ITN and IRS impact malaria vectors across Sierra Leone.

1306

IS INSECTICIDE RESISTANCE ASSOCIATED WITH SPECIES DIVERSITY IN *ANOPHELES GAMBIAE S.L.* IN CÔTE D'IVOIRE?

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Insecticide resistance in malaria vectors threatens the efficacy of vector control across sub-Saharan Africa. In Côte d'Ivoire, the *Anopheles gambiae* species complex, the country's predominant malaria vectors, are highly variable across ecological settings and in their levels of insecticide resistance. Here we analysed the association between the species distribution, diversity of *An. gambiae* s.l., and level of insecticide resistance in various ecological settings in Côte d'Ivoire.Larval and adult mosquitoes were sampled from July to October 2020, across three ecological settings in Côte d'Ivoire. Three to five-day old adult female *An. gambiae* s.l. were tested against deltamethrin (0.05%), permethrin (0.75%) and pirimiphos methyl (0.25%) using WHO susceptibility test kits. If pyrethroid resistance was detected, tests were done using 5x and 10x the diagnostic dose and with the synergist piperonyl butoxide (PBO) (4%). PCR was used to identify members of the *An. gambiae* s.l. species complex and the presence of insecticide resistance target site mutations (*Kdr* L1014F and *Ace-1*^{R} G119S). The distribution of species and insecticide resistance was compared across ecological settings.We found multiple resistance mechanisms present in *An. gambiae* s.l. across the three ecological settings in Côte d'Ivoire. Following pyrethroid exposure, mortality rates were significantly higher in *An. gambiae* s.l. collected in the savannah zone compared to those collected in the forest zone after ($p<0.05$). Looking at members of the species complex, *An. gambiae* was more abundant in the savannah area (97-100% of collected mosquitoes), whereas *An. coluzzii* was the predominant species in the transition (90-96%) and forest zones (34-70%). *An. coluzzii* greater resistance intensity to pyrethroids than *An. gambiae*. However, resistance mutation alleles were more common in *An. gambiae* (e.g. frequency of *Kdr* L1014F in *An. gambiae* was 82.19-91.57 % *vs* 58.47-61.79% for *An. coluzzii*). Variations in species distribution and insecticide resistance across ecological zones in Côte d›Ivoire must be taken into account when considering vector control methods.

1307

DISCOVERING NATURAL PRODUCTS FOR VECTOR CONTROL

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Vector-borne diseases (VBDs) represent a significant health burden worldwide, threatening the health of ~80% of the global population. Insecticide-based vector control is the most effective method to manage many VBDs but its efficacy has been declining due to high levels of resistance in vector populations to currently available insecticide classes. Therefore, the discovery of new chemistries from non-conventional chemical classes and with novel modes of action is a priority. Natural products (NPs) have been used as insecticides for many decades and served as inspiration for the development of synthetic insecticides. Hence, the discovery of novel NPs could lead to the development of highly effective insecticides in the future. Here, we describe a high-content phenotypic screen of more than 3,000 compounds from the AnalytiCon NP collection against first instar larvae of *Aedes aegypti* (Linnaeus, 1762). Compounds were screened in a 384-well plate format using the Perkin Elmer Opera Phenix and larvae were scored for lethal and novel phenotypic endpoints. Screening revealed four chemistries that caused high mortality of larvae, and nineteen chemistries that caused phenotypic changes, including atypical pigmentation and changes in body proportions. An overview of the phenotypic screening platform and secondary confirmatory assays will be presented. Work to investigate mode of action of screen hits using electrophysiology studies will be discussed and results considered in the context of insecticide development.

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PASSIVE SURVEILLANCE OF *AEDES* VECTORS IN THE SOUTHERN URBAN CITY ACCRA, GHANA

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Dengue, Zika and Chikungunya are *Aedes*-borne viral diseases that have become significant global health concerns over the past few years. Ghana shares borders with countries that have reported outbreaks of these diseases but, the country remains free of an outbreak. Recent studies have uncovered antibodies and viral RNA of the Dengue virus serotype-2 among individuals in some localities; an indication of silent transmission ongoing in the population, hence the need to test possible sustainable passive methods to assess the risk of transmission of these viruses in the country. This was a cross-sectional study that assessed the risk of transmission of Yellow fever, Dengue, Zika and Chikungunya viruses in four (peri-) domestic settings using ovitraps (a passive sampling method). Ovitraps to collect *Aedes* eggs were specially constructed with plastic water bottles. These were left for five days at collection points and sampling was done at three different time points. The eggs collected were identified and counted. This data was used for the estimation of the Positive Ovitrap Index (POI) and the Egg Density Index (EDI). Both risk indices recorded for all sites were higher than the WHO thresholds allowed for these indices; indicating that all sites had a high potential of an outbreak following the introduction of these viruses. Our results confirmed that ovitraps could successfully be used as a cost effective, sustainable passive sampling method in the country, and its use should be considered in the development of a well-structured surveillance system for the *Aedes* vectors in Ghana.

1309

INTENSITY OF PYRETHROIDS RESISTANCE IN DRY SEASON BREEDING *ANOPHELES GAMBIAE SENSU LATO* POPULATIONS ALONG THE NIGER RIVER IN MALI: IMPLICATION FOR SPREADING INSECTICIDES RESISTANCE

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Previous studies have shown that the riverbeds constitute suitable ecosystems for sustaining malaria transmission throughout the dry season. In addition, this dry season breeding *An. gambiae s.l.* population may harbor different insecticide resistance mechanisms they will spread in surrounding areas at the onset of the rainy season. This study explores the intensity of insecticide resistance in *An. gambiae s.l.* to pyrethroids during the dry season along the Niger River. Larvae were collected in water pockets distributed along the riverbed between Koursalé and Kenieroba. They were reared to adult stage at the insectary, and 3- 5-day-old females were submitted to the World Health Organization insecticide resistance intensity bioassay test. Mosquitoes were exposed to 1x, 5x, and 10x concentration of deltamethrin. They were also tested at 1x concentration after a pre-exposition to the piperonyl butoxide (PBO). The mortality rates of *An. gambiae s.l.* populations to deltamethrin ranged from 1% to 5.8% at 1x concentration, 27.2 to 57.8% at 5x, and 60.8% to 80.3% at 10x. Mortality rates at 1x concentration after exposure to PBO increased from 5.8 to 21.0% suggesting the presence of metabolic resistance mechanism together with other resistance mechanisms. *An. gambiae s.l.* populations

breeding in riverbeds during the dry season were highly resistant to pyrethroids (deltamethrin) and may serve as inoculum to build up resistant population in surrounding areas at the onset of the rainy season.

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ASSESSING THE ENTOMOLOGICAL PERFORMANCE OF PYRETHROID-CHLORFENAPYR NETS IN THE PRESENCE OF PYRETHROID-PIPERONYL BUTOXIDE (PBO) INSECTICIDE-TREATED NETS

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Pyrethroid-piperonyl butoxide (PBO) and pyrethroid-chlorfenapyr insecticide-treated nets (ITNs) are being scaled up in endemic countries. Some control programmes have deployed both ITN types in the same communities through multiple distribution channels. PBO inhibits enzymes associated with pyrethroid resistance, notably cytochrome P450 monooxygenases (P450s) while, chlorfenapyr is a pro-insecticide requiring activation by P450s. The inhibitory action of PBO against P450s may therefore, reduce the impact of chlorfenapyr when pyrethroid-PBO and pyrethroid-chlorfenapyr nets are used in the same household. We performed a series of experimental hut trials to evaluate the entomological impact of combining pyrethroid-chlorfenapyr and pyrethroid-PBO ITNs against a pyrethroid-resistant malaria vector population in Benin. Comparison was made to combinations with pyrethroid-only ITNs. All net types were also tested as single and double treatments. Susceptibility tests were performed to assess the resistance profile of the vector population during the trials. Susceptibility bioassays revealed high intensity pyrethroid resistance that was overcome with PBO pre-exposure but susceptibility to chlorfenapyr. Applied singly, pyrethroid-chlorfenapyr nets induced significantly higher vector mortality (82%) than pyrethroid-PBO ITNs (37%, $p<0.001$) and pyrethroid-only ITNs (22%, $p<0.001$). Except for pyrethroid-PBO ITNs, mortality in huts with two nets of the same type was similar to single nets. Applying two pyrethroid-chlorfenapyr ITNs in the same hut induced significantly higher mortality (85%) than combinations of pyrethroid-chlorfenapyr ITNs with pyrethroid-only ITNs (61%, $p<0.001$) and pyrethroid-PBO ITNs (74%, $p<0.001$). In conclusion, pyrethroid-chlorfenapyr ITNs induced highest levels of vector mortality. Combining these nets with pyrethroid-PBO or pyrethroid-only nets in the same households may reduce control of pyrethroid-resistant vectors compared to when deployed alone. Programmes should prioritise distribution of pyrethroid-chlorfenapyr ITNs to maximise control impact.

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ANOPHELISM WITHOUT MALARIA EXPLOITING HOST GENETIC BACKGROUND TO SPREAD OF A SYMBIONT THAT IMMUNIZES *ANOPHELES* AGAINST *PLASMODIUM*

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The discovery of a novel microsporidian symbiont from wild *Anopheles* mosquitoes and the finding that it protects against *Plasmodium* infection has led to the suggestion that it is a promising candidate for integrated vector management. However, field prevalence have remained relatively low (0-9%) suggesting that host genetic background could be hampering the spread of *Microsporidia MB* despite undergoing vertically and horizontally transmission in adults. We investigated *Microsporidia*-infected hosts' interactions with specific insecticides alleles and how this could be exploited to create a *Microsporidia MB* pandemic in the wild. Iso-female *Microsporidia*-infected lines from field infected females were exposed to standard and low dosages of deltamethrin and permethrin insecticides to establish phenotypic and genotypic profiles. Symbiont infections in F1, resistant alleles, and symbiont transmission were confirmed *posthoc* by qPCR. Microsporidia *MB* prevalence across areas with contrasting insecticides profiles suggest increased prevalence of symbiont in lowlands (12.69±2.4%) than highlands (1.03±0.001%). *Microsporidia MB* does not protect against deltamethrin and permethrin, but genotypic profiling suggests a bias of infection towards hosts with susceptible (65.90±18%) and heterozygous resistant (53.05±6.21%) alleles. Notably, sub-lethal exposure to permethrin and deltamethrin induced a sustained spike of *Microsporidia MB* in *Anopheles gambiae* s.s (86.267±8.43%; $p=0.001$), and *An. arabiensis* (91.035±12.72%; $p=0.02$). A significant transovarial transmission of spiked *Microsporidia*-infection to offspring from the pre-exposed females was observed ($p=0.001$), but the insecticide profiles of offspring and mothers were similar to non-spiked ($p=0.891$). These findings did not interfere with hosts' life history traits. Pre-exposing *Microsporidia*-infected *Anopheles* to lower dosages of classical insecticides is a possible dissemination strategy of the symbiont in areas where *kdr* alleles is fixed.

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MOSQUITODB: A COMPREHENSIVE-ELECTRONICALLY-BASED ENTOMOLOGICAL SURVEILLANCE SYSTEM FOR THE CONTROL AND ELIMINATION OF MOSQUITO-BORNE DISEASES

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Most National Disease Control/Elimination Program and researchers lack a robust entomological surveillance system that can manage field and laboratory based mosquito data leading to the inability to make timely informed decisions on the deployment of vector control tools. We have developed an electronic mosquito database management system (MosquitoDB) that can manage diverse entomological studies for the control and elimination of vector-borne diseases. The system is a freely and securely web application accompanied by its mobile version for data collection available in the Google Play Store - capable of validating and recording geolocation mosquito data even in the absence of an internet connection. The key functionalities include but not limited to standardized data collection forms, customizable forms variables, proper linkage of field and laboratory data, data sharing capabilities, multi-language support, and access to linked datasets with summarized reports in different formats. Moreover, an interactive dashboard to support making informed decisions on where, when, how, and which vector control tool(s) should be implemented. MosquitoDB can easily be integrated into other databases (eg. DHIS2) through its well-secured Application Programming Interfaces (APIs) with the ability to push key entomological indicators. Current users include mostly researchers and some national malaria control programs focusing on malaria vectors. MosquitoDB is an effective and comprehensive electronically-based entomological surveillance system that can support national diseases control with routine surveillance and researchers with complex diverse entomological studies.

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INSECTICIDE SYNERGISTS, SYNERGIZED INSECTICIDE PRODUCTS AND MOSQUITO RESISTANCE TO INSECTICIDES: A SYSTEMATIC REVIEW

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The extensive use of insecticides has led to widespread insecticide resistance in insects. Synergists have been discovered to combat the resistance. We aim to review the commonly applied synergists, the

purpose of usage, and the responses of different species of mosquitoes to the synergized insecticide products. The review compared the responses of different mosquito species to insecticides with/without synergists. Metrics included larval/adult mosquito mortalities, 50% and 90% lethal insecticide concentrations, and metabolic enzymatic activities pre- and post-exposure to synergists. We analyzed how mosquitoes' resistance levels affect their response to synergist exposure. This review collected 2,799 paired (insecticide and paired synergized insecticides) records covering six major types of synergists and 26 mosquito species (complexes) from four genera. Piperonyl butoxide (PBO) was the most tested synergist, and *Aedes* mosquitoes had been tested with the most diverse synergist types. PBO pre-exposure nearly fully restored the susceptibility of *Anopheles funestus* and *Anopheles arabiensis* to pyrethroid insecticides, but not with highly insecticide-resistant *Anopheles gambiae* sensu lato, *Culex*, and *Aedes* mosquitoes. PBO was also a good synergist for DDT and carbamate insecticides. S, S, S-tributyl phosphorotrithioate worked well with pyrethroids on adult mosquitoes but not on larvae. Triphenyl phosphate was not a good synergist for *Aedes* mosquitoes. PBO-treated long-lasting insecticidal nets (PBO-LLINs) significantly increased mosquito mortality compared to regular LLINs; however, their effect was compromised against highly insecticide-resistant mosquitoes. There was not enough evidence to examine how synergist exposure affects metabolic enzymatic activity in mosquitoes. In conclusion, certain species of high-level multiple insecticide-resistant mosquitoes are tolerant to PBO exposure and to PBO-LLINs. Potential development of mosquito tolerance to synergized insecticide products needs to be closely monitored.

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QUANTIFICATIONS OF CYTOCHROME P450S GENES INVOLVE IN *ANOPHELES GAMBIAE* S.L. METABOLIC RESISTANCE IN THE CASCADES REGION OF BURKINA FASO

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The most common vector control tools are Insecticide Treated Nets (ITNs) and Indoor Residual Spraying, both of which rely on insecticide treatments. With the development of resistance to the recommended classes of insecticides the efficacy of these tools is threatened. To mitigate this resistance, Burkina Faso, one of the ten-plus-one high malaria burden countries have successfully piloted new generation nets (NGN) including Piperonyl Butoxide (PBO)-pyrethroid and Interceptor G2 nets, deployed in two health districts. Subsequently, the country is planning a country-wide coverage of NGN only in the next mass distribution campaign. The current study assessed the variation in expression levels of known cytochrome P450s genes associated with metabolic insecticide resistance on data collected between 2020 and 2022. Mosquito populations were assessed using adults reared from larvae collected from different aquatic habitats from three villages with high insecticide resistance level in vector populations. Collections began in 2020 and ended in 2022. Mosquitoes were exposed to deltamethrin and alphacypermethrin after pre-exposure to PBO following WHO tube bioassay guidelines then stored in RNAlater. cDNA developed from extracted mRNA will be use during a multiplex TaqMan qPCR to assess for the variation in expression of the GSTE2 and seven (07) known cytochrome P450s genes level. The overall mean of mortality rate was < 20% after exposure to the diagnostic dose and varied between sites and insecticide used. The pre-exposure to PBO improved the mortality rate to between 79 and 86%, depending on collection site and insecticide. These results indicate an involvement of cytochrome P450 and esterase in the resistance among other mechanisms. The assessment of known cytochrome P450s genes is ongoing. Bioassay results indicate possible better performance of PBO-Pyrethroid nets. The multiplex qPCR results will inform on the presence of the given metabolic resistance genes and the variation in their expression level over years.

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NEXT GENERATION MOSQUITO CONTROL: REMOTE SENSING AND APPLIED MACHINE LEARNING TECHNIQUES ACCURATELY PREDICT *CULEX* SP. ABUNDANCE AND MOSQUITO BREEDING HABITATS

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Mosquitoes are the world's most deadly animal. The arboviruses they transmit result in an estimated 300 million infections and 500,000 deaths annually. With few effective therapeutics or preventative vaccine available, public health officials rely on targeted mosquito abatement efforts to reduce the burden of disease. Effective insecticides have been developed to reduce the mosquito population and therefore reduce disease transmission. However, widespread insecticide application is inhibited by limited budgets for mosquito control and the fear of inducing insecticide resistance in the mosquito population. Targeted mosquito abatement efforts are critical to effectively reducing the burden of disease in affected areas. Our current collaborative project is proof-of-concept study demonstrating the use of remote sensing and machine learning to effectively predict *Culex* sp. mosquito abundance in Harris County, Texas. Mosquito collection data from November 2017 to June 2018 was obtained from routine collection by Harris County Mosquito and Vector Control Division. Using Sentinel imagery, a U-Net convolutional neural-network machine learning algorithm was employed to generate land classification and land-use categories for seasonal images. Additionally, indices for vegetation and water were derived from the same images. A novel data extraction method was employed to ensure remote sensed variables were both temporally and geographically resolute to the mosquito data. A predictive model of mosquito abundance by these micro-environmental factors was developed using a suite of 5 different machine learning statistical techniques. Random Forest achieved the highest overall accuracy of 95% and was used to derive a predicated mosquito risk map for the entire county. This study demonstrates the utility of remote sensing and machine learning algorithms in large-scale vector control daily surveillance decision making. We believe integration of this technology into routine vector control activities will work to reduce the burden of mosquito-borne disease and limit insecticide residence through targeted abatement.

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GROUND MOSQUITO ADULTICIDE FIELD TRIAL OKLAHOMA

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Mosquito-borne diseases continue to pose a threat to public health worldwide. Assessing the level of insecticide resistance in a given mosquito population is essential for the efficient management and control of mosquito vectors. Three populations were analyzed in this pioneer study in Oklahoma: an adult Mixed wild population from the city of Bethany, and two laboratory-reared larvae populations of *Culex pipiens/quinquefasciatus* collected in suburban backyards from Tulsa and Oklahoma City. Our approach consisted of a ground adulticide field trial in a field station arranged in a 3x3 grid. The adulticides used were the organophosphate Fyfanon EW and pyrethroid PermaSease 4-4. Cages were collected 20-30 minutes following spray off and mortality readings were taken in the following 12hr and 24hr. Considers were considered dead if they were unable to right themselves or fly at the time of the mortality reading. Survivors were stored at -80 ºC and enzyme activity assays of P450 cytochrome, α- and β-carboxylesterases, and glutathione S-transferases

were determined using a laboratory susceptible strain as control. Mortality data was not adjusted using Abbott's formula because control mortality exceeded 20%. For all populations in response to Fyfanon EW, the highest 24hr mortality was achieved at 100 ft whereby the *Culex* population had the highest overall mortality in response to Fyfanon EW, ranging from 77.78%-84.13%. The 24hr mortality at all distances for all populations in response to PermaSease 4-4 was high (88.36-100%). The average 24hr mortality was greater than 90% for all populations at all distances with the exception of the Mixed population at 300 ft. Minute recovery was observed between the 12 and 24 hr mortality readings, suggesting that *kdr* is not an abundant insecticide resistance mechanism in these populations.

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IMPROVED GLUE FOR TRAPPING BLACK FLIES

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Esperanza Window Traps (EWTs) are useful for black fly monitoring and control. Preliminary studies in both Uganda and Nigeria revealed that a BanfieldBio Inc. (BBI) glue with an ultraviolet (UV) component performed equal to, or better, than the TAD (formerly Tanglefoot) formulations being used. Our team then compared the efficacy of six different glue types on EWTs in two separate locations per country (Nigeria and Uganda) to identify the optimal glue to be used on the EWTs. We tested two glues from Trecé Adhesives Division (TAD) (All-weather and Hand Applied) and four from BBI (BioGlue and Autocidal Gravid Ovitrap (AGO)). Both BBI formulas were tested with and without a UV pigment component. Using a Latin square design, glues were rotated between six separate sites per location each day for 30 days with a human landing catch standard. In Nigeria, the proportion of flies caught were evenly distributed among glue types. In Uganda, the TAD All Weather formulation outperformed the other glues for both sites. The BioGlue (UV) was the next best in the proportion of flies caught. Among the BBI formulations, the glues with a UV component outperformed their counterparts. In Nigeria, both TAD formulations and the UV-infused glues were deemed stable, only requiring a recoat occasionally compared to the regular BioGlue and AGO glues, which required a recoat once daily. In Uganda, the stability results were similar, but the UV-infused glues required more recoats than the TAD formulations. Based on the preliminary study, it was hypothesized that the UV-infused glues would outperform their counterparts and the TAD formulations, but, while the former was found to be true, the latter was not. Based on both the stability of the glue and the proportion of flies caught compared to the other glue formulations, the TAD All Weather formulation appears to have the highest efficacy for catching black flies. This study demonstrated that infusing a glue with UV can increase the efficacy of the glue, but other components of the formulation influence efficacy. Using the TAD All Weather formulation provided a demonstrated increase in EWT efficacy over the previous adhesives used.

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INSECTICIDE RESISTANCE OF *AEDES ALBOPICTUS* INVADED MOZAMBIQUE

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Aedes albopictus is an important vector of various arboviruses. This mosquito originated in Asia, and it has expanded its distribution around the world. Although *Ae. albopictus* has already established in West Africa, it had not established in the continental part of East Africa until its establishment was confirmed in southern Mozambique by 2019. A recent population genetic study suggests that the Mozambique population originated in Southeast Asia. Because Asian populations have acquired insecticide resistance, we examined whether the invasive population shows any signs of insecticide resistance by using techniques of genetic analysis and bioassay. In the analyses, we used *Ae. albopictus* samples collected at Maputo, the capital city of Mozambique in 2019. The genetic analysis found that some individuals had F1534C knockdown resistance (kdr) mutation. The WHO Tube Assay showed that the F10 generation with F1534C mutation are resistant to 0.25% permethrin, the organochlorine DDT, the carbamate propoxur and the organophosphorus fenitrothion. In the bioassay with 0.25% permethrin, the F1534C homozygous individuals had a higher survival rate (50%, n = 4) after 24 hours than the wild-type F1534 homozygous individuals (19%, n = 22). However, the number of homozygous individuals with the mutation was small, and nearly 20% of wild type individuals survived. We are conducting additional experiments with a larger sample size, and testing whether the population has another resistant mechanism such as metabolic resistance.

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CHARACTERIZING PYRETHROID RESISTANCE IN FIELD-COLLECTED *ANOPHELES GAMBIAE S.S* AND *AN. ARABIENSIS* FROM 11 DISTRICTS IN UGANDA

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Remarkable progress in malaria control, enabled in part by the scale-up of long-lasting insecticidal nets and indoor residual spraying (IRS) remains fragile and constantly threatened by insecticide resistance. Here, *An. gambiae s.s* and *An. arabiensis* were collected from 11 districts stratified by IRS status namely; No IRS, IRS stopped (2009-2014, then 2017) and IRS active (2014-2019). In *An. gambiae,* mosquitoes were genotyped for resistance mutations: *Vgsc-1014S*, *Vgsc-1014F*, *Cyp6aa1*, *Cyp6p4*, *ZZB-TE*, *Cyp4j5,* and *Coeae1d*. For *An. arabiensis* only *Vgsc-1014S* and *Vgsc-1014F* were genotyped. Overall, 2753 *An. gambiae* s.l were phenotyped with 40% (1105) *An. gambiae* s.s. and 60% (1648) *An. arabiensis.* Mortality to permethrin was significantly higher in *An. arabiensis* compared to *An. gambiae* in No IRS (67.7% vs 16.1%, OR 0.10, 95% CI:0.05-0.19, p<0.0001) and IRS stopped (63.6% vs 11.3%, OR 0.20, 95% CI: 0.10-0.38, p<0.0001). Higher mortality to deltamethrin compared to permethrin was found in *An. gambiae* s.s (25.6% vs 11.3%, OR 0.44, 95% CI: 0.27-0.71, p=0.001) and *An. arabiensis*. In *An. gambiae*, PBO showed partial restoration of susceptibility to permethrin (16.1% vs 54.5%, OR 6.80, 95% CI: 3.08-15.05, p<0.0001) and deltamethrin (24.6% vs 55.6%, OR 3.83, 95% CI: 2.01-7.31, p<0.0001) with near restoration of susceptibility in *An. arabiensis.* The *Vgsc-1014S* mutation approached fixation in *An. gambiae* and *Vgsc-1014F* allele frequency was significantly high relative to *Vgsc-1014L* (28.40 vs 3.43, fisher exact p=0.02). *An. arabiensis* were predominantly (~97%) wild type-*Vgsc-1014L*. Notably, *Vgsc-1014S/F* resistant alleles were associated with *An. gambiae* survival to deltamethrin (OR 3.44, 95% CI: 1.02-11.57, p=0.046. The *Cyp4j5* mutation and the triple mutation (*Cyp6aa1, Cyp6p4 and ZZB-TE*) were associated with survival to Deltamethrin + PBO (OR 2.27, 95% CI: 1.08-4.80, p=0.031) and Permethrin + PBO (OR 3.19, 95% CI: 1.16-8.80, p=0.025) respectively. In this study, molecular markers showed consistency with association to pyrethroid resistance advocating for the need to have resistance marker screening in entomological surveillance programs.

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ABSENCE OF INSECTICIDE SELECTION IN A PYRETHROID RESISTANT *AEDES AEGYPTI* STRAIN: RESPONSE IN SUSCEPTIBILITY, CROSS-RESISTANCE, *KDR* MUTATIONS AND EXOME

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Aedes aegypti populations from Mexico were subjected to intense permethrin selection between 1999 and 2010. This resulted in selection of resistance mechanisms that either reduced pyrethroid binding to their target site, the voltage-gated sodium channel (VGSC) or increased their metabolism by detoxification enzymes. Since few insecticide classes are available for public health, management of resistance has been proposed as a strategy to prolong their use to control mosquitoes. Management of resistance relies in the assumption that negative fitness is associated with resistance and when insecticides are no longer in use, susceptibility is restored. To test this hypothesis in the laboratory, we characterized the resistance profile of a pyrethroid resistant *Ae. aegypti* strain from Mexico (V_{F1}), then we tracked the pyrethroid susceptibility during 27 generations in absence of insecticides (V_{SUS}). In parallel, we maintained a permethrin resistant strain by artificial selection (V_{PERM}). By the 27th generation, V_{SUS} resistance ratio (RR) to permethrin declined from 55-fold to 2.4-fold and deltamethrin declined from 73 to 1.24-fold. Malathion RR was maintained at 2-fold. Chlorpyrifos RR declined from 6.8 to 0.85-fold whereas temephos declined from 21 to 1.8-fold. Knockdown-resistance mutations at the VGSC declined from 0.9 to 0.12. By comparing the exomes of the 27^{th} generation of V_{SUS} and V_{PERM}, we identified the serine/arginine protein, ovochymase-2|polyserase-2 and transmembrane serine protease 9 with high association values in chromosome 1. Insecticide detoxification genes included the glutathione S-transferase theta-1 and cytochrome CYP12F8. In chromosome 2, we identified a general odorant-binding protein 67, coenzyme Q-binding protein and superoxide dismutase. In chromosome 3, the mitochondrial genome maintenance exonuclease, angio-associated migratory cell protein, VGSC, CYP6AK1 and carboxy/choline esterase CCEunk1O differed significantly among strains. Further research will elucidate the functional role of these genes in conferring permethrin resistance.

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VECTOR COMPETENCE AND IMMUNE RESPONSE IN PYRETHROID-RESISTANT *AEDES AEGYPTI* FOR DENV-2 INFECTION

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The development of resistance to insecticides in *Aedes aegyti* prevents effective control of their field populations. Depending on their resistance levels and different mechanisms it is expected to affect the interaction between mosquitoes and the pathogens they transmit. In this study we investigated whether resistance to pyrethorids in *Ae. aegypti* has an effect on its vector competence and immune response to DENV-2. High levels of esterases and MFO enzymes, as well as kdr mutations (Ile 1016 and Cys 1534) were present in two field mosquito populations from Tapachula, Mexico, compared to the New Orleans susceptible strain. The field mosquitoes and the laboratory colony were infected with DENV-2. Viral load detection was performed in infected mosquito excreta at 2, 7 and 14 days post infection (dpi), as well as the detection of immune response markers using qPCR at 21 dpi. The statistical analysis indicated that the mosquitoes from one resistant field colony were more susceptible to viral infection in addition to presenting a lower expression of immune response markers. While the other resistant field colony presented a lower susceptibility to infection and a higher expression of immune markers. Our results indicated that these insecticide resistance mechanisms could potentially affect susceptibility to VDEN-2 infection. In addition to highlighting the importance of understanding the interaction of resistance mechanisms in the vector competence of *Ae. aegypti* to evaluate the possible consequences in the transmission of disease-causing pathogens in mosquitoes that survive the control methods commonly used in public health.

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A SHUT-DOWN IN EXPRESSION OF A MALE-SPECIFIC AMINOPEPTIDASE IMPEDES MALE REPRODUCTIVE SUCCESS OF THE MOSQUITO *CULEX PIPIENS*

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Understanding the developmental processes of male and female mosquitoes provides important information for sterile insect release programs and its importance for improving vector control strategies. However, little is known about the molecular functions of male accessory glands in this species. After using RNA-seq and qRT-PCR analysis to identify sex-specific genes during pupal and adult stages of the mosquito *Culex pipiens*, we then examined male accessory gland tissues of adult male mosquitoes using RNA-seq and qRT-PCR analysis to narrow down candidate genes related to the functions of male reproductive processes in this species, where relevant male-specific genes may be the most concentrated. RNAi knockdown of the male-specific gene aminopeptidase (CPIJ003539) was then performed to show the functional role in the male accessory glands in *Cx. pipiens*. Observations showed clear differences in knockdown tissue under light microscopy. In-cage fertility assays were also performed to assess fertility and fecundity of knock-downed *Cx. pipiens* males. At two days after first copulation, females were collected and dissected to quantify sperm insemination rate in their spermatheca. The percentage of sperm in the spermatheca was recorded after dissection to assess significant differences in insemination rate between knockdown versus wild type *Cx. pipiens* males.

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DIAPAUSE-SPECIFIC GENE EXPRESSION IN THE FAT BODY OF THE MOSQUITO *CULEX PIPIENS*

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Northern house mosquito *Culex pipiens* is a major disease vector for West Nile virus that enter mosquito diapause during winter to survive inimical conditions by inducing a series of unique diapause phenotypes such as stress tolerance, lipid accumulation, and extended longevity. Forkhead transcription factor (Foxo) has been identified as the master regulator of the diapause program in *Cx. pipiens*. Foxo protein is highly abundant in the fat body in diapausing females. Since the fat body plays a crucial role in the storage and release of nutrients, synthesis of hemolymph proteins, and cross-talk with the endocrine system, the fat body-specific genes play a key role in the diapause program in this species. Although gene expression profiles have been studied in diapausing and non-diapausing mosquitoes, tissue-specific transcriptomic profiling has not been done to study the formation of diverse diapause phenotypes in *Cx. pipiens*. Here, we use RNA sequencing to contrast gene expression profiles between non-diapause and diapause to identify transcriptional changes specific to the fat body of *Cx. pipiens*. Functional annotation of upregulated genes in diapausing mosquito fat body identified genes related to carbohydrate metabolism, pleckstrin homology domain, immunity, and cytoskeletal proteins. Quantitative real-time PCR validation of candidate genes from

RNA-seq analysis is used to verify the upregulation of these genes in the diapausing condition. Our findings provide promising insights into the discovery of potential regulators during diapause in *Cx. pipiens*.

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RAPID EVOLUTION OF TRANSCRIPTION REGULATION BETWEEN *ANOPHELES GAMBIAE* COMPLEX MEMBER SPECIES IMPACTS HYBRID STERILITY AND INTROGRESSION

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A major goal in evolutionary biology is to understand how genetic variation contributes to phenotypic variation in a natural context. While variation in complex traits has been mapped to quantitative trait loci, individual genes, amino acid substitutions, or *cis*-regulatory variants, our understanding of how most complex traits are regulated by interacting gene networks remains incomplete. Our ability to understand epistatic interactions between loci is hampered by an incomplete knowledge of standing genetic variation within populations and genetic variation that segregates between species. Gene expression differences between malaria vectors impact their behaviors, physiologies, and capacity to transmit malaria to humans. *Cis*-regulatory elements (CREs) and *trans*-acting factors (TAFs) interact to modulate the expression of their target genes. As species diverge, selection acts to fix genetic variation in CREs and TAFs to modulate gene transcription to selectively advantageous levels. In this study we compare allele-specific expression of *Anopheles gambiae* species complex F1 hybrids to pure species and quantify gene expression divergence in *cis*- and *trans*-. We integrate these results into a QTL analysis of hybrid female sterility between two *An. gambiae* complex member species and highlight putative sterility loci which serve as barriers to introgression between these important malaria vectors.

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ASSESSING THE ROLE OF FAMILY-LEVEL VARIATION AND HEAT SHOCK GENE EXPRESSION IN THE THERMAL STRESS RESPONSE OF THE MOSQUITO *AEDES AEGYPTI*

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Changes in global climate, which include, higher temperatures and more frequent extreme thermal events, are expected to cause dramatic shifts in the distributions of infectious diseases. The mosquito *Aedes aegypti* is the primary vector of many human disease-causing viruses worldwide, and its geographic range is expanding, in part, due to changing climate. The capacity for this species to respond adaptively to change will be a key component determining its success in warming environments. It is not clear how much heritable genetic variation in the mosquito may affect the upper thermal limits of populations over the long term. Nor are the physiological response underpinning thermal tolerance well understood. To cope with thermal stress, in the short term, cells induce a plastic response referred to as the Heat Shock Response (HSR). Heat Shock Proteins characterize part of the HSR, and the contribution of these thermotolerance genes to the variation seen in response to thermal stress remains unclear. Using a high throughput physiological 'knockdown' assay, we investigated mosquito thermal tolerance in the framework of a family-based breeding design, with the goal of characterizing the role of genetic variation for the trait. While families representing the extreme ends of the distribution differed in their knockdown time, the trait did not exhibit significant heritability. We then explored whether siblings in the families representing the extremes in performance for knockdown time differed in their heat shock response, as assayed via the expression of multiple Heat Shock Protein genes (*HSP's* 26, 83, 70). We discovered that after exposure to heat stress, families with higher thermal tolerance demonstrated less expression of two of their *HSP* genes than those from families with a low resistance to heat. This pattern suggests that other mechanisms of heat tolerance may be more important than *HSP's*, and that increased expression may be a sign of poor adaptation to heat stress. Dissecting the genetic mechanisms that underpin thermal tolerance is key to assessing the future impact that climate change will have on mosquito-borne disease transmission.

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RNA-SEQ-POP: EXPLOITING THE SEQUENCE IN RNA-SEQ - A *SNAKEMAKE* WORKFLOW REVEALS PATTERNS OF INSECTICIDE RESISTANCE IN *ANOPHELES GAMBIAE*

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The majority of transcriptomic studies primarily focus on differential gene expression, not making full use of the underlying sequence data, and often, are not reproducible. Here, we present a scalable *snakemake* workflow, *RNA-Seq-Pop*, which comprehensively analyses RNA-Sequencing data in a reproducible manner, performing quality control and differential expression analyses, as well as calling genomic variants and generating a range of useful statistics. We demonstrate the utility of the workflow by investigating pyrethroid-resistance in *Anopheles gambiae,* from Busia, Uganda, that underwent four generations of deltamethrin selections. We provide additional modules specifically of interest for *An. gambiae s.l.*

The workflow reports allele frequencies of variants of interest, detecting a dramatic shift in frequency of *VGSC*-995S (26→100%) and *Gste2*-119V (11→53%) during insecticide selections. *RNA-Seq-Pop* summarises genetic diversity, capturing effects of inbreeding, and estimates regions of the genome under selection, able to detect selective sweep signals over known insecticide resistance loci, such as the VGSC. *RNA-Seq-Pop* can estimate recent ancestry within the gambiae complex; we show that the reference *An. gambiae* Kisumu strain, contains a large degree of *An. coluzzii* ancestry on the autosomes. The workflow can also determine the karyotype of common chromosomal inversions - we show that the 2La chromosomal inversion rose in frequency from 33 to 86% in the Busia strain. The workflow is available here: https://github.com/sanjaynagi/rna-seq-pop. *RNA-Seq-Pop* is designed for ease-of-use, and does not require programming skills to configure and run. We hope that the workflow will be a useful tool to facilitate reproducible, comprehensive transcriptomic studies both in *An. gambiae*, and across other taxa.

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YEAST INTERFERING RNA LARVICIDES FACILITATE SCALED REARING AND SEX-SEPARATION OF ADULT MALE *AEDES, ANOPHELES,* AND *CULEX* SPP. MOSQUITOES

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Several emerging population-based mosquito control technologies, such as the sterile insect technique (SIT) and incompatible insect technique (IIT), will benefit from the establishment of effective and affordable sex-sorting methods in multiple species of mosquitoes. Small interfering RNA- (siRNA-) based screens conducted in *Aedes aegypti* larvae revealed multiple genes that are required for survival of female larvae or the development of female-specific traits. Several of the siRNAs identified significantly increased male:female sex ratios by causing female larval death, while other siRNAs led to higher than expected numbers of adult males at the expense of females. A number of the genes identified in the *A. aegypti* screen are well conserved in multiple species of Diptera, including vector mosquitoes. Silencing orthologs of these genes in other mosquitoes, including *Aedes albopictus, Anopheles gambiae, Culex pipiens,* and *Culex quinquefasciatus,* resulted in significantly increased adult male:female ratios. Larval consumption of *Saccharomyces cerevisiae* (yeast) strains engineered to express interfering RNA corresponding to these genes results in increased 5 male: 1 female ratios in surviving

adults. Incorporation of the yeast larvicides into mass rearing protocols for culturing each species of mosquito is facilitating the scaled production of fit adult males, indicating that yeast RNAi larvicides could potentially benefit mosquito population control programs that require mass male releases. Initial efforts to scale yeast fermentation and drying have been successful and are being further expanded to facilitate the global distribution of this technology to support mosquito control programs worldwide. These efforts, the putative functions of the genes identified in these screens, and the implications of these findings for the study of mosquito sex chromosome evolution will be discussed.

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A ZONE OF INHIBITION ASSAY TO SCREEN FOR HUMORAL ANTIMICROBIAL ACTIVITY IN *ANOPHELES GAMBIAE* HEMOLYMPH

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In insects, antibacterial immunity largely depends on the activation of signaling pathways leading to the production of humoral immune factors, such as antimicrobial peptides (AMPs). The transcription of innate immunity genes encoding for AMPs is highly dependent on several signaling cascade pathways, such as the Toll pathway. In mosquitoes, AMPs hold special interest as their upregulation limits the growth of variety of mosquito-borne pathogens, including malaria parasites. However, the regulation and identification of humoral immune factors regulating AMPs in mosquitoes remain mostly elusive, largely due to the lack of convenient assays. Here, we establish a zone of inhibition assay (ZOI) coupled with RNAi to identify the contribution of AMPs and components of the Toll pathway to humoral antimicrobial activity of *Anopheles gambiae* hemolymph. With this assay, we show that *Micrococcus luteus* challenge induces antimicrobial activity in the adult female mosquito hemolymph by increasing the ZOI against *M. luteus* six-fold, an increase that is solely dependent on Defensin 1. Moreover, by silencing *CACTUS*, *REL1* and *MyD88* we demonstrate that *CACT* kd induces antimicrobial activity in the mosquito hemolymph, whereas the antimicrobial activity in *REL1* kd and *MyD88* kd is reduced after challenge, formally establishing a role of *MyD88* upstream of *CACT* in antimicrobial immunity in *An. gambiae*. In addition, we establish that while injection of dsRNA in itself does not increase the ZOI, the injury itself functions as a priming event for future bacterial challenges. Together, our results establish ZOI assays as a scalable medium throughput assay to identify components of the humoral immune system and their regulation in this important mosquito vector species.

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IDENTIFICATION OF CYCLE TARGETS THAT CONTRIBUTE DIVERSE FEATURES OF CIRCADIAN RHYTHMS IN THE MOSQUITO *CULEX PIPIENS*

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Culex pipiens demonstrates robust circadian rhythms in adult eclosion, flight activity, mating and development. These rhythmic patterns are believed to be controlled by the functional endogenous light-entrainable circadian clock comprising positive and negative regulators that works in a transcription-translation feedback loop. Moreover, these mosquitoes undergo seasonal diapause in response to the short photoperiod of late summer or early fall. However, the exact genetic and cellular mechanism behind the clock gene-mediated activity pattern and developmental switching to diapause still need to be completely unraveled. To determine the possible linkage between clock genes and downstream processes, we used ChIP-sequencing to identify the direct targets of one of the core clock proteins, Cycle (CYC). The nearest genes corresponding to the peaks within the 1Kb upstream of the transcription start site in promoter with the predicted binding site, E box element (CACGTG), were extracted for each binding site, resulting in a dataset comprising the target genes possibly regulated by CYC. The top five hundred candidates with the highest fold enrichment were prioritized for the functional relevance assessment and validation. Genes related to different processes, including insect hormone synthesis, and feeding behavior regulation, were selected and tested. ChIP-quantitative PCR and quantitative real-time PCR validated ten candidate genes related to the behaviors mentioned above. These genes showed a significantly high expression in dawn compared to dusk in accordance with the expression pattern of *cyc* mRNA level and are thus strong candidates for mediating the circadian rhythmicity.

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A NEW DATABASE OF STAKEHOLDER AND PUBLIC ENGAGEMENT EFFORTS FOR BIO-CONTROL TECHNOLOGIES FOR CONTROLLING VECTOR BORNE DISEASES

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As research and development of biotechnologies for controlling vector borne disease advance, there is a need for community, public, and stakeholder engagement to inform ethical and successful research and development of these technologies. The effective and sufficient engagement is especially important for genetic bio-control technologies that involve mass releases of modified organisms, where potential risks and benefits are likely to spread past local circumstances and initial jurisdictions. While there are many examples of efforts to engage stakeholders in research and implementation of these technologies, the available examples are scattered geographically, and across different technologies and technology-developmental phases. This makes it difficult to learn from past efforts when assessing needs and opportunities in new contexts. We compiled documented examples of stakeholder, community and public engagement efforts for bio-control technologies for the control of vector borne diseases and developed a database to catalogue this information. This database organizes examples of past engagement activities which can be searched and sorted by characteristics such as location, technology, development phase, or purpose of engagement. The database will allow interested parties such as technology developers, vector control and public health specialists, regulatory and government officials, and funders to learn from past engagement efforts and identify opportunities for future work in different contexts.

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EXPERTS INSIGHTS ON THE ROLE OF STAKEHOLDER ENGAGEMENT IN DECISION MAKING IN RESEARCH AND IMPLEMENTATION OF GENE DRIVE TECHNOLOGIES

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Bio-control tools such as gene drives have an enormous potential to address some of the world's major public health threats. However, concerns and uncertainty surrounding these technologies have led to increasing calls to ensure sufficient and effective community and stakeholder engagement. This study aimed to explore insights and recommendations from key stakeholders on how community and stakeholder engagement (CSE) could be fed into decision-making for gene drive research and development. In-depth interviews (n=37) were conducted with gene drive developers, vector control specialists, and policy contributors. Discussions were centered around how CSE can be used to build partnerships and facilitate knowledge-sharing in different

contexts where these technologies will likely be deployed. Participants framed the role of CSE in informing decisions in different ways. Gene drive developers based their insights on how to develop products that are both effective and acceptable, and how CSE could lead to successful product development and deployment for research. On the other hand, vector control specialists focused their discussions on how the technologies could fit within current vector control contexts and complement ongoing efforts. Differently, policy contributors focused on how to build a sustainable process to ensure local ownership and sustainability of the technologies past the project timelines. This study indicates varying priorities and expectations among the different stakeholders based on their role and interest in disease control efforts. The findings point to the need for effective strategies for coordinating these priorities in order to develop gene drive technologies that are not only effective, but also meet the community needs and integrate with the ongoing local vector control efforts.

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AEDES AEGYPTI PHOSPHOLIPASE-C MUTANT LACKS LIGHT-EVOKED BEHAVIORAL RESPONSES

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The behaviors responsible for mosquito disease vectoring capabilities are driven by multiple sensory inputs, notably olfaction, vision, and heat detection. The Aedes aegypti β-class phospholipase C (PLCβ) is the ortholog of Drosophila NORPA PLCβ essential for light detection in both larval and adult photoreceptors. To study visual contributions to Aedes behaviors, we created CRISPR-CAS9 induced mutations within the Aedes aegypti PLCβ gene. A homozygous viable Aedes mutant, designated norpACAT, possesses a nonsense point mutation and two small deletions within the CRISPR-targeted region of the gene. The predicted 124 kD protein PLCβ was readily detected in protein blots of wild type head extracts but not norpACAT head extracts. In histological analysis of retinal tissue, PLCβ protein was detected in the rhabdomeres of wild type photoreceptor cells, the expected location, but not anywhere in the retina of norpACAT. Despite the absence of PLCβ protein in norpACAT, electroretinography detected a light-evoked electrical response in these animals. This response was diminished, being notably slow to respond and slow to recover from a light stimulus relative to the wild type control. To determine if the norpACAT mutant is deficient in visual responses, we developed assays to detect larval light-triggered startle responses, larval light-avoidance behavior, and adult light-triggered startle responses. Wild type mosquitoes, but not the norpACAT mutant, respond to the visual cues present in each of these behavior tests. The norpACAT mutant shows normal circadian activity and locomotion, demonstrating that the absence of immediate light-triggered responses is not due to general lethargy. Our results demonstrate that the norpACAT mutant is defective in acquisition of visual information and therefore provides a genetic model capable of discerning the role of vision in complex mosquito behaviors.

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GENETIC DIVERSITY AND POPULATION STRUCTURE OF *ANOPHELES FUNESTUS* BASED ON MITOCHONDRIAL DNA MARKERS (MTDNA-COI AND MTDNA-COII) IN WESTERN KENYA

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In this study, the mitochondrial markers, cytochrome oxidase subunits I (mtDNA-COI) and II genes (mtDNA-COII) were used to assess the genetic structure and diversity of *Anopheles funestus*, a very important malaria vector in Africa, that adapt and colonise different ecological niches in western Kenya. Adult mosquitoes were collected using mechanical aspirators in four sites (Bungoma, Port Victoria, Kombewa and Migori) across four counties in western Kenya. All samples were morphologically identified as *An. funestus s.l.* The *COI* and *COII* genes were amplified, sequenced and analyzed to identify sibling species and genetic structure of the *Anopheles funestus* population. Hundred and Sixty (160) *An. funestus s l* specimens (40 from each site) were used for species identification, genetic structure and gene flow. The *COI* gene showed that *An. funestus* constitutes 96% of all the specimens identified. Other members of the *An. funestus* complex identified includes *Anopheles funestus-like Anopheles longipalpis, Anopheles parensis* and *Anopheles vaneedeni*.Both genes exhibit high haplotype diversity (*COI*, Hd=0.99; *COII*, Hd=0.98) but low nucleotide diversity (*COI*, Π=0.03; *COII*, Π=0.02). A minimal level of genetic differentiation was observed between Port Victoria and Bungoma (F_{ST} = 0.01512, P= 0.00000), Port Victoria and Kombewa (F_{ST} = 0.03135, P=0.00000), Migori and Kombewa (F_{ST} = 0.03568, P=0.000), Migori and Bungoma (F_{ST} = 0.01621, P=0.01802) but no genetic differentiation between Port Victoria and Migori (F_{ST} = 0.00319, P= 0.180) and Kombewa and Bungoma (F_{ST} = 0.01121, P=0.0900). The high gene flow (Nm) was between Port Victoria and Migori (Nm=81.79) and low gene flow was observed between Migori and Kombewa (Nm=6.17). Neutrality tests suggest population expansion of *Anopheles funestus* with an excess of low-frequency variation. This is the first report on *Anopheles funestus-like* in western Kenya. No barrier to gene flow was observed in *Anopheles funestus* population. Population expansion suggests the high adaptability of this species.

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DETERMINING THE SPECIFICITY AND SELECTIVITY OF FLAVIVIRUS TARGET SEQUENCES BY NS3 PROTEASES IN *AEDES AEGYPTI* CELLS USING QUENCHED-GFP

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Aedes aegypti transmits viruses such as dengue, Zika, and yellow fever, all members of the Flavivirus genus. The flavivirus genome is a single stranded positive sense RNA that is translated as one polyprotein and cleaved by both cellular proteases and the virally encoded NS3 protease. We seek to exploit NS3 by developing a transgene that will result in the virus-induced death of *Ae. aegypti*. Our goal is to express an insect specific neurotoxin in the mosquito that is tethered to the endoplasmic reticulum via an NS3 cleavage sequence, only to be released by the protease in those insects that are systemically infected. In this study, our goal is to determine the cleavage efficiency of target sequences by flavivirus proteases in *Ae. aegypti* cells. The most widely recognized sequence will be incorporated into our final transgene construct. We designed a series of reporter plasmids that express a quenched or non-fluorescing eGFP. DENV2 derived NS3 target sequences were inserted at the eGFP-QP (quenching peptide) junction. Transfection of the reporters into A20 cells followed by fluorescent imaging showed effective suppression of eGFP fluorescence when fused to the quenching peptide. Expression of the protease via plasmid transfection was confirmed by Western blot. We are presently assessing the effect of introducing the protease into cells expressing the reporters and its ability to cleave eight target sequences from the DENV2 polyprotein. Our expectation is that when the protease is introduced either by viral infection or plasmid-based expression, the target sequence will be cleaved and eGFP released, leading to a measurable reversal of the quenching phenotype proportionate to the amount of cleavage occurring. If successful, we will be able observe and quantitate NS3 activity in vivo,

rendering this an effective method for evaluating cleavage by NS3 derived from multiple viruses. This should allow us to develop a transgene with the potential to kill mosquitos infected with any flavivirus.

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THE POPULATION GENOMICS OF AN. DIRUS AND AN. BAIMAII IN CAMBODIA, THAILAND, AND BANGLADESH

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Forest dwelling mosquitoes in the *An. dirus* complex are some of the most important malaria vectors in Southeast Asia. Whole genome sequencing can provide important insights into the unique malaria transmission dynamics in this region, where many malaria vectors feed and rest outdoors. Wild collected female specimens of *An. dirus* [A] and *An. baimaii* (formerly *An. dirus* species D) from Bangladesh (n=47), Thailand (n=223), and Cambodia (n= 264), and were sequenced using Illumina deep whole genome sequencing. We used PCA of these whole genomes to visualize the population structure of these specimens and define unique populations of both *An. dirus A* and *An. baimaii* across collection sites. We used Fst scans in 1000 SNP windows across contigs representing 80% of the *An. dirus* genome to look for signals of increased differentiation and potential signals of selection in each population comparison. We describe the underlying genetic diversity and divergence of these populations and investigated the genetic variation in genes known to be involved in insecticide resistance. Understanding the population structure, patterns of evolutionary selection, and epidemiology of insecticide resistance within *An. dirus* will enable us to inform malaria control in this region of extremely complex outdoor malaria transmission. These data will be publicly available as part of the MalariaGEN Vector Observatory, an open access resource of genome sequence data.

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CRYOPRESERVATION OF *ANOPHELES GAMBIAE* AND GENETICALLY MODIFIED STRAINS OF *ANOPHELES STEPHENSI*

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Maintenance of multiple strains of genetically modified mosquitoes is expensive and fraught with issues such as cross-contamination, genetic drift or even complete loss of lines due to lack of resources or catastrophic events such as equipment failure or colony crashes. It is a given that at some point after a strain is discarded, it will be needed again, and the cost of recreating that same strain re-incurred. For years, the mosquito field has been crying out for a methodology that will allow curation biobanks of *Anopheles* mosquitoes without the need for culture. Sanaria has developed a unique method for the cryopreservation of *Anopheles* eggs, which provides such a breakthrough technology for the mosquito research field. We have used this technology to cryopreserve six strains of genetically modified *A. stephensi*. In work silencing mosquito immune genes, lines with LRIM1, TEP1 or LL3 genes knocked by CRISPR/Cas9 methodology were each revived after cryopreservation. The LRIM1 knock out line was particularly fragile due to its immune compromised status, and while recovery from liquid nitrogen vapor phase was poor, we could still re-establish the line which was confirmed by molecular characterization. We have similarly cryopreserved *A. stephensi* strains modified with a Y-chromosome linked lox docking site, an effector line harboring EGFP- dnRel2, and a line expressing BziP-rtTA created by Piggyback transposon-mediated insertion. For these strains and the successful cryopreservation of *A. gambiae*, we have successfully scaled down the cryopreservation method to account for the reduced needs and sometimes limited numbers of eggs available from mosquitoes that are not as fecund or robust as wild types.

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MICROBIAL CONTRIBUTION OF RNAS IN MOSQUITOES

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RNA Interference in mosquitoes plays vital roles in endogenous gene regulation (using micro, miRNAs), antiviral immunity (using short interfering, siRNAs) and regulation of genomic parasites (using Piwi-interacting or piRNAs). siRNAs, in particular, are usually derived from dsRNA present during viral infection, however in a survey of small RNAs in *Anopheles stephensi*, we identified siRNAs with sequence homology to a bacterial plasmid. It is possible that these siRNAs originate from bacteria, but their presence is puzzling, since these siRNAs have the size and chemistry of DICER-dependent processing, but bacteria do not have a DICER homolog.To investigate the origin of these siRNAs, we will perform several experiments. We plan to rear mosquitoes with and without antibiotic treatment. By using the antibiotic treatment, we will be able to completely deplete the organism of the bacteria. We, then, plan to isolate siRNAs from adult mosquitoes from both groups. If siRNAs disappear from the aseptically reared mosquitoes, this will support bacterial origin. However, if they appear on the aseptically reared mosquitoes, it will disprove our hypothesis of bacterial origin of siRNAs.

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ANTI-AEDES NEST1 AND AGBR1 SALIVARY PROTEIN ANTIBODIES AND DENGUE SYMPTOMS

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Dengue fever, caused by dengue virus (DENV) currently threatens about half of the world's population. DENV is transmitted to the vertebrate host through the bite of an Aedes female mosquito while taking a blood meal. During this process, salivary proteins are introduced in the host skin and blood to facilitate blood acquisition. Such salivary proteins modulate skin and systemic immune responses. Among immunogenic salivary proteins, AgBR1, and NeSt1 have shown modulatory properties in Zika and West Nile virus infections. The objective of this study was evaluating whether human IgG antibodies against these proteins are associated with different clinical presentation of infections with DENV. For this, we tested 253 serum samples from participants residents of a dengue fever endemic area in Colombia. Our preliminary results showed that DENV infected volunteers presented lower IgG antibody titers against AgBR1 than the healthy controls. We also found that the levels of IgG anti-salivary proteins were associated with the risk of developing certain dengue symptoms which could be an indicator of disease progression to severity.

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EVALUATION OF ENVIRONMENTAL AND ENTOMOLOGIC LA CROSSE VIRUS RISK FACTORS IN WESTERN NORTH CAROLINA

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La Crosse Virus (LACV) is the most prevalent arboviral cause of encephalitis in children in the United States. In North Carolina, La Crosse Encephalitis (LACE) is the most commonly-reported arboviral disease in humans. Epidemiologic evidence suggests LACV risk is highly focal, perhaps persisting at the residential level. From June through September 2021, we collected *Aedes eggs* and resting adult mosquitoes at 6 residential LACE case/non-case residential household pairs in order to: a) compare LACV infection rates in mosquitoes, b) compare known LACV environmental and entomologic risk factors, and c) compare LACV infection rates and risk factors between case and non-case residences. A total of 97,982 *Aedes eggs* were collected over 5,761 trap days at the 12 sites. On average, there were more eggs collected at LACV case sites (20.8 eggs/trap/day) than at non-case sites (12.9 eggs/trap/day). We reared 27,677 mosquitoes (28.2% of the total eggs collected), held adults for 7 days, and pooled them for virus testing. The vast majority (84%) of reared adults were *Ae. triseriatus* (n=23,236), the native and primary LACV vector. *Aedes japonicus* (11%) and *Ae. albopictus* (5%), invasive secondary LACV vectors, accounted for the remaining collections; a small number (<100) of *Ae. hendersoni* were identified microscopically as larvae. Resting adults were collected via large bore aspirator during the study period resulting in a minimum of 11 collections at each paired site. Our results indicate that *Ae. triseriatus* remains highly abundant relative to invasive vectors, and includes evidence of residential-level LACV transovarial transmission. Multivariate analyses to assess site-specific environmental and entomologic risk factors will be presented.

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AEDES AEGYPTI THERMAL PREFERENCE IN TEMPERATURES AND RELATIVE HUMIDITY RELEVANT TO THE SOUTHWESTERN UNITED STATES

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Mosquitoes are ectotherms that depend on temperature for their survival. While many studies have focused on how temperature affects critical life history traits of disease relevant mosquito species, few studies have focused on the actual temperatures at which *Aedes aegypti* mosquito species might be found, and furthermore, what their preferred optimal temperature preferences are. In this study, we investigate *Aedes aegypti* temperature preference using young and old females both blood-fed and unblood-fed as well as often overlooked young and old males. Additionally, in consideration of the potential impact of humidity on preference, all studies were conducted at 40% relative humidity. Temperature preferences were investigated using a thermal gradient plate and an acrylic channel, into which *Aedes aegypti* were individually placed. The temperature gradient ranged between 17°C - 47°C. The channel was designed to be 4 millimeters high so that mosquitoes had no choice except to physically walk along the temperature gradient and rest at the temperature they preferred. We found that all mosquitoes avoided hot temperatures above 40°C, and exhibited preferences for cooler temperatures. However, male mosquitoes tended to prefer the coolest temperatures and rest closer to 17°C, while the female mosquitoes showed a preference for slightly warmer temperatures, resting around 20°C - 25°C. These results can be used to better understand where in specific microclimates we can expect to find *Aedes aegypti* resting in order to carry out more targeted control efforts and to build more accurate arbovirus forecasting models.

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HOW MOSQUITOES INTERACT WITH VECTOR CONTROL TOOLS - BEHAVIORAL ANALYSES USING 3D VIDEO TRACKING

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Vector control has substantially contributed to the reduction of the malaria disease burden and is key in the prevention of other mosquito-borne infectious diseases, such as dengue or lymphatic filariases. However, the development of resistance to insecticide-based interventions and outdoor biting mosquitoes, that may not be targeted with conventional insecticide-based approaches, pose a challenge, requiring the development of new and improvement of existing tools. The development and evaluation of tools in vector control still relies on simple endpoints such as the number of dead or blood-fed mosquitoes in simplified bioassays. Yet, these assays and endpoints provide little or no information about the behavioural search or avoidance strategies employed by mosquitoes. To improve vector control products, knowledge of how mosquitoes use chemical, visual, acoustic or mechanosensory cues and interact with vector control tools is essential. To quantify mosquito behaviour we have built different set-ups in combination with an infrared 3D video tracking system that records the flight paths of mosquitoes in real time as they interact with vector control products. We will present and discuss the experimental laboratory set-ups and results from the behavioural analysis of testing topical repellents in the arm-in-cage test, measuring the efficacy of long-lasting insecticidal nets in the World Health Organization tunnel assay and evaluating the attractiveness of attractive toxic sugar baits.

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RIFT VALLEY FEVER VIRUS REASSORTMENT IN THE CULEX TARSALIS MOSQUITO VECTOR

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Rift Valley Fever Virus (RVFV; order *Bunyavirales*; family *Phenuiviridae*) is a mosquito-borne pathogen of humans and ruminants. While historical transmission is endemic to Africa, co-circulating genotypes have been detected outside this geographic range, posing risk to naïve populations as well as potential for formation of reassortant viral genotypes. Indeed, RVFV reassortant genotypes have been isolated from naturally-infected humans, cattle, and mosquitoes. We have previously shown that reassortment occurs in co-infected vertebrates at low levels. However, data regarding reassortment in mosquitoes and impact on transmission cycles is limited. We hypothesized that if RVFV-infected mosquitoes are co-infected with RVFV then reassortment with occur with high frequency. We utilized the laboratory-competent mosquito *Cx. tarsalis* to query the reassortant potential of an attenuated RVFV vaccine (MP-12) and two wild-type virulent (SA01-1322 or KEN128B-15) strains *in vitro* and *in vivo*. Reassortment was determined via an established genotyping assay. Infection in CxTxR2 *Cx. tarsalis* cells demonstrated that reassortment between MP-12 and KEN128B-15, or KEN128B-15 and SA01-1322, represented a minority of viral plaques isolated (approximately 2%) at 3 days post-infection (dpi). In co-infected *Cx. tarsalis* mosquitoes, at 14 dpi, reassortant viruses of MP-12 and KEN128B-15 in the midguts (MG) and salivary glands (SG) represented 80% and 60% of plaque isolates, respectively. Co-infection with KEN128B-15 and SA01-1322 resulted in 60% virus reassortants in the MG, and 2% recovered in SG. A majority of the reassortment was revealed to be comprised of M and S segments.

The S segment of WT strain KEN128B-15 and the M segment of vaccine strain MP-12 were preferentially represented among in the majority of reassortant genotypes. Future work endeavors to evaluate the phenotype, kinetics, and pathogenicity of the reassortant viruses. Results of these studies will provide key data regarding mechanisms and frequency of viral reassortment in order to evaluate risk and develop mitigations strategies.

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METAVIROME CHARACTERIZATION IN *ANOPHELES DARLINGI* FROM THREE DIFFERENT GEOGRAPHICAL REGIONS OF COLOMBIA

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Next-generation sequencing technologies have increased knowledge about the diversity and ubiquity of viruses in arthropod hosts; yet, there is a lack of knowledge in the composition of the neotropical anopheline virome. Thus, this work aimed to characterize the metavirome of *Anopheles darlingi* from Colombia. Mosquitoes were collected in the Bajo-Cauca (BAC), the Pacific (PAC), and the Amazonas (AM) regions. Mosquitoes were grouped into pools and RNA was extracted and sequenced by RNA-Seq Illumina. The *An. darlingi* reference genome (A darlingi v1) was used to map the reads to exclude mosquito transcripts whit Bowtie2. Transcripts were assembled using SPAdes and RNA virus-derived sequences were retrieved through a BLAST search against the Reference Viral Database. Also, a sensitive taxonomic classification of the reads using the Kaiju NCBI-nr+euk database was carried out to determine the read counts by viral family. Bray-Curtis dissimilarity (BC) was estimated from normalized datasets. From 357M PE-reads, 101700 were classified as of viral origin, distributed in 16 viral families and two unclassified groups. A high proportion of reads was assigned to unclassified-*Ortervirales* (52%), *Chuviridae* (10%) and *Baculoviridae* (8%). A similar viral composition was found in *An. darlingi* from all regions. Regarding the distribution of viral read counts by family, a high similarity was observed at the intra-region level (BC>0.84); and among regions, a greater similarity was observed between PAC and BAC (BC=0.74) than in BAC and PAC compared to AM (BC=0.41 and 0.43, respectively). Furthermore, seven RNA virus families were identified from virus-derived sequences. The similarity found in the *An. darlingi* virome between BAC and PAC and its difference with AM may be due to the Andes; this mountain range acts as a geographical barrier separating *An. darlingi* population from the northwest and southeast. Also, the differences may be due to environmental specific conditions in each region. This work contributes knowledge on the *Anopheles* virome composition and on the ubiquity of insect-specific viruses that could be used as biological control agents

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ANOPHELES GAMBIAE S.L. HOST PREFERENCES DURING RIMDAMAL II; A CLINICAL TRIAL FOR MALARIA CONTROL IN BURKINA FASO

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It is well known that mosquitoes have exhibited behavioral changes in response to control methods. Some of these behaviors include biting outdoors more frequently and biting during the day from the introduction of insecticide treated bed nets. RIMDAMAL II is a double-blind, cluster randomized trial in Burkina Faso designed to test whether repeated high-dose ivermectin mass drug administrations (MDAs), paired with seasonal malaria chemoprevention, can reduce childhood malaria incidence. In the context of this trial, we analyzed host preferences of An. gambiae s.l. in a subset of study clusters to determine whether this changed depending on cluster arm, across MDAs, or during the span of the two season intervention (summers of 2019-2020). Our working hypothesis was that mosquitoes from treated villages will change their feeding preferences (avoiding ivermectin), and the frequency of mosquitoes feeding on non-human hosts will increase. Bloodfed *Anopheles* mosquitoes (n=650) were collected from different households within six clusters (3 intervention and 3 control), and their abdomens were analyzed to identify the host species the mosquitoes had fed on prior to capture. Bloodmeal analysis of the engorged midguts was performed by PCR using primers for common hosts present in the area. *Anopheles* primarily fed on humans across all MDAs with no significant host species changes across time, although mixed bloodmeals (DNA from more than one host species), and bloodmeals from non-human host species were also present. Analysis of changes between arms will be tested after trial unblinding. The preliminary data suggest no shift to non-human hosts to avoid ivermectin. Further analyses are pending to determine if they might have avoided ivermectin by preferentially biting the non-treated humans in intervention clusters, or if more time may be necessary for mosquitoes to adapt and show behavioral changes to this intervention.

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UTILIZING A BITE DIARY APP IN A CITIZEN SCIENCE PROGRAM TO QUANTIFY HUMAN-MOSQUITO CONTACT RATE AND REDUCE MOSQUITO-BORNE DISEASE RISK

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Complex socio-environmental processes such as landscape change, economic inequality, human movement, and climate change are rapidly transforming mosquito-borne disease transmission dynamics globally. As a result, it is important that disease control efforts are informed of anthropogenic factors that drive mosquito-borne disease transmission. Unfortunately, a majority of current research and surveillance programs narrowly focus on the mosquito populations and overlook the critical human-mosquito contact dynamics that drive disease spread. To fill this gap, we broaden research and surveillance efforts to quantify human exposure to mosquito bites, and characterize the human behaviors that are key drivers of disease transmission. The shift in focus is facilitated by our novel development of focused bite surveys that allow us to quantify human-mosquito contact for the first time. Our pilot study used self-administered standardized survey instruments to assess human-mosquito contact rates in two study sites in southern Louisiana. The result showed that the human-mosquito contact levels were influenced both by the mosquito density and human behaviors, and a dengue virus transmission model demonstrated that the observed differences in the contact rates lead to differential virus transmission risk. Built on our experience, we designed a citizen science program that combines a prospective mobile app-based survey with an evidence-based education to estimate bite exposure rates, address how socio-environmental factors influence the dynamic of human-mosquito contact, and pioneer a sustainable

community-based mosquito control approach in Florida. We highlight the practicality of using mobile app-based surveys to investigate human-mosquito contact rate in relation to socio-economic factors. A renewed focus on human-mosquito contact dynamics contributed new insights into the mechanisms behind mosquito-borne disease emergence and guide future research directions that inform disease prevention and control.

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THE INSECT-SPECIFIC EILAT VIRUS CAUSES SUPERINFECTION EXCLUSION AGAINST WEST NILE VIRUS IN MOSQUITO CELLS

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West Nile virus (WNV) is a mosquito-borne pathogen that can cause febrile illness and fatal neurological disease in infected individuals. There is no vaccine or specific treatments available for WNV. WNV is prevalent worldwide, including in the United States of America (USA). *Culex* mosquito species predominantly transmit WNV, and in the USA, *Culex tarsalis* is a major WNV vector. Our data shows that *Culex tarsalis* is a competent vector for Eilat Virus (EILV), an insect-specific alphavirus. EILV cannot infect mammals and is a prime candidate to target pathogenic viruses in their mosquito vector. We tested the potential for EILV to modulate WNV replication *in vitro*. C6/36 cells were infected with EILV-eGFP at an MOI of 10. Three days post-EILV infection, EILV-infected C6/36 cells, and uninfected C6/36 cells were infected with WNV strain NY99 and 02-1956 at two MOIs (0.1 and 0.01), and WNV titers assayed at timepoints 0, 4,8, 12, 24, 48, 72, and 120 hours post-WNV infection. EILV significantly suppresses WNV 02-1956 titers at both MOIs at all tested time points. EILV suppressed WNV NY99 at MOI 0.01 at 24, 48, and 72 hours post-WNV infection but not at 96 hours post-WNV infection. However, WNV NY99 at MOI 0.1 was not suppressed by EILV at any time point. In conclusion, EILV causes superinfection exclusion against the unrelated flavivirus WNV, especially strain 02-1956. This effect is potentially due to resource depletion or induced immune responses triggered by EILV.

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LARVAL PERFORMANCE, BREEDING HABITAT PREFERENCE, AND INTERSPECIFIC COMPETITION BETWEEN AEDES ALBOPICTUS AND AEDES AEGYPTI IN MADAGASCAR

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In Madagascar, *Aedes aegypti* and *Aedes albopictus* are potential vectors of *Flavivirus* and *Alphavirus*. Historically, both species were found allopatric (*Ae. albopictus* abundant in eastern and highlands areas and *Ae. aegypti* in western and southern regions). Recent unpublished data showed an unexpected co-occurrence of these two species in all five bioclimatic domains, suggesting larval adaptation of both species to different larval sites and absence of larval interspecific competition. This study is the first attempt to evaluate the effect of larval habitat types on the emergence rate of both species and the occurrence of interspecific competition between them in Madagascar. In a first experiment, 30 first-instar larvae of *Ae. albopictus* and *Ae. aegypti* were placed separately in plastic containers, metallic containers, coconut shells or tires. In a second experiment, first-instar larvae of both species were transferred in a ratio of 15:15 into each habitat. Each container received 0.03g of rat cookies every two days. Each experiment was conducted simultaneously and replicated three times. The total number of emerged adults and the first day of appearance of adults were estimated by species in each habitat. Larvae from both species were able to develop in all habitats. Both species' emergence rate was unaffected by interspecific competition in plastic containers ($p = 0.279$), tires ($p = 0.328$) and coconut shells ($p = 0.095$). Competitive effects of *Ae. albopictus* on *Ae. aegypti* were observed only in metallic drums ($p = 0.049$). No significant difference was detected in the appearance of the first adult in the four habitats for *Ae. aegypti* [8.42 days (± 0.57), $p = 0.940$] and *Ae. albopictus* [7.75 days (± 0.54), $p = 0.242$]. These results showed the presence of ecological plasticity with stable coexistence in many container types, except in metallic containers. This may explain the large co-occurrence of these species in several areas of Madagascar, that might nevertheless be influenced by additional factors.

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MARK-RECAPTURE OF WEST NILE VIRUS VECTOR CULEX TARSALIS IN COLORADO, USA USING NOVEL DNA-LOADED NANOPOROUS PROTEIN CRYSTALS

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Mosquito mark-release-recapture (MMRR) studies provide essential information on mosquito dispersal patterns that inform vector control and arbovirus prevention strategies. Such insights into vector ecology are increasingly valuable as climate change alters distribution of arthropod vectors and associated pathogens, which remain a global threat to human health. Current MMRR tagging methods are limited by durability, effects on mosquito fitness, cost of labor or materials, and small number of distinguishable markers available. Recently, a cross-linked protein crystal was developed that readily uptakes and protects short strands of DNA. Consumption of these DNA-loaded crystals by larval *Culex tarsalis* does not affect mosquito survivorship, and the crystals persist in the mosquito from immature to adult stages. Here we describe a pilot implementation of a scalable mark-recapture field study in collaboration with existing vector surveillance and control networks in Colorado. Eighty-four protein crystal batches loaded with unique DNA barcodes were deployed at 12 known larval breeding sites for *Cx. tarsalis* and *Cx. pipiens*, the primary vectors for West Nile virus (WNV). Adult mosquitoes trapped as part of an existing WNV surveillance program were subsequently screened via PCR for crystal-protected DNA barcodes. We successfully recovered, amplified, and sequenced deployed DNA barcodes in adult mosquito pools, providing promising evidence for the use of DNA-loaded protein crystals as a marking method of larval habitats. Preparations for a larger scale field trial in the summer of 2022 are ongoing.

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CO-DETECTION OF *PLASMODIUM FALCIPARUM* IN CHILDREN HOSPITALIZED WITH DENGUE FEVER IN THE DOMINICAN REPUBLIC

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Hispaniola is the only remaining malaria-endemic region in the Caribbean. Cases of malaria and dengue in the Dominican Republic spiked in 2019, but their rates of co-detection are poorly characterized, especially in children. Our aim is to investigate the presence of *Plasmodium falciparum* in a cohort of children admitted with dengue fever and the differences in clinical presentation and outcomes. We performed a prospective, observational study during 2019 at the Hospital Infantil Dr. Robert Reid Cabral Hospital in Santo Domingo, Dominican Republic. Children with serological evidence of acute dengue were enrolled and blood samples were collected via dried blood spot using FTA cards to inactivate pathogens and preserve DNA. We used qPCR to detect the presence of *Plasmodium falciparum* DNA. Clinical and laboratory data were recorded from each child's hospitalization. Univariate analysis was performed to evaluate

the association between co-detection and clinical outcomes. The overall co-detection of dengue and malaria in our cohort was 1.4% (6/429). The median age was 4 years (IQR 1-7 years) in children with dengue and 5.5 years (IQR 4-6 years) in children with dengue-malaria. There were no significant differences in fever duration or presence of vomiting, abdominal pain, and rash between the groups. However, children with dengue-malaria were more likely to present with headache (50% vs 19%, p=0.053). Children with dengue-malaria were more likely to be admitted to the ICU (OR=6.79, 95%CI 1.18-39.23), and be classified with severe dengue (OR=2.61, 95%CI 0.47-14.60). Deaths were rare in this cohort (4 in children with dengue and 0 in children with dengue-malaria) which did not allow for comparison between groups. The co-detection of malaria and dengue in children was overall uncommon in our Dominican Republic cohort despite the rise in cases in 2019. Co-detection may be associated with a more severe clinical course and recognition of these cases may be important. Further epidemiological studies to characterize the risk of both pathogens as case numbers fluctuate will be important to better understand the dynamics of coinfections.

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THE IMPACT OF DEMOGRAPHIC TRANSITION AND SOCIO-ECONOMIC FACTORS ON DENGUE CIRCULATION IN BRAZIL, 2001-2020

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Since the mid-1950s, Brazil has experienced a demographic transition with observed declining birth rates and increasing life expectancy. At the same time, dengue viruses (DENV) became endemic with varied transmission across Federal Units. Building on previous observations, we assessed how demographic transition impacted the shift to dengue hyper-endemicity in Brazil. We used reported symptomatic and severe dengue case data at the Federal Unit level from 2001-2020 and a Bayesian catalytic model to estimate yearly changes in DENV transmission intensity and the age at which individuals are most at risk of secondary infection. We used general linear regression models to identify factors associated with changes in age of highest risk of secondary infection, including demographic, socioeconomic and climatic factors. Nationally, peak susceptibility to secondary infections decreased from age 51 (95% CI: 35-74) in 2001 to age 18 (95% CI: 8-54) in 2020 ($p<0.01$), with variability in risk across Federal Units. Units with decreasing age were associated with smaller population size ($p<0.01$), while units with increasing age were associated with longer life expectancy ($p<0.01$), and a non-linear increase in births ($p<0.01$). Changes in births suggest that Units are still undergoing demographic changes that may impact the rate at which younger individuals become susceptible to secondary infections. We also found signals of large dengue outbreaks in 2007 and 2015, coinciding with DENV-2 replacing DENV-3 and the introduction of Zika virus in Brazil, respectively. Shifts in estimated age of susceptibility to secondary infections suggest that the risk is becoming higher among younger age groups. Changes in life expectancy and birth rates were associated with the age of highest risk of secondary infection and suggest that demographic changes may be driving how population susceptibility changes over time. Though we have not evaluated the impact of serotype-specific immunity, these demographic factors will be key to understanding their impact on dengue periodicity and intensity.

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ARBOVIRUSES AS AN UNAPPRECIATED CAUSE OF NON-MALARIAL ACUTE FEBRILE ILLNESS IN WESTERN CAMEROON

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Acute febrile illness is a common problem managed by clinicians and health systems globally, particularly in the Tropics. In many regions, malaria is a leading and potentially deadly cause of fever; however, myriad alternative aetiologies exist. Identifying the cause of fever allows optimal management, but this depends on many factors including thorough knowledge of circulating infections. Arboviruses such as dengue cause fever and may be underdiagnosed in sub-Saharan Africa where malaria is a major focus. We examined cases of fever in western Cameroon that tested negative for malaria and found 13.5% (13/96) were due to dengue, with 75% (9/12) of these being dengue 2 infections. Two complete dengue 2 genomes were obtained and clustered closely to recent isolates from Senegal and Burkina Faso. The seroprevalence of dengue in this region was 24.8% (96/387). Neutralizing antibodies to dengue 2 were detected in all (15/15) seropositive samples tested. Chikungunya is an arthritogenic alphavirus that is transmitted by *Aedes* mosquitoes, the same principal vector as dengue. The seroprevalence for chikungunya was 15.7% (67/427), and being seropositive for one arbovirus was associated with being seropositive for the other ($[[\text{Unsupported Character - Symbol Font } \&\#935;]]^2=16.8$, $p<0.00005$). Interestingly, chikungunya did not cause a single case of fever in the 96 subjects tested. Taken together, these data indicate that *Aedes*-transmitted arboviruses are endemic in western Cameroon and are likely a common but underappreciated cause of febrile illness. This work supports the need for additional study of arboviruses in sub-Saharan Africa and efforts to improve diagnostic capacity, surveillance systems, and arbovirus prevention strategies.

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MOLECULAR EPIDEMIOLOGY OF TYPE 4 DENGUE VIRUS OUTBREAK IN PARAGUAY, 2019-2020

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Dengue virus type 4 (DENV-4) was first detected in Paraguay in 2012, and since that year, had persisted in the country as a non-predominant type. However, in 2019-2020, DENV-4 became predominant and caused an outbreak in Paraguay that spanned two waves: a smaller first wave in mid-2019 and a larger second wave between late 2019 and early 2020. We investigated the molecular epidemiology of the DENV-4 outbreak to understand its origin and evolution. Patients with suspected dengue were enrolled in a cross-sectional study between January 2019 and March 2020 from two clinical facilities in Asunción, Paraguay. We selected DENV-4 positive samples for complete viral genome sequencing and phylogenetic analysis. Epidemiologic metadata were collected through

a survey. We sequenced complete DENV-4 genomes from 61 patients, largely concentrated in the Greater Asunción metropolitan area (56/61; 92%). Phylogenetic analysis revealed that outbreak viruses from 2019-2020 belonged to genotype II, which has been responsible for outbreaks in South America and the Caribbean. The samples sequenced in this study were closely related to a small number of DENV-4 viruses detected in Paraguay in 2018, differing by only two nucleotides (synonymous mutations in NS3 and NS5). The closest sequence outside of Paraguay was from a sample collected in Brazil in 2013, and the shared ancestor between this and the Paraguay sequences dated to October 2010 (95% HPD: Mar 2010-May 2011). Among the outbreak sequences, we observed two clades, which diverged from a common ancestor in August 2017 (95% HPD: May 2017-Nov 2017), differed by three nucleotides (synonymous mutations in the E, NS3, and NS5 proteins), and were not separated by time or geography. We did not find a significant difference in the percentage of severe dengue cases between the clades (17% vs 11%; p=0.70). Overall, our results suggest that lineages of DENV-4 may have been circulating undetected in South America since 2010. We did not find evidence for substantial viral genomic differences between outbreak and pre-outbreak DENV-4 sequences, or between the first and second wave.

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PRE-EXISTING EXPOSURE TO DENGUE ALTERS HOST RESPONSE TO A TETRAVALENT DENGUE VACCINE, TAK-003

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TAK-003 (TDV) is a tetravalent live attenuated/chimeric dengue vaccine candidate that has completed a pivotal phase III clinical trial showing efficacy in preventing virologically confirmed dengue. Sub-analysis of the phase III trial data also showed that the efficacy against the dengue serotypes differed by baseline serostatus of vaccine recipients. To investigate the possibility that qualitative differences in activation of the innate immune response following vaccination in baseline seropositive and seronegative recipients may be a contributing factor, we performed genome-wide microarray profiling of whole blood RNA at baseline and following two doses of TDV, given 90 days apart. After the first dose, genes related to antiviral response and dendritic cell activation were induced; these changes were greater in those seronegative than those seropositive at baseline. The magnitude of expression of a subset of genes in the innate immune and dendritic cell activation pathways also tended to positively correlate with magnitude of neutralizing antibody titers induced following TDV vaccination in those seronegative at baseline. Interestingly, gene sets for T cell activation, cell cycle and mitochondrial function were induced after the first dose in baseline seropositive recipients, suggesting differentiation and expansion of memory T cells from prior dengue exposure, in response to vaccination. The second dose in those seronegative at baseline induced mostly genes related to Toll-like receptor and inflammatory signaling as well as dendritic cell and monocyte activation. In comparing the gene expression response in those baseline seronegative after the second dose with those baseline seropositive after the first dose, we found few overlapping differentially expressed genes.

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IDENTIFICATION OF ARBOVIRUS AS CAUSE OF NEUROLOGICAL DISORDERS IN HOSPITALIZED PATIENTS IN SÃO JOSÉ DO RIO PRETO, SÃO PAULO, BRAZIL

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Arbovirus (arthropod-borne virus) infections are increasingly important causes of neurologic disease. The spectrums of neurological manifestations linked to these viruses are not fully known. This study aimed assessing retrospectively the incidence of arboviruses as neurotropic agents in cerebrospinal fluid samples from patients with neurological symptoms to make a differential diagnosis and establish profiles of the etiological agents associated with disorders of the central and peripheral nervous system. A total of 255 cerebrospinal fluid (CSF) samples collected from July to December/2017 were tested for Dengue virus (DENV 1-4), Zika virus (ZIKV), Chikungunya virus (CHIKV), Rocio virus (ROCV), Saint Louis virus (SLEV), West Nile virus (WNV), Mayaro virus (MAYV), Ilheus virus (ILHV), Yelow fever virus (YFV), Bussuquara virus (BSQV), Iguape virus (IGUV) and Madariaga virus (MADV) using the RT-qPCR and RT-nested-PCR methodologies to assess the presence of viral RNA and ELISA for serological analysis of DENV, ZIKV and CHIKV. Among the 255 CSF samples analyzed, 3.92% (10/255) were positive for arboviruses. ZIKV infection was detected in 2.74% (7/255), six detected by RT-qPCR and one by ELISA. DENV was found in 0.78 % (2/255) being identified by RT-qPCR. ILHV infection was identified in 0.39 % (1/255) through RT-qPCR (published data) and the other investigated viruses were not found. Our findings highlight to the scientific and clinical community the importance of occurrence of neurological syndromes associated with arboviruses, showing the relevance of using specific methodologies to perform accurate diagnosis.

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THE EFFECT OF AGE ON DENGUE PRESENTATION AND THE PERFORMANCE OF THE 2015 PAHO CASE DEFINITION IN A PUERTO RICAN COHORT

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We leveraged a cohort of Puerto Rican patients to evaluate age associated variability in dengue presentation, examine the performance of the 2015 PAHO criteria, and identify signs/symptoms that differentiate between dengue and other febrile illnesses. Patients with fever ≤7 days were recruited in the Sentinel Enhanced Dengue Surveillance System at 3 emergency departments from May 2012 - December 2015. Serum samples were tested for dengue, chikungunya, and Zika viruses by RT-PCR and IgM ELISA. Nasopharyngeal samples were tested for respiratory viruses. A total of 10,408 patients are included in the analyses. Frequencies of dengue signs/symptoms were assessed by age including older and younger than 5 years, the age associated with speech development completion. We used generalized linear mixed models to visualize how dengue signs and symptoms change with age. LASSO (least absolute shrinkage and selection operator) regressions identified the variables that best predicted dengue. The performance of the 2015 PAHO and alternative dengue diagnostic

criteria were compared. Nausea and headache/retro-orbital pain had the strongest associations with speech development, while the estimated proportion of patients with aches/pains rose until age 20 years. Children aged < 5 years were less likely to have leukopenia compared to older children and adults, but the frequencies of rash, vomiting, and petechiae were similar across age groups. The 2015 PAHO criteria had a sensitivity and specificity of 96% and 10% in adults and 89% and 35% in children. LASSO models showed that the specificity of the PAHO criteria could be improved by: 1) using any two of four observable PAHO criteria: vomiting/nausea, petechiae, rash, leukopenia (specificity 68%, sensitivity of 70%), or using the established ≥ 2/6 PAHO criteria plus either: 1) AST > 50 IU/L or platelet count < 100,000 cells/mL (specificity 89%, sensitivity 74%) or 2) absence of: throat pain, rhinorrhea, or cough (specificity 46%, sensitivity 81%). This is the first study to describe how dengue signs/symptoms change by year of age and to independently assess the performance of the 2015 PAHO dengue case definition.

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VIROLOGIC AND IMMUNOLOGICAL CHARACTERISTICS OF A DENGUE VIRUS 3 HUMAN CHALLENGE MODEL

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Dengue virus (DENV) infections are a significant source of morbidity and mortality throughout the tropics and subtropics. Over 400 million infections are estimated to occur every year, resulting in nearly 100 million symptomatic infections and over 20,000 deaths. Despite decades of effort there are no vaccines currently available for use in individuals without pre-existing dengue immunity and no antiviral available for prophylaxis or as a therapeutic. Accordingly, new models and tools are urgently needed to accelerate dengue countermeasure development. Dengue human infections models presents an opportunity to explore a vaccine or antiviral's potential for clinical benefit in a controlled and highly reproducible setting. Herein, we report the virologic and immunologic outcomes of a phase 1, open-label assessment of a dengue virus-3 challenge study. In this study, 9 participants received a subcutaneously inoculation with 0.5 mL of a $1.4x10^3$ PFU/ml solution of the attenuated DENV-3 challenge strain CH53489. All subjects developed detectible RNAemia within 7 days of inoculation, with peak titers ranging from $3.13x10^4$ to $7.02x10^8$ GE/ml. Infectious viral titers ranged from $5.3x10^3$ to $3.0x10^7$ PFU/ml during the same period, and all subjects experienced quantifiable NS-1 antigenemia. DENV-3 specific seroconversion was observed after day 14 post infection, and all subjects developed DENV-3 specific memory T cell responses by 28 days post infection. Multiplexed serum cytokine analysis revealed production of IP-10, IFN-A2a, IFN-b, and IL-1Ra following inoculation. RNAseq analysis of whole blood revealed the presences of an antiviral transcriptional response to infection that overlapped with the period of serum cytokine production and viremia. This analysis provides a detailed description of the virologic and immunologic features of DENV-3 strain CH53489 infection, and identifies biologically relevant biomarkers of infection that can inform future studies assessing the efficacy of candidate dengue countermeasures.

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DEVELOPMENT OF A NONHUMAN PRIMATE MODEL OF DENGUE VIRUS INFECTION

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Research on dengue virus (DENV) has long been hampered by the fact that a robust animal model does not exist for this disease. Mouse models are limited by the strict species specificity of the virus, as well as major differences between mouse and human immunology. Development of a nonhuman primate (NHP) model for DENV infection has so far been problematic, as experimental infections cause only transient viremia with inconsistent presentation of the hemorrhagic or inflammatory symptoms that are characteristic of human disease. The recent disappointing performance of the DENV vaccine, Dengvaxia, illustrates the hazard of relying on viremic reduction in NHPs as the sole measure of efficacy. Although Dengvaxia demonstrated >90% protection in preclinical testing in NHPs, efficacy dropped to below 60% in clinical trials, and vaccination of DENV naïve individuals resulted in an *increased* risk of hospitalization upon subsequent infection. Thus, the utility of current DENV/NHP models is limited, and the field is in dire need of one that more accurately recapitulates human disease. The role of innate immunity, specifically the interferon response, has been shown to be crucial for control of DENV replication in the host, as demonstrated by the lack of viral replication in interferon-intact mice. Although DENV is able to modulate aspects of the rhesus macaque (RM) interferon response (e.g., STAT2 degradation) similarly to what is observed in human cells, we hypothesize that transient suppression of interferon prior to infection may allow a more robust infection of the RM and subsequent pathogenesis. We have produced a rhesusized IFN-a receptor (RhIFNAR) blocking antibody in an *in vitro* system and confirmed its neutralization capacity in RM cells. The ability of this antibody to block signaling *in vivo* is currently being investigated, and future studies will focus on investigating whether suppression of type I IFN signaling via this treatment promotes establishment of a robust infection and recapitulation of hemorrhagic symptoms that are the hallmarks of human DENV disease.

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SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF AT-752, A NOVEL NUCLEOTIDE PRODRUG WITH PAN-SEROTYPE ACTIVITY AGAINST DENGUE VIRUS: RESULTS FROM A FIRST-IN-HUMAN DOSE-ESCALATION STUDY

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AT-752 is a novel guanosine nucleotide prodrug inhibitor of the polymerase of flaviviruses with sub-micromolar, pan-serotype antiviral activity against dengue. Preclinical evaluation showed good safety and high efficacy against dengue virus infection in animal models, prompting this first-in-human (FIM), double-blind, randomized, placebo-controlled study of the safety, tolerability, and pharmacokinetics of escalating single (Part A) and multiple (Part B) oral doses of AT-752. Eligible healthy males and females 18-65 years of age were randomized to receive oral AT-752 as: Part A) single ascending doses (250, 500, 1000 and 1500 mg; n=31) or placebo (pooled n=10); or Part B) once daily dose (1000 mg QD x 7 days, n=6), twice daily dose (750 mg BID x 4.5 days, n = 6) or three time daily dose (750 mg TID x 4.3 days, n=6), or placebo (pooled n=6). Food effect evaluation was studied within a single-dose cohort. A group of healthy participants of Southeast Asian origin contributed to pharmacokinetic ethnic sensitivity data. Plasma samples were collected at pre-determined timepoints for the pharmacokinetics of AT-752, and its freebases (AT-273, surrogate for the intracellular active triphosphate). AT-752 was well tolerated. Most adverse events were mild. Sporadic cases of gastrointestinal related events including mild to moderate vomiting occurred mostly at higher doses. Plasma exposure of AT-281 (metabolite of AT-752) and other metabolites was approximately dose proportional over the studied dose range. A high-fat/high-calorie meal did not impact the total exposure of AT-281 while slightly increased plasma exposure of AT-273. No pharmacokinetic ethnic sensitivity was detected. The 750 mg TID dose led to a rapid increase in plasma AT-273 levels to exceed the 90% effective concentration of the drug in inhibiting dengue viral replication in vitro (0.64 uM) and maintained such levels over the treatment period. The overall safety and pharmacokinetic results obtained in this FIM study support further clinical development of AT-752 for the treatment and/or prophylaxis of dengue.

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THE BITING RATES AND PATTERNS OF *AEDES AEGYPTI*: A SYSTEMATIC REVIEW (1970 - 2021)

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Transmission models have a long and important history in the study of mosquito-borne disease dynamics. Mosquito biting rate (MBR) is an important parameter in these models, however, estimating its value empirically is complex methodologically. With the goal of identifying appropriate MBR estimates for the mosquito vector for dengue, Chikungunya, and Zika, we performed a systematic review using terms such as biting rate and biting frequency combined with *Aedes aegypti*, *Ae. aegypti*, and *A. aegypti*. We screened 1,324 articles from PubMed and ProQuest databases among which 19 articles met our inclusion criteria. Researchers have used several approaches to estimate biting rates, each with its strengths and limitations. Human landing studies provide relative estimates of biting rates and have been successful in characterizing how rates vary over time, space, and climatic conditions. However, human landing studies are labor and resource intensive. The approach used in most modeling studies to estimate the mosquito's daily biting rate is the inverse of the length of the gonotrophic cycle. Several studies, however, including mark-release-recapture and histological studies have shown that *Ae. aegypti* females bite multiple times within a gonotrophic cycle. Histological studies in particular provide useful data to estimate the per mosquito biting rate, the specific parameter used in transmission models. We propose an approach that combines multiple biting rate studies and studies estimating the gonotrophic cycle to obtain rigorous estimates of the per mosquito biting rate. These results reinforce the importance of engaging with vector biology when using mosquito's daily biting rate data in modeling studies on arbovirus transmission. For *Ae. aegypti* this includes understanding the variation in the number of bites per gonotrophic cycle, as well as recognizing the potential for spatial and temporal variability in these estimates within and between geographic sites.

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DIFFERENCES IN EXPOSURE TO DENGUE AND CHIKUNGUNYA VIRUSES AND ASSOCIATED RISK FACTORS IN WESTERN AND COASTAL KENYA

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Despite severe illness caused by dengue (DENV) and chikungunya (CHIKV) viruses, little is known about the risk factors for their exposure in urban Kenya. To fill this gap, we recruited children (up to 18 years old) and adults from two urban areas in Ukunda [coast] and Kisumu [west] in Kenya. Participants were followed up at any time of febrile illness and every 6 months for 2 years. At baseline (2020), 1,969 participants from Ukunda and 1,809 participants from Kisumu were enrolled including 2,119 (56%) adults and 1,659 (44%) children. During the follow-up period (2021), 491 participants, including 270 adults and 221 children were newly enrolled due to COVID attrition. Questionnaire data were collected to describe the demography, socioeconomic status, and household environment of participants. Blood samples were collected for the detection of IgG against CHIKV and DENV by in-house ELISA. Risk factors associated with exposure to DENV and CHIKV in both study sites were assessed. There was significantly more exposure to DENV in Ukunda than in Kisumu at both the baseline and first follow-up time points ($p<0.01$). At baseline, there was more exposure to CHIKV in Kisumu than in Ukunda ($p<0.01$). Gender, water source, and home/livestock ownership were not associated with exposure to either virus at any time point. In Ukunda, having less education was associated with DENV and CHIKV exposure ($p<0.01$). From baseline to first follow-up, there were more DENV and CHIKV seroconversions in Ukunda than in Kisumu ($p<0.01$ and $p=0.04$, respectively). While there were no risk factors associated with DENV seroconversion, having less education and having an outdoor occupation were associated with CHIKV seroconversion in both Ukunda and Kisumu ($p<0.01$). Our data show common ongoing transmission of both CHIKV and DENV in Kenya; although DENV is more common in coastal Kenya and CHIKV in western Kenya. Interventions mitigating the burden of DENV and CHIKV need to be site-specific.

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REVISITING DENGUE DIAGNOSTICS FOR AFRICAN COUNTRIES

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Dengue fever is underrecognized and underreported in African countries. Dengue virus (DENV), which causes dengue fever, is a mosquito-borne flavivirus consisting of four serotypes. Millions of dengue virus infections are reported every year, mostly in South American and Asian countries. Routine dengue surveillance is lacking across many African countries, enabling the misdiagnosis of dengue fever as malaria. Dengue diagnostics include nucleic acid amplification tests, such as those developed by the US CDC. Low and middle-income countries can request access to lyophilized PCR diagnostics through the US CDC, including the CDC Trioplex Assay and the CDC DEN1-4 RT-PCR. We undertook an in silico analysis of commonly used Dengue virus PCR primers and probes to investigate the homology of the primer and probe sequences to circulating variants within countries on the African continent. We found that the CDC DENV1-4 RT-PCR primers and probe had 1-2 mismatches against all DENV1 African sequences, 0-4 against DENV2, and 0-1 against DENV3. In contrast, the CDC Trioplex assay exhibited greater homology to DENV1 and DENV3, with no mismatches between the primers and probe and African sequences. However, the Trioplex primers and probe had 2 mismatches in almost all DENV2 sequences from African countries, which is likely sufficient to severely impact diagnostic sensitivity.Using phylogenetic analyses, we determined that DENV1, 2, and 3 had been circulating on the African continent for 8, 40, and 12 years, respectively, ample time for the development of viral diversity unique to the African continent, especially in the case of DENV2.These data raise the possibility that dengue is underdiagnosed in Africa due to inadequate diagnostics rather than a lack of dengue infections. Therefore, dengue diagnostics must be designed and evaluated to include the unique viral diversity circulating on the African continent to ensure the stark absence of dengue virus in Africa is not merely due to inappropriate molecular diagnostics.

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OPTIMIZATION OF A NOVEL DENGUE DIAGNOSTIC METHOD BASED ON CRISPR-CAS ASSAYS

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Dengue is major arthropod-borne viral disease in humans caused by dengue virus (DENV, *Flaviridae*) inflicting a vast public health burden. Prevention and mitigation of dengue outbreaks rely on vector control and effective epidemiological surveillance aiming early viral circulation

detection using timely and affordable diagnostic tools. Reverse transcriptase real time PCR (RT qPCR) is the gold standard method for DENV identification and serotyping, however, it requires equipment and infrastructure mostly unavailable at the point of care in resource limited endemic urban districts. CRISPR-Cas method emerged as a proven low cost and portable diagnostic tool in viral diseases. We have been working in the proof of concept of a CRISPR-Cas method for dengue diagnostics, as reported previously. In this work, we aimed to evaluate its performance in an increased sample size and by reducing protocol complexity and costs. DENV presence in RNA extracted from febrile patients' blood samples was initially assayed by RT-qPCR. cDNA from these samples was then amplified by PCR and RPA (Recombinase Polymerase Amplification) and mixed with dengue specific sgRNA-CRISPR-Cas12 assembly. Dengue infected samples were detected by measuring the fluorescent signal released by the enzyme nuclease collateral activity using single strand oligo reporters. In the comparative analyses we assessed sensitivity, specificity and the Kappa concordance index. Results from processing 98 samples with both, RT-qPCR and CRISPR-Cas12 protocols, showed 81.6% concordance, 70% CRISPR-Cas12 assay sensitivity and 97.5% specificity. The kappa index for detection (0.64) indicates moderate agreement between tests. Our results indicate that the CRISPR based diagnostic tool evaluated and improved in this work is highly specific and potentially portable. This initial evaluation allowed us to identify sensitive steps in the original protocol incorporating key solutions. Further experimental work is necessary to increase sensitivity, to determine limit of detection and to achieve complete portability required for the implementation of this assay in early diagnostic surveillance.

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AGE, POVERTY AND INEQUITY ARE KEY DETERMINANTS OF DENGUE SEVERITY IN COLOMBIA

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Age has been a major risk factor for death and complication due to dengue infection (DENV). Although antibody-dependent enhancement (ADE) has been proposed as an explanation, other variables could shape disease outcomes. We aimed to analyze the role of age as a risk factor for disease severity across departments (first administrative level), and epidemic years in Colombia considering poverty and inequity indexes. We conducted a retrospective study analyzing DENV epidemiological data from Colombia between 2012 to 2017, and monetary poverty, extreme poverty, and GINI indexes. Total cases, incidence, incidence of severe DENV, mortality, case-fatality rates (CFR), and complication rates (CR) were calculated for each department and year. The effect of age, department, year of infection, monetary poverty, extreme poverty, and GINI on CR and CFR was evaluated by using a generalized additive model. After adjustment, age ($p<0.001$), GINI ($p<0.001$), monetary poverty ($p<0.001$), and extreme poverty($p<0.001$) indexes were significantly associated with the CR, but age was the only variable significantly associated with CFR ($p<0.001$). Our results revealed a first peak of CR in patients younger than 5 years old, the second peak in patients between 27 to 34 years old, and a third peak after 45 years old. Our work has important implications for future designing of human cohorts analyzing the risk of complications in adults and provides evidence for improving clinical DENV risk assessment. Our findings are consistent with similar observations linking ADE with severe DENV in childhood and suggest protective antibody decay during adulthood. The interplay of biological and socioeconomic factors shaping clinical outcomes in DENV is complex and should be further analyzed.

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HETEROGENEITY IN DENGUE RISK IN A COHORT IN SOUTHERN PUERTO RICO

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Serosurveys using neutralizing antibody tests represent the gold standard for measuring dengue (DENV) seroprevalence. Such studies can be used to estimate historical force of infection as well as age-specific seroprevalence, both critical inputs for evaluation of cost-effectiveness of dengue vaccination programs. A DENV vaccine has been approved for use in children aged 9-16 years old living in endemic areas of the United States who had a previous DENV infection. We used DENV neutralizing antibody results from 718 participants aged 1–16 years in the Communities Organized to Prevent Arboviruses (COPA) cohort study in Ponce, Puerto Rico, together with case data from Ponce from 2003-2018 reported through a passive surveillance system, to estimate annual dengue force of infection using a catalytic model. In this model, individuals are assumed to undergo annual hazard of DENV infection from each of the four serotypes, and to seroconvert upon infection, with durable same-serotype protection and no cross-protection between serotypes. We allowed the hazard of infection to vary with demographic variables and spatially. Overall, 37.4% of children had evidence of previous DENV infection, and 43.7% of children aged 9-16 years. The seroprevalence and case data were consistent, identifying 2007, 2010, and 2012 as years of major dengue outbreaks in Ponce. In addition, we identified markers of higher socioeconomic status as being associated with lower dengue hazard, including having private insurance, higher household income, and having screens in all windows and doors. Finally, we found that the proportion of children with evidence of multiple prior infections was greater than expected according to the model. One hypothesis for this observation is that there is significant heterogeneity not captured by these variables. Such heterogeneity would have implications for cost-effectiveness of vaccination programs, as the benefit of vaccination is strongest in individuals who have had a single infection. Our findings indicate that large dengue outbreaks occurred in 2007, 2010, and 2012 in Ponce, PR and that dengue risk was heterogeneous in the population.

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ARBOBIOS - A BRAZILIAN COHORT OF DENGUE WARNING SIGNS PATIENTS DURING 2019 EPIDEMICS

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It is known that 3.6 billion people worldwide live in areas that place them at risk of DENV infection, 400 million overall are exposed to DENV infection. Around 2 to 5 % of infected individuals progress to Severe Dengue (SD). The mortality can be reduced to less than 1% if robust early predictor ofprogression to SD exists. To establish a warning signs

cohort for identification and validation of prognostic biomarkers for the severe DENV infection. During the 2019 epidemic in Brazil, a prospective longitudinal cohort of warning signs (WS) DENV patients was constitute in the following cities: Araraquara, SP; Arcos, MG; Campo Grande, MS; Nova Serrana, MG; Palmas, TO and São José do Rio Preto, SP. Two following-up visits were programmed at days 7 and 14. The presence of RNA DENV viruswere done by in-brew qPCR after RNA extraction with EasyMag (bioMérieux)and serological responses were evaluate by IgM ELISA (PanBio) only for samples negative in qPCR. For this study, we used SMS data banking. A total of 1117 patients were enrolled and 48 refused to participate. 1069 were analyzed and from those 1016 were adults. The virus RNA was detected in 36.2% of the samples (387) most of them were serotype 2, and out of 682 negative for virus RNA, 444 were reactive in the serological test (65.10%), it is assumed that 77.7% (831) of the participants presented DENV infection at the time of the study. Only 1.59% (17) were not detected by both tests. The follow-up were realized in 984 and 960 patients for days 7 and 14, respectively. This is the biggest WS DENV clinically well characterized cohort in Brazil. As expected, we detected the presence of DENV virus in a low number of WS DENV patients, however IgM serological test were positive in most of negative samples for qPCR. The follow-up were concluded but each medical record should be analyzed and revised to estimate the number of SD.

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POPULATION-BASED SEROPREVALENCE OF DENGUE IN URBAN AND SEMI-URBAN NEPAL

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Clinical cases of dengue have been increasing in Nepal since 2009 however the population-level burden is undescribed. Initially, outbreaks were limited to urban/semi-urban areas in low elevation regions. However, the geographic zones of transmission have been increasing and in 2019 a large outbreak affected many parts of Nepal including higher elevation regions. The objective of this study was to investigate the seroprevalence of dengue among children and young adults in an urban and semi-urban setting of Nepal to understand the population-level burden in densely populated high-altitude regions. We conducted a community-based cross-sectional serosurvey among children and young adults 0 to 25 years old in Kathmandu metropolitan city and municipalities of Kavre, a peri-urban district outside of Kathmandu. Eluted dried blood spots were tested with commercially available indirect ELISA (InBios, DENV Detect) for IgG responses to dengue-derived recombinant antigen. We used finite mixture models to determine seropositivity cutoffs. We tested dried blood spots collected from 659 participants enrolled between 2019 and 2021. The median age was 11.9 years (IQR 6 - 17). 40 participants were seropositive for an overall seroprevalence of 3.2%. The highest seroprevalence was among 15-25 years old (4.4%, 10/229) followed by 0-5 years old (2.4%, 3/125) and 5-15 years old (1.3%, 4/305). Seroprevalence was higher in Kathmandu (6%, 17/284) compared to Kavre (1.1%, 4/375). The study reveals a high burden of dengue in a high-altitude, densely populated region of Nepal justifying immediate public health attention and mitigation efforts. The increasing geographic scope of dengue in Nepal may be a result of changing temperature and weather patterns due to climate change and warrants continued vector and population-level surveillance.

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CROSS-REACTIVE CD8 T CELLS DISPLAY UNIQUE TRANSCRIPTIONAL PROFILES, LEADING TO ENHANCED CYTOLYTIC POTENTIAL AND INCREASED IMMUNE-MEDIATED PATHOGENESIS DURING ZIKA INFECTION

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Zika virus (ZIKV) spread explosively throughout the Americas in 2015, leaving in its wake a devastating and ever-expanding list of sequela associated with infection. Since this epidemic, substantial effort has been put forth to understand the emergence of ZIKV in the Americas, the course of disease and importantly, the correlates of protection. In addition to circulating in mosquito populations in the same geographic regions, flaviviruses share a substantial degree of genetic, and consequently antigenic similarity. This begs the question: In areas of endemic flavivirus circulation, how does immunity to one flavivirus shape immunity to the next? The purpose of this research study was to define how exposure to a heterologous flavivirus shapes the functional T cell response to ZIKV in a mouse model of infection and how those T cells, in turn, impact pathogenesis. We generated data showing that effector CD8+ T cells generated during infection with any flavivirus functionally cross-react with at least one ZIKV CD8+ T cell epitope, which we termed a "pan-flavivirus" epitope. We found that prior infection with a heterologous flavivirus results in altered phenotypic responses to this cross-reactive epitope during a subsequent ZIKV infection compared to a homologous ZIKV prime-boost challenge or a primary ZIKV challenge in the form of altered transcriptional profiles driving enhanced cytolytic potential. We found that this altered cytolytic capacity had the potential to enhance ZIKV disease in an adoptive transfer model. Our findings provide a mechanistic understanding of cross-reactive T cell control during heterologous infection and have important implications for vaccine design, as these results define the functional consequences of priming a cross-reactive T cell response for a pan-flavivirus vaccine.

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PERSISTENT DENGUE SYMPTOMS IN UMPHANG DISTRICT, TAK PROVINCE, THAILAND: A PROSPECTIVE COHORT STUDY

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While dengue has been considered an acute illness, emerging evidence finds that some symptoms can last for months or longer, similar to mounting evidence for long COVID. However, the share of cases with long symptoms, their duration, and associated characteristics are poorly understood and likely impacted by location and the prevalence of other diseases, such as COVID-19. We conducted a prospective cohort study in Umphang District, Tak Province, Thailand, to investigate this. Dengue and COVID-19 are endemic in this hilly district, exacerbated by migration from bordering Myanmar. We sequentially screened district hospital patients with NS1, enrolling 22 (6 inpatients and 16 outpatients) from 5/4/2021 through 7/1/2021 who tested positive for dengue. Their median age was 34 years (range 7-76). Diagnoses included dengue hemorrhagic fever (DHF, 3) and dengue fever (DF, 19). We ascertained the persistence of symptoms through up to 10 interviews over the 6-month follow-up period, analyzed their association with patients' observable characteristics, and present preliminary key results . Overall, symptom duration from enrollment averaged (± standard error of the mean) 125±5 days (range 56-140). The average symptom duration in older (above median age) patients (135±3 days) was significantly longer than in younger patients (115±9), t=3.05, p=0.011. Inpatients averaged significantly shorter illnesses (107±9 days) than outpatients (131±6), t=3.66, p=0.004, despite similar average ages (38±4 versus 41±5), t=0.42, p=0.68. However, DHF (121±9 days) and

DF (125±6), t=0.61, were simlar.p=0.55. Further study and comparisons with COVID-19 and other viral illnesses would be useful to understand whether immune system characteristics, age, severity of illness, clinical management, or other factors explain the lower persistence in inpatients and why diagnosis appears unimportant. In Umphang, as in other settings (Wu Zeng et al., AJTMH, 2018), the high prevalence and duration of dengue contribute substantially to dengue's overall disease and economic burden and highlight the potential benefit of effective prevention strategies.

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SURVEILLANCE AND EVOLUTIONARY ANALYSIS OF DENGUE VIRUSES AND THE IMPACT ON EPIDEMIOLOGICAL DYNAMICS IN A DENGUE HYPEREDEMIC BRAZILIAN CITY, SAO PAULO, BRAZIL

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In São José do Rio Preto (SJdRP), São Paulo, Brazil, the circulation of DENVs is characterized by frequent serotype/lineages replacement and changes in the epidemiological patterns of the disease, which turn the city an ideal scenario to study DENVs diversity, and its impact in epidemiology. Our lab has conducted molecular surveillance for over ten years, demonstrating the prevalence of DENV1 (2012-2017) and DENV2 (2018-2019). In this context, we screened for DENVs a total of 1,914 samples in 2020, 2,164 samples in 2021, and 1,129 samples in 2022, totalizing 5,207 serum samples collected from patients with dengue-like symptoms. The overall positivity rate for dengue in 2020 was 20.9%, with the prevalence of DENV2 circulation. In 2021, DENV2 was detected in 5.4% of samples, and DENV1 in 8.7%, showing an overall positivity rate of 14.1%. The results demonstrate a serotype replacement in the municipality, with DENV2 being replaced by DENV1. Additionally, we screened all samples received in 2022, and DENV1 was detected in 15.7% of the samples and DENV2 in only 0.5%. Genomic sequencing of DENVs is being conducted to better understand the evolution of the virus in SJdRP and the recent clade replacement event. So far, we have sequenced 103 DENV1 and DENV2 genomes. The sequencing libraries were generated using Nextera XT DNA Library Prep and genome de novo assembly in Geneious Prime. Phylogenetic analyses evidence that all DENV2 genomes are grouped within the American/Asian (III) genotype, BR3 and BR4 lineage, and all DENV1 genomes are grouped within genotype V, L1 lineage. Further information is being collected to compose the epidemiological database analyses. We are sequencing a greater number of DENV positive samples to reconstruct the phylodynamic of each serotype and analyze the genetic diversity of dengue circulating lineages in SJdRP during these past years and correlate it to epidemiological and clinical data. Our findings demonstrate a DENV1 serotype replacement event and reinforce the critical role of molecular and genomic surveillance in dengue hyperendemic municipalities where different strains circulate simultaneously.

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STRAINS OF DENGUE CIRCULATING IN THE WESTERN PROVINCE OF SRI LANKA DURING THE COVID-19 PANDEMIC

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Dengue is endemic to Sri Lanka since 1989 and subsequently affected by regular dengue epidemics. We sought to identify the dengue strains and the circulating serotypes from July 2019 to January 2021 during the COVID-19 pandemic. Samples were obtained from 277 consenting patients presenting with febrile illness from an ongoing study at the Colombo North Teaching Hospital, National Institute for Infectious Diseases and University Hospital- Kotelawala Defence University of the western province. All samples were tested by Reverse transcriptase polymerase chain reactions (RT-PCR) and/or Real time-PCR tests to determine dengue positivity and serotype. Sequencing (NGS) was carried out on samples with adequate viral load followed by phylogenetic analysis using the Geneious software. The testing showed 51.6% were positive for dengue virus. The serotyping showed 14.0 % of the positives were DENV-1, 44.1% DENV-2, 37.1% DENV-3 and 4.9% DENV-4 respectively. Sequencing showed two genotypically distinct variants of the DENV-3 and DENV-1 containing samples. The DENV-2 sequencing showed one cluster of a similar genotype and DENV4 samples are yet to be sequenced. One of the identified DENV-3 variants was similar to that reported in 2017/18 in Sri Lanka while the other variant was similar to one reported in India, 2016. One of the identified DENV- 1 variants was similar to the 2018 strain found in Sri Lanka while the other was similar to the variant reported in China in 2016. The DENV-2 is similar to the one reported in 2017. According to our data, two genotypically distinct variants of DENV-3 and two DENV-1 serotypes, plus a DENV-2 serotype were simultaneously circulating in this area from July 2019 to January 2021. The DENV-1 strain like the 2018 DENV-1 from India and the DENV-3 strain similar to the one reported from China in 2016 have not been previously reported in Sri Lanka. Our data suggest that during the COVID-19 pandemic multiple strains have been circulating in the western province even though no serious epidemic has been reported.

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ISOLATION OF YELLOW FEVER VIRUS AND SAINT LOUIS ENCEPHALITIS VIRUS FROM *AEDES* MOSQUITOES IN AN URBAN AREA OF SOUTHWESTERN REGION OF SAO PAULO STATE, BRAZIL

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Flaviviruses (Flaviviridae family, genus Flavivirus) are considered a serious threat to public health in many parts of the world, as many are highly pathogenic to humans and animals and may cause encephalitis or hemorrhagic fever in their hosts. Many of them have spread to different geographic regions where their circulation had not been detected previously, causing new outbreaks. Brazil is a great source of arbovirus diversity, mainly in the Amazon Region. However, other biomes, such as Cerrado and Atlantic Forest, may be also a hotspot for emergent/reemergent viruses. For instance, Saint Louis Encephalitis virus (SLEV)

was isolated in different parts of the country, but no outbreak was ever reported. In the other hand, from 2016-2018, a large outbreak of Yellow Fever (YF) occurred in the southeastern region, with thousands of human and neotropical primates deaths registered. During this period, a total of 3,764 mosquito pools were collected at sites with YF ongoing epizootic events and human cases. Mosquitoes were captured in different municipalities at ground level between 9 am and 3 pm, using an entomologic net and bottle-type manual vacuums in green areas, while Nasci's Aspirator was used in urban dwellings; they were identified morphologically, grouped into pools according to their taxonomic category, macerated and tested by RT-qPCR for both YFV specific and a pan flavivivirus assay. Positive mosquitoes were inoculated into C6/36 cells, followed by IFA, and sequenced by NGS. Two pools collected in November 2016 at Aracatuba zoo, located in an urban area, were positive: YFV was detected in Aedes scapularis and SLEV was detected in Aedes aegypti. Both pools were isolated in C6/36, showing high virus load. Full genome sequencing revealed that YFV belongs to South American genotype I, in a cluster within SP lineages that has caused the earlier outbreak. SLEV isolated belongs to genotype III, and seems to be restricted to Atlantic Forest biome. To our knowledge, this is first isolation of SLEV in Aedes aegypti, and its role must be further investigated.

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EVALUATING THE POTENCY OF YELLOW FEVER VACCINE SERUM NEUTRALIZING ANTIBODIES (≥ 10 YEARS POST-VACCINATION) AGAINST WILD TYPE YELLOW FEVER AND VACCINE STRAIN VIRUSES IN A NON-ENDEMIC COHORT

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Yellow fever virus (YFV) is an enveloped single-stranded RNA virus and the prototype flavivirus, transmitted via mosquitoes of the *Aedes* and *Haemagogus* species causing ~200,000 yellow fever (YF) annual worldwide cases with a fatality rate ranging from 20-60%. A live-attenuated YFV vaccine (17D) has successfully offered protection and contained outbreaks since the 1940s. In 2013, the World Health Organization Strategic Advisory Group of Experts on immunization concluded that a single dose of 17D offers lifelong immunity and protection, and removal of the booster dose requirement, previously administered every 10 years, was enacted in 2016. However, recent outbreaks in Africa and South America (2016-2018) and wide variability in real-world neutralization data from vaccinees highlight knowledge gaps in our understanding of the potency and durability of 17D based YFV protection beyond the 10 years. Neutralization test (NT) antibody titers are widely used and the best correlated surrogate of immunity. However, most studies characterize NT titers against the homotypic vaccine strain 17D and the potency of vaccinee YFV specific neutralizing antibodies (Nabs) against currently circulating WT YFV is rarely characterized. This limits our understanding on the durability of 17D Nabs against WT YFV infection. Here we examine serum NT titers against 17D and WT YFV viruses (of African and South American lineage) in a non-endemic cohort of YFV vaccinees ≥ 10 years post-vaccination, recruited to a study of long-term immunity to arthropod-borne viruses. We utilize the focus reduction neutralization test (FRNT) to determine the serum dilution that neutralizes 90% of our control input virus ($FRNT_{90}$). Subjects have well documented travel history, characterized immunity profiles against relevant flaviviruses including dengue, Zika and chikungunya. These studies contribute to our limited knowledge on human immune response to a simulated WT YFV infection and the durability of YFV specific serum Nabs, thereby, informing the role of vaccine boosters.

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SPACE SPRAY EFFICACY OF FLUDORA CO-MAX EW AGAINST INSECTICIDE-RESISTANT *AEDES AEGYPTI* AND *CULEX QUINQUEFASCIATUS* MOSQUITOES FROM CÔTE D'IVOIRE: A SEMI-FIELD EVALUATION

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Space spray of insecticides against arboviruses is threated by resistance in mosquito vectors. We evaluated the space spray efficacy of a new product, Fludora Co-Max EW (a combination of flupyradifurone and transfluthrin, with Film Forming Aqueous Spray Technology (FFAST)), against insecticide-resistant *Aedes aegypti* and *Culex quinquefasciatus* from Côte d'Ivoire. Insecticide-resistant *Ae. aegypti* and *Cx. quinquefasciatus* mosquito larvae were collected in Abidjan, Côte d'Ivoire from August to December 2020. Emerged adult females were tested against Fludora Co-Max EW and K-Othrine EC using ultra-low volume cold fogging (ULV) and thermal fogging (TF) both outdoors and indoors. Evaluation cages were placed at 10, 25, 50, 75 and 100 m from the spraying line for outdoors, and at ceiling, mid-height and floor in a house for indoors Knockdown and mortality were recorded and compared by treatment. Overall, Fludora Co-Max EW induced significantly higher knockdown and mortality effects in *Ae. aegypti* and *Cx. quinquefasciatus* compared with K-Othrine EC. With both species, Fludora Co-Max EW mortality rates were above 80% (up to 100%) for outdoor ULV spray at each distance checkpoint (10 to 100 m), and 100% for indoor ULV and TF sprays at all level checkpoints (ceiling, mid-height and floor). K-Othrine EC induced high mortality indoors (97.9-100%), whereas outdoor mortality rapidly declined in *Ae. aegypti* from 96.7% to 36.7% with ULV, and 85.0% to 38.3% with TF, from 10 to 100 m. For outdoor Fludora Co-Max EW spray, ULV showed both higher knockdown and killing performance *Ae. aegypti* and *Cx. quinquefasciatus* compared with TF. Fludora Co-Max EW performed better against *Cx. quinquefasciatus* compared with *Ae. aegypti*. Fludora Co-Max EW induced high mortality and knockdown effects against wild insecticide-resistant *Ae. aegypti* and *Cx. quinquefasciatus* strains and performed better than K-Othrine EC. The presence of flupyradifurone and transfluthrin and FFAST technology in Fludora Co-Max EW may have broadened its killing capacity. Thus, Fludora Co-Max EW is an effective adulticide and a promising tool for the control of mosquito-borne arboviruses.

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CLIMATE CHANGE IMPACTS ON ZIKA AND DENGUE RISK: PROJECTIONS USING A TEMPERATURE-DEPENDENT BASIC REPRODUCTION NUMBER

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Recent work characterizing the temperature dependencies of the basic reproduction number R_0 for vectorborne disease highlights how climate change may impact geographic spread. Of particular importance is understanding how newly emerging diseases, like Zika, might be affected by changing temperature. We applied a temperature-dependent $R_0(T)$ to characterize Zika (and, for comparison, dengue) transmission potential under specific future climate change scenarios in three diverse regions of Brazil, a country that has been profoundly impacted by Zika. The $R_0(T)$ for Zika and dengue were derived from a compartmental transmission

model. We obtained temperature projections for 2040 by fitting cubic spline interpolations to historical temperature data and projecting those data using temperature-change predictions under different climate change scenarios. We applied this approach to three Brazilian cities (Manaus, Recife, and Rio de Janeiro) representative of a diverse set of climates. We calculated seasonal $R_0(T)$ for each city for each climate change scenario for both diseases. Our model predicts that the $R_0(T)$ for Zika peaks at 2.8 around 30 degrees Celsius while for dengue it peaks at 7.0 around 31 degrees Celsius. We predict that, regardless of the specific climate change emission scenario, there will be an increase in arbovirus disease pressure in Brazil. For Manaus, we predict the annual R_0 range, currently 1.2-2.8, to shift to 1.6-2.8, for Recife we project the range to shift from 0.8-2.4 to 1.3-2.7, and for Rio de Janeiro to shift from 0-1.2 to 0-1.7. In the hotter climates, like Manaus, the increases will be attenuated during the months of highest transmission. In the cooler climates, like Rio de Janeiro, where transmission cannot be sustained year-round, projections suggest an increased number of months where $R_0 > 1$. As Zika immunity wanes and temperatures increase, there will be increasing epidemic potential, especially in regions where transmission is currently marginal. Surveillance systems should be implemented and sustained for early detection.

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VARIABLE NEUTRALIZATION OF SYLVATIC DENGUE BY HUMAN PRIMARY DENGUE IMMUNE SERA

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Approximately one-half the global population is at risk of infection with dengue virus (DENV), with countries in the tropics and sub-tropics bearing the highest burden of disease. DENV is sustained in two ecologically discrete non-human primate sylvatic and human urban transmission cycles in west Africa and southeast Asia. As global population expands, increased urbanization and deforestation increase human proximity to mosquito vectors and non-human primate reservoirs involved in maintenance and transmission of sylvatic DENV. Although the central dogma of dengue immunity asserts protective immunity of homotypic reinfection following primary dengue infection, specific risk of zoonosis by homotypic sylvatic DENV has yet to be fully characterized. Sylvatic DENVs form independent clades and are genotypically distinct from other endemic variants within a given serotype. Despite genetic differences, it is expected that human primary immune sera arising from endemic DENV infection will potently neutralize sylvatic DENV. Here we quantify neutralizing potency of DENV-specific primary immune sera against sylvatic strains of DENV-1, DENV-2 and DENV-4. Using virus neutralization assays, sera from endemic (N=14) and non-endemic (N=24) subjects1-47 years post infection were assayed against genetically diverse homotypic serotypes of sylvatic DENV to characterize potency and breadth of protection against non-endemic strains of DENV. We found most primary immune sera neutralized homotypic sylvatic variants but with highly variable potency: greater than 20-fold differences in neutralization titers between sylvatic and clinical strains with several sylvatic strains poorly neutralized in comparison with their homotypic counterparts. These results highlight a potential vulnerability within endemic populations with an increased susceptibility of zoonosis by peoples residing in semi-urban settings. Our findings within this work supports a global demand for increased disease surveillance of dengue emergence as human migration widens.

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EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF PREGNANT WOMEN EXPOSED TO THE 2016 ZIKA VIRUS EPIDEMIC IN LATIN AMERICA: A DESCRIPTIVE ANALYSIS OF THE ZIKALLIANCE PREGNANT WOMEN COHORT

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A prospective cohort of pregnant women (PW) was set up to measure the impact of Zikavirus (ZIKV) infection during pregnancy as part of the ZIKAlliance project. We conducteda descriptive analysis of the 9,024 PW enrolled in the study and exposed to the ZIKVoutbreak that began in 2015 in eleven sites over nine countries (BOL, BRA, COL, CUB,ECU, GUA, MEX, PER, VEN). PW older than 16 years were enrolled. A systematic dataand biological sample collection were performed during monthly follow-up visits, usuallycoinciding with antenatal visits, regardless of clinical manifestations suggestive ofarboviral infection until delivery. Data on sociodemographic, epidemiological, clinicaland risk factors for mosquito exposure were collected. Most PW were enrolled duringthe second trimester of pregnancy and had a median age of 26 years. Most PW (37%)reported a monthly income between USD 100-300, although ECU reported the highestincome (> USD 1000/month). Active and passive smoking as well as alcohol and drugconsumption during the current pregnancy were most frequent in BRA. Hypertensionwas the most frequent comorbidity, mainly in PER. We found that over half of thepopulation in CUB and MEX planned their pregnancies during the outbreak. BRA andECU observed the highest frequencies of previous preterm births while BOL reportedthe highest known familial disorders. Sexual transmitted diseases were reported in lowfrequencies being syphilis the more frequent infection mainly in BRA. Zika, dengue andchikungunya virus circulated in the study countries. We found that nearly 90% of peoplein CUB and VEN stored water indoors while they also reported the lowest frequency ofgarbage disposal service. In-house insecticides and window screen were the mostfrequent type of mosquito protection overall in 65% of the population. Nearly 85% ofthe COL site did not use any type of mosquito protection at enrollment visit despite theZIKV outbreak. We will present a comparison of the different sociodemographic andpregnancy-related characteristics between the countries to better understand theepidemiological scenario of PW exposed to ZIKV outbreak in Latin America.

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CHARACTERIZING THE IMMUNE RESPONSE TO ZIKA VIRUS USING EPITOPE MAPPING, REPORTER VIRUS PARTICLES, AND ANTI-ZIKV ANTIBODIES

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We have characterized the immune response to ZIKV infection and vaccines by epitope mapping over 90 anti-ZIKV MAbs at amino acid-resolution, using a comprehensive ZIKV prM/E library of 672 single alanine mutants expressed in human cells. Published studies include epitopes of MAbs isolated from a Brazilian patient, with a highly neutralizing MAb protective in animal models of ZIKV fetal disease. Epitope locations suggest that some MAbs act by binding across adjacent E proteins, preventing rearrangements necessary for ZIKV infectivity. Mapping also reveals epitopes specific for ZIKV or common to DENV, information that can help create better vaccines and therapeutics. We have also identified mutations that increased ZIKV RVP budding, which may aid the design and production of anti-ZIKV vaccines, by screening each individual ZIKV library prM/E variant for ZIKV particle budding and infectivity. To provide critical reagents, we developed ZIKV reporter virus particles (RVPs) capable of one round of infectivity, with luminescent or fluorescent readout, and demonstrated reproducible neutralization titer data (NT50 values) across different RVP production lots, volumes, time frames, and laboratories. We also isolated anti-ZIKV MAbs for ZIKV-specific immunodetection, diagnostic applications, and ZIKV neutralization studies. After immunization with DNA and sub-viral particles, and phage library panning with RVPs, we isolated 48 ZIKV-specific conformational MAbs against prM/E, including one that potently neutralized ZIKV RVPs (IC50 45 ng/ml) with a quaternary epitope spanning adjacent E proteins. We have also used ZIKV RVPs to identify cellular receptors and attachment factors that enable ZIKV entry. ZIKV RVPs were tested on our Membrane Proteome Array (MPA), comprising 6,000 unique human membrane proteins individually expressed in live human cells. Known receptors and attachment factors were identified (validating the approach), as well as a number of membrane proteins not previously known to enable ZIKV entry. These newly identified proteins help explain viral tropism and pathogenesis, and may be useful as therapeutic targets.

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BREADTH AND POTENCY OF NEUTRALIZING ANTIBODIES TO YELLOW FEVER VIRUS (YFV), UP TO 10 YEARS POST-VACCINATION

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Yellow fever is a severe disease caused by the prototypic flavivirus, yellow fever virus (YFV), which is a transmitted by *Aedes aegypti* and *Haemogogus* spp. mosquitoes. Significant control of YFV has been achieved through vaccination with live attenuated vaccine, 17D, which was first developed in 1937. In 2016 the historical vaccination regime of prime followed by boost every 10 years was amended to a single vaccination by both the CDC and WHO based in part on data that demonstrate long-term persistence of YFV neutralizing antibodies. However, analyses of neutralizing antibodies titers following single-dose vaccination estimate that approximately 20% of individuals have neutralizing antibody titers that fall below assay limits of detection by 10 years post-vaccination. Furthermore, the neutralization assays used to establish antibody titers typically only assess neutralization against the attenuated 17D vaccine strain virus and the correlation between 17D based titers and neutralization against clinically relevant wild-type (WT) YFVs remains largely unknown. Using a panel of immune sera from a non-endemic human cohort vaccinated with 17D, one to nine years prior (n = 20), we investigated breadth and potency of neutralizing antibodies against a panel of WT YFVs, representative of the seven YFV genotypes found globally. To further understand the variables that may play a role in directing antibody responses one to nine years post vaccination, we employed multiple variable regression evaluating the effects of time since vaccination, age at vaccination, and Zika and dengue virus infection history, on immune sera potency and breadth. Importantly, for subject serum samples with neutralization titers against 17D at or just above the neutralization threshold of detection, we define the limits potency against WT YFV, a more authentic and stringent test of potential neutralization limits of protection.

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CHARACTERIZING THE IMMUNOGENICITY AND EFFICACY OF A CHIMERIC INSECT-SPECIFIC VIRUS VACCINE AGAINST ZIKA VIRUS

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Zika virus (ZIKV) reemergence remains an important public health threat, and presently has been reported in eighty-six countries worldwide. Although ZIKV infection often results in an acute undifferentiated febrile illness, severe Zika infection can lead to Guillain Barré Syndrome in adults and congenital zika syndrome, which is a pattern of birth defects in infants. Aripo virus (ARPV) is a newly discovered insect-specific flavivirus, that genetically clusters with pathogenic flaviviruses; like Zika; but is apathogenic in vertebrate cells. We developed an Aripo-Zika chimeric virus (AZ) containing the pre-membrane and envelope genes of ZIKV and the nonstructural proteins of ARPV as a vaccine candidate. We analyzed AZ's ability to induce a robust immune response and provide protection from ZIKV disease. We evaluated optimal immunization doses, effects of boosters on immunogenicity and efficacy, and explored the rates and efficacy of maternally transferred passive immunity. Our results indicated that an immunization dose of 10^{10} genome copies is the most effective dose in our immune-competent murine models, and boosters significantly increased AZ immunogenicity. Passive transfer of maternal antibodies to pups, resulted in complete protection from a lethal ZIKV challenge. We next assessed the impact of co-infection with a vertebrate pathogenic flavivirus on AZ's inability to replicate in vertebrate cells. When co-infected with ZIKV, AZ and ARPV showed no growth in African green monkey kidney cells (i.e., Vero-76) over a 120-hour period. Conversely, we evaluated the immunity to the ARPV backbone in murine models. Our data suggests when vaccinated with similar chimeric vaccines (i.e., AZ and Aripo-West Nile), murine retain their immunogenicity. Overall, our data suggests chimeric vaccines using this insect-specific platform are a safe and effective method for the development of flavivirus vaccines.

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MATERNAL ZIKV INFECTION AND RISK OF DIFFERENT CONGENITAL ABNORMALITIES IN NEWBORNS - RESULTS FROM THE ZIKALLIANCE CONSORTIUM

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The ZIKAlliance consortium was created in response to the Zika virus (ZIKV) epidemic that raged through the Americas between 2015 and 2017 with the goal to investigate the impact of ZIKV infection during pregnancy and subsequent abnormalities in newborns. In Latin America and the Caribbean, pregnant women (PW) and children (CH) cohorts were established in 14 sites in 8 countries. Eligible participants were PW over the age of 16 years, willing to attend study visits, and able to provide informed consent. Among 3866 PW, a total of 3852 (99.6%) were enrolled by ZIKAlliance partners between 2017 and 2019. PW were followed over the course of the pregnancy every ~4 weeks during routine antenatal care visits, including collection of serial blood/urine samples and assessment of rash/fever illness episodes. All PW were revisited at delivery for birth outcomes. Investigations included a comprehensive assessment of potential co-factors or effect modifiers for the risk of congenital malformations in ZIKV-infected PW, such as demographics, socio-economic status, TORCHS infections, and previous flavivirus infections or vaccines. Out of 3852 enrolled PW, 820 (21.3%) only attended the enrollment visit, 540 (14.0%) had one additional follow-up visit, and 2492 (64.7%) had more than 1 follow-up visit. Out of the PW with more than 1 follow-up visit, 2045 (82.1%) had a pregnancy outcome recorded, with 1952 babies born alive and 38 suffering from abortion or stillbirth (65 lost to FU). Preliminary results show that 2.7% of the PW were confirmed or highly suggestive for a ZIKV infection during pregnancy, while 3.4% of newborns were diagnosed with microcephaly, defined as -2SD for gestational age (according to WHO Intergrowth). Major abnormalities, including abortion or stillbirth, extreme prematurity, and structural abnormalities occurred in 11.9% of the newborns. Univariate and multivariable logistic regression was conducted to assess the relationship between ZIKV infection and birth outcomes. Diagnostic information was not available on all PW at the time of submission. Data analysis is on-going, and results will be updated in the coming months.

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ZIKA VIRUS (ZIKV) DIAGNOSTIC TESTING IN EIGHT LATIN AMERICAN COUNTRIES IN 2017-2019: RESULTS OF THE ZIKALLIANCE PROSPECTIVE COHORT STUDY

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Zika virus (ZIKV) emerged in 2015 as a public health issue, spreading from Brazil to the rest of Latin America. ZIKV impact is mainly related to congenital Zika syndrome that can occur in case of infection during pregnancy. European Commission-funded ZIKAlliance prospective cohort study was set up in 2017 to investigate incidence of adverse outcome of ZIKV infection in pregnancy. Overall, 3852 pregnant women (PW) were enrolled in 2017-2019 from 14 sites in 8 countries in Latin America and Caribbean and followed up during pregnancy until delivery. Here we present results of laboratory testing performed using a standardized diagnostic algorithm. Molecular and serological tools used (Transcription-Mediated Amplification assay, TMA; IgG and IgAM ELISA; Virus Neutralization test, VNT) allow to have high sensitivity (and thus detect ZIKV low viral charges) and specificity (avoiding cross-reactivity with co-circulating Flaviviruses). Because of the cross-reactivity of serological tests for flaviviruses, we developed criteria to classify PW according to their likelihood of having contracted ZIKV during pregnancy, developing categories from 'confirmed' over 'highly suggestive' to 'possible' or 'indeterminate'. Preliminary findings on 1084 PW from 8 sites show that a small proportion of the PW (~1%) had confirmed evidence of ongoing ZIKV infection (TMA+ result or VNT seroconversion between enrolment and delivery), while a larger group had markers of recent (presence of IgAM) (~9%) or past infection (presence of IgG, confirmed by VNT) (~26%), suggesting an intense spread of ZIKV among PW. The need for diagnostic categories based on likelihood of infection status will be a challenge for the analysis of associations between congenital abnormalities and infection status. However, our results allow to estimate ZIKV circulation in a broad region of Latin America and Caribbean, through an efficient and standardized diagnostic process. This estimation, generally made difficult by the high proportion of asymptomatic ZIKV infections, will be useful to guide future public health interventions.

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COXSACKIEVIRUS A6 CAUSING HAND FOOT AND MOUTH OUTBREAK IN NORTHEASTERN BRAZIL 2018

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Hand foot and mouth disease (HFMD) is highly contagious acute viral disease commonly associated to Enterovirus (EV). During 2018, Brazil faced massive HFMD outbreaks scattered across the country. The aim of the present study was to characterize the EV responsible for the HFMD outbreak occurred in Paraiba State, Northeastern, Brazil in 2018 followed by phylogenetic analysis to gain information on its genetic diversity. A total of 49 serum samples (one of which patient) collected from children under 15 years old clinically diagnosed with HFMD were tested for EV using conventional nested RT-PCR and RT-qPCR. Oropharyngeal swabs were not available. EV infection was laboratory confirmed in 71.4% of samples (35/49). Twenty-six of viremic cases were detected within the first three days of disease (74.3%; 26/35). The mean and median ages were 1.83 years and 1 year, respectively. All 49 children were considered immunocompetent and neurological complications or fatalities were not observed. Twenty-two EV-positive samples were successfully sequenced and classified as CV-A6 genotype. Phylogenetic analysis (VP1 region) of three samples revealed that the detected CV-A6 strains belonged to sub-lineage D3. CV-A6 strains detected here clustered with South American, European and West-Asian strains also involved in HFMD cases during 2017-2018 seasons, and apart from previously Brazilian CV-A6 strains detected from 2012 to 2017, therefore suggesting a globally co-circulating pool of different CV-A6 strains introduced into the country at distinct time-points. The increasing circulation of the emerging CV-A6 associated to HFMD, along with the detection of more severe cases worldwide; suggest the need for a more intense surveillance system of HFMD in Brazil. The present study reinforces the importance of the emergence of CV-A6 causing HFMD in Latin America. This investigation was performed exclusively in serum, highlighting that blood samples should be considered as an important and valuable specimen type when diagnosing enteroviral HFMD outbreaks.

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SEROPREVALENCE OF SARS-COV-2 INFECTION AFTER THE SECOND WAVE IN KINSHASA, DEMOCRATIC REPUBLIC OF THE CONGO

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The Democratic Republic of the Congo (DR. Congo) has experienced four waves of the Corona Virus Disease-2019 (COVID-19) epidemic, with Kinshasa, the capital city, being the epicenter. As observed across African countries, the second wave in DR. Congo was severe compared to the first wave, partly due to the lightening of stringent public health countermeasures implemented during the first wave and the spread of the severe acute respiratory syndrome (SARS-CoV-2) beta variant (B.1.351). However, the burden of COVID-19 in DR. Congo and especially in Kinshasa is likely underestimated because Polymerase Chain Reaction (PCR) testing is mainly conducted on symptomatic persons meeting the case definition, while many infected persons are either asymptomatic or paucisymptomatic. After the first wave, a household-based survey conducted in Kinshasa estimated at least 292 infections going undiagnosed for every laboratory-confirmed case. To ascertain the cumulative population exposure in Kinshasa after the second wave, we conducted a prospective population-based cross-sectional study targeting all the 35 health districts of Kinshasa. A multistage cluster sampling was used to recruit two thousand five hundred sixty eligible consenting participants from 585 households. Participants were administered a structured pre-tested questionnaire on a smartphone application, Epicollect 5. Three to five mL of venous blood was collected and analyzed using a highly sensitive and specific Enzyme-Linked Immunosorbent Assay detecting total antibodies against the Receptor Binding Domain of the spike protein. Data were analyzed with STATA 15.1 using the svyset command. Female participants represented 55.2%. The overall population-weighted; test kit adjusted SARS-CoV-2 seroprevalence was 76.5% (95% CI 74.5 - 78.5%). The seroprevalence was 4-fold higher than the first wave and was associated with age, household income, and education level. Evidence generated from this population-based survey is critical to adjusting COVID-19 control measures and especially vaccination campaign strategies in the context of vaccine shortage and hesitancy.

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IMMUNOGENICITY AND EFFICACY OF ADVAX-2 ADJUVANTED PSORALEN-INACTIVATED SARS-COV-2 VACCINE IN NONHUMAN PRIMATES

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The World Health Organization declared COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a global pandemic in March 2020. Since then several SARS-CoV-2 variants of concern (VOCs) with mutations in the spike protein have emerged. Most of the currently available COVID-19 vaccines target the SARS-CoV-2 spike protein. Mutations in the receptor binding domain (RBD) of SARS-CoV-2 spike protein could potentially lead to immune evasion of these vaccines. Development of a safe and effective vaccine that protects against SARS-CoV-2 VOCs is a high priority. Inactivated whole-virus vaccines target several viral antigens and can elicit broader immune responses to potentially overcome this issue. We prepared a psoralen-inactivated whole-virus SARS-CoV-2 vaccine (SARS-CoV-2 PsIV) by treating SARS-CoV-2 nCoV/USA-WA1/2020 with the psoralen compound 4′-Aminomethyltrioxsalen (AMT) and UVA irradiation. SARS-CoV-2 PsIV was purified by chromatography and evaluated for its immunogenicity in nonhuman primates (NHP), using 10^8 - $5x10^{10}$ particles/dose with Advax-2 adjuvant. We also evaluated SARS-CoV-2 PsIV as a booster shot in animals vaccinated with a DNA vaccine encoding SARS-CoV-2 spike glycoprotein. Advax-2 adjuvanted SARS-CoV-2 PsIV elicited a dose dependent neutralizing antibody response in NHPs, as measured by serum microneutralization assay against SARS-CoV-2 Washington strain as well as the delta variant. Animals vaccinated with the DNA vaccine followed by a booster dose of SARS-CoV-2 PsIV exhibited the highest neutralizing antibody responses. SARS-CoV-2 PsIV also elicited immune responses to more than one antigen (spike and nucleocapsid proteins) suggesting that Advax-2 adjuvanted SARS-CoV-2 PsIV has the potential to protect against COVID-19 from emerging SARS-CoV-2 variants either by itself or as a booster shot to other nucleic acid (NA) vaccines. Preliminary results from vaccinated NHPs challenged with delta variant suggests that SARS-CoV-2 PsIV protected the animals from SARS-CoV-2 infection, when administered as a booster shot to DNA vaccines.

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COVID-19 VACCINE HESITANCY: VACCINATION ACCEPTABILITY IN SOWETO, SOUTH AFRICA

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Governments worldwide are rolling out vaccination programmes to curb the global spread of COVID-19. Drawing on data collected prior to vaccine availability, this article explores public proclivity to accept and receive vaccination in Soweto, South Africa. We measured 'acceptability' qualitatively among adults over eighteen years of age in three categories, namely acceptance, refusal, and hesitancy. In these categories, 55 percent were open to vaccination, some 35 percent were not, and about 10 percent hesitated. Reasons given for outright refusal were mostly grounded in concerns over safety and survival, faith in traditional medicines, cultural practices, or religious beliefs. Hesitators generally wished to initially monitor the vaccines' effects on others before 'getting jabbed' themselves. Meanwhile, dis- and misinformation on social media platforms fostered and fuelled vaccine hesitancy considerably. Here, we argue that whereas COVID-19 vaccine acceptance is normative, it remains crucial to unveil and address factors detrimental to acceptability, especially in the huge lower-income groups excessively affected by this virus in South Africa. Dissemination of adequate and timely information about vaccination alongside a debunking of counterfactual claims (or so- called 'conspiracy theories') may be crucial in driving forward vaccine efforts.

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CLINICAL EVALUATION OF A RAPID DIAGNOSTIC TEST FOR THE DETECTION OF SARS-COV-2 IN NASAL SAMPLES

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Molecular assays such as RT-PCR have been established as the gold standard method for detection and identification of viral pathogens. However, the Covid-19 pandemic which started in late 2019 has further highlighted the need for more affordable, easy to use yet reliable rapid diagnostic assays. This would improve the control of outbreaks by more rapidly identifying and isolating infected individuals at a wider population scale in order to break the chain of transmission. Lateral flow assays would be a good candidate for this as they are cheaper, easier to use by

both professionals and the general public and have a much faster time to result, hence why they have been widely used alongside RT-PCR to detect SARS-CoV-2 infection. Though, it is important to understand how well these tests perform to determine whether they can be used for diagnosis as an alternative to the current gold standard methods. A case study was thus put in place in Senegal using a lateral flow test which detects SARS-CoV-2 antigen in nasal swab samples and nasopharyngeal swab samples. A clinical evaluation of this test was done on a cohort of 383 patients, including symptomatic and asymptomatic cases, who were also tested using an RT-PCR kit authorised for emergency use by the FDA. The sensitivity and specificity of the rapid Covid-19 antigen test, in comparison to the RT-PCR method, were respectively 85% and 99% across all patient samples tested. These results which meet the WHO requirements for diagnostic methods in response to the Covid-19 pandemic of ≥80% for sensitivity and ≥99% for specificity therefore suggest that the rapid antigen test can be used in the diagnosis of acute SARS-CoV-2 infection.

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DYNAMICS OF THE IMMUNE HUMORAL RESPONSE IN COVID-19 VACCINATED INDIVIDUALS: A POPULATION-BASED STUDY ACROSS THE 46 MUNICIPALITIES OF BOLÍVAR, COLOMBIA, 2021

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The impact of the COVID-19 pandemic in the Colombian Caribbean region has been devastating. As of late March 2022, Bolívar was one of the most affected departments in this region, with dominant and registered circulation of Gamma, Mu, Delta, and Omicron variants that caused over 196K laboratory-confirmed cases, and over 3K COVID-19 associated deaths. Also, as of March 2022, the vaccination coverage across the 46 municipalities of Bolívar was heterogeneous; 23.9% to 68.9% of people have received one dose, and 21.4% to 73.2% have received two doses. The dynamics of the immune humoral response (IHR) has been scarcely studied in localities with large ethnic variability. Herein, we describe the dynamics of the IHR in individuals from all Bolívar's municipalities. During June to November 2021, we conducted a cross-sectional and population-based study with a convenience sample with proportional probability to the population size of each municipality, resulting in 8 to 880 samples per locality. Blood samples were collected from a total of 4079 individuals that were partially (22/4079, 0.5%) or fully vaccinated (4057/4079, 99.5%) with mRNA (mRNA-1273, or BNT162b2), non-replicating viral vector (Ad26.COV2.S, or ChAdOx1 nCoV-19), or inactivated virus (CoronaVac) COVID-19 vaccines. Anti-spike IgG antibodies were evaluated by ELISA, and the log10(ratio of signal-to-cut off [S/Co]) was used as a proxy for IHR titer. Time elapsed between sample collection and administration of the last vaccine dose was used to monitor the dynamics on a monthly basis. Among individuals, the median age was 42.8 years (IRQ: 23.8), 62.2% were women, and 41.6% self-reported a previous COVID-19 diagnosis. Overall, the dynamic changes of IHR titers were greater in partially vaccinated compared to fully vaccinated individuals. Furthermore, different dynamic patterns were observed according to the type of vaccine, age group, previous COVID-19 diagnosis, and municipality. Our results contribute reliable and real-world information on the dynamics of the IHR, and could inform vaccination strategies and prioritization of population groups with lower antibody titers.

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ETHICAL ISSUES OF PUBLIC HEALTH POLICIES TO FIGHT AGAINST COVID19 IN MALI

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The COVID19 pandemic has challenged public health policies. The magnitude of the challenge means that public policy makers must make a significant number of decisions every day. Some of these decisions will involve tensions between societal and individual values. In a pandemic such as COVID19, there is a strong ethical assessment need to consider how to do the greatest good. Tensions can be alleviated by an ethical analysis of the situation that allows for the arbitration between values to find balance leading to justifiable decisions. The present work, which is a point of view on public health policies for the fight against COVID19 in Mali, aims to illustrate the ethical issues related to social distancing, isolation, closing of the borders and quarantine and to provide benchmarks for action in line with the ethical analysis. Isolation, distancing, and quarantine are among the measures that restrict people's freedom. These measures are also the most coercive of all the actions available to public health authorities to limit the spread of the disease. Their justifiability lies in the expected beneficence and prudence adopted by public health authorities. The acceptability of these measures raises ethical issues between the value of beneficence or prudence and that of freedom. It also reveals the tension between beneficence and the values of justice and non-maleficence. However, examining COVID19 public policies provides a useful insight into the trade-offs faced by decision-makers and contributes to the necessary reflection on the meaning of actions taken by both decision-makers and the population.

1389

ROTAVIRUS GENOTYPES OVER TIME IN VACCINE-INTRODUCING AND NON-INTRODUCING COUNTRIES

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Rotavirus vaccines have substantially lowered the global rotavirus gastroenteritis burden in children aged <5 years. However, vaccines may offer less protection against some rotavirus genotypes, including G2P[4], and vaccine introduction may also exert vaccine-induced selective pressures on circulating rotavirus strains. To examine if strains that vaccines may be less effective against became more dominant over time, we systematically reviewed literature of rotavirus surveillance reporting genotype distributions between 2002 and 2019. We included data from countries with at least 6 years of surveillance data and, if a rotavirus vaccine was introduced into their national immunization program during the time period identified in the data (between 2002 to 2019, specific surveillance period varied by country), at least 2 years of data pre- and post-introduction. We estimated odds of infection by a particular rotavirus genotype (G1P[8] was the referent) over time for each country using a multinomial logistic regression with surveillance year as the exposure. The final dataset included four vaccine-introducing countries (Ethiopia, Kenya, South Africa, and Zimbabwe) and five non-introducing countries (Argentina, China, Myanmar, Nepal, and Ukraine). For vaccine-introducing countries, the odds of infection with G2P[4] increased each year in South Africa [adjusted odds ratio (aOR): 2.47, 95% confidence interval (CI): 2.47-2.48] and Kenya (aOR: 4.24, 95% CI: 4.24-4.25). For non-introducing countries, the odds of infection with G2P[4] increased each year in China (aOR=1.46, 95% CI 1.46-1.48) and Ukraine (aOR=1.93, 95% CI 1.93-

1.95). G2P[4] infection odds increased over time in some introducing and non-introducing countries; however, introducing countries had much higher odds of G2P[4] infection as time went on than non-introducing countries. These findings highlight the need for continued surveillance in both vaccine-introducing and non-introducing countries to monitor circulating rotavirus genotypes and assess potential impacts of vaccine introduction.

1390

HEMIN DRIVES PLASMA CELL DIFFERENTIATION AND VIRAL REACTIVATION OF EBV LATENTLY INFECTED MUTU I CELLS

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The connection between Epstein-Barr virus (EBV) and *Plasmodium falciparum malaria* coinfection roles in the development of Burkitt lymphoma (BL) in Sub-Saharan Africa has long-been accepted by the scientific community, yet the mechanisms involved remain unknown. A major hallmark of malarial disease is hemolysis and bystander eryptosis of uninfected red blood cells, which causes the release of heme in large quantities. In murine models, heme has been shown to bind specifically to Bach2, an important regulator of B cell proliferation and differentiation. This binding event can cause Bach2 to become unstable and degrade. Importantly, Bach2 is a repressor B-cell terminal differentiation. We hypothesized heme released during acute malaria infection drives differentiation of latently infected EBV-positive B cells resulting in viral reactivation and release of infectious virus. To test this hypothesis, Burkitt lymphoma cell lines were treated with hemin, the oxidized form of heme, and analyzed to measure cellular and viral changes. Hemin treatment degrades Bach2, followed by an increase in expression of CD138, a plasma cell marker. Additionally, RNA sequencing of hemin-treated cells revealed a large shift from B cell transcripts to plasma cell transcripts. Antibody production (IgM) was measured in culture supernatant by ELISA, which demonstrated these plasma cells are non-functional. Reactivation of EBV following hemin treatment was indicated by expression of immediate early, early, and late lytic transcripts followed by production of complete virions released in culture supernatant. This observation demonstrates heme can drive EBV reactivation through modulation of B cells, with greater implications for early events in BL pathogenesis and the impact of hemolytic events on immune cells.

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ADAPTING A COVID-19 ELISA FOR DRIED BLOOD SPOT TESTING IN MALI, WEST AFRICA

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Serosurveillance is an important method to help monitor COVID-19 in the community in Mali. We have previously adapted and qualified a two-antigen ELISA for use in local laboratories using venous blood samples from the local population. To further optimize the assay, we assessed testing using dried blood spot samples. Venous blood and dried blood spot samples were collected from a subset of participants in an ongoing longitudinal cohort serosurvey. Samples were tested in parallel to assess concordance and the performance of the dried blood spot samples. We present the results of preliminary concordance testing. Thirty-six participants from the rural town of Bancoumana had paired venous blood and dried blood spot samples for testing (median age 10 years (IQR 7 to 16.5); 55.6% male (20/36). Of these, 31/36 of venous blood samples and 31/36 of dried blood spot samples were COVID-19 seropositive (two category kappa 1.0). When assessing individual antigens, venous blood and dried blood spot signals correlated strongly for spike and RBD (Pearson r=0.9050, p<0.00001 and r=0.9524, p<0.0001 respectively). Compared to paired venous blood, one dried blood spot sample had a discordant positive RBD result, one had a discordant negative spike result and one had a discordant positive spike (four category weighted kappa 0.864). Overall, dried blood spot elution and testing was comparable to venous blood testing in the Malian population. Additional testing and analysis will be presented.

1392

ACQUISITION OF SARS-COV-2 NEUTRALIZING ANTIBODIES IN RURAL KENYA: A 24-MONTH PRE- AND PERI-PANDEMIC COMMUNITY COHORT STUDY

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At the beginning of the Covid19 pandemic, the SARS-CoV-2 burden in sub-Saharan Africa was unexpectedly moderate, leading to speculation about potential interactions or cross-protective immunity conferred by endemic pathogens, such as malaria. We hypothesized that SARS-CoV-2 sero-conversion in malaria-endemic Africa is pauci-symptomatic and mediated by co-infection with *Plasmodium falciparum*. We investigated the spread of SARS-CoV-2 in a large, densely-sampled sero-epidemiologic study in rural Kenya over 24 months with more than 500 participants. To do this, we measured the acquisition of SARS-CoV-2 neutralizing antibodies (nAbs) that block interactions between the receptor binding domain (RBD) on the SARS-CoV-2 spike S1 protein and human ace 2 using a surrogate virus neutralization test (sVNT) on dried blood spot eluates. Sero-prevalence of these nAbs was measured from January 2020 to December 2021 in 3-month intervals, and individual seroconversion was determined with 1-month resolution by testing samples in the intervening months after their last nAb-negative sample. In this community cohort, 95% of participants had at least one malaria infection in the year prior to the start of the Covid19 pandemic. We observed no evidence of pre-existing SARS-CoV-2 neutralizing antibodies in January - March 2020 samples collected prior to the first detected Covid-19 infection in Kenya in March 2020, indicating it is unlikely that *P. falciparum* exposure induced cross-protective neutralizing antibody-mediated immunity against SARS-CoV-2 infection at the beginning of the pandemic. We also determined the rate of sero-conversion within our cohort and associations of sero-conversion with symptomatic illness and *P. falciparum* malaria. By understanding SARS-CoV-2 sero-conversion in a community setting in Kenya and its interaction with endemic *P. falciparum* transmission, we can better assess risk for future possible pandemics as well as help to resolve the paradox of the initial limited impact in Africa.

1393

MUCH NEEDED INCIDENCE STUDIES IN SUPPORT OF LASSA FEVER VACCINE DEVELOPMENT: METHODS AND ENROLLMENT

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As we prepare for imminent Lassa fever virus (LASV) vaccine trials, an improved understanding of Lassa fever (LF) epidemiology is needed. The Kenema Government Hospital (KGH) in Sierra Leone participates in prospective observational epidemiology studies to characterize the prevalence and incidence of LASV seropositivity. Here we present an update on a large cohort study in Sierra Leone building on prevalence studies completed in 2018 (The PEER Health Study). Briefly, after community engagement efforts, study teams recruited randomly selected households in randomly selected villages from high prevalence districts. Study data were enumerated, including demographic data, medical history, and blood was collected using finger-sticks and dried blood spots.

Samples were tested by pan-LASV ELISA (GP-NP, Zalgen Labs, MD, USA). Volunteers will be followed to collect blood at 12 months following enrollment. Study participants extended across Sierra Leone, including 18 villages in six of Sierra Leone's 14 districts. Districts were selected based on higher reported numbers of cases from these areas. Between April 2021 and February 2022, 5,710 residents over one year old were enrolled (enrollment is ongoing, with a study target of 8,000 participants). Participants included 3019 (53%) women, 1646 (29%) children aged 2-11, and 754 (13%) adolescents aged 12-17 from 614 total households. 13 villages had previously participated in the PEER Health Study. Of the volunteers from those villages, 53% (2139/4061) reported participating in this previous study. Preliminary LASV ELISA data shows high levels of seropositivity; data from 1184 samples (782, 66% positive) across five villages with data available at this time shows per-village seropositivity rates of 46%, 68%, 69%, 74%, and 78%. The KGH LF team has successfully enrolled thousands of volunteers in one of the first studies to systematically study population-based LASV epidemiology. Initial data shows very high rates of seropositivity, suggesting high exposure to LASV. These data will support site selection and trial development as planned Lassa fever vaccine trials get underway.

1394

FACTORS ASSOCIATED WITH PERCEIVED SUSCEPTIBILITY TO COVID-19 IN THE DEMOCRATIC REPUBLIC OF CONGO

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Perceived susceptibility to COVID-19 is critical in disease prevention behavior. This assessment investigates perceived susceptibility to COVID-19 in selected regions of the Democratic Republic of Congo (DRC) and identifies associated factors. We are conducting an ongoing country-wide longitudinal phone survey using non-random sampling, and participants are contacted every two months. Rolling enrollment began in August 2021; this analysis includes those enrolled through March 25, 2022 (N=6157). Perceived susceptibility to COVID-19 is measured by the question: How susceptible do you consider yourself to COVID-19? Responses were dichotomized as susceptible (susceptible or very susceptible) and not susceptible (a little, not susceptible at all, neutral). A mixed-effect logistic regression with individual-level random effects was used to identify factors associated with the perceived susceptibility to COVID-19. The median age of respondents was 40 years (IQR: 17); 66% were healthcare workers (HCW). The proportion of participants reporting perceived susceptibility to COVID-19 fluctuated, but was similar at the beginning and end points: 54% (95%CI: 45.5, 62.6) in August 2021 to 54% (95%CI: 51.0, 56.4) in March 2022, with a peak of 65% (95%CI:64.9 - 70.7) in November 2021. Being single, a HCW, living rurally, having or living with someone with a comorbidity, belonging to a revival religion, and completing a survey during a COVID-19 wave in DRC were associated with a significant increase of perceived susceptibility. Participants living in provinces with a high cumulative burden of COVID-19 (>10,000 confirmed cases by March 2022) and who had at least a high school education were significantly less likely to report perceived susceptibility to COVID-19. Perceived susceptibility to COVID-19 in DRC is relatively low and fluctuating. Our findings highlight the need for tailored interventions to heighten the perceived susceptibility especially in provinces with high burden of COVID-19. More research is needed to investigate if the perceived susceptibility correlates with the compliance to preventive measures against COVID-19 in DRC.

1395

ASSESSING URBAN DRIVERS OF VARIATION IN DENGUE RISK IN COLOMBO CITY, SRI LANKA USING POINT PROCESS SPATIAL MODELLING

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Colombo, the capital of Sri Lanka, is densely populated with a population of 752,993 and an area of 37km^2 and has varied residential land use. Endemic for dengue transmission with two seasonal peaks, it has the highest yearly burden of dengue in the country. As part of their dengue surveillance and control system, the Colombo Municipal Council records the location of confirmed cases in Colombo city to pinpoint areas of high incidence and to administer vector control measures. The aim of the study was to investigate the spatio-temporal heterogeneity of dengue within the city at a high geographic resolution and relate this to ecological risk covariates of type of residential area, residential density, land use, and proximity to known vector breeding risk sites such as construction sites, markets, and schools. Particular focus was on how the built environment and land use changes relate to dengue incidence. Spatio-temporal analysis of individual, confirmed, geolocated dengue cases was done for the period 2000-2017 using point pattern analysis methods to develop a spatially continous map of disease risk. A point process model was fitted using Integrated Nested Laplace approximation with the R-INLA package. The model estimated dengue incidence (case counts with a population offset) at 100m x 100 m x month grids and was used to map risk across the city. From the model, we found a range of spatial correlation (the distance value above which spatial dependence becomes negligible) of 7.21km (6.89-7.54), which can inform intervention. The model was validated on 50% of the data. The analysis highlighted that there was persistent high incidence in certain areas of the city. These findings will help the dengue control program better target its activities.

1396

UNDERSTANDING COVID19 VACCINE HESITANCY IN THE JOHNSONVILLE PEPPER WULU TOWN COMMUNITY, LIBERIA, A QUALITATIVE STUDY

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The COVID-19 pandemic has had widespread morbidity and mortality, with nearly 6.2 million deaths globally. In Liberia, fewer cases and deaths have been reported than in other countries, but the limited healthcare resources in this low-income country makes the population vulnerable, in the event of more virulent variants. The COVID-19 is no exception. To protect against the COVID-19 virus, vaccines are being distributed; yet coverage targets have not been met. The objectives of this research were to understand COVID-19 vaccine hesitancy among people in the Johnsonville Pepper Wulu Town community, and to gather community feedback on what can be done to encourage the uptake of COVID-19 vaccines. A qualitative study was conducted with purposive sampling identifying 12 community members who were expected to have knowledge and understanding about the COVID-19 vaccine. All participants were aged 18 years or older and had resided in the community for not less than six (6) months. Audio recordings of in-depth interviews were transcribed and manually coded; thematic analysis was undertaken. From the study conducted, three themes were generated to group participants' statements into category which better explained what they know about the COVID-19 vaccine. Out of the 12 participants interviewed, 10 said they have not gotten any dose of the COVID-19 vaccine and were not willing to take the vaccine due to reasons like fear to die in two years after taking the vaccine and

lack of trust in Government. Eight indicated that they are not prepared to recommend the vaccine to their child/children, friends or relatives. The results of the study showed that COVID-19 vaccine hesitancy exists in the community and it comes from issues such as misinformation, lack of information, and/or mistrust. Mobilization through prominent individuals and Community based-Organizations along with building emotional support, and increased knowledge to overcome misinformation would help to alleviate the myths of death, and liaising with stakeholders to address concerns around trust could help improve uptake.

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INTRAHOST DIVERSITY OF SARS COV-2 IN UNVACCINATED AND VACCINATED PATIENTS FROM SAO JOSE DO RIO PRETO, SAO PAULO, BRAZIL

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The transmissibility and the escape of immunity of SARS-CoV-2 variants can influence the infection's natural history and impact the morbidity and mortality of COVID-19. We analyzed SARS-CoV-2 intrahost diversity in unvaccinated (Uv) and vaccinated (V) patients from São José do Rio Preto and surrounding cities. COVID-19 samples were obtained from April to July 2021 and divided into two groups: samples from Uv patients and V (patients vaccinated with CoronaVac - Butantan/Sinovac). Total RNA was extracted and the whole-genome sequencing was performed using Illumina CovidSeq. Using Pangolin COVID-19 Lineage Assigner Tool, genomes were classified, and only Gamma (P.1-like) lineages were used. Thus, for each group, we analyzed a total of 60 sequences. Intrahost single nucleotide diversity analysis was carried out using LoFreq, and annotation and prediction of genetic effects were annotated using the SnpEff. The inference of selective pressures was performed using HyPhy to detect codons evolving on diversifying (DS) or purifying selection (PS). Our results evidenced that the frequency of mutations (downstream, nonsynonymous, start lost, stop gained, synonymous and upstream) between both groups demonstrated statistically significant difference for NSP7a and S protein. The frequency of transitions (Ts) and transversions (Tsv) mutations was 207 and 76 for Uv and 243 and 95 for V group, respectively. The frequency of allele composition for each site was also analyzed, and the most common substitution is C>T in the ORF1ab region, followed by C>T and G>T in the S region for both groups. Regarding the selection analysis, on Uv individuals, 18 proteins showed PS, while 5 proteins showed DS. For V individuals, 16 proteins showed PS, while 4 proteins showed DS. The PS was mostly identified in the ORF 1ab proteins (non-structural proteins) from V group. Furthermore, our findings show that vaccination with CoronaVac favors the occurrence of PS, especially on non-structural proteins, preventing further SARS-CoV-2 genetic diversification and reinforcing the importance of vaccination to reduce virus transmission and divergence.

1398

USING A PROSPECTIVE COHORT OF AGRICULTURAL WORKERS TO QUANTIFY HOUSEHOLD TRANSMISSION OF SARS-COV-2, GUATEMALA 2021-2022

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We established a prospective, community-based, household cohort in rural southwest Guatemala to determine SARS-CoV-2 incidence and household transmission dynamics by demographic and clinical characteristics, environmental risk factors, vaccination status, and SARS-CoV-2 variant. A purposive sample of households was selected from an existing cohort of agricultural workers undergoing COVID-19-like illness (CLI) surveillance. Households undergo routine surveillance consisting of twice weekly symptom screening for CLI, defined per CDC case definition, and weekly saliva collection. Participants reporting ≥2 days of CLI or a known COVID-19 exposure are tested for SARS-CoV-2 by RT-PCR. A positive test result leads to intensive household surveillance, whereby all household members undergo CLI symptom screening and saliva collection for SARS-CoV-2 RT-PCR testing 3 times a week for four weeks. We will calculate secondary infection rate (SIR) and evaluate individual- and household-level risk factors for index case-patient infection and secondary transmission using generalized estimating equation models. We enrolled 339 participants from 74 households (Sep 2021-Jan 2022). Median household size is five (IQR: 4-6), with 0.5 persons per square meter (IQR: 0.3-0.7). Median age of participants is 21 years (IQR: 10-34), 48.1% are male, and 26.6% have ≥2 COVID-19 vaccine doses. Between January 20, 2022–March 4, 2022, during the Omicron wave in Guatemala, 23 (31%) households had at least one SARS-CoV-2 infection. Saliva samples collected during routine and intensive household surveillance are undergoing analysis and will be used to estimate the SIR and risk factors for secondary transmission within households; preliminary results will be updated and available by August 2022. In conclusion, during a 44-day period, nearly one-third of households were infected with SARS-CoV-2 Understanding SARS-CoV-2 transmission dynamics in household settings can help public health officials target interventions. Future analyses will estimate SIR from saliva and examine risk factors for primary and secondary infection.

1399

INFECTIONS DUE TO *CHLAMYDIA TRACHOMATIS, UREAPLASMA UREALYTICUM* AND *MYCOPLASMA GENITALIUM* ASSOCIATED WITH HUMAN PAPILLOMA VIRUS IN ASYMPTOMATIC SEXUALLY ACTIVE WOMEN FROM CAJAMARCA, PERU

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To determine the prevalence and risk factors of sexually transmitted infections (STIs) including *Chlamydia trachomatis*, *Ureaplasma urealyticum* and *Mycoplasma genitalium* among asymptomatic women with human papillomavirus (HPV) infection. A cross-sectional study was performed in 842 asymptomatic women from Cajamarca, Peru. The pathogens were detected using polymerase chain reaction (PCR) and the results were analyzed according to the HPV status: high-risk HPV, low-risk HPV and negative for HPV. Demographical and gyneco-obstetric data was analyzed to identify risk factors. We found that 23.99% (202/842) women were positive for HPV, of whom 79.21% (160/202) were infected with a high-risk genotype. Co-infections were evaluated and 14.38% (23/160) were positive for *Ureaplasma urealyticum*, 9.38% (15/160) for *Chlamydia trachomatis* and 1.25% (2/160) for *Mycoplasma genitalium.* We found a significant association between HPV genotype and the number of children, partners, and history of sexual abuse. The co-infection between high-risk HPV and *Chlamydia trachomatis* was associated with number of abortions,

number of sexual partners and no use of condom. Finally, co-infection between high-risk HPV and *Ureplasma urealyticum* was associated with no use of condom and history of STIs. HPV infection continues to be a highly relevant problem in Peru, particularly due to the high prevalence of high-risk genotypes. In addition, we report high rates of co-infections with other STIs, such as *U. urealyticum* and *C. trachomatis*. We highlight the importance of active surveillance to promptly diagnose these infections, since they may lead to persistent HPV infections.

1400

EVALUATION OF TEST STANDARD Q COVID-19 AG (SD BIOSENSOR INC., KOREA) FOR THE SARS-COV-2 DETECTION AMONG SYMPTOMATIC PATIENTS AND HOUSEHOLD CASE AT THE CENTRE DE TRAITEMENT AMBULATOIRE D'ANGONDJÉ, LIBREVILLE, GABON

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COVID-19 is caused by the novel coronavirus SARS-CoV-2, that leads to acute and severe respiratory syndrom. For rapid and effective patient care, simple antigen tests have been developed following the example of the reference technique, the Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) which is more expensive, which requires a qualified personnel and which has a longer execution time. These tests must be evaluated and compared to RT-PCR for deployment on Gabonese territory. At the Angondjé Outpatient Treatment Center, oro- and nasopharyngeal samples were taken from patients with suspected COVID-19 and from case-contact persons. The Standard Q COVID-19 Ag test (SD Biosensor, Republic of Korea) for the detection of SARS-CoV-2 N antigen was compared to RT-PCR, from June to October 2021. Of 76 respiratory samples, 4 (5.3%) were positive by RT-PCR while 7 (9.2%) were positive by antigen testing. The sensitivity and specificity of the Standard Q COVID-19 Ag test for the detection of SARS-CoV-2 N antigen were 75.0% and 98.4%, respectively. A total of 5 discrepancies were identified. The false negative result came from a sample with a high RT-PCR amplification threshold cycle and the other four false positive samples came from symptomatic patients. The sensitivity of the Standard Q COVID-19 Ag test was less than 80.0%, invalidating it for use as a first-line test for the Covid-19 diagnosis.

1401

SPECIFIC TRANSMISSION BLOCKING OF SARS-COV-2 USING NEUTRALIZING SULPHATED POLYSACCHARIDE FORMULATIONS TO SATURATE ACE2 RICH MUCOSA

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The inhibition of interactions between the spike protein (S) RBD and human angiotensin-converting enzyme 2 (hACE2) is crucial towards blocking the pathway of *SARS-CoV-2* invading host cells. With constant threat of evolving *SARS-CoV-2* associated with higher transmission as well as evading memory of immunizations from recurrent infections. The current trend of dominant strains tends to be "more transmissible form of *SARS-CoV-2*". We have recently reported nanomolar range activity of heparin (Unfractionated) in *SARS-CoV-2* entry. To advance its use, we adopted lipid formulation strategy to develop topically applicable transmission blocker of *SARS-CoV-2*. Lipid-based formulations are very promising due to their indispensable properties, including the biocompatibility with skin lipids, its GRAS grade characters, amphiphilic nature enabling the efficacious loading, penetration, and delivery of heparin across the skin/mucosal barriers attaining optimum neutralizing effect with minimal side effects. Our preliminary data generated with Spike-RBD-ACE2 interaction blocking experiments show the lipid formulations greatly increase the bioavailability of heparin molecules in *in-vitro*. This blocking combined with nano molar anti-viral activity is variant proof as heparan sulfate has a critical role in viral internalization post spike-receptor binding. Additionally, our *in-silico* studies point to heparin being critical to stabilizing open state of spike protein indispensable for the fusion. Further these formulations prolong exposure time acting as reservoirs of heparin which is a highly potent neutralizer of *SARS-CoV-2*. Such a well-absorbed formulation can also be exploited for the control of other diseases, for example, *HIV* transmission-blocking as well as conventional usage of heparin for varicose vein/hemorrhoids venous thrombosis.

1402

IN VITRO BIOLOGICAL CHARACTERIZATION OF THE SARS-COV-2 VARIANT P.4 AND THE CORRELATION WITH EPIDEMIOLOGICAL ASPECTS

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Since the beginning of the SARS-CoV-2 pandemics, Brazil became an important epicenter for virus dispersion, and this allowed the uncontrolled transmission of the virus in the Brazilian territory, which led to the emergence of innumerous SARS-CoV-2 variants, including variants of concern (VOCs). In this process, some VOCs that had important impact in the public health system emerged, such as variants Zeta (P.2) and Gamma (P.1). In order to follow the emergence of new VOCs, an epidemiological surveillance program was created and led to the identification of P.4, a SARS-CoV-2 variant with possible association with an increase in the number of cases in the Sao Paulo state. Therefore, this study aims to describe the biological features of P.4 variant in cell culture. After isolation of P.4 from a nasopharyngeal clinical sample, a plaque assay formation was performed to compare the plaque morphology of this variant with lineages P.1 and B.1.1.33 (the first variant detected in Brazil). Similar to P.1, the size of plaques formed by P.4 infection were larger than plaques from Lineage B.1.1.33. Furthermore, the number of plaques generated after P.4 infection was 1.6 times lower than lineage B.1.1.33 and 3.1 times higher than the observed in P.1 infection. The virus growth kinetics showed that P.4 and P.1 have a similar pattern, with a decrease in viral titer after 6h of infection, followed by a recover after 12h. Viral titers of P.4 and P.1 were similar and slightly lower than lineage B.1.1.33 48h post-infection. In the immunological aspect, a viral microneutralization assay showed that, for all variants, neutralizing antibodies induced by CoronaVac vaccination were capable to inhibit infection. No difference was observed in neutralization titers when comparing P.4 to P.1 and B.1.1.33. To complement these data, a phylogenetic analysis is in progress to evaluate the origin and introduction of P.4 in the state, correlating with a possible impact in the number of cases, hospitalizations and deaths. This combination between biological and epidemiological data will allow the better comprehension of the SARS-CoV-2 evolution dynamics.

1403

CLINICAL EVALUATION OF THE BIOFIRE® COVID-19 TEST 2

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Coronavirus Disease 2019 (COVID-19) is a contagious respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Diagnosis of COVID-19 is critical to public health efforts to identify infectious individuals and reduce the spread of disease. The BioFire® COVID-19 Test 2 was developed by BioFire Defense LLC in cooperation with the US Department of Defense (Contract Nos. W81XWH20C0076 and W81XWH21C0003) and has been cleared by the US FDA. The test targets three regions of the SARS-CoV-2 genome and is run on the easy-to-use BioFire® FilmArray® platform. Analytical sensitivity of the BioFire COVID-19 Test 2 was determined to be 2.2E+02 GE/mL with inactivated SARS-CoV-2 virus demonstrating that the BioFire COVID-19 Test 2 is a highly sensitive molecular test for the detection of SARS-CoV-2. A prospective clinical study at three different sites within the US evaluated performance of the BioFire COVID-19 Test 2 using nasopharyngeal swab specimens collected from individuals suspected of COVID-19 and the BioFire Respiratory Panel 2.1 as a comparator. The positive percent agreement (PPA) was determined to be 98.6% and the negative percent agreement (NPA) was determined to be 99.6%. In addition to the three assays included in the FDA-cleared version of the test, the test contains four additional SARS-CoV-2 assays that have not yet been reviewed by FDA and are currently masked by software. Due to the continued evolution of the SARS-CoV-2 genome, BioFire Defense has reevaluated the data obtained during the clinical evaluation with the four additional assays included. The reanalyzed data demonstrate that unmasking the additional four assays does not significantly affect sensitivity or specificity of the BioFire COVID-19 Test 2 (98.6% PPA and 99.1% NPA). An in silico analysis of currently circulating variants (as of March 14, 2022) predicted that 99.9% have perfect complementarity to three or more of the seven assays. These data indicate that unmasking the additional four assays maintains sensitivity and specificity while ensuring robust detection of evolving SARS-CoV-2 virus variants with the BioFire COVID-19 Test 2.

1404

INVESTIGATING TRANSMISSION DYNAMICS OF SARS-COV-2 IN A LARGE UNIVERSITY COMMUNITY

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The SARS-CoV-2 pandemic continues to create public health challenges across the globe, which warrants sustained research into viral transmission. One of the tools that has allowed for a better understanding of SARS-CoV-2 transmission is whole viral genomic sequencing surveillance, leading to the characterization of genome variants. Many studies have been conducted in institutional settings like healthcare, but a gap remains in studying the dynamics of variants in campus populations with in-person instruction. The goal of this study was to investigate local transmission of SARS-CoV-2 in a large university and understand the introduction events and dynamics of variants during two semesters when in-person classes had resumed, and where various control measures had been implemented. First, we sequenced 677 SARS-CoV-2 viral genomes collected through passive and active surveillance at Purdue University in Indiana throughout the first 18 weeks of 2021. We show that there were 36 distinct variants identified in this community during this period, including the presence of multiple variants of concern. For instance, Alpha and Iota reached rapid dominance, and Gamma had just emerged at the end of the semester. In addition, we conducted phylodynamic analysis of Gamma genomes in context of >21,000 other publicly available genomes and inferred that there were at least ten independent introductions into the Purdue community for this variant. These introductions were from within the state of Indiana and from other states such as Illinois, Washington, and New York, suggesting domestic spread. We also compared variant temporal trends to the state as a whole and other universities in Indiana and the Midwest and found that the overall pattern of variants over time was similar. Last, we document the rise, spread and dynamics of Omicron variant in a highly vaccinated university population. These findings shed light on the transmission dynamics of SARS-CoV-2 variants on a fine temporal scale and demonstrate the ability of sustained surveillance programs to provide important insights that can inform mitigation strategies for continued emerging variants.

1405

PERCEIVED SELF EFFICACY FOR PREVENTING DENGUE FEVER IN TWO CLIMATICALLY DIVERSE MEXICAN STATES

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Research about how knowledge and self-efficacy influence mosquito control in Mexico is limited. Our study aimed to bridge this knowledge gap by assessing individual-level variables that affect the use of mosquito control measures. Our study utilized an online cross-sectional survey with 623 participants in Colima and Sonora, Mexico. It was observed that individuals in Sonora had lower scores in knowledge and mosquito control outcomes when compared to those living in Colima. Multiple linear and logistic regression models were separately used to explore factors that predicted the mosquito control scale and the binary outcome of taking measures to control mosquitos, respectively. Self-efficacy (β=0.323, p-value = <.0001) and knowledge about dengue reduction scale (β=0.316, p-value= <.0001) were the most important predictors of mosquito control scale. The model explained 24.9% of the mosquito control scale variance. Age (OR= 1.064, p-value = <.0001) and self-efficacy (OR= 1.020, p-value = 0.0024) were both associated with an increase in the odds of taking measures against mosquitoes in the previous year. Dengue fever prevention interventions may focus on improving general knowledge about mosquito control measures in younger individuals, and people in Sonora.

1406

STOP HEP B @ BIRTH: A COMMUNITY-ORIENTED CARE MODEL FOR MICRO-ELIMINATION OF MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B IN PERI-URBAN YANGON: A SINGLE ARM PROSPECTIVE STUDY

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Mother-to-child transmission (MTCT) accounts for most chronic hepatitis B virus (HBV) infections in Southeast Asia. Elimination of MTCT of HBV is theoretically possible, but evidence is lacking for implementation strategies that provide cost-effective, equitable access to a comprehensive suite of interventions in low- resource settings. We conducted a single arm trial of a community-oriented primary care model for micro-elimination of MTCT of HBV in a population of 80,093 in peri-urban Yangon, Myanmar. Between August 2018 to December 2021 local antenatal care (ANC) clinics screened 17,718 pregnant women for chronic HBV (HBsAg), 561 (2.9%) of whom tested positive. Among 107 HBsAg positive women resident in the study area, 62% had less than high school education; all 19 (18%) with a viral load >200,000 IU/mL were initiated on tenofovir (TDF) therapy starting at 20 weeks gestation (55%) or their first ANC visit, whichever was later. Among 102 live births, 93 (92%) of newborns

received timely (less than 24 hours after birth) HepB birth dose vaccination, including 26 (24%) born at home. Among 19 women eligible for TDF, 16 (84%) achieved viral suppression (<200,000 IU/mL) at delivery; all of their newborns received timely hepatitis B immune globulin (HBIG). Among 64 (63%) of infants tested at 24-28 weeks of age, none were HBsAg positive. Our findings demonstrate the feasibility of delivering HepB birth dose vaccine, TDF and HBIGto prevent MTCT in a defined population in a low resource peri-urban setting where at least one in four women deliver at home. Although initiation of TDF at 20 weeks gestation may suppress viral load for most pregnant women, residual risk for MTCT of HBV likely will persist until a higher proportion of women present to their first ANC visit before 20 weeks gestation. Active community participation likely enhanced the resilience of the approach during the dual shocks of the SARS-CoV2 pandemic and the military takeover in 2021.

1407

DEFINING PROTECTIVE ANTIBODY RESPONSES TO A RECOMBINANT SUBUNIT EBOLA VIRUS VACCINE: THE SEARCH FOR A CORRELATE OF PROTECTION

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Ebola virus (EBOV) causes lethal hemorrhagic fevers with case fatality rates of up to 90%. Outbreaks are sporadic and unpredictable and vaccination has been key to controlling disease. However, due to limited stocks of approved vaccines and requirement of cold-chain storage, there is a need to continue developing new vaccines with more appropriate product characteristics. In addition, although all vaccine candidates use the surface glycoprotein as the main antigen, the method of protection induced by the EBOV glycoprotein remains unclear. We have developed a recombinant subunit vaccine that has an increased safety profile and thermostability, allowing easier deployment in endemic regions. Our vaccine has shown high efficacy in the gold standard non-human primate model, with 3 doses showing 100% protection. Characterizing these protective antibody responses is ongoing. Subunits of the EBOV glycoprotein (GP) have been produced in *Drosophila* S2 cells including full length GP, GPΔmucin-like domain, GP1, GPcl, sGP, and GP2. These subdomains were used to explore the binding patterns of antibodies using a multiplex immunoassay, in order to analyze specific GP subregions antibody populations are targeting. Neutralizing titers were also obtained via microneutralization assay using pseudotyped rVSV-EBOV-GP-GFP. While vaccination elicited potent antibody titers, we found no significant relationship between overall IgG titer and protection. However, our data indicate that quality of the overall immune response may be correlated to protection. We found significantly higher neutralizing titers in NHPs that survived EBOV challenge while IgG binding patterns to the EBOV GP subunits suggested that increased binding to GPΔmucin-like domain over full-length GP was detrimental to protection. We are further exploring the relationship between targeted regions and other functional qualities of the antibody response. Currently, mechanisms of protection do not have a clear pattern between vaccine platforms. Our findings will be an important step towards establishing universal correlates of protection for Ebola virus and other filoviruses.

1408

CLINICAL AND ECONOMIC IMPACT OF COVID-19 ON PLANTATION WORKERS: PRELIMINARY RESULTS FROM THE GUATEMALA AGRICULTURAL WORKERS AND RESPIRATORY ILLNESS IMPACT (AGRI) STUDY

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The clinical and economic impact of COVID-19 and other respiratory pathogens on agricultural workers is poorly understood, especially in the global South. In the AGricultural workers and Respiratory Impact (AGRI) study, we evaluated the clinical and socioeconomic burdens of respiratory disease in a cohort of Guatemalan banana plantation workers in southwest Guatemala. All eligible workers were offered enrollment from June 15-December 30, 2020, and annually, then followed for influenza-like illnesses (ILI) through: 1) self-reporting to study nurses, 2) sentinel surveillance at health posts, and 3) absenteeism. Workers with ILI submitted nasopharyngeal swabs for influenza, RSV, and SARS-CoV-2 testing, then completed surveys at days 0, 7, and 28. Through October 10, 2021, 1,833 workers developed 169 ILIs (12.0/100 person-years) and 43 (25.4%) of these ILIs were laboratory-confirmed SARS-CoV-2 (3.1/100 person-years). Workers with SARS-CoV-2-positive ILI reported more anosmia ($p<0.01$), dysgeusia ($p<0.01$), difficulty concentrating ($p=0.01$), and irritability ($p=0.01$), and greater clinical and well-being severity scores (Flu-iiQ) than test-negative ILIs; they also had greater absenteeism ($p<0.01$) and lost income (median US$127.1, $p<0.01$; monthly median household income=US$363.2; monthly food basket price in Guatemala=US$386.3). Guatemalan plantation workers in this cohort experienced a substantial burden of acute respiratory illness during the COVID-19 pandemic, of which one in four tested positive for SARS-CoV-2. Those with COVID-19 had greater disease severity, absenteeism, and economic losses than workers with SARS-CoV-2-negative ILI, and they lost approximately one-third of their monthly household income, placing them well below the monthly food basket price in Guatemala.

1409

ASYMPTOMATIC SARS-COV-2 INFECTIONS, BNT162B2 MRNA COVID 19 VACCINE-RELATED SYMPTOMS, AND CORRELATES OF IMMUNITY IN POST-VACCINATION BREAKTHROUGH INFECTIONS IN THE PROSPECTIVE ASSESSMENT OF SARS-COV-2 SEROCONVERSION (PASS) STUDY

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To evaluate clinical and immunological outcomes of SARS-CoV-2 infection and vaccination, we have been conducting a single-center, observational cohort study of healthcare workers. 271 participants were enrolled between August 25, 2020 and March 24, 2021. Testing for IgG antibodies against SARS-CoV-2 spike protein is conducted using a microsphere-based multiplex immunoassay interpolated against an internal standard curve for binding antibody units (BAU) and has been performed on serum samples collected at monthly visits between September 2020 through August of 2021, and quarterly since that timepoint. Neutralizing antibody titers against wild-type virus are determined by microneutralization assays and against wild-type, delta, and omicron variants by lentiviral pseudovirus neutralization assays. For the first 6 months of the study participants completed a symptoms questionnaire every day they had any symptoms different from baseline. During this period, 12 participants were diagnosed with SARS-CoV-2 infection. All 12 had at least mild symptoms of COVID, demonstrating that asymptomatic SARS-CoV-2 infection is likely rare. Of 206 participants evaluated for adverse effects after 1st and 2nd vaccine doses of the BNT162b2 mRNA COVID vaccine, no relationship was observed between vaccine-associated symptom scores and antibody titers 1 month after the 2nd vaccination. Longitudinal studies demonstrate that anti-spike IgG binding antibodies decrease from a geometric mean (GM) of 1929 BAU/mL at 1 month post-vaccination to a GM of 442 BAU/mL at 6 months post-vaccination ($P < 0.001$, n=187), and that boosting greatly enhances IgG BAU to spike protein. While only 5 of 39 participants had detectable neutralizing activity against Omicron 1 month after 2 BNT162b2 vaccinations, booster vaccination resulted in detectable neutralizing activity in the serum of all participants. Ongoing studies are evaluating serological and cellular immune responses immediately prior to 13 post-vaccination and 25 post-booster breakthrough infections in an attempt to identify immune correlates of protection and will be reported at the conference.

1410

RECONSTRUCTING THE SARS-COV-2 EPIDEMIC IN EASTERN UGANDA: INSIGHTS FROM A MALARIA LONGITUDINAL STUDY

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Understanding population-level exposure and immunity to SARS-CoV-2 is necessary to inform future public health responses to new variants. However, estimating the proportion of the population that has been infected is complicated by asymptomatic or sub-clinical infections, inadequate testing capacity, and challenges in collecting routine surveillance data. Seroprevalence surveys can bridge this gap by identifying antibody responses to prior SARS-CoV-2 infection. We leveraged an ongoing malaria cohort in Tororo and Busia Districts, Uganda, to measure SARS-CoV-2 seroprevalence after each pandemic wave. Notably, this cohort involves monthly serum collection and continuous passive surveillance for all illness at a dedicated study clinic. We tested a total of 1,093 samples from 434 individuals aged 0.5 to 73 years using a standardized Luminex assay to detect IgG against the SARS-CoV-2 Spike protein. Specificity of the assay was 100% and sensitivity was 93%. Round 1 samples (n=245) were obtained from October-November 2020, round 2 (n=414) samples were obtained from March-April 2021 (post-Alpha), and round 3 samples (n=434) were obtained in August-September 2021 (post-Delta). Overall seroprevalence was 22% in round 1 samples, 38% in round 2 samples, and 60% in round 3 samples; seroprevalence was consistently higher with increasing age, with adults in the final round having a seroprevalence of 77%. There was no association between seroconversion and malaria incidence, household wealth, household construction, or sanitation. Cough, headache, any GI diagnosis, and number of unscheduled visits were all associated with a higher risk of seroconversion. Seroprevalence as assessed in this longitudinal cohort in eastern Uganda suggests a substantially higher level of population exposure to SARS-CoV-2 than indicated by case count data and is consistent with a meta-analysis of seroprevalence studies in Africa that estimated seroprevalence at 65% in Q3 2021 (Lewis et al.). We are currently generating data from an additional serosurvey round in February-March 2022 to estimate the attack rate of the Omicron wave in this population.

1411

GENOMIC SURVEILLANCE OF SARS-COV-2 IN PUERTO RICO REVEALS EMERGENCE OF AUTOCHTHONOUS LINEAGE AND VARIANT TURNOVER DYNAMICS

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Since the start of the COVID-19 pandemic in 2019, genomic surveillance has been critical to track the global transmission and evolutionary changes of SARS-CoV-2 emergent variants. We conducted a genomic surveillance study through a partnership with local health agencies and academic institutions to understand the emergence and molecular epidemiology of SARS-CoV-2 in Puerto Rico. During March 2020-March 2022, we collectively sampled COVID-19 cases monthly and sequenced over 4,379 SARS-CoV-2 genomes, accounting for more than 50% of the genomes from Puerto Rico published in GISAID, to reconstruct the local epidemic in a regional context using phylogenetic inference. Our analyses revealed that multiple importation events from the continental United States propelled the emergence and spread of the virus throughout the study period, including the introduction and spread of most SARS-CoV-2 variants detected world-wide. Lineage turnover cycles through various phases of the local epidemic were observed, including the emergence of the Omicron variant, where the predominant lineage was replaced by the next competing lineage or variant after approximately 4 months of circulation locally. We also identified the emergence of lineage B.1.588, an autochthonous lineage that predominated circulation in Puerto Rico from September to December 2020 and subsequently spread to the

United States. This collaborative approach highlights the importance of partnerships, timely collection of samples and analysis of SARS-CoV-2 genomic surveillance data to inform public health responses.

1412

A DESCRIPTIVE LOOK AT COVID CASE INVESTIGATIONS AND CONTACT TRACING IN BRAZOS COUNTY, TEXAS FROM MARCH 2020 TO JULY 2021

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To aid local capacity, Texas A&M University partnered with the Brazos County Health District to conduct COVID case investigations and contact tracing. Investigators interviewed persons testing positive for SARS-CoV-2 (cases). We analyzed epidemiologic and clinical factors using STATA 16, Poisson regression to estimate prevalence ratios (PR [95%CI]) across age groups. During Mar 2020 through Jul 2021, 30126 cases were reported. Most were white (66%), non-Hispanic (52%), young (median age 24 yrs, range 0-101.), with 48% young adults (18-29 yrs). Cough (43%), headache (40%), fatigue (34%), and aches (33%) were the most common symptoms. Clinical presentation was unknown for 24% while 68% were symptomatic. Asymptomatic infections were less common in teens (12-17 yrs; PR 0.6 [0.5–0.8], p<0.01) and older adults (≥65 yrs; PR 0.7 [0.6–0.8], p<0.01) than children. Children (0-11 yrs) had fever (45%), cough (38%), rhinitis (31%), while young adults (18-29 yrs) had cough (59%), pharyngitis (55%) and fatigue (53%). Influenza-like illness (PR 1.4 [1.3-1.4], p<0.01), gastroenteritis (PR 1.7 [1.5-1.9], p<0.01), or loss taste/smell (PR 2.0 [1.8-2.3], p<0.01) were more common in adults (≥18 yrs) than children (<18 yrs). Incubation period was 2 days from test date (median; range 0-101), symptoms lasted 6 days (range 0-21), and was resolved in 2 days (range 0-94). Few individuals (3.3%) were hospitalized, and 281 (0.9%) deaths occurred. Contact tracing revealed a range of 0-300 close contacts per case (household contacts range 0-18), with information provided on 18138 total close contacts. Most contacts were exposed in their households (69%) or via family members (56%). During interviews, close contacts were given post-exposure testing guidance, but testing prior to interview was more common when exposures resulted from co-workers than from other sources, such as family members (PR 1.7 [1.3-2.3], p<0.01). In summary, asymptomatic SARS-CoV-2 infection were uncommon. Clinical presentation varied by age group, with syndromes more prevalent in adults than children, which could direct syndromic surveillance and testing recommendations.

1413

ORACOV: AN IMPROVED VACCINE PLATFORM TO DELIVER A ROOM TEMPERATURE STABLE, ORALLY ADMINISTERED VACCINE AGAINST SARS-COV-2 AND OTHER EMERGING INFECTIOUS DISEASES

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OraCOV is a foam dried, room temperature stable SARS-CoV-2 vaccine administered orally as a drink. We used Ty21a, the attenuated *Salmonella Typhi* vaccine, to stably express and secrete SARS-CoV-2 antigens. Ty21a is administered orally in 3-4 doses over 6 days, has an excellent safety record in >150M recipients, and induces protection against typhoid fever for 3-7 yrs. Oral administration induces protective IgA and IgG antibodies and T cells through exposure of the oral and GI mucosa. We have developed a Ty21a vaccine strain, stably expressing and secreting SARS-CoV-2 antigens. One of the challenges for Ty21a-based vaccines is to achieve robust expression and secretion of heterologous antigens that are stable. To do so, we integrated the SARS-CoV-2 spike ectodomain (eS) and the receptor binding domain (RBD) into the Ty21a chromosome, using the lambda-Red recombineering system. We 1st integrated the eS, along with the *E. coli* α-hemolysin (HlyA) secretion apparatus, to the viaB locus. To further increase the expression, we have integrated an additional copy of the different antigens in alternative positions in the genome. This resulted in a dramatic increase in expression and secretion of the antigens that is anticipated to significantly improve humoral and cellular responses to immunization. For better survival of the vaccine in the acidic digestive tract, we introduced a *Shigella sonnei* acid-resistance gene cassette and demonstrated acid resistance *in vitro*. We achieved stable, bioactive viability of the bacterial-based vaccine for several months at room temperature and 4 °C through foam drying. This was accomplished through optimizing foam drying protective additives that shield the vaccine from oxidation, swings in pH, and other chemical reactions. Our Ty21a-vaccine vector platform is excellent at expressing foreign genes. Thus, success in this project will establish the Ty21a platform as universal for responding to many emerging, re-emerging and current infectious diseases.

1414

NON-NEUTRALIZING ANTIBODY-MEDIATED RESPONSE TO SARS-COV-2 INFECTION

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The role of neutralizing antibodies to SARS-CoV-2 as correlates of immunity has been extensively studied, however, the function of non-neutralizing antibodies in contributing to viral clearance and immunity is poorly understood. Studies have shown that up to 40% of individuals following COVID-19 fail to generate detectable neutralizing antibodies but successfully clear SARS-CoV-2 infection suggesting other mechanisms for viral clearance. We hypothesize that non-neutralizing antibodies eliminate virus-infected cells by binding to the cell surface to trigger functions such as antibody-dependent cellular cytotoxicity (ADCC). To examine this hypothesis, we infected VERO cells with the wild virus at different multiplicities of infection. We examined antibody reactivity to the cells with sera from naturally infected individuals, immunized individuals without prior COVID, and immunized individuals with prior COVID by surface immunofluorescence staining and flow cytometry in non-permeabilizing conditions. We show sera from individuals following COVID infection have greater reactivity to virally infected cells compared to sera from immunized individuals normalized for antibodies to Spike (S) protein. Using monoclonal antibodies and sera following COVID infection we demonstrate S, N, and M but not E SARS-CoV-2 structural proteins are recognized on the surface of infected cells. We have developed an ADCC killing assay of infected cells using NK cells. Studies are underway to evaluate the relative opsonic killing with antibodies from COVID infected, vaccinated, and vaccinated with prior infection from a longitudinal cohort study of nursing home residents and health care workers. We will explore whether this opsonic killing differs among viral strains. In conclusion, we show virally infected cells express SARS-CoV2 structural proteins on their surface that are recognized by sera from COVID infected and or vaccinated individuals that may mediate opsonic killing of the cells.

1415

SEROLOGICAL REACTIVITY AND FUNCTIONAL IMMUNITY AGAINST SARS-COV-2 IN VARIOUS COMMUNITIES IN LIBERIA

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The ongoing COVID-19 pandemic has highlighted the global need for rapid and effective surveillance of emerging infectious viruses. While full-scale testing of SARS-CoV-2 and its variants has been conducted globally, Liberia remains largely neglected. This has left a gap in knowledge as to what variants are in Liberia and how widespread exposure is within the country. Our previous efforts in Liberia have led to the development of a mobile scientific laboratory located at the University of Liberia, Fendell campus. We developed a multiplexed immunoassay (MIA) to assess exposure to several SARS-CoV-2 variants along with the seasonal coronavirus, NL63. Additionally, we investigated unrelated viral exposures to Dengue serotype 2 (DENV-2) and Chikungunya virus (CHIKV). This serological study was conducted in collaboration with the National Public Health Institute of Liberia (NPHIL) over the summer of 2021 on available samples from four counties within the country (n=188). To assess anti-SARS-CoV-2 antibody functionality we developed a novel multiplexed inhibition test (MINT) which assesses the ability of antibodies to inhibit the Spike-ACE2 interaction. Overall, our study suggests elevated reactivity in urban counties compared to rural regions for Wuhan-Hu1, Alpha, and Beta variants. MINT also demonstrated the presence of functional antibodies inhibiting receptor-binding of these variants. Furthermore, antibodies to viruses previously not reported in Liberia were detected (DENV-2 & CHIKV). Collectively this study highlights the feasibility of conducting large-scale immunosurveillance studies in Liberia with a substitute for neutralization assays. This work further serves to encourage broader studies to investigate the viral landscape of Liberia and allows capacity building for future pandemic preparedness in the region.

1416

MULTI-ORGAN NATURAL EXPRESSION OF HUMAN ACE2/TMPRSS2 RECEPTOR COMPLEX FOR SARS-COV-2 IN A HUMAN IMMUNE SYSTEM-HUMANIZED DRAGA MOUSE (HLA-A2. HLA-DR4. RAG1 KO. IL-2RGC KO. NOD)

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Beyond mild to severe acute respiratory distress syndrome induced by SARS-CoV-2 infection, a frightening aspect is the potential of lingering multi-organ pathologies long after infection may have been cured. Thus, clinically relevant animal models for SARS-CoV-2 infection that will allow investigations on the mechanisms of multi-organ human-like pathogenesis are urgently needed. The human immune system (HIS)-humanized DRAGA mouse (HLA-A2.HLA-DR4.Rag1KO.IL-2RgcKO.NOD) was recently reported as an *in vivo* surrogate human model for COVID-19. Using immunofluorescent microscopy, immunoblotting and quantitative measurements in ELISA, we here report that the HIS-DRAGA mice express naturally the main human (h)ACE2/(h)TMPRSS2 receptor complex for SARS-CoV-2 to different extends in the lungs, liver, kidneys, cerebellum cortex and small intestine. Hence, this preclinical new model for COVID-19 may offer unique advantages for studying the mechanisms of multi-system complications including human-like immunopathological events at different stages of infection and later after infection has been cured.

1417

SARS-COV-2 NEUTRALIZING ANTIBODY REPERTOIRE AFTER INFECTION AND VACCINATION

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The individual subunits of the spike protein are the targets of a strong neutralizing antibody response from both SARS-CoV-2 natural infection and vaccination. It is known that mRNA vaccination generates a more balanced neutralizing antibody response between the spike subunits: spike subunit 1 (S1), spike subunit 2 (S2) and the receptor binding domain (RBD), while infection tends to result in a skewing of the response toward RBD. The questions of how infection with SARS-CoV-2 variants might skew the antibody response to SARS-CoV-2 and if disease severity impacts the strength of the response toward RBD are highly relevant in understanding protective responses to SARS-CoV-2. Here, we functionally define the role SARS-CoV-2 spike subunits RBD, S1, and S2 play as a target of the human neutralizing antibody response to the initial SARS-CoV-2 circulating strains versus variants of concern. In this study, we identify the spike protein subunits that contain antigenic determinants and examine the neutralization capacity of polyclonal sera from a cohort of SARS-CoV-2$^+$ patients, ranging in disease severity. Using an ELISA format, we assessed binding of human sera to S1, RBD and S2. To functionally identify the key target of neutralizing antibody, we depleted sera of subunit-specific antibodies (S1, RBD and S2) to determine the contribution of these individual subunits to the neutralization of WA-1 and B.1.351. We demonstrate that epitopes within RBD are the target of a majority of the neutralizing antibodies in the human polyclonal antibody response after infection, although both infection and vaccination, induce S2 neutralizing antibodies in many individuals. The targets of antibody neutralization differs between infection and vaccination, suggesting that mechanisms of virus neutralization may differ as new variants arise. These data confirm the RBD of spike as susceptible to polyclonal antibody mediated neutralization and demonstrates the ability of the human B cell response to generate a broad antibody repertoire, providing critical information for the next generation of vaccines.

1418

SEROSURVEILLANCE FOR SARS COV-2 ANTIBODY IN FERAL HOGS AND WHITE-TAILED DEER IN TEXAS

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Serological evidence of SARS CoV-2 infections have been reported in white-tailed deer (WTD) in the United States. Even though WTD are susceptible to SARS CoV-2 infection, there is no evidence of SARS CoV-2 infection in other mammal species that might inhabit and interact with WTD in nature. WTD and feral hogs are widely distributed in Texas and generally overlap in their range. The aim of this study was to determine SARS CoV-2 antibody seroprevalence in feral hogs and WTD in Travis County, Texas during 2018 (prepandemic period) and from March 2020 to March 2021 (pandemic period). Sera samples were tested for neutralizing antibody in Vero cells to SARS-CoV-2 using a constant dose of SARS-CoV-2 virus and a 1:10 dilution of each sample. SARS CoV-2 antibody was not detected in any of the 166 feral hog sera samples collected during the prepandemic and pandemic period. In contrast, 11.83% (20/169) of the WTD sera samples collected during the pandemic period were positive for SARS CoV-2 antibody, while no antibody was detected in the 40 WTD samples collected during at the prepandemic period. Interestingly, SARS CoV-2 prevalence in WTD was null during October to December 2020 and

increased to 28% and 52% in January and February 2021 respectively, suggesting a rapid spread of the virus. These results provided the first evidence of SARS-CoV-2 infection in WTD in Texas and no evidence of infection among feral hogs.

1419

SENORINEURAL HEARING LOSS IN SARS COV-2 INFECTION

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SARS CoV-2 Virus infection mainly affects the respiratory tract leading to pneumonia. However neuronal inflammation leading to sensory neural hearing loss is quite rare but has been reported. Pathogenesis is not known, theories like immune-mediated process related to viral infection, neurotropic and neuroinvasive properties of virus, and the affinity of virus to ACE2 recptors whose abundance is seen in haering centre leading to local cytokine release, etc have been postulated. We report a case of a 22-year-old woman with no prior known co-morbidities and a history of cesarean section two weeks back who presented with insidious onset gradually progressive bilateral painless pitting pedal edema for 10 days associated with decreased urine output for two days. She was hospitalized due to the development of sudden onset breathlessness and sudden onset bilateral hearing loss. There was no history of any trauma, vomiting, vertigo or any drug intake before this episode. On examination, she was tachypneic, with bilateral diffuse crepts on lung auscultation and required 4-liters of supplemental oxygen via nasal prongs. Her CT thorax showed bilateral peripheral ground-glass opacities and consolidations suggestive of COVID-19. Her throat swab for SARS CoV-2 RT-PCR came out to be positive. Her blood investigations showed severely deranged renal function with prerenal azotemia, metabolic acidosis, and hyperkalemia, and was given one session of hemodialysis for the same. ENT evaluation suggested sensorineural pattern of hearing loss and she was started dexamethasone along with supportive management. However, she continued to deteriorate and was intubated and put on mechanical ventilator support in view of worsening type 1 respiratory failure. She went into cardiopulmonary arrest and succumbed to death. This case emphasizes one of the rarely reported manifestations of COVID-19, in the form of sudden-onset sensorineural hearing loss. Early detection of same may help in early initiation of steroid with mortality benefit.

1420

VARICELLA ZOSTER ENCEPHALITIS IN AN IMMUNOCOMPETENT LADY

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Human alpha herpesvirus 3 (HHV-3), referred as *Varicella zoster* virus causes chickenpox (varicella) commonly affecting children and young adults, and shingles (varicella zoster) in adults but rarely in children. It rarely causes encephalitis in adult around 1 in 33,000-50,000 varicella cases and very rare in immunocompetent. A 49-Year-old woman without any prior co-morbidity presented to emergency department with complaints of intermittent holocranial throbbing type headache for six days relieving on over-the-counter medications, associated with single episode of non-bilious, non-projectile vomiting four days back. Following that there is altered mental status for last two days in the form of decreased responsiveness and one episode of generalised tonic clonic seizure. On examination patient was found to have vesicular rash on the left upper abdomen and medial side of left thigh. CE-MRI revealed features of viral encephalitis. CSF analysis showed total leucocyte counts of 1920/cumm (80% monomorphs), high protein levels, low sugar levels, and Biofire (multiplex PCR) yielded positive result for *Varicella zoster* virus. IV acyclovir was started for the same. On due course, she recovered and is doing good in follow-up. Usual risk factors like HIV, malignancy, elderly, history of organ transplant, any recent psychological stress, immunosuppressive drugs/steroid intake were absent in this patient. Hence it is important to thoroughly examine the patient for varicella and to keep the suspicion of CNS involvement in patient's having headache, as it was there during the initial course in this patient. Timely identification in CSF with Biofire leads to delay in treatment initiation in immunocompetent as CSF picture was not suggestive of typical viral encephalitis.

1421

EXPLORING THE ROLE OF *PF*CORONIN IN WILDTYPE AND ARTEMISININ-RESISTANT *PLASMODIUM FALCIPARUM*

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The frontline artemisinin (ART) drug class has been critical to malaria control. However, treatment failures of ART combination therapies (ACTs) in some parts of the world threaten their efficacy. ACT treatment failures in Southeast Asia have been attributed to mutations in the *Plasmodium falciparum* (*Pf) kelch13* locus. Mitigating the spread or emergence of ART resistance in Africa, where malaria is most prevalent, is a critical global public health priority.Previously, we found that *Pfcoronin* mutations drive in vitro evolved ART resistance in Senegalese isolates, as measured by the ring-stage survival assay (RSA). To investigate whether this resistance could be attributed to decreased *Pf*Coronin levels, as previously reported for *Pf*Kelch13, we performed immunoblot-based quantification analysis using parasites in which either WT or mutant *Pf*coronin was tagged with spaghetti monster-HA (smHA). Consistent with the RSA phenotype, we found 61-77% less Coronin in the mutant than in WT ring stage parasites, while protein levels were unchanged in late-stage parasites. However, complete loss of *Pf*coronin (knockout) was insufficient to confer ART resistance. This indicates that *Pfcoronin*-mediated ART resistance is more complex and likely involves dynamic changes. To explore the role of *Pf*Coronin, we undertook interaction studies. We immunoprecipitated smHA-tagged *Pfcoronin*, followed by mass spectrometry. In both WT and mutant parasites, the major interacting partner of *Pf*Coronin was *Pf*Actin-1 in both rings and trophozoites stages. By contrast, the second most enriched protein in WT parasites was *Pf*Polyubiquitin (*Pf*PUb), but only in ring stage. *Pf*PUb in rings was significantly less enriched in the mutant than in the WT. In trophozoites, *Pf*Ub was equally enriched, with no significant difference between mutant and WT. These results highlight the role of protein turnover in modulating *Pfcoronin*-mediated ART resistance. One speculation is that the reduced protein turnover rate in mutant parasites likely modulates *Pfcoronin*-mediated ART resistance via the ubiquitin-proteasome system.

1422

PREVALENCE OF SULFADOXINE-PYRIMETHAMINE RESISTANCE MARKERS OF *PLASMODIUM FALCIPARUM* AMONG PREGNANT WOMEN IN AN AREA OF HIGH MALARIA TRANSMISSION: NCHELENGE, ZAMBIA

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Malaria infection has devastating consequences on pregnancy. To protect against adverse outcomes, the World Health Organization recommends the provision of intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP) at monthly intervals from the second trimester to delivery among asymptomatic women resident in areas of moderate to high malaria transmission. However, high levels of malaria parasite resistance compromise the therapeutic efficacy of SP,

underscoring the importance of monitoring SP-resistance markers in the *Plasmodium falciparum* population. As part of a 3-arm, parallel, partially placebo-controlled, individually randomised, phase-3, superiority trial involving 5,436 pregnant women in an area of high malaria transmission and high SP resistance in Nchelenge District of Zambia between 2019-2022, the first 200 falciparum-positive samples collected at enrolment from asymptomatic women were analysed for the frequency of the dihydropteroate synthase (*dhps*) 540 mutation and dihydrofolate reductase (*dhfr*) 581 mutation. The prevalence of the *dhps*540 mutation was 66.8% (95% CI: 59.8, 73.3). Sample analysis is currently underway for the prevalence of the *dhfr*581 mutation and will be presented. Results of Day 28 parasite clearance by slide microscopy and polymerase chain reaction assay will also be presented. These results are consistent with findings from a random selection of 96 malaria-positive samples analysed from a pregnancy cohort of 1,084 women conducted in the Nchelenge district between 2013-and 14. At that time, 70.8% (95% CI: 60.8, 79.2) of samples expressed the *dhps*540 mutation, and 9.4% (95% CI: 4.2, 16.0) had the *dhfr*581 mutation. The prevalence of *dhps*540 resistance markers remains high among pregnant women in Nchelenge and is relatively unchanged over the past decade, underscoring the continued need for a more efficacious preventive treatment for use in IPTp in malaria-endemic areas of high resistance to SP.

1423

DESIGNING CHEMOPREVENTION TRIALS TO MEASURE PROTECTIVE EFFICACY AND EFFECTS OF RESISTANCE: INSIGHTS FROM SIMULATION

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Malaria chemoprevention, involving the administration of sulfadoxine-pyrimethamine (SP) alone or in combination with other antimalarials, is an important component of malaria control efforts in vulnerable groups. The duration of SP protection against new infections is likely dependent on the prevalence of mutations in the *dhfr* and *dhps* genes that confer or facilitate parasite resistance to SP, but this effect has not been fully quantified. Studies that characterise parasite genotypes at multiple time points after SP treatment can help to determine the impact of these mutations on parasite clearance and the duration of protection against new infections. Here we use a simulation approach to determine the required sample size for such studies to detect a difference in protective efficacy between resistant and sensitive parasite strains. Assuming a 50% frequency of a resistance marker (e.g. *dhps* 540E) in the parasite population, an infection rate of one infection per person per year, and an expected difference of 15 days in prophylaxis, preliminary findings suggest that a sample size of approximately 490 children without malaria symptoms treated with SP would be required to detect a difference between the proportion of infections with a resistant or sensitive parasite by 63 days of follow-up, with a power of 90%. The respective sample size required to detect a difference in the mean time to new infection is approximately 230 asymptomatic children. Higher transmission settings are associated with more reinfection events; hence, a smaller sample size would be required. In addition, the observed proportions of resistant or sensitive reinfections, and sample size required, depend on the frequency of the parasite strains as well as drug efficacy against each type. We explore the robustness of the results with and without a control group, though appreciating that this may not be ethically possible. Further, loss to follow-up will be considered in our ongoing work on sample size calculations.

1424

THE MYSTERY OF THE ADAPTIVE PROLINE RESPONSE SOLVED: LOSS OF FUNCTION OF THE *PLASMODIUM FALCIPARUM* MFR4 MEDIATES HALOFUGINONE RESISTANCE

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We have previously shown that resistance to halofuginone (HFG), a potent antimalarial that targets the *Plasmodium falciparum* cytoplasmic prolyl tRNA synthetase (*Pf*cPRS), can be achieved by the parasite through two different mechanisms: The Adaptive Proline Response (APR) and mutation in the target gene. The APR confers low level resistance to HFG by increasing the intracellular proline levels in the parasite up to 20-fold, thereby competing with HFG for binding of *Pf*cPRS (PMID: 25395010, 25995223, 30773881). We identified that arginine is the most important source for the increased proline levels in the resistant parasites and we hypothesized that disruption of the arginine-proline biosynthesis pathway would inhibit parasites from becoming HFG resistant through APR. We disrupted ornithine δ-aminotransferase (OAT), a critical enzyme in this pathway, and thereby eliminated arginine as source of proline in OAT knockout parasites (ΔOAT). Surprisingly, these parasites could still become moderately resistant to HFG and their proline levels were still elevated, albeit not through arginine. To understand the genetic changes underlying the phenotype, we performed whole genome sequencing of these resistant lines and revealed mutations in the major facilitator superfamily related protein 4 gene (*pfmfr4*, PF3D7_0914700) resulting in predicted frameshift and nonsense mutations. To demonstrate that MFR4 loss of function is the cause of APR, we generated *Pf*MFR4 knockout parasites (ΔMFR4). ΔMFR4 parasites showed a moderate HFG-resistance phenotype despite never having been exposed to HFG. Metabolomic profiling revealed a 20-fold increase in proline levels similar to what was observed in the APR. In addition, we reverted one of the observed loss of function mutations in a previously selected line back to its WT allele which restored *Pf*MFR4 protein levels and rendered the parasites susceptible to HFG again. We present *Pf*MFR4 as a novel proline exporter and demonstrated that *Pf*MFR4 loss of function leads to a buildup of intracellular proline causing the APR.

1425

EVALUATION OF IN VITRO AND MOLECULAR ANTIMALARIAL SUSCEPTIBILITY PRIOR TO AND DURING COVID-19 PANDEMIC 2018-2019 TO 2021-2022

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The potential effects of SARS-CoV-2 (Covid-19) on antimalarial susceptibility and drug markers-*Plasmodium falciparum* multidrug resistance gene-1(*Pfmdr1* and *Plasmodium* chloroquine resistance transporter *(Pfcrt)* in a setting of high malaria transmission remains unknown. The COVID-19 pandemic imposed an additional burden in malaria-endemic regions where health systems were struggling to deter the spread of antimalarial resistance already reported in South East Asia. This study sought to evaluate *in vitro* and molecular antimalarial susceptibility prior to and during Covid-19 pandemic. A total of 400 clinical samples from individual presenting with uncomplicated malaria enrolled under our ongoing malaria drug resistance surveillance study in 2018-2022 were screened against a panel of antimalarials namely chloroquine (CQ), quinine (QN), atovaquone (AV), primaquine

(PQ) and artemisinin (ART), halofantrine (HAL) artemether (AR) and dihydroartemisinin (DHA). Each sample was also characterized for polymorphisms in selected drug resistance genes.Inhibition curves in, *in vitro* assays, were obtained from the relative fluorescence units (RFU) using Graph Pad Prism (San Diego, CA, USA). Prior to Covid-19 pandemic chloroquine, quinine, atovaquone, Primaquine, artemisinin, artemether and dihydroartemisin had stable median (IC50) and during the pandemic period the median (IC50) of each elevated to 2-4 fold with a $p<0.0001$. However this was below the resistance threshold. While Lumefantrine, Artesunic acid and tafenoquine medians remained unchanged prior and during Covid-19 period. *Pfmdr1* codon 86 were wild type prior and during the pandemic while codon 184 had mixed infections during the same period. *Pfcrt* codons 72 and 76 were predominantly wild type before and during the pandemic period. Analysis of other markers that could have resulted in elevated median (IC50) is still under way.

1426

PROMPT TREATMENT SEEKING BEHAVIOR AMONG CAREGIVERS OF CHILDREN WITH MALARIA RELATED FEVER IN RURAL MALAWI

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Malaria is a major public health problem in Malawi, where it is responsible for 40% of hospital deaths. Majority of malaria cases are due to *Plasmodium falciparum (Pf)* of which fever (temperature >37.5°C) is a common clinical sign. Prompt diagnosis and effective treatment (treatment within 24 hours of fever onset) is critical to prevent progression from uncomplicated to severe disease and to reduce transmission. As part of a baseline household survey in large evaluation of Malaria Vaccine Implementation Program (MVIP), we investigated whether prompt treatment-seeking behavior is clustered at community-level (villages) according to socio-economic demographics. From 4,563 households included in the survey, 4,856 children aged 5-48 months were enrolled. Out of 4,732 children with documented gender, 2,472 (52.2%) were females and 2,260 (47.8%) males. Among the 4,856 children, 1,700 (35.0%) reported fever in the two weeks prior to the survey. Fever prevalence was higher in communities with high percentage of caregivers with no formal education (37.0% [95% CI: 34.0%, 40.1%] compared to those with post-primary education (31.0% [95% CI: 28.4%, 33.8%]). Among children with fever, 677 (39.8%) sought treatment promptly. Children were more likely to be taken for prompt treatment if were from communities with high percentage of: caregivers having post-primary education than those with no formal education (aOR:1.37, 95% CI: 1.11-3.03); high percentage of households in high socio-economic status (SES) than those from low SES [aOR: 2.78, 95% CI: 1.27-6.07]. Children were less likely to be taken for prompt treatment if were in communities far (>5 km) than those near a health facility [aOR: 0.53, 95% CI: 0.28 –0.98]; and if were under Muslim guardians compared to non-Muslim [aOR: 0.21, 95% CI: 0.06 –0.74]. The high heterogeneity in prevalence of fever and prompt treatment-seeking behavior underscore the need to promote community-level interventions (such as use of long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), intermittent preventive therapy (IPT), presumptive treatment, and education) in order to eradicate malaria.

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IDENTIFICATION OF NOVEL DETERMINANTS ASSOCIATED WITH QUININE AND CHLOROQUINE RESISTANCE IN A *PLASMODIUM FALCIPARUM* GENETIC CROSS

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The genetic basis of *Plasmodium falciparum* resistance to quinine (QN), a drug used to treat severe malaria, has long been enigmatic. To gain further insight, we conducted a *P. falciparum* genetic cross between Cam3.II (QN-resistant) and NF54 (QN-sensitive) parasites using FRG-NOD human liver-chimeric mice. These parents also differ in their susceptibility to the former front-line drug chloroquine (CQ), making it possible to map the determinants of CQ resistance. We obtained 119 independent recombinant progeny from our initial round of cloning and after pressuring bulk cultures with QN or CQ. 72-hour drug susceptibility assays, whole-genome sequencing, and quantitative trait locus (QTL) analyses were conducted on 74, 45, and 64 progeny for QN, CQ, and the active CQ metabolite monodesethyl-CQ, respectively. QTL analysis of these three drugs revealed peaks on chromosomes 7 and 12. A shared 140 kb region on chromosome 12 was mapped to resistance to all three antimalarials, with this region appearing to be co-inherited with *pfcrt*. As expected, CQ and md-CQ resistance mapped to a ~60 kb region on chromosome 7 harboring the CQ resistance determinant *pfcrt*. QTL mapping of high-grade QN resistance (elevated IC_{90}) identified a novel ~20kb chromosome 7 peak that was 282 kb downstream of *pfcrt,* of which the drug/metabolite transporter (*pfdmt1)* is a promising candidate. Bulk segregant analysis comparing a progeny bulk culture pressured with QN 95nM and then 180nM vs a no-drug control also mapped to a single non-*pfcrt* chromosome 7 peak. We have successfully generated NF54- and Cam3.II-edited parasites with mutant or wild-type DMT1 alleles, and expect to soon profile these edited parasites against CQ, QN, and other clinically relevant antimalarials. Studies are also underway to characterize new progeny that we recently obtained after pressuring bulk cultures with 140nM, 180nM, and 240nM of QN, to tag DMT1 with 3xHA for subcellular localization studies, and to edit mutations in the candidate chromosome 12 genes and profile edited lines. Our studies will deliver novel insights into the mechanisms of action and resistance to QN, CQ, and related antimalarials.

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REDUCTION IN MALARIA MORBIDITY IN CHILDREN UNDER FIVE FOLLOWING INTEGRATED COMMUNITY CASE MANAGEMENT IMPLEMENTATION, NORTHERN UGANDA, 2015 TO 2017

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Malaria is the third leading cause of death among children under five years globally. In Uganda, integrated community case management (iCCM) is one of the key interventions used to manage malaria at community level as a way of ensuring care within the first 24 hours of sickness. In this study we assessed the effect of iCCM on malaria morbidity in children under five years between 2015 and 2017. We conducted a retrospective analysis of routine monthly health facility malaria data to evaluate the impact of iCCM on malaria burden in children under five as reported at health facilities. A Generalized Estimating Equations model was fitted for

fractional response variables due to the nature of Test Positivity Rate (TPR) and reported average marginal effects as measures of effect. A total of 904 health facilities was considered. Between 2015 and 2016, 9 (28%) of the 32 districts in the study were implementing iCCM covering 115 (14%) of the facilities in the area in 2015 and 161 (19%) in 2016. In 2017 however, the number of districts implementing iCCM increased to 19 (59%) covering 510 (56%) of the health facilities in the study area. A twenty percent (20%) difference in TPR was observed in districts where iCCM was implemented compared to where it was not. We observed that TPR at heath facilities was significantly associated with implementation of iCCM (margin: -0.121, 95% CI: -0.14, -0.10). The iCCM intervention was associated with 12% reduction in TPR. A reduction in TPR of 3% due to implementation of IRS is observed (margin: -0.030 CI 95%: -0.06, 0.00) and a reduction of 2% due to LLIN implementation (Margin: -0.02, 95% CI: -0.03, -0.01). We also observe expected monthly variation in TPR. We observe that a combination of interventions leads to higher reduction in TPR. This study shows that TPR was lower in facilities located in districts where iCCM was implemented compared to facilities in districts with no iCCM. Even with LLIN and IRS implementation, iCCM has a value in reducing Malaria morbidity in children under five years of age.

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ELUCIDATING THE EFFECT OF FALCIPAIN2A POLYMORPHISM ON ARTEMISININ DRUG RESISTANCE

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The emergence of ART resistance in the Greater Mekong subregion marked a major setback for malaria elimination worldwide. It is clinically manifested as delayed parasite clearance and captured in a novel ring-stage survival assay. Although Kelch 13 has been proposed as the primary marker and determinant of artemisinin resistance in *Plasmodium falciparum*, many other genes and proteins with variable degrees of influence on resistance phenotype have been identified. One such effecter is falcipain 2a (FP2a), a principal hemoglobinase of the malaria parasite, whose disruption in the asexual stages diminishes parasite susceptibility to artemisinins, suggesting that hemoglobin digestion is required for artemisinin activity. Intriguingly, in addition to acquiring a K13 mutation (M476I), parasites selected *in vitro* for artemisinin resistance also acquired a nonsense mutation at codon 69 of FP2a. In another study, S35stop mutation was introduced in FP2a as a result of repeated ART exposure for over two years. Our previous study displayed altered FP2a activity contributes to artemisinin resistance since certain FP2a mutant parasites presented reduced FP2a activity, decreased hemoglobin digestion, enlarged food vacuoles, and enhanced ring-stage survival after treatment with dihydroartemisinin. To understand this further in depth, we generated CRISPR/Cas9 mediated FP2a knockout (KO) parasites in 3D7, Dd2, and two Southeast Asia origin field isolates (F09A13, F09A44). The introduction of different FP2a haplotypes in these KO parasites revealed variability in their artemisinin resistance profiles. This work would help us elucidate the role of hemoglobin digestion in artemisinin resistance and identify novel FP2a haplotypes associated with it.

1430

THERAPEUTIC EFFICACY OF DIHYDROARTEMISININ-PIPERAQUINE FOR THE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* AND *P. VIVAX* INFECTION IN ETHIOPIA

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WHO recommends monitoring of antimalarial drug efficacy for early detection of drug resistance and to inform local policy implementation. In Ethiopia, the national treatment guidelines employ a species-specific treatment approach. Artemether-lumefantrine (AL) and chloroquine (CQ) are the first-line schizonticidal treatments for *Plasmodium falciparum* (Pf) and *P. vivax* (Pv), respectively. This study reports the efficacy of dihydroartemisinin-piperaquine(DHA/PPQ) as an alternative treatment for uncomplicated Pf and Pv. High efficacy for DHA/PPQ for adults (>18yrs) was reported in Ethiopia in 2018. The study assessed the clinical and parasitological efficacy in two sites with sufficient Pf and Pv cases to meet therapeutic efficacy study requirements. Patients over six months with uncomplicated Pf and Pv mono infection in each site were recruited and allocated to Pf and Pv groups , treated with standard DHA/PPQ and followed for up to 42 days according to the WHO guidelines for monitoring antimalarial drug efficacy. PCR-uncorrected estimates were analyzed by Kaplan-Meier survival and per-protocol analysis methods. A total of 90 patients for Pf and 88 patients for Pv were enrolled respectively from the two sites. Adequate clinical and parasitological response (ACPR) rates were reported: 95.3 % (CI:88.5-98.7) for Pf cases and 100% (CI: 95.5-100) for Pv cases at 42 days follow up. PCR classification of recrudescence and reinfection, in addition to sequencing of molecular markers of drug resistance, is pending. Seven patients (7.8%; CI: 3.2-15.4) had Pf parasitemia on day three after DHA/PPQ treatment; however, 100% of patients cleared parasites for the Pv site. No serious adverse event was reported in both sites.The study results confirm high efficacy DHA/PPQ reported for Adults in Ethiopia. The 92.2% day three parasite clearance for Pf warrants continuous monitoring of DHA/PPQ therapeutic efficacy and detailed investigation of molecular markers of resistance.

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MICROSATELLITES REVEAL HIGH POLYMORPHISM AND A LACK OF POPULATION STRUCTURE AMONG MALARIA PARASITES FROM AREAS WITH DIFFERENT TRANSMISSION INTENSITIES IN MAINLAND TANZANIA

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The World Health Organization recommends conducting therapeutic efficacy studies TES) to monitor the performance of antimalarials in all countries. In TES, WHO has recently recommended genotyping polymorphic coding genes (*msp1, msp2*, and *glurp*) and neutral microsatellites in *Plasmodium falciparum* to distinguish reinfection from recrudescence for adjusting antimalarial efficacy. This study assessed polymorphism of six neutral microsatellite markers (Poly-α, PfPK2, TA1, C3M69, C2M34 and 2490) for potential use in Tanzania. Ninety-four dried blood spots (DBS) samples were collected from four sentinel sites of Kibaha (Pwani), Mkuzi (Tanga), Mlimba (Morogoro) and Ujiji (Kigoma) from

April to September 2016. Parasite DNA was genotyped using these six markers to determine the extent of polymorphisms and genetic diversity at the four sites. Overall, 83 (88.3%) samples were successful genotyped (with positive results for ≥50.0% of the markers) and >50.0% (range = 47.6-59.1%) were polyclonal with mean multiplicity of infection (MOI) ranging from 1.68 to 1.88 among the four sites. There was high genetic diversity with limited variability among the four sites; based on mean allelic richness (R_S = 7.48, range= 7.27-8.03, for an adjusted minimum sample size of 18 per site) and mean expected heterozygosity (H_e = 0.83, range= 0.80-0.85). Cluster analysis of haplotypes using STRUCTURE, principal component analysis and pairwise genetic differentiation (F_{ST}) did not detect population structure and isolates clustered independent of their geographic origin. Poly-α was the most polymorphic marker followed by C2M34, TA1 and C3M69 while 2490 was the least polymorphic suggesting that Poly-α, C2M34 and TA1 which were the topmost could be adopted as validated markers for use in TES in Tanzania.

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ELUCIDATING THE PATH TO *PLASMODIUM* PROLYL-TRNA SYNTHETASE INHIBITORS THAT OVERCOME HALOFUGINONE-RESISTANCE

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The development of next-generation antimalarials that are efficacious against the human liver and asexual blood stages is recognized as one of the world's most pressing public health challenges. In recent years, aminoacyl-tRNA synthetase (aaRS) enzymes, including cytoplasmic prolyl-tRNA synthetase (ProRS), have emerged as attractive targets for malaria chemotherapy. We have developed a novel, single-step, Time-Resolved Förster Resonance Energy Transfer (TR-FRET) based ligand displacement biochemical assay platform for *Plasmodium falciparum* and human ProRS that overcomes critical limitations of existing technologies and enables quantitative inhibitor profiling in high-throughput screening format with unprecedented sensitivity, robustness, and flexibility. Guided by our TR-FRET assay, we developed a diverse set of high-affinity ProRS inhibitors, including several proline-uncompetitive and proline-noncompetitive compounds which are the first ProRS inhibitors that are demonstrably not cross-resistant to previously reported ProRS drug resistance mechanisms (altered proline homeostasis and ProRS mutations) and are refractory to drug-resistance development. Several compounds, including the proline-uncompetitive inhibitors and the first triple-site ligands for aaRS enzymes that simultaneously engage all three substrate-binding pockets, exhibit potent dual-stage activity against *P. falciparum* and favorable cellular selectivity. Using our TR-FRET assay, we show how ProRS paralog›s differential substrate binding affinities drive cellular parasite selectivity in the absence of biochemical selectivity. Our data inform the inhibitor requirements to overcome existing resistance mechanisms and, supported by representative inhibitor-target co-crystal structures, promise to accelerate rational development of ProRS-targeted anti-malarial therapies. Our novel TR-FRET assay strategy will enable the adaptation to other aaRS isoforms and related enzymes, providing a general platform to facilitate and accelerate aaRS drug discovery efforts, including those indicated for pathologies beyond malaria.

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EFFECTIVENESS OF DIHYDROARTEMISININ PIPERAQUINE FOR SEASONAL MALARIA CHEMOPREVENTION AMONG CHILDREN UNDER TEN YEARS OF AGE IN KOULIKORO, MALI A CLUSTER RANDOMIZED TRIAL

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Since 2012, seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine (SP-AQ) targeting children under 5 years old was recommended as policy for malaria control in sub-Saharan Africa by the World Health Organization (WHO). We Conducted a district-wide cluster randomized study to compare dihydroartemisininin-piperaquine [DHA PQ] as alternative to SP-AQ, the standard of care drug treatment for SMC in children <10 years old in the Koulikoro Health. The primary efficacy endpoint was malaria incidence while asymptomatic *Plasmodium falciparum* infection and adverse effects to SMC drugs were secondary endpoints. Probability proportional to size sampling of 49 out of 71 health centers was used with a sampling ratio of 2:1 for the DHA-PQ and SP-AQ comparison groups, respectively. The proportion of children receiving the first dose under directly medical observation was 91% and 88% for the DHA-PQ and SP-AQ groups, respectively. Malaria cumulative incidence was significantly lower in DHAPQ treatment arm in September (RR: 0.68, 95% CI: [0.57–0.82]); October (RR: 0.60, 95% CI: [0.51–0.70]) and November (RR: 0.55, 95% CI: [0.40–0.74]) compared to SP-AQ treatment arm. Overall prevalence of asymptomatic malaria infection was similar in both treatment arms (12.3% for DHA-PQ and 12.0% for SP-AQ ($p > 0.05$). Vomiting was frequently reported as self-reported drug side effects (0.5% for DHA-PQ vs. 3% for SP-AQ; $p < .001$). Our results suggest that DHA-PQ is an effective alternative drug for SMC in the study area, and given the low proportion of self-reported adverse events, it could significantly improve both children›s compliance to treatment and community adherence to the strategy.

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ASSOCIATION OF LUMEFATRINE PHARMACOKINETICS AND RESISTANCE SELECTION FOLLOWING ARTEMETHER-LUMEFANTRINE TREATMENT IN CHILDREN WITH AND WITHOUT HIV IN UGANDA

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Artemisinin-based combination therapies (ACTs), the primary treatment for malaria, are now threatened by the multisite emergence of artemisinin resistance in Africa. We present a population pharmacokinetic/pharmacodynamic model using trial data from a study of artemether-lumefantrine in HIV-uninfected and HIV-infected children (aged 0.5-8 years) living in a high transmission region of Uganda. HIV-infected children were on trimethoprim-sulfamethoxazole (TS) prophylaxis in conjunction with either efavirenz (EFV), nevirapine (NVP), or lopinavir/ritonavir-based (LPV/r) antiretroviral regimens, known to cause significant drug-drug interactions with ACT components. A total of 264 children contributed 364 episodes, with recurrent parasitemia detected in 176 episodes (48%)

by day 42. A two-compartment population PK model with first-order absorption best fit the data. Lumefantrine exposure was highest in those on LPV/r, lowest in those on EFV, and equivalent in those on NVP or HIV-uninfected, with HIV status and lumefantrine concentration significantly associated with recurrence risk. Following treatment, time to recurrence in HIV-uninfected children was 35 days versus 48, 51 and 58 days for HIV-infected children receiving TS and either EFV, NVP, and LPV/r, respectively. Drug resistance typing was conducted for pfmdr1 N86Y and Y184F, and pfcrt K76T. Comparing pre- and post-treatment recurrent matched pairs, significant selection was demonstrated for pfmdr1 N86 and pfcrt K76 in recurrent infections, with no evidence of selection seen for pfmdr1 Y184F. Using a time to event PK/PD model, more resistant (pfcrt K76) parasites were able to tolerate concentrations 3.5-fold higher than more sensitive parasites (pfcrt K76T mixed + mutant). This is the first population PK model of lumefantrine in HIV-infected children and provides evidence that wild-type K76 parasites are able withstand higher lumefantrine concentrations, which may help explain how selection is occurring in high transmission settings over repeated ACT treatments, a concern as we try to combat the recent emergence and spread of artemisinin resistance in Africa.

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CHEMOPREVENTION EFFICACY STUDIES DETERMINING IF SEASONAL MALARIA CHEMOPREVENTION IS EFFICACIOUS IN MOZAMBIQUE, UGANDA AND SOUTH SUDAN VIA A NOVEL RESEARCH PROTOCOL

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Chemoprevention efficacy is a function of a chemopreventive drugs ability to clear existing sub-patent malaria infection and to prevent new infections from establishing themselves over the desired period of protection. In the case of seasonal malaria chemoprevention (SMC) a combination of drugs, traditionally sulfadoxine, pyrimethamine and amodiaquine (SPAQ), should clear these sub-patent infections and prevent new infections over a 28 day period from day 0 of a 3 day drug administration. These studies evaluate the chemopreventive efficacy of SPAQ, and in the case of Uganda also dihydro-artemisinin piperiquine (DP), to clear sub-patent infection and prevent new *P. falciparum* infections from establishing themselves in SMC eligible age children (3-59 months) in Mozambique, Uganda and South Sudan. These studies also aims to determine that if protection is not afforded for a duration of 28 days whether this is as a result of drug resistance or drug dosing. The inclusion of a pharmacometric assessment of chemopreventive drugs, particularly drug elimination, in the context of drug resistant halplotypes has not been studied before.

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DYNAMICS OF ANTIMALARIAL DRUG EFFICACY IN THE GREAT LAKES REGION OF AFRICA: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

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Malaria is a life-threatening vector-borne disease known to be endemic for more than 80 countries and affects around 249 million people, with 607 000 deaths worldwide each year. Antimalarial drug resistance is a globally recognized threat to malaria control and elimination. Nowadays, the artemisinin combination therapies (ACTs) recommended by the World Health organization (WHO) to treat *Plasmodium falciparum* are threatened by the development of resistance. However, resistance has emerged and spread in the Greater Mekong Sub region (GMS), and more recently in East Africa, in Rwanda and Uganda, following the path of chloroquine resistance. It is therefore crucial to implement surveillance systems to monitor and control the emerging resistance in different endemic regions. The systematic review and meta-analysis will assess the spatio-temporal dynamics of ACTs efficacy and molecular markers of resistance in East Africa over the last twenty years.

1437

THE DEVELOPMENT OF NOVEL 4-AMINOQUINOLINES AS THERAPEUTICS AGAINST MULTI-DRUG RESISTANT *PLASMODIUM FALCIPARUM*

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The emergence of multi-drug resistance threatens the utility and efficacy of current frontline combination therapies. To overcome this increasing problem, two novel 4-aminoqunolines have been developed to be active against multi-drug restraint strains of *Plasmodium falciparum*. Patterning the novel scaffold after isoquine, a 4-aminoquinoline (4AQ) developed to circumvent the metabolic-stability issue with amodiaquine, we have successfully developed two novel 4AQ scaffolds, amodiachin (ADC) and amodiapiperaquine (APQ). Lead compounds from both scaffolds, ADC-017 and APQ-002 exhibit low nanomolar inhibitory activity against drug sensitive D6 and multi-drug resistant strains Dd2 and 7G8 of *P. falciparum*. Assessment of *in vivo* efficacy in *P. yoelii* murine malaria model produced sub 1 mg/kg/day ED_{50} for both scaffolds and a 10 mg/kg/day non-recrudescence dose for APQ-002. The continued optimization of these two novel scaffolds will be presented and discussed.

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GUT BARRIER INTEGRITY IN MACAQUES INFECTED WITH *PLASMODIUM KNOWLESI*

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Malaria continues to be a significant public health burden in a large portion of the world. *Plasmodium knowlesi*, which causes zoonotic malaria in Southeast Asia, can cause severe illness akin to that of *Plasmodium falciparum*. In both diseases, the gastrointestinal tract is a location of significant parasite burden and inflammation. Recently, our group demonstrated evidence of gut pathology in both a natural macaque host (*Macaca fasicularis*) and a non-natural host (*Macaca mulatta*) during experimental infection with *P. knowlesi*. In the natural host *M. fascicularis*, despite having relatively low parasitemia, parasites were observed throughout the gut, particularly in the colon, while gut pathology was most striking in the stomach. Importantly, such disturbances may explain gastrointestinal symptoms reported by patients with malaria. In the non-natural host, *M. mulatta*, higher parasite loads and adhesive interactions were observed throughout the gut, a finding that was associated with the expression of *P. knowlesi* Schizont-Infected Cell Agglutination (SICA) variant proteins. While these studies point to the importance of the gut in malaria pathogenesis, it is not clear how sequestration and inflammation in the gut impact malaria disease severity. Here, we investigate the impact of *P. knowlesi* infection on gut barrier integrity within these host species by performing immunohistochemistry-based labeling of tight

junction proteins occludin and claudin-5 on archived gut tissue from our previous studies. Tight junctions play an important role in maintaining the intestinal epithelial barrier by regulating paracellular permeability. Our results suggest that *P. knowlesi* infection contributes to the degradation of tight junctions in the colon, which could ultimately contribute to a loss of intestinal barrier integrity and worsen disease. We also identified species-specific differences in intestinal structure using high-dimensional image analysis. Future research will continue to focus on these differences to understand the relationship between sequestration, inflammation, and disease severity in the gut during malaria.

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TWO SAFE AND ORALLY ADMINISTERED DRUGS TO BLOCK THE TRANSMISSION OF MALARIA INDUCING SPLENIC RETENTION OF MATURE GAMETOCYTES

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The spleen clears rigid erythrocytes from the circulation. Drugs that would increase the rigidity of *Plasmodium falciparum*-infected red blood cells would therefore induce the specific clearance of circulating parasites. We screened more than 13k compounds with filters that mimic how the spleen senses mechanically altered red blood cells. 82 compounds that target mature gametocytes, the circulating transmission stages of *P. falciparum*, were identified.NITD609, an orally administered PfATPase inhibitor with known effect on all *P. falciparum* stages, killed and stiffened mature gametocytes *in vitro* at nanomolar range. TD-6450, an orally-administered and safe drug, stiffened mature gametocytes *in vitro* after short exposures and killed asexual parasite stages at high nanomolar range. Concentration-time simulation ofTD-6450 in healthy volunteers showed that these concentrations can be reached in almost all subjects with a single-dose oral administration. NITD609 and TD-6450 are strong candidates for clinical trials in human volunteers.

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EXPOSURE TO MOSQUITO BITES AS STIMULUS FOR *PLASMODIUM FALCIPARUM* GAMETOCYTE PRODUCTION

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Gametocytes are essential for onward transmission of malaria to mosquitoes. There are many factors that may influence gametocyte production, including a hypothesized role for exposure to uninfected mosquitoes in stimulating gametocyte production at the start of malaria transmission seasons. In a high-endemic area in Burkina Faso during the dry season when there is no measurable mosquito exposure, we recruited 120 individuals aged 10 to 50 years who were infected with *P. falciparum* with >= 100 parasites/µL. This cohort was randomized to two groups and followed for 28 days with blood sampling on days 0, 6, 12, 14, 20, 26 and 28, thus spanning 2 cycles of gametocyte production. The first group (Cohort 1) participated in membrane feeding using venous blood and direct skin feeding, resulting in exposure to ~60 mosquito bites on one occasion at d14. The second group (Cohort 2) followed the same procedures but without direct skin feeding and thus had no exposure to mosquito saliva. Gametocytes were quantified in both cohorts by qPCR, targeting male and female gametocyte transcripts. In cohort 1, mean gametocyte density pre-exposure (days 0 to 4) was 32.07 gametocytes/ µL (95% CI 19.67- 52.29) and this declined to 28.64 gametocytes/ µL (95% CI 17.80- 46.06) during follow-up (days 20 to 28) (p = 0.057). A similar decline was observed in cohort 2 who were not exposed to mosquito bites: mean density 27.38 gametocytes/ µL at enrolment (95% CI 18.43-40.67), declining to 20.72 gametocytes/ µL (95% CI 13.70- 31.34) during follow-up (p = 0.0538). The proportion of individuals with gametocytes at d14 (baseline) and d28 (14 days after exposure) were respectively 84% and 88% in Cohort 1 and 86% and 88% in Cohort2. We observed no evidence that gametocyte density increases after mosquito exposure. We are currently examining gametocyte commitment markers, but our preliminary conclusion is that mosquito saliva-induced gametocytogenesis is not a likely explanation for the infectivity to mosquitoes of human parasite carriers at the start of the transmission season.

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KINETICS OF TRANSMISSIBILITY TO MOSQUITOES FROM CLINICAL *PLASMODIUM VIVAX* INFECTIONS IN ETHIOPIA: COMPARISON BETWEEN PRIMARY AND RECURRENT INFECTIONS

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The hypnozoite liver stage of *Plasmodium vivax* causes relapsing infections. The rapid production of *P. vivax* gametocytes renders relapsing infections transmissible. The precise contribution of relapses has yet to be quantified. We compared the infectivity of recurrent and primary *P. vivax* infections. Patients (n=241) with microscopy confirmed *P. vivax* infections were followed monthly in Arba Minch (Ethiopia). Direct membrane feeding assays (DMFA) were done at primary and recurrent infections, using *An. arabiensis* colony mosquitoes. Treatment was administered by the health facility; the study did not have control. Parasite and gametocyte densities did not differ between primary and recurrent infections. Of the patients that completed the 6th month follow-up, 44% (70/159) had at least one recurrent infection (range 1-5 times) within 66 days (range 13-183 days). Recurrence did not differ (P=0.63) between patients who received CQ + PQ (42%, 43/102) and those who received only CQ (49%, 25/51). Recurrent infections were observed more (P=0.04) in men (51%, 49/97) than women (34%, 21/62). Of the 377 DMFAs that were done using 42,661 mosquitoes, 68% (156/230) were infectious to at least one mosquito at recruitment and 75% (110/147) at recurrence (P=0.146) with a median of 45% mosquitoes infected (range, 3-97%). The mean oocyst density in infected mosquitoes was higher (P=0.031) in recurrent (18; 5-53) infections compared to recruitment infections (12; 4-33). This work provides the most comprehensive assessment of parasite kinetics and transmissibility in natural *P. vivax* infections to date, quantifying the importance of relapse infections to the infectious reservoir and informing the optimization of malaria control and elimination strategies. Follow-up of patients will be completed in July 2022. We are quantifying parasite and gametocyte densities by qPCR and antibody responses to gametocyte antigens. Advanced genotyping tools to determine the genetic associations between the incident and recurrent infections in humans and subsequent mosquito infections are being deployed and results will be ready before the meeting.

1442

PROSPECTIVE EVALUATION OF POST-ARTEMISININ HEMOLYTIC ANEMIA IN AFRICAN CHILDREN WITH SEVERE MALARIA

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Artemisinin is the first-line treatment of severe malaria in adults and children but is induces by far the most antimalarial adverse event: the post-artesunate delayed hemolysis (PADH). PADH is generally mild in adults but some severe cases with complications and a fatal case in absence of blood transfusion had been reported. The incidence of PADH in adults is well documented and has been associated with pitting of infected RBC by the spleen. The link between pitting and the incidence PADH in African children is still elusive. We recently explored the occurrence and incidence post artemisinin hemolytic anemia (PAHA) in children living in endemic areas and analyzed preliminary data. Between November 2020 to July 2021, we conducted a prospective study in the pediatric department of the in Cotonou. In the 1081 patients screened, 351 children with severe malaria, treated with injectable artesunate were included. An epidemiological survey was done at admission and the children were followed at D0, D3, D5, D14, D21 and D28 for pitting, hematological, epidemiological and clinical data. From the 351 children included 47.9% declared self-treatment before coming to the hospital, 72.6% had hemoglobin beyond 7 g/dL and required transfusion, 14 died before D14 and 323 were followed up to D28. PAHA occurs with an incidence of 22.9% (76 children) between D5 and D28. 14.5% of patients with PAHA required transfusion versus 4.3% in non-PAHA (p=0.002). Indeed, infectious events were observed in 9.2% of PAHA patients versus 2.7% in non-PAHA (p=0.03). This study showed that PAHA in children living in endemic areas is as frequent than PADH in adults. The management of this delayed hemolysis is complicated by the fact that, compared to adults, a deeper existing anemia is observed at admission in children. Preliminary data did not show severe complications, but the design of this study allows to closely follow children and provide hospital cares when needed. In endemic areas this follow up would be difficult and thus a predictive test such as the PADH prediction test by HRP2-based dipsticks would be helpful to avoid severe complications following patients discharge at hospital.

1443

PREVALENCE AND GENETIC CHARACTERISTICS OF *PLASMODIUM VIVAX* GAMETOCYTES IN DUFFY-POSITIVE AND DUFFY-NEGATIVE AFRICANS

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Plasmodium parasites replicate asexually in the human host, and, in each replication cycle, a portion of the asexual stages develops into sexual gametocytes. The proportion of infections that carries gametocytes is a proxy for human-to-mosquito transmissibility. The documentation of *P. vivax* infections in Africa where the predominant population is Duffy-negative demonstrates the ability of *P. vivax* to replicate asexually in Duffy-negative hosts, causing malaria symptoms. However, it is unclear what proportion of *P. vivax* infections in Duffy-negatives carries gametocytes. This study aims to determine the prevalence of *P. vivax* in Duffy-negatives across broad regions of Ethiopia and characterize parasite stages including gametocytes among *P. vivax* infections. Of the 258 *P. vivax* confirmed samples collected from southwestern, northwestern, and eastern regions of Ethiopia, 13 (5%) were from Duffy-negatives, with the highest number observed in the southern nations and Benishangul-Gumuz areas. Of the 13 *P. vivax* cases in Duffy-negatives, four (30.8%) were detected with gametocytes, similar to the percentage of gametocyte-positive samples in Duffy-positives (38.4%). These gametocyte-positive samples in Duffy-negatives were also found in the southern nations and Benishangul-Gumuz areas. A wide difference in parasitemia is observed among *P. vivax* samples in Duffy-negative individuals. Infections in Amhara (north) and Oromia (southwestern) show high parasitemia comparable to Duffy-positives. In Oromia, mixed rings and trophozoites were most common in the *P. vivax* cases. Our finding is the first to report the presence of gametocytes in *P. vivax* from Duffy-negatives. Ongoing work examines genetic variations in *Pvs*25, *Pvs*28, *Pvs*48/45, and *Pvs*230 in gametocyte-positive samples from Duffy-positive and Duffy-negative infections. Findings will help prioritize transmission blocking vaccine candidates against vivax malaria.

1444

USE OF EX VIVO BRAIN ORGANOIDS TO MODEL THE EFFECTS OF MALARIA AND SICKLE CELL DISEASE-ASSOCIATED HEMOLYSIS ON FETAL BRAIN

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Sickle cell disease (SCD-HbSS and HBSC genotype) and sickle cell trait (SCT-HbAS genotype) overlaps *Plasmodium falciparum* cerebral malaria (HCM) in sub-Saharan Africa. SCD and malaria are associated with erythrocyte lysis and free circulating heme which increases when RBCs are parasitized. Heme levels are regulated by heme scavengers including (Hemopexin (HPX), Haptoglobin (HG), and Hemeoxygenase-1 (HO-1). Patient-derived adult somatic cells reprogramming into induced pluripotent stem cells (iPSC) provides opportunities to differentiate them into brain organoids. They can be used as non-invasive models to determine the effects of heme on the developing brain during disease-induced hemolysis and to develop novel therapeutics. We hypothesize that cells from urine, a non-invasive source, collected from children with HCM, SCD and SCT can be reprogrammed to iPSCs and then differentiated to 3D brain organoids to model the hemolysis effects on neuronal cells. We extracted clinical data from children (3-8 years) with SCD, SCT and HCM presenting at the Child Health Department (CHD), Korle-Bu Teaching Hospital in Accra, Ghana using a data abstraction instrument that documents clinic attendance/visits, *Plasmodium* parasitemia, hematological parameters and complications. Urine and blood samples from children with HCM, SCD, SCT and HbAA (control) from CHD were collected. Next, urine mesenchymal stem cell were isolated and assessed by flow cytometry and immunofluorescence. We determined parasitemia, complete blood count (CBC), hemoglobin levels and brain cell injury markers (CXCL10, BDNF, S100b, Tau, and heme), heme scavengers (Hemopexin, Haptoglobin, HO1), and angiogenic markers (Ang-2/Ang-1) in HCM, SCD,SCT and HbAA patients. The results show that the UDC were CD73+/CD146+/CD105+ and rare smooth muscle cells (SMA+/calponin+) were present. Biomarkers of heme-induced brain injury (CXCL10, Ang-2/Ang-1, BDNF, S100b, Tau) predicted HCM and SCD severity compared with controls. We conclude that urine-derived *ex vivo* brain organoids can be utilized to model the effects of malaria and SCD-associated hemolysis on fetal brain.

1445

STRUCTURAL EQUATION MODEL OF MOLECULAR PERTURBATIONS IN ASYMPTOMATIC INFECTION WITH *PLASMODIUM FALCIPARUM*

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Clinical immunity to malaria can be conferred after repeated episodes, resulting in infections during which the host shows few symptoms while parasitemic. These asymptomatic infections serve as reservoirs for transmission and contribute to anemia and chronic inflammation. Identifying molecular pathways that are uniquely perturbed by asymptomatic malaria infections using blood transcriptomics can help elucidate the mechanisms associated with inflammation due to malaria. However, detecting transcriptomic signatures specific to asymptomatic infections is often difficult using conventional approaches given the modest signals. Here, we apply structural equation modeling (SEM) with

the aim of reducing gene sets to the most representative genes, while also exploring transcriptomic differences in asymptomatic children infected with *Plasmodium falciparum* (*Pf*) relative to uninfected children beyond variable expression of gene sets. Specifically, we use confirmatory factor analysis (CFA) to reduce gene sets to the most representative genes by systemically removing collinear genes within or between gene sets and genes that are poorly correlated to others within their gene set. Subsequently, SEM path analysis helps determine the relative contributions of gene sets in the immune response to asymptomatic infections. Relevant blood transcription modules (BTMs) are included for analysis based on previous work to differentiate transcriptomic signatures of 80 children with incident *Pf* infections in 3 categories: with concurrent fever, with delayed fever, or asymptomatic. We apply CFA to these BTMs to determine the optimal set of genes attributed to each module, and path analysis to validate their importance in identification of infection. This work provides proof of concept that SEM can be used to create optimized gene sets from transcriptomic data to be used for downstream analysis. Combining SEM with machine learning, we attempt to determine whether truncated gene sets can reliably distinguish asymptomatically infected from uninfected individuals and identify disease-specific molecular signatures unique to these infections.

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DISRUPTING THE BLOOD BRAIN BARRIER: A ROLE FOR HEME-LADEN *PLASMODIUM FALCIPARUM* HISTIDINE-RICH PROTEIN II PARTICLES

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Severe malaria manifests as severe anemia, cerebral malaria, and respiratory distress. Children under age 5 are disproportionately affected by severe malaria and the most vulnerable to death from malaria. Children who survive cerebral malaria can go on to develop neurodevelopmental impairments. Cerebral malaria is characterized by cerebral edema and sequestration of infected red blood cells in cerebral microvasculature. It was previously shown that the Plasmodium falciparum secreted protein histidine-rich protein II (HRPII) is sufficient and necessary to induce vascular leakage in blood-brain barrier (BBB) models. We found that HRPII from cultured parasites and serum of infected patients forms large multimeric particles that are richly heme bound. Using an in vitro culture model of the BBB, we found that HRPII:heme particles are internalized in a caveolin-dependent process and that early inflammatory signaling is mediated by heme oxygenase 1. This subsequently leads to induction of the NLRP3 inflammasome and IL1β secretion, resulting in loss of BBB integrity. Inhibition of these pathways with anti-inflammatory drugs mitigated BBB disruption by HRPII:heme. We propose that HRPII:heme induced endothelial dysfunction significantly contributes to cerebral edema during malaria infection and that disrupting this process is an opportunity for new adjunctive therapies for severe malaria.

1447

HIGH RESOLUTION LIPIDOMIC PROFILING OF HOST RESPONSE TO *PLASMODIUM FALCIPARUM* MALARIA

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Intraerythrocytic forms of *Plasmodium falciparum* parasites rely heavily on host-derived lipids for the remodeling of infected red blood cells (iRBCs), maturation, replication and survival. To investigate *P. falciparum*-induced lipid metabolism perturbations *in vivo* and their impact on the parasite development, we used a multi-omics integrative approach to generate and analyze 200 high-resolution joint host and parasite lipidomic and transcriptomic profiles of 100 West African children sampled before and during natural *P. falciparum* infection in Burkina Faso. We analyzed approximately 1000 serum lipid molecules and provide evidence for significant associations between parasitemia and specific sub-classes of lipids. Integrative lipidomic-transcriptomic analysis revealed a set of lipid-gene networks linked to lipid metabolism of the *P. falciparum* parasite. These findings provide the first detailed *in vivo* blueprint of *P. falciparum* infection-triggered lipidome changes and parasite gene expression events that implicate core parasite lipid remodeling and biosynthesis pathways.

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PLASMODIUM FALCIPARUM-INDUCED ACTIVATION OF IMMUNOMETABOLISM PATHWAYS IN VIVO

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The Immune response during *Plasmodium* infection is orchestrated by an interplay between pro-inflammatory and anti-inflammatory responses. The pro-inflammatory response that controls infection can also induce tolerogenic mechanisms to control the over-reactivity of the immune system and prevent host damage. One of these mechanisms is mediated by amino acid catabolism. To investigate the impact of *P. falciparum* infection on immuno-metabolic networks and its effect on the disease progression, we analyzed the serum metabolome of 100 Burkina Faso children sampled before and during natural infection. Using high-resolution metabolomic and transcriptomic profiling, we identify a pattern of upregulation of immune-tolerogenic pathways in association with *P. falciparum* infection and parasitemia. These findings expand our understanding of the host immune response and the interplay between immunogenic and tolerogenic responses to *P. falciparum* infection in vivo.

1449

EFFECTIVENESS OF BASIC MALARIA DIAGNOSTIC REFRESHER TRAINING ON THE ACQUISITION OF SKILLS AMONG LABORATORY TECHNICIANS IN MALI

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The WHO recommends confirming all suspected malaria cases by microscopy or rapid diagnostic tests. In Mali, a baseline microscopy assessment demonstrated poor performance in most health facilities within intervention zones; 32% of assessed providers reached the competency threshold of 90% or above in slide preparation, staining and reading. The US President's Malaria Initiative Impact Malaria project supported the National Malaria Control Program and the National Institute of Public Health (NIPH) to conduct eight basic Malaria Diagnostic Refresher Training (bMDRT) sessions between February and June 2021. Parasite detection (PD), species identification (ID), and parasite counting (PC) were assessed. Each bMDRT lasted five days and was held at the Parasitology Department of the NIPH in Bamako. 96 laboratory technicians (59% male, 41% female) from referral health centers (27%), community health centers (70%) and other health facilities (3%) were trained. They were given 15 slides to read at pre-test and 45 at post-test. Between pre and post-test, the mean score of participants improved in PD (51% to 78%), ID (31% to 35%), and PC (5% to 30%). About 45 days after the training, twelve recent bMDRT participants were randomly visited for an on-the-job

evaluation with proficiency testing (PT) during two rounds of Outreach Training and Supportive Supervision Plus (OTSS+) which occurred between March-August 2021. PD improved after two rounds of OTSS+ from an average score at post-test of 75% to 82% during OTSS+. ID improved from 38% to 51% during OTSS+. A decline in PC was observed from 19% to 8% during OTSS+ likely due to the absence of manual counters at most of the facilities visited. bMDRT and OTSS+ were effective at improving the skills of laboratory technicians when the right tools were available in the workplace. Lab technicians who were evaluated during the two rounds of OTSS+ and scored below 80% during the bMDRT and below 80% in PD during PT were invited to attend another bMDRT.

1450

ASSESSING THE RISK OF MALARIA RAPID DIAGNOSTIC TESTING FAILURE AS A RESULT OF PF HRP2 GENE DELETION

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The spread of *Plasmodium falciparum* that evades detection by rapid diagnostic tests (RDTs) threatens progress toward malaria control and elimination in Africa. WHO recommends that countries assess the prevalence of *pfhrp2/3* gene deletions. In Senegal with the collaboration of NMCP (National Malaria Control Program) we established a pilot HRP2/3 surveillance study with the objective of collecting samples in regions with different transmission profiles to assess the potential risk of "diagnostic failure" as a result of *hrp2/3* deletion. These results will guide Sénégal NMCP for procurement and implementation of appropriate malaria RDTs.During the 2021 malaria transmission season, we recruited 763 symptomatic patients with fever and negative HRP2 RDT results in Kolda, Kédougou, Kaolack and Diourbel. For each patient, an RDT-HRP2 test (SD BIOLINE), a blood slide thick/thin smear and a filter paper were prepared. We used the PET-PCR assay to confirm the *P. falciparum* infection status. Microscopy slides were read by an expert microscopist for PET-PCR positive result samples, and *msp2* genotype to check for DNA quality. The deletion of the *hrp2* gene was studied using the One-step PCR. All samples were blinded for each independent evaluation. Preliminary findings reveal that among the 763 symptomatic participants 34 (~ 4.4%) had RDT-/PET-PCR positive. Microscopy slide screening of these RDT-/PET-PCR+ revealed 2 of these samples had non-*falciparum* species *P. ovale* and *P. malariae* with low parasite density (40 and 4400 parasites/ul). Using the One-step PCR method, we found 7 of the remaining 32 RDT-/PET-PCR positive samples (0.9%) had preliminary evidence of *pfhrp2* gene deletion. These preliminary results are currently being independently verified to determine if indeed they have the *pfhrp2* gene deleted. This work shows the importance of monitoring the HRP2 deletion and is in line with the process of quality control and assurance of malaria diagnosis.

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ANALYZING THE DISTRIBUTION AND REPORTING OF SEVERE MALARIA DIAGNOSIS IN MALI

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Mali's national malaria control program updated its guidelines in 2020 for more accurate diagnosis, treatment, and reporting of severe malaria. Specific updates include dropping high fever and vomiting as signs of severe malaria. Regular training and supervision of service providers is conducted; however, data continue to show large numbers of severe malaria cases. To understand the drivers of this, we extracted 2019-2020 severe malaria data from the District Health Information Software, version 2 (DHIS2) database to examine reported severe malaria cases. We utilized the following variables: population group (children < 5 years, ≥5 years excluding pregnant women, and pregnant women); transmission intensity (very low, low, moderate, and high); dry and wet season; and seasonal malaria chemoprevention (SMC) implementation period. On average, 33% of malaria cases were classified as severe, with no difference between 2019 and 2020. Of all severe cases, 29% were children under five, 64% were five years and older, and 7% were pregnant women. Pregnant women with malaria were more likely to receive a severe malaria diagnosis (41%) compared to children under five (34%) and those five years and older (31%). Unlike children under five and pregnant women, severe malaria among the population five years and older decreased with increasing transmission (from 78% in very low to 57% in high transmission districts). The proportion of cases classified as severe malaria was 29% during the dry season and 36% during the rainy season. During the SMC implementation period, 39% of children under five with malaria were classified as severe cases, compared to 31% in the period without SMC. The number of severe malaria cases reported through the routine health information database are unexpectedly high, especially during the dry season and SMC implementation, which has important implications for the use of resources for the management of severe malaria. This may suggest poor-quality data and/or noncompliance with national guidelines. Additional data and further analyses are needed to understand the drivers of over diagnosis of severe malaria.

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HEMOZOIN CLEARANCE RATES POST TREATMENT WITH COARTEM USING MAGNETO-OPTICAL DETECTION, MOD

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Hemozoin is partially magnetic by-product of malaria digestion of hemoglobin. By using a system of magnets and red light (Magneto-Optical Detection, MOD) this substance can be used as a biomarker for the presence of malaria. Still in question is the length of time hemozoin remains detectable in the blood stream post-treatment using modern day drugs. For this study 67 Patients who were seen at the Chulimbo Health Clinic in Kisumu, Kenya for uncomplicated malaria were asked to join a follow up blood draw study. All patients were confirmed to have malaria by Microscopy and RDT and all were treated with CoArtem, the first line drug of choice for uncomplicated malaria. Finger stick blood samples were collected on Days 0, 2, 7, 14, 21, and 28. Each patient sample was tested by standard RDT, Microscopy, and MOD for the presence of malaria. Previously there was concern about using hemozoin as a biomarker for

malaria disease because of accumulation in the spleen, however this study indicates that it becomes quickly undetectable in circulating blood in an average of 9 days after treatment. This information helps to define the utility of the new MOD technology by defining the window in which patients can be malaria negative but hemozoin positive.

1453

LOW PREVALENCE OF *PLASMODIUM FALCIPARUM* INFECTION WITH *PFHRP2/3* DELETION IN A LONGITUDINAL STUDY IN KINSHASA PROVINCE, DEMOCRATIC REPUBLIC OF CONGO

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Histidine-rich protein 2 (HRP2) rapid diagnostic tests (RDTs) are widely used to detect *Plasmodium falciparum* (*Pf*) in sub-Saharan Africa. The high prevalence of *P. falciparum hrp2* (*pfhrp2*) gene deletions in the Horn of Africa raises concerns about the ongoing use of HRP2-RDTs in other regions. We previously reported 6% *pfhrp2* deletion prevalence among asymptomatic children in a 2013-14 national survey in the Democratic Republic of Congo (DRC), but found no evidence of false-negative HRP2-RDTs due to *pfhrp2* and/or *pfhrp3* (*pfhrp2/3*) deletions in a 2017 follow-up study of symptomatic children and adults. To evaluate changes in *pfhrp2/3* deletion prevalence over time, we performed a longitudinal study of 1,662 individuals across seven sites in Kinshasa Province, DRC, from 2018-2021. Samples collected during biannual household visits that had ≥100 parasites/µL by qPCR were selected for genotyping using a recently developed multiplex real-time PCR assay that detects *P. falciparum* lactate dehydrogenase *(pfldh)*, *pfhrp2*, *pfhrp3*, and human *beta-tubulin*. *Pfldh*+ samples that were *pfhrp2*- or *pfhrp3*- in duplicate, and *Pf* beta-tubulin+ in another confirmatory real-time PCR assay, were classified as harboring *pfhrp2/3* deletions. Mixed infections of *pfhrp2/3*-intact and -deleted strains were defined conservatively as samples with a *pfhrp2/3*-*pfldh* cycle threshold (Ct) difference >3. Among 1,285 *Pf* infections with ≥100 parasites/µL collected during the study period, mono-infection by parasites with *pfhrp2/3* deletion was uncommon. Only one *hrp2*-deleted and one *hrp3*-deleted mono-infection were detected; no dual *hrp2*- and *hrp3*-deleted mono-infections expected to escape detection by HRP2-RDTs were identified. Mixed infections were not identified based on the defined Ct threshold. Low *pfhrp2/3* deletion prevalence supports the ongoing use of HRP2-RDTs in the Kinshasa Province, DRC.

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OUTREACH TRAINING AND SUPPORTIVE SUPERVISION IN PUBLIC HEALTH FACILITIES OF BIOKO ISLAND TO IMPROVE MALARIA DIAGNOSTICS AND CASE MANAGEMENT

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Outreach training and supportive supervision (OTSS) can help improve the quality and performance of staff in malaria diagnosis and clinical management, both being key elements of the suite of interventions implemented by the Bioko Island Malaria Elimination Project (BIMEP) and the National Malaria Control Program (NMCP) to control and eventually eliminate malaria from the island. Capacity building of public health personnel for clinical management and diagnostics has taken place since 2004 on Bioko, however there has been no systematic process to assess and document weaknesses in these areas. The BIMEP/NMCP introduced OTSS as a pilot program on Bioko in 2022 to address this gap, allow for providing more context specific training and mentoring, improve adherence to guidelines and collect evidence for adjusting interventions. OTSS checklists were created to assess health worker performance for malaria microscopy, RDT use, management of simple and severe malaria cases, malaria in pregnancy and laboratory readiness. These checklists were field tested by BIMEP staff, reviewed, and validated by a working group from the Ministry of Health and Social Welfare. The Campaign Information Management System (CIMS) and the District Health Information System (DHIS2) were used for data collection and analysis, and real-time dashboards were designed to allow for monitoring and decision-making. Process and output indicators for both laboratory and clinical supervisions are expressed as the percentage of satisfactory responses and observations, and impact indicators include, among others, the percent of suspected malaria cases tested for malaria; percent of suspected malaria cases confirmed as malaria; and percent of confirmed malaria cases treated as per national guidelines, both for outpatient consultations and hospitalized cases. The results of the first OTSS implementation on Bioko Island will be compiled and presented using descriptive statistics, along with a description of challenges and lessons learned that can be useful for similar efforts in other countries setting up OTSS.

1455

CLINICAL EVALUATION OF AN INNOVATIVE AUTOMATED MICROSCOPE SOLUTIONS (AUTOMIC, MILABTM) FOR THE DETECTION OF MALARIA PARASITES IN PATIENTS WITH SYMPTOMS SUGGESTIVE OF MALARIA IN SUDAN

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Microscopy, despite being the gold standard for malaria diagnosis, has been shown to have limitations in low-resource settings, particularly in areas with a shortage of skilled microscopists. The advancement of automated microscopy could allow microscopy to be performed in such areas, as well as improve mixed infection or even low parasitemia detection. In this study, we conducted a clinical evaluation of an artificial intelligence-driven fully integrated automated microscopy, miLab™ (Noul Inc., Korea). This is a health facility-based case-control study conducted in a malaria-endemic area of rural Khartoum in 2020. The study included 190 patients aged >5 years with malaria symptoms (100 positives and 90 negatives) confirmed by expert microscopy. miLab™ testing was performed according to the manufacturer's instructions, using 5 µL capillary blood. The device performs all required steps of smearing, staining, and imaging. The results in the automated mode are reported as negative or suspect. The suspected samples were examined further and confirmed positive or negative by the operator in the corrected mode. The reference standard test was PCR and the comparator test was expert microscopy. miLab™ identified 104 positives and 86 negatives out of 190 patient samples in the corrected mode, while nested PCR identified 112 positives and 78 negatives. The comparator test identified 100 positives and 90 negatives. When compared to PCR sensitivity, specificity and accuracy were 96.2%, 69.1%, and 85%,, respectively (PPV=81.6%, NPPV=92.7%) in the automated mode and 90.2%, 96.2% and 92.6% respectively (PPV=97.1%, NPPV=87.8%) in the corrected mode. The respective results of comparator expert microscopy 89.3%, 100%, 93.7% (PPV=100%, NPPV=86.7%). In conclusion, when used in a clinical context, miLab™ microscope solutions demonstrated high sensitivity but low specificity

when used in automated mode. The expert intervention was shown to be required to improve the device's specificity. The corrected results of miLab were comparable with those of the comparator expert microscopy.

1456

REAL-TIME PCR TO DETECT *PLASMODIUM OVALE CURTISI* AND *WALLIKERI* WITHIN MIXED SPECIES INFECTIONS

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Plasmodium ovale curtisi (*Poc)* and *P. ovale wallikeri* (*Pow*) represent distinct non-recombining malaria species that are increasing in prevalence throughout sub-Saharan Africa. We adapted and refined separate 18S rRNA real-time quantitative PCR (qPCR) assays that detect *Poc* (Perandin 2004) and *Pow* (Calderero 2012) to determine the species of *P. ovale*-positive samples and identify mixed *Poc*/*Pow* infection within clinical samples. Using 18S plasmid controls ranging from 10^5 to 10^{-1} copies/µL and running each qPCR to 50 cycles, *Poc* and *Pow* were reliably detected at 10^0 and 10^1 plasmid copies/µL, respectively. Cross-reactivity between the *Poc* and *Pow* qPCR assays was observed at concentrations greater than 10^4 copies/µL. However, this represents a parasite density greater than that found in the vast majority of natural infections (~>5,000 parasites/µL). Using mock mixtures of plasmid controls with *Poc:Pow* ratios up to 10-fold different, we developed species-specific classification criteria that prevented false-positive detection while maintaining sensitive detection of the minority ovale species down to 10^0 copies/uL (< 1 parasite/µL) at a ratio of 1:10. Compared to a traditional nested PCR (nPCR, Snounou 2002), the adapted qPCR assays successfully determined parasite species for a greater proportion of *Po*-positive clinical samples from Tanzania and Cameroon, even when nPCR cycles were extended to 50+50 cycles (78% (29/37) vs. 66% (25/38) for qPCR and nPCR, respectively). Four discordant findings between qPCR and nPCR in the 20 samples with speciation results in both assays were attributable to detection of mixed *Poc*/*Pow* infection by qPCR whereas nPCR detected only one *Po* species. This real-time PCR approach can be used to improve our understanding of *P. ovale* malaria epidemiology and differences between species.

1457

THE CHELEX AND WASH (C&W) METHOD: AN INSTANT TOTAL NUCLEIC ACID EXTRACTION FOR MALARIA FROM BLOOD THAT IS COMPATIBLE WITH LOOP MEDIATED ISOTHERMAL AMPLIFICATION AT THE POINT OF CARE

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Malaria elimination requires point of care compatible diagnostic tools that can detect submicroscopic parasitemia. Loop mediated isothermal amplification (LAMP) is a prime candidate for this, however the extraction approaches used are equipment-intensive, costly and time consuming. This study presents an innovative method - the chelex and wash (C&W). The extraction is equipment-free and involves homemade filter paper-based dipsticks that are dipped in room-temperature stable lysis and wash buffers which only requires heating to 65ºC for 10 minutes. C&W is paired with reverse transcriptase (RT) LAMP detected DNA and RNA from *Plasmodium spp* (Pan), *P. falciparum* (Pf), and human actin (internal control). The mean time to positivity for a 0.1% parasitemia sample was 11.8 (±1.1) minutes for Pan, 13.4 (±0.9) minutes for Pf assay, and 14.8 (±0.3) minutes for human actin control. The Limit of Detection was 0.5 parasites/uL of whole blood for Pan and 1 parasites/uL for Pf with a 30-minute cutoff time. When paired with a device that can be implemented at the point-of-care, finger-pricked blood extracted with the CW method is compatible with lyophilized RT-LAMP and can be visually detected in under 1 hour. Unlike other extractions, C&W requires only one consistent temperature for both extraction and LAMP, thus allowing one to use a simple heating device, such as the "Black Pearl" point-of-care device (in-house device at the University of Calgary that allows for incubation and visualization of samples). C&W performances are currently being compared to two index tests (boil and spin and commercially available options) and will be presented at the conference. The C&W extraction method can be used effectively at the point-of-care in resource-limited settings, as it is equipment-free, ultrasensitive, fast (under 1 hour total), inexpensive (0.50 USD), minimally invasive (requires only 10 uL of blood) and easy-to-use. The test also uses minimal single-use plastic, thus making it an environmentally friendly option. Further developments include pairing this extraction method with a microfluidic cartridge for single-use testing.

1458

CHARACTERIZATION OF POLYCLONAL ANTIBODIES AGAINST *PLASMODIUM VIVAX*-SPECIFIC TARGETS

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The development of more sensitive and specific antigen detection assays for *Plasmodium vivax* (Pv) is required. To address this need we selected, expressed, and purified five *P. vivax*-specific antigens using self-assembled protein nanoparticles (SAPNs) to generate polyclonal antibodies in rabbits to develop a rapid diagnosis test (RDT) for *P. vivax*. These targets (PvDBP, PvEBP2, Pvs25 and PvLDH) which span the different stages of the parasite life cycle in the blood were selected due to their specificity for *P. vivax* as opposed to other Malaria species. To validate their selectivity, we performed cross-reactivity assays using whole parasite lysate for Western blots, flow cytometry, immunofluorescence microscopy, and Imagestream analysis using *Pv, P. falciparum (Pf), and P. knowlesi (Pk)*. These assays have shown a higher signal for *P. vivax* at various stages of the parasite life cycle relative to *Pf* or *Pk*. The WHO requires the detection of <200 *P. vivax* parasites/µl blood for rapid diagnostic tests. Our current technology shows a detection limit of 1 parasite per µl of infected blood in an ELISA-based assay and <10 parasites per µl in a paper-based assay. Additionally, experiments using artificially mixed infections with *P. falciparum* indicate that 100x excess of *P. falciparum* can be tolerated in our assays. The polyclonal antibodies with the highest affinity and specificity will eventually be selected for the development of monoclonal antibodies to be used in a new RDT for *P. vivax* infection detection which is critical for proper disease treatment to eliminate liver-stage hypnozoites that cause recurrent blood stage infection. Furthermore, antibodies that exhibit protection against *P. vivax* in proof-of-concept assays can be used as monoclonal therapies or to develop vaccines against the respective target proteins.

1459

COST-EFFECTIVENESS AND SENSITIVITY OF POOLED PCR TESTING STRATEGY FOR MALARIA SURVEILLANCE IN LOW TRANSMISSION SETTINGS

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Intensive malaria control measures in the past two decades have significantly reduced malaria disease burden in many countries worldwide, and many countries and regions have shifted the goal of malaria control to elimination. A number of national malaria control programs in Africa have developed strategies to stratify the countries based on malaria transmission intensity to implement malaria elimination program in phases. When malaria transmission is reduced to a low level, detecting the parasite carriers, particularly the low parasitaemia asymptomatic carriers presents a big challenge. Samples pooling strategy has been used to identify malaria parasite carriers, but the cost effectiveness and loss to detect low parasitaemia infections are not well known in settings with different malaria prevalence. This study was to examine the optimal pool size without significant loss of detection sensitivity in pooled PCR testing strategy, and to what prevalence the pooled PCR testing strategy is cost-

effective. To determine optimal pool size, pre-screened asymptomatic samples were used to test pool size of 5, 10 and 15 sample. Dry blood samples total from 110 asymptomatic malaria carriers from Kenya were used for this test. The qPCR in triplicate were conducted to quantify parasitaemia. We found that pooling sizes of 5, 10 and 15 increased cycle threshold (Ct) values by 0.16, 0.35 and 0.72 respectively, leading to 97.6%, 94.0% and 81.9% detection sensitivities. Our data indicated that pooling up to 10 dried blood samples into one PCR detection provides more than 90% sensitivity. We are currently analysing labour and molecular reagent saving from pooled PCR testing strategy in malaria surveillance in several counties in western Kenya with low transmission.

1460

DESIGN AND VALIDATION OF A LOW-COST ELECTRICITY-FREE DEVICE FOR AUTOMATED THIN SMEARING OF WHOLE BLOOD

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High-throughput microscopy plays a crucial role in diagnostics of infectious diseases, including malaria - with more than 200 million thin-smear samples imaged every year. High quality thin blood smears enable sensitive and specific detection and speciation of malaria parasites, as compared to thick smear microscopy and RDTs. However, practical implementation of making high quality blood thin smears in field conditions remains elusive. Current manual methods lack consistency and do not provide a uniformly dense monolayer of RBCs, even when prepared by trained experts. Existing devices for assisting in making thin smears are either prohibitively expensive, electrically powered, or unvalidated for producing high quality whole blood smears. Here we present Inkwell - a low-cost, purely mechanical, electricity-free, compact blood smearing device which uses passive dynamics of an air-spring to produce high quality whole blood smears of tunable density, with minimal training requirements. The prototype of this device, which uses a $0.01 US empty syringe and a spring for velocity control, enables users to easily and reliably smear a drop of whole blood into a dense monolayer of roughly 12 million individually distinguishable red blood cells on a single slide. We present measurements of the consistency and reliability of our prototype device across hundreds of smears and match them to theoretical predictions from Landau-Levich thin film coating. We anticipate that Inkwell; our open-source thin-smear making device - in conjugation with our Octopi: high throughput automated microscopy system can achieve a detection limit below 10 parasites per microliter.

1461

GENERATION OF RIBOSOME DISPLAY SCFV ANTIBODIES FOR MALARIA DIAGNOSTICS

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Malaria infections are a major cause of morbidity and mortality throughout the world, with 198 million cases and 584,000 deaths globally in 2013. Microscopy and nucleic acid amplification tests are costly and need expert testers. Rapid antigen based diagnostic tests have aided diagnosis of malaria, particularly in resource poor settings. Accurate *Plasmodium* species identification has therapeutic implications for *P. vivax* and *P. ovale*, which have dormant liver stages. Current RDTs are based on detection of 3 different types of *Plasmodium* antigens; The first is *Plasmodium* histidine rich protein (HRP) 2 (pHRP-2), which can be specific to *P. falciparum* or *P. vivax*, the other two are *Plasmodium* lactate dehydrogenase (LOH) (pLDH) specific to *P. falciparum or P. vivax* or be a variant that is common to all *Plasmodium* species (panspecific) and *Plasmodium* enolase, which is also pan specific. In this study, five antibodies that were generated against Plasmodium LDH (Lactate Dehydrogenase) from *P. vivax* and *P. falciparum*, and three antibodies raised against HRP II (Histidine Rich Protein II) from *P. falciparum*. Our advanced technology was used to generate unique thermostable antibodies with the goal of suitability for superior diagnostic assay development. The recombinant ribosome display library was subjected to stress conditions (heat and denaturants) prior to antibody selection. This specialized guided selection process resulted in antibodies which exhibited thermostability T(m) up to 80°C as measured with CD spectroscopy. These heat-stable antibodies are suitable to develop robust malaria diagnostic tools for use in tropical climates and remote areas.

1462

DRIED BLOOD SPOTS: THE IDEAL MOLECULAR DIAGNOSTIC SAMPLE FOR MALARIA FIELD STUDIES

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Molecular diagnostic endpoints are increasingly used in controlled human malaria infection studies and field efficacy studies of malaria vaccine and drug candidates. Molecular diagnostic biomarkers include *Plasmodium* 18S rRNA, the 18S rRNA-coding genes, and other DNA gene targets. Many such assays rely on the collection of whole blood specimen, which can be challenging to cold store. One assay is an 18S rRNA-based quantitative reverse transcription PCR (qRT-PCR)-based approach that achieves analytical sensitivity which allows for detection down to a single infected erythrocyte in just 50 microliters of blood, a volume that can be collected as dried blood spots (DBS). When this qRT-PCR is performed on DBS, the strategy offers advantages over liquid blood samples in terms of collection, storage, and shipping. Here, the stability of the *Plasmodium* 18S rRNA biomarker on DBS was evaluated using short- and long-term storage at -80°C, -20°C, room temperature, and 37°C. Stability was evaluated using both the *Plasmodium* 18S rRNA and the endogenous human control TBP mRNA. In separate analyses, human 18S rRNA integrity was also evaluated as the TBP mRNA is more labile than parasite or human derived 18S rRNAs. The data showed that the *Plasmodium* 18S rRNA targets were stable for 12 months at -20°C (P=0.4), with minimal increase in TBP cycle number (1.47 cycles; 95% CI: 1.13-1.81 cycles). Although target degradation was evident for low positive specimen stored 12 months at 37°C (P=0.01) or room temperature (P=0.005), they were still reliably detectable with minimal loss (-0.61 ± 0.73 $\log_{10}$ copies of 18S rRNA, -0.12 ± 0.85 $\log_{10}$ copies of 18S rRNA, respectively) which speaks to the resilience of *Plasmodium* 18S rRNA when collected as DBS. Other DBS aspects potentially useful for malaria trials were also evaluated including the diagnostic accuracy of sample pooling and the collection volume reliability, as well as stability of at-home, self-collected DBS. Given the stability of DBS and their compatibility with rRNA and DNA assays, DBS samples are thus the preferred diagnostic matrix for malaria field studies where ease of sample handling is of paramount importance.

1463

CLINICAL PERFORMANCE EVALUATION OF BINAXNOW MALARIA PFPAN RAPID DIAGNOSTIC TEST FOR THE PARASITOLOGICAL CONFIRMATION OF MALARIA IN LAGOS, NIGERIA

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Malaria Rapid Tests (RDTs) are recommended diagnostic tests, in addition to malaria microscopy for the parasitological confirmation of all suspected malaria cases before treatment. This is the recommendation by WHO and has been adapted by Malaria Control Programmes. Histidine Rich Protein-2 (HRP-2) and plasmodium lactate dehydrogenase (pLDH) are commonly used analytes among the RDTs for malaria. However, there are variability in the performance of these RDTs in different epidemiological settings. Presumptive diagnosis and poor trust on the RDT results are major challenges among healthcare providers in the implementation of RDTs in malaria case management. Overdiagnosis and overtreatment of malaria have been well documented and these may be responsible given

the changing epidemiology of malaria in Nigeria over time. We assessed the BinaNow Malaria HRP-2 pLDH in Lagos, Nigeria in patients suspected to have malaria at presentation. The study was conducted in six healthcare centers located in Ikorodu and Somolu Local Government Areas of Lagos state from July 2013 through February 2014. The study assessed the performance characteristics of the rapid tests against microscopy results under different settings. The Binax Pf and Binax Pan tests detected malaria in 676 (40%) and 368 (22%) of the study participants respectively. The sensitivity of the Binax Pan was (80% [95% CI: 76, 84]) and was significantly lower than Binax Pf of (98% [95% CI: 96, 98]) (p<0.001). The positive predictive value of the Binax Pf and Binax Pan was 50% and 74% respectively. Similarly, the negative predictive value for Binax Pf and Binax Pan was (99% [95% CI: 99, 100]) and (95% [95% CI: 94, 96]) respectively, and were similar (all p>0.932). Fever, chills, headache and vomiting were significantly associated with positive results by both tests. However, there was no significant association with test positivity and age, gender, season, parasitaemia and duration of illness among febrile and afebrile participants. The malaria RDTs performance indicate the utility and relevance in the case management of malaria and should be used by Healthcare providers without any doubt.

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CLINICOPARASITOLOGIC CONSIDERATIONS IN THE IMPLEMENTATION OF THE NATIONAL GUIDELINES ON DIAGNOSIS AND TREATMENT OF SUSPECTED MALARIA PATIENTS IN LAGOS STATE, NIGERIA

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One of the major challenges with malaria is the non-specificity of associated symptoms and signs. Current best practice in malaria case management in the National Guidelines on Diagnosis and Treatment of Malaria is mandatory parasitologic confirmation of suspected cases by either microscopy or malaria Rapid Diagnostic Tests (RDTs) before treatment. Despite the existence of this guideline since 2010, the implementation has remained a challenge as healthcare providers still rely on presumptive diagnosis coupled with unreliable microscopy test results that has resulted to overdiagnosis and overtreatment of malaria. Accurate diagnosis ensures only parasitologically confirmed cases of malaria receive the recommended treatment to avoid waste of medicines, glossing over of potential ailments that could be treated presumptively as malaria and poor patients' outcome. We conducted a cross-sectional study among to determine malaria parasite confirmed rates in 1621 patients, 2 years and above that presented with suspected malaria symptoms in semi-rural health facilities in Ikorodu and Somolu Local Government Areas of Lagos State, Nigeria. Parasite positive rate of 20% was recorded with *P. falciparum* being the predominant species (99.1%) and *P. malariae* (0.9%). Fever, body pain, headache, vomiting, and anorexia were associated with malaria positivity. Febrile participants were more than 4 times likely to test positive for malaria by microscopy than afebrile (OR: 4.06 [95% CI: 3.15, 5.25]). Participants with vomiting had a 2.5-fold increased risk of having detectable malaria parasites (OR:2.48 [95% CI: 1.83, 3.35]), while body pain and headache increased the odds of testing positive by microscopy by 2.18 (95% CI: 1.63, 2.94) and 1.91 (95% CI: 1.34, 2.77) respectively. Cough and catarrh were associated with decreased odds of testing positive by microscopy by 54% and 62%, respectively. Presumptive diagnosis and nonimplementation of current guidelines may impede expected treatment outcomes in non-malaria patients and promote overtreatment with subsequent pressure on antimalarial medicines that could trigger resistance.

1465

EFFICACY AND SAFETY OF PYRONARIDINE-ARTESUNATE (PYRAMAX), A NEWLY-REGISTERED ARTEMISININ-BASED COMBINATION FOR THE TREATMENT OF MALARIA INFECTION IN AFRICAN PREGNANT WOMEN

PYRAPREG Team

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Malaria in pregnancy is a major public health problem in endemic countries, resulting in an increased risk of maternal anaemia, low birth weight and infant death. Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) are the most widely deployed artemisinin-based combination treatments (ACT) in sub-Saharan Africa. However, there is a need for alternative therapeutic options for treating malaria during the 2ndand 3rdtrimester of pregnancy. Pyronaridine-artesunate (PA), a newly registered ACT, may be a potential candidate but data on its safety and efficacy during pregnancy are scarce. We are implementing a non-inferiority, multicentre, randomized, open label clinical trial comparing PA with AL and DP for treatment of pregnant women with *P. falciparum*malaria infection in the 2ndand 3rdtrimester of pregnancy. The trial is conducted in 5 African countries: Burkina-Faso, The Gambia, Democratic Republic of Congo, Mali, Mozambique. The primary endpoint is treatment efficacy (PCR-adjusted cure rate at day 42) and the main secondary endpoint is safety during the 63 days post treatment, at delivery, and the status of the baby one year after birth. The trial will recruit 1,875 (ratio of 1:1:1) pregnant women. Recruitment started in January 2021 and by 1stApril 2022,782 pregnant women were enrolled, with 546 (69.8%) having completed the 63-day follow-up, and 480 (61.4%) delivered. Recruitment is planned until December 2022. Since the beginning of the study 35 cases of serious adverse events have been registered. In conclusion, results of this trial will establish the safety and efficacy of PA when administered to pregnant women with malaria.

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COHORT PROFILE: PARTICIPANT BASELINE CHARACTERISTICS FOR THE KINSHASA MALARIA COHORT STUDY

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Few malaria longitudinal studies combine epidemiological and entomological data at varying transmission intensities. Here we present the baseline household and individual characteristics for a longitudinal study conducted in three health areas in Kinshasa Province: an urban area with low prevalence (Voix du Peuple), a semi-urban area with moderate prevalence (Kimpoko), and a rural area with high prevalence (Bu). The baseline survey collected data on socio-demographics, mosquito net ownership and use, housing characteristics, asset ownership, and proximity to ecological risk factors. At baseline and each active surveillance visit, each participant provided information on the history of febrile illnesses, malaria symptoms, diagnosis, and treatment. Participants also provided a blood sample for rapid diagnostic testing, microscopy, and molecular testing at every visit. The baseline sociodemographic and clinical data were analyzed to generate descriptive statistics. From April to October 2018, 239 households (1,662 participants) were enrolled, with 475 participants in Voix du Peuple, 596 in Kimpoko, and 591 in Bu). Over half of the participants were female (56%). Children under five represented 16% of the study population. The mean number of mosquito nets per household was 2.3 (95% CI: 2.1 - 2.5). Most study households (78%) owned at least one mosquito net, but ownership varied by site (Voix du Peuple 18%, Kimpoko 33%, Bu 28%). Net use was high, with 90% being used the

night before the interview. The primary net source was mass distribution campaigns (68%). Most participants (43%) reported having at least one malaria episode in the previous six months. At baseline, the overall malaria rapid diagnostic test positivity rate was 33% (Voix du Peuple 3%, Kimpoko 35%, Bu 54%). Baseline data will be combined with data from six active household surveillance visits and nine entomological surveys to provide a broad picture of malaria prevalence and transmission in Kinshasa Province over four years at three endemicity levels.

1467

EVALUATING THE IMPACT OF HETEROGENEITY OF PREVALENCE AND INCIDENCE IN MALARIA CLUSTER RANDOMISED CONTROL TRIALS: CAN TRIALS BE DESIGNED MORE EFFICIENTLY?

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Cluster randomised control trials (cRCTs) remain the gold standard for evaluating the community-level impacts of control interventions against malaria. Numbers of such trials have increased in the past 40 years and have been instrumental in influencing health care policy. In 2021 alone, over 20 malaria vector cRCTs were published. However, cRCTs are expensive and logistically challenging. To enable cRCTs to detect the expected effect size of control interventions, investigators must account for heterogeneity within (known as the intracluster correlation coefficient) or between (known as the coefficient of variation, or k) clusters. Often, baseline data needed to estimate these coefficients are absent when cRCTs are designed, thus figures are obtained from other settings or simply guessed. Consequently, trials can be underpowered, meaning that they are unable to detect the impact of intervention(s) under consideration. Malaria transmission is notoriously heterogenous, owing to factors such as uneven geographical distributions of mosquito populations and housing type. These factors have contributed to several recent malaria vector cRCTs being underpowered. We conducted a systematic review of malaria cRCTs to better understand factors that influence variation in the effect size of interventions and to generate guidelines that could assist investigators in designing future malaria cRCTs. We compared estimated and retrospectively calculated coefficients of variation among previously conducted cRCTs. We then assessed which factors influenced the coefficient of variation, focusing particularly on those that might be available to investigators during the design phase. Lastly, we investigated how the coefficient of variation changes during the course of cRCTs in the presence and absence of different control interventions to determine whether sample size calculations should be tailored according to different control strategies. These findings have the potential to optimise the design of future malaria cRCTs and help ensure interventions are accurately evaluated to help in the global fight against this disease.

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COMMUNITY PERCEPTIONS AND RESPONSES TO IVERMECTIN MASS DRUG ADMINISTRATION FOR MALARIA CONTROL IN MOPEIA, MOZAMBIQUE: THE ACCEPTABILITY OF THE BOHEMIA TRIAL

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Malaria is preventable and treatable, and yet it remains a significant public health problem around the world, particularly in Africa. New tools and strategies are needed to address this persistent burden. The BOHEMIA consortium (Broad One-Health Endectocide-based Malaria Intervention in Africa) has undertaken a trial of the impact on malaria of mass drug administration with ivermectin at the start of the malaria transmission season in Mopeia, Mozambique. Evidence of the acceptability of malaria MDA in Africa is scarce and the BOHEMIA project included a social science work package the focus of which was to identify and understand the likely drivers and challenges to high uptake of the ivermectin MDA and to explore the acceptability of the approach as a strategy for malaria prevention. The qualitative exploratory study used an ethnographic approach with social science researchers living in ten of the trial communities prior to the intervention (phase 1) and during the implementation of the trial (phase 2), collecting data through non-participant observations, in-depth interviews, focus group discussions and photovoice. Following the completion of the trial, focus group discussions were undertaken in an additional 20 communities (phase 3) as a retrospective assessment of the intervention acceptability and to triangulate the findings from the 10 in-depth communities. This approached allows for the development of rich descriptions of community experiences and responses to the ivermectin MDA and an in-depth understanding of the local challenges and opportunities for the use of this tool for malaria prevention. The results of phase 1 and the effects of the COVID-19 pandemic are discussed elsewhere. This presentation will present the results of phase 2, community experiences and responses to the ivermectin MDA, and discuss the broader implications of the acceptability of ivermectin MDA as a malaria control strategy.

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AN UNEXPECTED TURN: A 4-AMINOQUINOLINE ANTIMALARIAL COMPOUND INHIBITS *PLASMODIUM* SEXUAL STAGES IN *VITRO*

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The emergence of drug-resistant *P. falciparum* strains poses a timely need for the development of new antimalarials that are not compromised by existing resistance mechanisms. We used a QSAR-based virtual screening strategy to search for candidate molecules with potential activity against *P. falciparum*. By coupling *in silico* and phenotypic screenings, we identified a 4-aminoquinoline compound, named LDT-623, which showed potent activity against asexual blood stages in both chloroquine-sensitive (3D7) and multidrug-resistant (Dd2) *P. falciparum* strains (mean IC_{50}s of 23 and 37 nM, respectively). This compound showed selectivity indexes of 21.3 and 54.8 for the parasite when compared with COS-7 and HepG2 cells. LDT-623 shared a few important features with chloroquine, a representative compound of the 4-aminoquinoline antimalarial drugs, as both are fast-acting compounds that inhibit β-hematin formation *in vitro* (mean IC_{50}s of 1.6 and 10.3 μM for LDT-623 and chloroquine, respectively). We tested whether LDT-623 inhibited parasite transmission stages using a luciferase-expressing *P. berghei* line with an ookinete stage-specific promoter. Interestingly, by inhibiting gamete fertilization and ookinete conversion, LDT-623 showed good dose-response curves with a mean IC_{50} of 1.6 μM, while chloroquine inhibited ookinete conversion by only ~ 50% at 10 μM. We next aim to explore whether LDT-623 also inhibits *P. falciparum* gametocytes *in vitro*. Selection of compound-resistant *P. falciparum* lines *in vitro* will also be carried out to investigate other genes involved in the mode of action of this particular compound, other than *pfcrt* and *pfmdr1* themselves, given its unusual asexual and sexual dual-stage antimalarial activity.

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DESIGN AND DEVELOPMENT OF AN ELQ-300 BACKUP BASED ON THE STRUCTURE OF ELQ-596

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A new series of endochin-like quinolones are three- to four-times more effective than ELQ-300 and share the same mechanism of action, inhibition of the Q_i site of *Plasmodium falciparum* cytochrome bc_1. ELQ-300 exhibits low nM IC_{50}'s vs. multidrug resistant *Pf* strains including field isolates, pan-antimalarial activity against the various Plasmodium species that infect humans, potent activity against replicating parasites in the liver, blood and vector stages of infection, excellent metabolic stability and extended pharmacokinetics in preclinical species, and a clean safety profile. An ELQ-300 prodrug, ELQ-331, was accepted as a preclinical candidate by the MMV in October of 2020. A representative of this new structure-activity relationship program, ELQ-596, exhibits low- to sub-nM IC_{50}'s against *Pf* reference strains that are three- to four-times lower than recorded for ELQ-300 in side-by-side in vitro testing, with extensive cross resistance observed in the ELQ-300 resistant D1 clone, which indicates selective Q_i targeting. An alkoxycarbonate ester prodrug of ELQ-596, ELQ-598, provides effective dose values that are also approximately three- to four-times lower than recorded for ELQ-331 in the same murine malaria model. Given that pharmacology experts predict that a single 30 mg oral dose of ELQ-331 will protect adults from malaria infection if taken weekly, we believe that a compound from this new series could provide the same degree of long-term protection at a significantly lower dose, perhaps 5 to 10 mg on a weekly or biweekly schedule.

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PARASITE HEXOSE TRANSPORTERS (HT) TARGETED BY HYDROXYETHYLAMINE ANALOGS: A PIVOTAL DISCOVERY OF BROAD-SPECTRUM COMPOUNDS WITH LOWER NANOMOLAR RANGE ACTIVITY AGAINST *PLASMODIUM FALCIPARUM* AND *LEISHMANIA DONOVANI*

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Pathogenic kinetoplastids as well as apicomplexans use a wide range of different strategies to gain access to the carbon sources of their human hosts. Glucose, an almost universally used energy and carbon source, is processed through several well-known metabolic pathways, primarily glycolysis. With both N and C terminals exposed to intracellular, parasite hexose transporters have literally no loose ends and are protected from host immune recognition. Here, we present the identification of novel hydroxyethylamine (HEA) based hexose transporter inhibitors specific to the parasites binding to their signature domains and blocking both *Plasmodium falciparum (PF)* and *Leishmania donovani (LD).* Proteins (GLUT2) PF3D7_0204700 and LdBPK_330310 from PF and LD, respectively have 80% homology. The extracellular loops are very compact potentially to burry immune determinants and evade host defenses. This gives rise to a highly hydrophobic outer pore that is exposed and making it an excellent dug target owing to characteristic central cavity/lumen of the transporter. Virtual screening was performed with the grids constructed covering the consensus regions using our in-house synthetic libraries (n=>5000). There was a high hit rate specifically from HEA compounds, particularly piperazine derivatives (HEA39). Upon testing for anti-parasitic activity, the results showed highly potent activity with IC50 values of 80 nM and 190 nM against *PF* and *LD*, respectively. The target specificity of HEA-39 was validated by impaired uptake of fluorescent non-metabolizable glucose analogue 2-NBDG under concentration dependent pressure of the compound. Additionally, *in silico* studies reveal possible activity against Toxoplasma and Trypanosoma demonstrating potential application of HEA based compounds against broad spectrum anti-protozoal agent. Further, evaluation showed no apparent cytotoxicity in HEK-293, A529, HEPG2 and PBMCs. Currently, we are in expanding to derivatize HEA-39 for more active analogs targeting HT.

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SAFETY AND EFFICACY OF KAF156 (GANAPLACIDE) IN COMBINATION WITH LUMEFANTRINE-SDF IN CHILDREN 2-12 YEARS WITH UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA. PART B OF A PHASE 2 CLINICAL TRIAL

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With resistance to current antimalarials constantly evolving, there is an ultimate medical need for novel antimalarials with previously unexploited modes of action. Ganaplacide belongs to a novel class of drugs called the imidazolopiperazines. The aim is to develop ganaplacide in combination with a solid dispersible formulation of lumefantrine (LUM-SDF) for the treatment of uncomplicated *P. falciparum* malaria, allowing for once-a-day administration. To study safety and efficacy of this combination, a Phase 2 study (NCT03167242) was performed in several Asian and African countries with a total of 524 patients in order to determine the most effective and tolerable dose of this new drug combination. Part B of this study included 175 pediatric patients, aged 2 to 12 years and is reported here. Patients meeting the inclusion- and none of the exclusion criteria were randomized to a 1-,2- or 3-day QD dose regimen of 400mg ganaplacide combined with 960mg LUM-SDF, or control (Coartem®). Dosing was adjusted according to body weight bands. PCR corrected cure rates at Day 29 were 77.1%, 91.3%, 95% and 95.5% respectively for the 1-,2- and 3-day regimens and control. Mean parasite clearance time was 36 hours for all arms. Tolerability was good and there were no safety observations of concern.

It was concluded that the treatment arm of 400mg ganaplacide combined with 960mg LUM-SDF, given QD daily during 3 days, met the predefined criteria for success (lower limit of 2-sided 95% exact CI > 80% for ACPR rate).

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REPURPOSING DRUGS TO TARGET ENDOTHELIAL DYSFUNCTION IN CEREBRAL MALARIA

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Endothelial dysfunction is a problem underlying different deadly diseases, including sepsis and cerebral malaria. Fatality in cerebral malaria is associated with cerebral coagulopathy, breakdown of the blood-brain barrier (BBB), and severe brain swelling. Currently, there are limited strategies to stabilize the BBB during inflammatory damage and new therapeutic strategies are critical. To identify new therapeutics for damaged blood vessels, we are screening FDA-approved kinase inhibitors (KI) drugs for treatment of cerebral malaria dysfunction. We first screened *in vitro* the effect of KIs in primary microvascular brain endothelial cells monolayers challenged with thrombin and down selected promising

candidates with barrier protective activity into the experimental cerebral malaria model (ECM). From the *in vitro* screen, the BCR-ABL family of drugs showed different barrier phenotypes ranging from protective, neutral, to barrier disruptive due to different off-target kinase targets. Of the three BCR-ABL drugs tested so far in the ECM model, one showed an impressive protection against neuropathologic injury, measured by a rapid murine coma and behavior score, associated with BBB protection and without affecting parasite growth. Our work demonstrates that kinase inhibitors are an attractive drug-repurposing option to pursue for cerebral malaria adjunctive therapy.

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IN VITRO ANTIPLASMODIAL ACTIVITY OF BIOSYNTHESIZED SILVER NANOPARTICLES USING *PANDANUS AMARYLLIFOLIUS* ROXB. AGAINST MALARIA PARASITE, *PLASMODIUM FALCIPARUM*

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The utilization of various plant resources for the biosynthesis of nanoparticles is called green nanotechnology. In present study, the plant mediated synthesis of silver nanoparticles using the leaf extract of *Pandanus amaryllifolius*, which acts as a reducing and capping agent. The aim of the present study was to assess the anti-plasmodial activity of synthesized AgNPs against the malaria parasite, *Plasmodium falciparum*. The obtained nanoparticles were characterized using UV-visible spectroscopy; EDX (energy-dispersive X-ray), SEM (Scanning electron microscope), XRD (X-ray diffraction) and Fourier transform infrared (FTIR) analysis. The efficacy of green synthesized AgNPs at different concentrations (25, 50, 75 and 100µg/ml) were tested on *P. falciparum*. Synthesized AgNPs particles were confirmed by analysing the excitation of surface plasmon resonance (SPR) using UV-vis spectrophotometer at 422 nm.The scanning electron micrograph showed structures of spherical, cubic shape, and the size range was found to be 40-60 nm. The EDX spectra showed the purity of the material and the complete chemical composition of the synthesized AgNPs. XRD study shows that the particles are crystalline in nature with face centered cubic geometry. The FTIR analysis of the nanoparticles indicated the presence of proteins, which may be acting as capping agents around the nanoparticles. The parasitic inhibition was dose-dependent. The synthesized AgNPs showed significant anti-plasmodial activity when compared to aqueous leaf extract of *P. amaryllifolius*. The maximum efficacy was observed in synthesized AgNPs against *P. falciparum* (IC_{50}=100 µg/ml; 100%) respectively. In conclusion, this method is considered as a new approach to control the malaria parasite, *P. falciparum*. Therefore, this study provides report on the anti-plasmodial activity of synthesized AgNPs using *P. amaryllifolius* against *P. falciparum*.

1475

THE IMPACT OF EXTENDED TREATMENT WITH ARTEMETHER-LUMEFANTRINE ON ANTIMALARIAL EXPOSURE AND REINFECTION RISKS IN UGANDAN CHILDREN WITH UNCOMPLICATED MALARIA

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Artemether-lumefantrine (AL) is the most used artemisinin-based combination therapy in Africa. Studies show lumefantrine (LUM) exposure is lower in young children and associated with poorer treatment outcomes. LUM exhibits dose-limited absorption; pharmacokinetic (PK) modeling predicts improved exposure with extended AL duration rather than dose escalation which may reduce reinfection risks. We conducted a randomized prospective PK/PD study of AL in children with uncomplicated *P. falciparum* malaria in high transmission Uganda. Children received either a 3-day (standard 6-dose) or 5-day (extended 10-dose) AL regimen with PK sampling for artemether (AR), DHA, and LUM through day 21 and clinical follow-up to day 42. Children aged 16 mo-16 yrs were enrolled, contributing 226 episodes of malaria (n=113 episodes for each regimen). Terminal median LUM concentrations were significantly increased in the 5-day vs 3-day regimen on days 7, 14, and 21 (816, 186, 89 ng/mL vs 363, 122, 65 ng/mL, respectively; p-values <0.001). A day 7 LUM target threshold of 280 ng/mL was predictive of recurrence risk at 28 and 42 days (55% and 25% higher risk of recurrence if below this threshold, respectively; p<0.001). Children in the lowest mg/kg dosing weight band were 3-fold as likely to be below 280 ng/ml in the 3-day vs 5-day regimen. 42-day risk of recurrent parasitemia did not significantly differ between 3- and 5-day regimens (73.5% and 66.4%). Overall, 7.1% of recurrent episodes were recrudescent. No significant toxicity occurred with either regimen. Extending the duration of AL was safe, and significantly enhanced LUM exposure in children. Although trends in reduced risk were seen at 28 days, they were no longer evident by 42 days in our high transmission setting. Day 7 levels were strongly predictive of recurrent parasitemia risk at 28- and 42-days. Data further suggest that those in the lowest weight-band are at higher risk of underdosing with the standard regimen. Additional study in other transmission settings and in settings of emerging resistance are warranted.

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ENGAGING THE PRIVATE SECTOR USING A TOTAL HEALTH SYSTEM APPROACH TO ELIMINATE MALARIA IN NEPAL: AN ASSESSMENT OF APPROACHES, TOOLS AND LESSONS

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In Nepal, despite the provision of free malaria diagnosis and treatment in the public sector, 60-80% of patients in Nepal seek care at a private health facilities (PHFs). Previous assessments have found that the capacity of PHFs is limited in malaria diagnosis, treatment and surveillance; thus, stalling Nepal's goal of reaching zero indigenous malaria cases by the end of 2023. The goal of this multi-method assessment is to understand private sector malaria practices and identify ways to enhance the engagement with private sector to ensure availability and access to quality diagnosis, treatment and case-based surveillance at the PHFs. To support the implementation of the National Malaria Private Sector Engagement Guidelines 2020, a multi-method assessment of malaria service provision and surveillance in PHFs in urban and semi-urban locations is currently ongoing to assess and implement a total health system approach to malaria elimination. It leverages private sector opportunities related to 1) landscaping to understand the coverage and quality challenges across PHFs, 2) managing malaria cases by engaging PHFs to expand access to and use of quality diagnosis and case management, and 3) timely and accurately reporting all malaria cases. Findings from this assessment will be presented on the status of PHFs. This will include PHF's capacity and commodity supplies for malaria diagnosis and treatment, their awareness about the national malaria treatment guidelines; their capability to manage malaria cases and refer when necessary, their awareness of where and how to record and report malaria tests and cases, and their willingness to engage in the national malaria elimination program. As a result of targeted and intensified engagement of PHFs, we expect that 1) all malaria cases detected at PHFs are reported to the national information systems to timely trigger case-based surveillance; 2) all malaria suspected cases are tested using quality diagnostics and treated following the national protocols; 3) test results are reported to the national information systems; and 4) ownership by the private sector of the national malaria elimination program.

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EXPLORING THE EXPECTED SYNERGY AMONG NEW MALARIA CONTROL TOOLS IN HIGH-BURDEN VERSUS NEAR-ELIMINATION SETTINGS

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New malaria prevention and control tools, deployed in conjunction with existing malaria interventions, may constitute an essential part of the long-term strategy to eliminate malaria in settings that currently have high malaria burden. However, the development and deployment pipeline for these new tools is often lengthy, uncertain, and expensive. Decisions on which tools to invest in and how far to continue investments depend not only on the anticipated cost of a tool and the tools' efficacy, but also on how a tool is expected to perform when used alongside other interventions and across diverse settings. Unfortunately, anticipating the extent of synergy or antagonism among different interventions, and how that relationship may differ in high-burden versus near-elimination settings, is not straightforward. Furthermore, even when studies exist that quantify the amount of synergy in a high-burden setting, it is not clear whether the same relationship would be expected in a near-elimination context. To help guide intuition and expectations for these relationships, we use the agent-based malaria transmission model EMOD to simulate the impact of several malaria interventions, including monoclonal antibodies, endectocides, and ATSBs, in both high-transmission and near-elimination settings. By adding interventions alone and in combination, we quantify the synergy or antagonism between pairs of interventions in different contexts and identify groups of interventions that follow similar patterns. The results can be used not only to identify the types of interventions that could most effectively be combined across different transmission strata, but also to help prioritize research and development investments to arrive at a portfolio of tools that will lower the barrier for malaria elimination.

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PREVALENCE OF SUBMICROSCOPIC MALARIA, VECTOR SPECIE COMPOSITION AND SEASONAL DISTRIBUTION IN A LOW TRANSMISSION AREA OF NEPAL: A SILENT THREAT TO MALARIA ELIMINATION

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Nepal's Malaria Strategic Plan 2014-2025 has set a vision eliminate malaria by 2025. Substantial progress has been made, however, sub-microscopic cases are still of concern. Following six malaria cases of *Plasmodium vivax* reported from a single ward, a cross-sectional, case-based surveillance and foci-investigation study was carried out in Shivanath-5 ward of Baitadi district in 2016 to identify additional malaria cases and classify the malaria foci. A household survey was conducted in 27 households within the circumference of the cluster of reported malaria cases. All febrile cases and 20% asymptomatic individuals were tested using a systematic random sampling method. Diagnostics used were antigen based RDTs, microscopy and PCR. Malaria, travel and clinical history was recorded. Information on geo-ecology, vulnerability, receptivity, and vector identification was also collected. A retrospective exercise using malaria data from the last three years from the health-facility level was also conducted. Results showed that the mean API of the study site from 2014-2016 was much higher (17.67/1000 in 2014/2015 and 37.10/1000 in 2015/2016) than the national average (0.10/1000) and there was substantial evidence of local transmission. The most affected group was ages14 years and with male to female proportion of infection of 30%:70%. The symptomatic sub-microscopic prevalence of *Plasmodium vivax* at the community level was found to be 4.88% by microscopy and 15.38% by PCR. No asymptomatic prevalence was seen in this study. *Plasmodium vivax* was found to be the predominant species in the region. The entomological study showed local transmission in terms of receptivity, vulnerability and geo-ecological factors. *An. fluvitilis* and *An. willmori* were the predominant species found in the study. Seasonal transmisison was found mainly in the months of May, June, July, and August. Our study showed that all cases investigated were indigenous which confirmed local transmission. Sub-microscopic prevalence calls for immediate actions and it can be a silent threat for driving residual transmission in the community.

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STRENGTHENING DISTRICT CAPACITY ON DATA USE TO IMPROVE MALARIA PRODUCT AVAILABILITY IN THE NORTH AND FAR NORTH REGIONS OF CAMEROON

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Background: Recurring stockouts of malaria products in health facilities (HFs) affected management of malaria in the North and Far North regions of Cameroon. The U.S. President's Malaria Initiative (PMI) funded Global Health Supply Chain Program-Procurement and Supply Management project (GHSC-PSM) identified low logistics data availability & quality in DHIS2, a health management information system, and inappropriate or non-ordering by HFs as the main root causes of stockouts. Methodology: In October 2020, with the National Malaria Control Program (NMCP), GHSC-PSM trained 101 staff from 45 districts in the North and Far North regions to analyze data on DHIS2 for its availability, quality, and use to make key supply chain decisions. GHSC-PSM developed an Excel-based tool that uses DHIS2 data to produce color-coded dashboards that highlight completeness, coherence, and stockouts across multiple supply chain variables. GHSC-PSM continues to provide coaching to districts on data analysis and feedback to HFs. GHSC-PSM also provides monthly airtime to facilitate districts' access to DHIS2 and data entry for relevant HFs. Results: Due to the training and improved knowledge on using data for distribution, in November 2020 the regional NMCP shifted from a pull distribution system, based on individual facility requests, to a push system, based on both facility and entire system needs. Between August 2020 and April 2021, the DHIS2 reporting rates increased from 70% to 95%. Through the End Use Verification surveys (EUV), we found that the stock cards (the original source of DHIS2 data) updating rates for the four presentations of Artemether/Lumefantrine (AL) increased from 44%-52% to 61-66% over the same period. The stockout rates reduced from 24%-42% in August 2020 to 12%-27% in April 2021, as observed through the EUV. DHIS2 data showed stockout reduction from 14%-23% to 10-17% showing increased data quality, better alignment between the EUV and DHIS2 over this period, and proof that the shift in systems based on improved data availability and quality led to improved stock availability.

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THE EFFECTIVENESS OF SCALED-UP INTERVENTIONS FOR MOBILE MIGRANT POPULATIONS ALONG THE VIETNAM-CAMBODIA BORDER: FINDINGS FROM A QUALITATIVE STUDY

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Despite the scaling-up of interventions targeting mobile and migrant populations (MMPs) in Vietnam, residual transmission and widespread

artemisinin resistance challenge current malaria elimination goals. Between 2018 and 2022, we conducted a qualitative study in six villages of By Gia Map along the Vietnam-Cambodia border to understand the social factors related to the effectiveness of MMP interventions. The study employed ethnographic methods, theoretical sampling and retroductive data analysis. The area is inhabited by the ethnic minority Stieng and M'nong that live in a combination of residences, large companies' plantations and their own farms in the forest. Working on these farms and subsistence activities are considered illegal by the government and expose people to malaria. Another group in the forest are the so-called MMPs, consisting of undocumented migrants and illegal forest workers. Various ongoing projects targeting MMPs in the area require village health workers (VHWs) to test MMPs or "forest goers". However, the focus on MMPs is not very effective for several reasons. VHWs are all women for whom it is a taboo to be in close contact with men, limiting their capacity to reach out to MMPs who are almost exclusively men. The demand for reporting illegal forest activities puts health workers at risk of betraying members of the ethnic minorities in their struggle for livelihood. Without negotiation power, LHWs' only way out is to fabricate data to report to the projects. In addition, the increase in testing has led to people's unwillingness toward blood sampling and an association between malaria and government control. Available surveillance data show that the MMPs are not present in the area during the period of high malaria cases suggesting they are not the main at-risk group. The study shows that the standardized supranational strategy of testing and treating MMPs is not effective in the study area as it misses ethnic minorities' vulnerabilities to malaria and other local socio-ecological factors. The study makes the case for localizing interventions, embedding them in the local context, based on knowledge of its particularities.

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PATHWAYS TO MALARIA ELIMINATION - OPPORTUNITIES FOR STRENGTHENING MALARIA SURVEILLANCE AND DATA-DRIVEN PROGRAM PLANNING AND IMPLEMENTATION IN GHANA

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The success of malaria elimination in Ghana is dependent on strong surveillance that enables evidence-based program planning, implementation, monitoring, and evaluation at all levels of the health system. The National Malaria Control Program (NMCP), together with its partners, conducted an assessment in 2021 to identify key surveillance gaps and develop actionable recommendations to strengthen the system. The mixed method, cross-sectional study included a desk level document review, key informant interviews (n=31), data quality audits, and an operational and service level survey (n=203). Tools were adapted from the WHO malaria surveillance assessment toolkit. Performance metrics (such as system coverage, data completeness and timeliness and data use) and contributing factors (such as system integration and use of dashboards) were assessed. Reported malaria cases from the public and private sector are housed within a central database, the District Health Information and Management System (DHIMS2); however, cases presenting at pharmacies are not captured in DHIMS2, contributing to low system coverage (approximately 35% of all malaria cases are captured in DHIMS2). Among reporting facilities, reporting completeness and timeliness were high (98% and 94% respectively); however, the health facility participation rate was difficult to determine due to outdated master facility lists. Use of data for decision-making remained focused at the national level, with less than half of intermediate areas reporting use DHMIS2 dashboards for data analysis and only 29% of facilities indicating that actions were triggered by data. Based on these key findings, priorities to strengthen surveillance include 1) mobilization and inclusion of pharmacies in malaria surveillance, 2) development of a single and comprehensive malaria repository with an updated master facility list and 3) capacity strengthening on use of dashboards for action-planning at operational levels.

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A PHASED RESEARCH APPROACH TO EVALUATING NOVEL BITE PREVENTION TOOLS FOR MALARIA ELIMINATION AND IDENTIFYING ENTOMOLOGICAL CORRELATES OF PROTECTION

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Volatile pyrethroids and etofenprox treated clothing are promising new tools for bite prevention for malaria elimination in areas where vectors bite outdoors or during waking hours. New classes of vector control interventions are typically evaluated for protective efficacy based on epidemiological endpoints. However, it is necessary to understand the effects on mosquitoes to ensure that additional products within a class function in the same way, without the need to conduct an epidemiological trial each time. Volatile pyrethroid products and etofenprox treated clothing with and without picaridin topical repellent first were evaluated in two semi-field systems (SFS) in Thailand, and then in an entomological field trial in Cambodia. The SFS studies used the standard measure of human landing rates but also included additional endpoints of disarming, blood feeding inhibition, and mortality, which cannot be measured in the field and are often not measured in any evaluation of vector control products. Data from these studies indicates that the standardized measure of human landing rates does not capture the overall and cumulative intervention impact on mosquito behavior and will underestimate protective efficacies. These interventions cause a range of 'secondary effects' that directly affect vectorial capacity, indicating protection may extend from the individual to the community. An entomological study using human landing catches was conducted in the field in Cambodia to evaluate the impact of the products on mosquito landing among wild vector populations. The study found that all products and combinations (n=6) reduced risk of mosquitoes landing by at least 50%, and the passive volatile pyrethroid product and the combination of products reduced risk by nearly 95%. Combined, these studies indicate strong entomological protective efficacy of these novel bite prevention tools and the utility of a phased research approach to evaluating bite prevention and vector control tools in the future. The addition of 'secondary effects' should also be considered for future research to provide insights into public health value of these tools.

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APPLYING SEROEPIDEMIOLOGY TO SUPPORT DECISION-MAKING FOR MALARIA ELIMINATION IN FIVE ELIMINATION SETTINGS

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A growing understanding of the longevity of malaria biomarkers in the immune system makes it possible to characterise an individual's recent and past exposure to *Plasmodium falciparum* and *P. vivax*. Rather than solely capturing concurrent infections using PCR or RDT diagnostics, serology measures specific antibody responses which reflect previous exposure to

pathogens. Assessing the presence or absence of anti-malarial antibodies in populations provides important insights for supporting decision-making for malaria elimination. The aim of this study was to evaluate the application of serology as a tool to support decision-making in five elimination settings in West Africa, Southeast Asia and South America. Serological responses to 7 *P. falciparum* and 4 *P. vivax* antigens were measured in 13,000 individuals across Cape Verde, Vietnam, Lao PDR, the Philippines, and Peru using a multiplex bead assay. Unsupervised machine-learning methods were applied to classify seropositivity, and population level historic and recent malaria exposure seroprevalence were estimated. This research highlights the added benefit of including serological assays in active surveillance in low-transmission or elimination settings. Preliminary results suggest that population-wide seroprevalence to recent exposure markers of *P. falciparum* in the Philippines and Lao PDR were 1% and 2% respectively, which is within the known range of sensitivity of the assay. As is common in elimination settings, recent exposure to *P. vivax* was higher in both populations, 10% and 7% seroprevalence. A positive correlation between age and recent exposure was found. Predictive mapping was used to identify clusters of recent exposure. The research demonstrates the advantages of serology, as opposed to infection diagnostics, in low transmission settings as a tool to confirm elimination. In addition to aiding elimination confirmation, serological estimates of exposure can help programs target areas which may have residual transmission. This research is a vital step in the proof-of-concept for including serology as a tool to aid decision making for malaria elimination.

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RETROSPECTIVE DESCRIPTIVE ANALYSIS ON THE IMPROVEMENT OF THE QUALITY OF MALARIA DATA IN 26 PROVINCIAL HEALTH DIVISIONS IN THE DEMOCRATIC REPUBLIC OF CONGO FROM 2017 TO 2021

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The Health Management Information System (HMIS) is one of the pillars of the health system contributing to evidence-based decision making. In 2013 DRC adopted District Health Information Software 2 (DHIS 2) as the only data management and reporting platform HMIS, and in 2016, 516 Health Zones from DRC were fully integrated in the platform, followed with data quality workshops at all levels of the Health System, regular data review meetings, regular feedbacks on data quality, and so forth. We performed a retrospective descriptive analysis to assess the change of the quality of malaria data in 26 provinces of the DRC from 2017 to 2021. An internal data congruence study aims to assess change of quality key elements, including completeness of basic service reports entered into DHIS2, number of rules violated in malaria data, and the ratio of data rule violated per 100 reports entered. In 2017, with 88.5% of completeness, 13.000 malaria data rules were violated for 189.141 reports entered in the system (ratio of 7) compared to 10,761 violations out of 226,980 reports in 2021 (ratio of 5), with 97.6% of completeness. Most provinces have significantly improved the quality of their data in DHIS2. The Lualaba province the ratio errors-data report decreased from 10 in 2017 with 82% of completeness to 3 in 2021 with 86% of completeness. The Bas Uele Province had a ratio decreased from 25 in 2017 with 94% of completeness violated rules to 2 in 2021 with 99.5% of completeness. Continued support for interventions related to data quality improvement, especially regular data quality assessment, data analysis and use, remain important to sustain gains and address remaining gaps.

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HAVING A PARENT WORKING IN AGRICULTURE IS ASSOCIATED WITH TESTING POSITIVE FOR MALARIA AMONG CHILDREN LIVING IN URBAN NIGERIA

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In 2018, 23% of children under the age of five years (U5) tested positive for malaria in Nigeria. Despite implementing several malaria-control interventions, Nigeria is still the world's highest malaria-burden country. Malaria is heterogeneous over fine scales in urban areas likely due to livelihood practices that promote mosquito breeding and exposures to vector biting, such as urban farming. Malaria infections acquired by agricultural workers increase transmission risk for household members. We aimed to evaluate the association between parental occupation and *Plasmodium falciparum* malaria infection status, as determined by microscopy, in U5 children living in areas administratively defined as urban. Data from the Nigeria 2018 Demographic Health Survey and geospatial data was used for this study. Rural-urban stratified descriptive and multivariable logistic model analyses were conducted. In this study, parents working in agriculture refer to males only. In urban areas, 4,644 U5 children were included in the analysis, of which 3,956 tested negative while 688 tested positive for malaria during the survey. 17% (n = 714) of the U5 children had parents working in agriculture, and of these, 25% (n = 179) tested positive. In rural areas, 6,860 U5s were analyzed, and 51% (n=1,127) of positive tests had parents working in agriculture. We found that urban children with parents working in agriculture had higher odds of testing positive for malaria in the unadjusted (cOR 2.78, 95%, CI: 1.96, 3.92) and adjusted analysis (aOR 2.80, 95%, CI: 1.70, 4.64) but insignificant in rural areas. Other risk factors significantly associated with malaria were children's age, poor health practices, lower education attainment, and poor access to media. Our study results align with studies conducted in other countries and area-specific studies conducted within Nigeria. These studies emphasize preventive measures such as net use and treatment in areas where agriculture is practiced. However, improved understanding of how agricultural practices contribute to malaria burden in urban areas is needed to better inform control programs to reduce transmission.

1486

USING GEOSPATIAL APPROACHES ON ROUTINE MALARIA SURVEILLANCE DATA FOR MICROSTRATIFICATION OF MALARIA RISK IN MAINLAND TANZANIA

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The increased access to malaria diagnosis at health facilities (HF), coupled with the adoption of improved reporting systems (DHIS2), has strengthened the value of routine data. Compared to cross-sectional community-based surveys of infection prevalence, routine HF data represents a richer source of information in time and space. In mainland Tanzania, several malaria-metrics from HFs were used to develop a council-level risk map (macrostratification) used for tailoring of interventions. Recently, this was further extended to the ward level to account for the intra-council heterogeneity and develop a microstratification risk map.

This is valuable to further target community-based interventions. The employed approach was pragmatic relying entirely on HF data, and can be easily used by council health teams. However, routine data are often accompanied with limitations such as incomplete, missing and inconsistent reporting that necessitate processing to obtain reliable estimates of risk. For this reason, out of the total 7,878 HFs, the laboratory reports from 1,208 (15%) HFs across 141 (5%) wards and antenatal reports from 684 (10%) HFs across 70 (2%) wards had to be excluded from the analysis. The microstratification was performed for 3,065 (93%) wards, whilst for the remaining 246 wards with no HFs, modelled prevalence estimates ($Pf PR_{2-10yrs}$) were used to inform on the malaria risk. Although Tanzania has high reporting rates, the raw routine data often do not account for the missing values, underlying heterogeneous population distribution, or other biases. Advances in statistical tools have used spatiotemporal modelling and imputation methods to handle incomplete routine data thus leveraging the value of routine data and its high resolution. A Bayesian spatiotemporal model was therefore applied on routine data using test positivity rate, to predict the estimates and quantify the heterogeneities at ward level. The outputs of the analysis complement the country's microstratification risk map by filling the spatial and temporal missing values, and thereby allowing for further improvements in the targeting of interventions.

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ANALYSIS OF HOSPITAL DATA TO ESTIMATE THE NUMBER OF MALARIA CASES

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Malaria is an endemic disease that occurs in Mali. Information on cases is provided by surveillance. Data are used to monitor malaria evolution and allocate resources. It is therefore important to ensure that it reflect the reality. Cases can be influenced by accessibility and collection. Data review from 2013 to 2017 in Diré, showed that more than 19% of malaria cases were notified by the hospital. In general, patients come from villages of health areas. This situation creates a recording bias and may affect the analysis of incidence data, which are generally anonymised and aggregated weekly. We proposed a method to correct this bias. The study carry out in Diré, composed by 18 health areas. The study covered all notified malaria cases. The analysis of the data consisted to estimate the number of malaria cases from health areas having consulted hospital. For this purpose, we defined the share of each health area using the mobility impedance model based on the principe of electric current. The P_i population corresponds to the population of the different health areas. The constant α represents the human mobility rate which corresponds to the proportion of patients consulting the hospital. The number of people likely to travel to the hospital *Fij* weekly would be calculated:Number patients attending the hospital is calculated as the sum $Fij = \alpha(P_i+P)/D_{ij}^2$ The weight of each health area in the weekly hospital data: $pi=F_{ij}(i)/\sum Fij$ The malaria case in the health area, xi=pi*weekly hospital case. The result shows: a gain in the number of malaria cases for the majority of the health areas. The 19% power loss of the data was considered. Two health areas fell into the 750 to 1450, and one into 3000 to 4000 cases per year class. The sensitivity of the results was satisfactory at 80-90% compared to the actual individual data for 2018-2020. Bias correction increased the analyse power. This simple method using the principles of human mobility can be a tool to help improve routine data for malaria and other diseases.

1488

COUNTRY-SPECIFIC INDIVIDUAL-BASED MALARIA MODEL: A STANDARDIZED WORKFLOW FOR NATIONAL APPLICATION

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Malaria individual-based dynamical models are increasingly used for country-specific decision making, for better understanding of past and current malaria trends, as well as the impact of malaria-related interventions. Not only can the effect of interventions be simulated but different strategic plans can be compared and assessed using epidemiological impact and cost-benefit analyses. Although many models are open-source, their intrinsic complexity requires highly technical and internal knowledge to operate them efficiently. Therefore, we have developed an interactive workflow which allows the user to utilize the OpenMalaria modelling suite for specific geographies in a transparent manner. The workflow is written in the widely used R programming language and publicly available under the GNU General Public License v3.0 (GPL 3). Standardization and modularity are among the main development goals in order to ensure robustness and reproducibility as well as flexibility and versatility. The workflow consists of three modules: i) generating the input for OpenMalaria, ii) running one or more simulations and iii) collecting and aggregating the results. The OpenMalaria simulation platform takes for each simulation a file written in the Extensible Markup Language (XML). Even though human-readable, writing and modifying XML files by hand can be tedious, especially if hundreds of files need to be processed. Thus, the first module of our workflows helps the user to generate valid XML files from R which can be used by OpenMalaria, with multiple functions to fill in the requested information. Such input files will be handled by the second module which provides the capabilities to run OpenMalaria on the local user machine or on a high-performance computing cluster if thousands of simulations need to be performed. The final step involves the collection and aggregation of the OpenMalaria outputs for their use in country modelling analyses. We believe that our R workflow greatly lowers the barriers for new modelers to use the OpenMalaria simulation platform for country-specific applications and will foster new input and more engagement in the community.

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QUANTIFYING SEASONAL MIGRATION AND ITS EFFECTS ON MALARIA TRANSMISSION IN DISTRICTS OF HIGH, MODERATE, AND LOW RISK IN ETHIOPIA

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Seasonal migration plays a significant role in the importation and spread of malaria in moderate- and low-risk areas. In Ethiopia, large movements of seasonal workers between areas of low and high malaria risk have complicated efforts to reduce the malaria burden in both source and destination regions. Efforts to estimate the impact of these movements on transmission intensity have been hampered by a lack of data at spatial resolutions relevant to malaria control. In this study, we used five-year, survey-based migration data from 78 zones in all regions and city administrations of Ethiopia covering the period 2009-2013 to develop a spatial interaction model and quantify five-year migration estimates between all pairs of districts in Ethiopia. By using these estimates along with other secondary data on seasonal migration, we were able to quantify seasonal migration between pairs of districts in northwestern Ethiopia where large-scale seasonal migration has historically taken place. These estimates were further used to fit a spatially explicit malaria transmission model between large seasonal migration nodes, which enabled the quantification of the effects of different combinations of malaria control interventions across origin and destination districts. Ethiopia has adopted a malaria elimination strategy that targets low and moderate transmission areas. A national malaria strategy incorporating modeling based on local data could help guide sub-national tailoring of malaria intervention mixes for optimal burden reduction as well as accelerate the progress toward elimination.

1490

USING INDIVIDUAL-LEVEL DATA TO ASSESS RISK FACTORS ASSOCIATED WITH CLINICAL MALARIA AT HEALTH FACILITIES IN CHILDREN UNDER FIVE YEARS IN BURKINA FASO

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In high-transmission settings such as Burkina Faso, the likelihood of clinical malaria in childhood varies with age. Understanding how factors such as weight, sex, malnutrition status, and distance to care modulate the relationship between age and clinical incidence can inform targeted interventions to improve case management. We analyzed retrospective data from Burkina Faso's Integrated Management of Childhood Illness electronic registry, which provides individual information on pediatric visits to participating health facilities, including diagnosis of malaria and other pathologies. The database included medical consultations data from over 1.6 million children under five who experienced over 2 million malaria episodes. We used a Generalized Estimating Equation (GEE) model with a binomial distribution to assess individual-level risk factors on the probability of having a malaria episode. To examine effect modification, interaction between age and others variables was introduced. The probability of having a malaria episode was significantly associated with age (OR=1.09), weight (OR=1.05), height (OR=1.01), and distance from the child's home village to the health facility (OR=1.2 and 1.31 respectively for children living 4-10km and >10km from the health facility compared to <4 km). The probability of having a malaria episode was higher in females (OR=1.4), higher in children with moderate, severe, or global acute malnutrition (OR=1.08, OR=1.66, OR=1.13 respectively), and lower for HIV^+ children (OR=0.87). Spatial effects were observed by district (OR=0.8 to 2.6). Although some of the observed associations may be driven by malaria risk, others may be due to differential rates of treatment-seeking for malaria compared to other childhood illnesses. For example, caregivers of female children and children living far from the facility may be less likely to seek care for milder illness, leading to greater odds that they have a malaria episode. Greater understanding of treatment-seeking for malaria episodes and for non-malarial illness is needed to make full use of passive surveillance data and identify vulnerable populations.

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MALARIA PERSISTENCE AFTER WEEKLY ACTIVE CASE DETECTION (ACD) IN A NATIVE COMMUNITY IN THE PERUVIAN AMAZON

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Malaria in native communities represents a significant challenge for Peru's national elimination program due to their hard-to-reach location. Nueva Jerusalén (NJ) is a native Achuar community in the Loreto region. Here, we describe the short-term effect of active case detection (ACD) on reducing malaria cases in NJ. In November 2019, three consecutive ACD visits were conducted at intervals of 7 days. Blood samples were collected for light microscopy (LM) and molecular detection (PCR). Species-specific treatment following the national guidelines was provided to any microscopy-confirmed malaria infection, regardless of the symptoms. Weekly positive rates were compared to determine if the ACD could change the malaria prevalence in NJ. Out of the 521 inhabitants, the mean coverage in the weekly ACD was 39.4% (range: 38.8 - 39.9%). Overall, 83 (13.4%) and 123 (20%) malaria infections were detected by LM and PCR. More than 90% of the infections detected by LM or PCR were due to *Plasmodium vivax*. The 1st ACD visit (n = 202) had the lowest positive rate by LM (9.9%) and PCR (15.3%) compared to the others (2nd: n= 206, 14.9 and 22.1%; 3rd: n = 208, 15.5 and 22.3%). There was no significant difference in the positive rate by LM or PCR among the three visits, indicating that ACD was unsuccessful in reducing malaria cases in NJ. This is the first report of malaria molecular surveillance in a native community in Loreto, Peru. Compared to other Amazonian endemic areas in Peru, NJ presented a high prevalence of malaria infections after each ACD visit. The positive malaria rate did not decrease after consecutive ACDs for two weeks. A profound understanding of the transmission dynamics, parasite and vector population, and human mobility patterns is required to provide insights into the persistence of malaria in remote, indigenous areas.

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RISK OF MALARIA FOLLOWING A SUB-PATENT INFECTION: A 29-MONTH LONGITUDINAL COHORT STUDY IN A HIGH TRANSMISSION AREA IN WESTERN KENYA

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In high-transmission settings, people with suspected malaria often harbor sub-patent *Plasmodium falciparum* infections, defined as those that are present by molecular detection but absent by clinical diagnostics like microscopy or rapid diagnostic test (RDT). Because they are undiagnosed, they are untreated, and the impact of missing sub-patent infections on the risk of future clinical illness is not fully understood. Conventional RDTs are believed to adequately detect parasites at densities that routinely produce clinical symptoms. We estimated, among patients with suspected malaria, the effect of sub-patent *P. falciparum* infections on subsequent clinical malaria using a longitudinal cohort of 268 people from three villages across 36 households in Western Kenya in a traditionally high-transmission setting. We tested all participants with symptoms suggestive of malaria using a conventional RDT, treated those that were positive with Artemether-Lumefantrine, and tested samples from all episodes using real-time PCR for *P. falciparum*. Our hypothesis was that, compared to uninfected people with suspected malaria, sub-patently infected people would have a similar risk of malaria. Over 29 months of observation, we observed 1,061 symptomatic episodes of suspected malaria, of which 586 were RDT negative. Among these RDT negative episodes, there were 232 episodes among 126 people with suspected malaria that harbored sub-patent infections, defined as negative by RDT but positive by PCR. We used weighted Kaplan-Meier curves to compare the two-month risk of RDT positive symptomatic malaria between these symptomatic and sub-patently infected participants and symptomatic but uninfected participants. Secondary outcomes included a symptomatic visit, fever, and RDT positivity with fever. The results of this analysis describe the natural course and clinical implications sub-patent malaria infections among people with symptoms suggestive of malaria. These findings can inform decision-making in high-transmission settings for treatment of people with suspected malaria and for the choice of diagnostics to evaluate suspected malaria.

1493

NEUTRAL VS. NON-NEUTRAL GENETIC FOOTPRINTS OF *FALCIPARUM* MALARIA MULTICLONAL INFECTIONS

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At a time when effective tools for monitoring malaria control and eradication efforts remain crucial, the increasing availability of molecular data motivates their application to epidemiology. The multiplicity of infection (MOI), defined as the number of genetically distinct parasite strains co-infecting a host, is one key epidemiological parameter for evaluating malaria interventions. Estimating MOI remains a challenge however for high-transmission settings where individuals are typically afflicted by multiple concurring infections. Given the relevance of MOI to malaria surveillance, several quantitative approaches have been developed to estimate MOI, including two cost-effective ones relying on molecular data: i) THE REAL McCOIL method is based on neutral single nucleotide polymorphism (SNP) loci, and ii) the *var* coding method relies on the *var* multigene family which encodes for the major *Plasmodium falciparum* blood-stage antigen PfEMP1 and is therefore under selection. In this study, we assess the robustness of the MOI estimates generated with these two approaches by simulating *P. falciparum* malaria dynamics under distinct transmission settings using an extended stochastic agent-based model. We specifically extended a previously developed computational model to incorporate neutral bi-allelic SNPs which, together with the *var* genes, can be used for MOI estimation. We demonstrate that these approaches are complementary and best considered across distinct transmission intensities. While *var* coding can underestimate MOI, it allows robust estimation under high-transmission where the *var* gene family exhibits high diversity and low repertoire overlap from negative frequency-dependent selection. In contrast, THE REAL McCOIL often considerably overestimates MOI, but provides better estimates for low and moderate transmission intensities. As many countries pursue malaria elimination targets, defining the most suitable approach to identify MOI based on local transmission intensity is highly recommended for monitoring intervention program effectiveness.

1494

PUTTING MOBILITY ON THE MALARIA INCIDENCE MAP: ACCOUNTING FOR HEALTH FACILITY TRIPS ACROSS THE COVID-19 PANDEMIC WHEN MAPPING MALARIA BURDEN

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The COVID-19 pandemic has induced dramatic changes in human mobility that affect our understanding of how much and where malaria remains. First, overall travel reductions may make case data less reliable and complicate incidence mapping, as people become less likely to travel to seek treatment or testing during adverse events. Second, changing travel patterns may mean different communities are at risk of infection, directly affecting transmission.

Distinguishing between these factors is critical for intervention planning, as it is necessary to determine if reported drops in cases are due to real reductions in burden, or due to reductions in health-seeking. Using mobile phone data collected from South Africa and Mozambique throughout the COVID-19 pandemic, we measure how trips to health facilities changed across the course of the pandemic, and how these changes affected health facility catchment populations. Using this understanding of health facility catchment populations with passively-collected malaria case data, we quantify changes in malaria burden across Mozambique and South Africa, accounting for changes in health-seeking behavior. Critically, these countries experienced very different COVID-19 interventions and subsequent changes to mobility, which influenced health-seeking behavior across communities. Finally, we compare our results with a more traditional incidence mapping approach, which estimates health facility catchment populations using fixed travel time measures, to identify and characterize communities that were most likely to have inaccurate burden estimates due to low health-seeking behavior.

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CHANGES IN VECTOR BIONOMICS MAY BE PARTLY RESPONSIBLE FOR THE CURTAILMENT OF MOSQUITO CONTROL EFFECTIVENESS ON BIOKO ISLAND

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Vector control interventions on Bioko Island for the past 17 years have been centered around indoor residual spraying (IRS) and long-lasting insecticidal bed nets (LLIN). Thanks to these interventions, malaria prevalence dropped significantly until 2016 and stalled through 2018 before increasing in 2019. However, insecticide resistance, which could result from intensive pressure, can affect the effectiveness of malaria control interventions. Beyond resistance, indoor interventions can also cause mosquitos to change biting hours and places. Therefore, Malaria programs must adapt and respond to insecticide resistance and investigate changes in vector bionomics. Several factors are suspected of reversing the diminishing trends in Malaria transmission on Bioko. Land-use changes and deforestation due to rapid urban growth and increased rainfall could be the most critical factors. This study aims to investigate the contribution of vector bionomics changes to malaria prevalence increase on Bioko Island. Entomological data between 2016 (the lowest historical point prevalence estimate) and 2022 will be analyzed to show the changes in mosquitos' density and biting patterns. Using logistic regression, we will investigate the relationship between malaria prevalence and the change in mosquito bionomics (biting place and time), adjusting for demographic factors from the malaria indicators survey (MIS). These factors include age, sex, off-island travel, time at which residents go indoors and to bed, bed net use, and household spraying status.

1496

EVALUATION OF THE MALARIA EPIDEMIOLOGICAL SURVEILLANCE SYSTEM IN 2021 IN THE HEALTH DISTRICT OF TAMBACOUNDA, SENEGAL

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Epidemiological surveillance (ES) is one of the main pillars of the global technical strategy for the fight against malaria. In southeastern Senegal, where malaria is a major public health problem, ES has been neglected, especially during the COVID-19 pandemic. In order to accelerate the reduction of malaria morbidity and mortality, an evaluation of the malaria ES system (ESS) was carried out in the health district of Tambacounda in 2021, in order to provide corrective measures and recommendations.

A retrospective descriptive study of the ESS was conducted in this district where the incidence of malaria has varied over the last five years between 112‰ and 193‰ for a population of 305,801 inhabitants in 2021. This

study covered the period from week 1 to week 52 in 2021. All the 27 health facilities (HF) with an area of responsibility within the health district were surveyed from February to March 2022.

Overall, the district's ESS was acceptable, with 96.3% of facilities completing the tools correctly and 92% of reports being complete despite 77% reporting on time. The data collected at the ES level showed 100% representativeness with an increased risk of malaria cases between W28 and W50. ESS was also considered simple by 74.1% of HF managers, even though only 55.6% of them were trained in ESS. However, the stability of the system was low since 55.6% of the HF had staff to ensure the continuity of the ES service despite the availability of management tools (100%) and the telephone network (96.3%). The same goes for the usefulness of ES since only 25.9% of HF managers analyzed the data they produced. On the other hand, the ESS was responsive with 96.3% rapid transmission of information and 100% of rapid diagnosis tests and drugs for treatment of malaria cases available.The ESS for malaria in the Tambacounda district health centers was found to be acceptable, simple, representative and responsive. However, the strengthening of health posts with qualified personnel, the training of personnel on ES and the quarterly formative supervision of the HF staff are essential levers on which action must be taken to make the district malaria surveillance system more effective.

1497

SPATIOTEMPORAL MAPPING OF MALARIA PARASITE PREVALENCE IN GHANA FROM 2011-2019 FOR RISK STRATIFICATION

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Ghana has made significant strides towards the control of malaria over the last decade, yet despite efforts to expand and implement malaria control interventions, the country remains a high burden country, with a vast majority of the population remaining at risk. The recent global technical strategy from WHO has highlighted the importance of moving away from a 'one-size-fits-all' approach to a sub-national risk stratification focus; optimizing the limited resources that are available for countries whilst continuing to reduce morbidity and mortality. Maps of malaria prevalence are a fundamental tool for risk stratification. We collate cluster level national malaria parasite prevalence surveys from 2011 to 2019. A suite of high-resolution satellite images and spatial covariates are pooled together at 1km resolution and passed through a causal inference algorithm for a robust and parsimonious model. A Bayesian hierarchical Spatio-temporal model is applied using R-INLA and TMB, to predict malaria prevalence at 1km resolution in unknown locations and timepoints. Prior to prediction, a 5-fold cross-validation using random holdouts of 20% was performed. A total of 18 covariates static and dynamic covariates were selected. Model predictions reflect a clear decline in prevalence nationally from 54% to 21% highlighting that significant progress has been made nationally. However, maps highlight that whilst previously known regions in the north had the highest-burden this has somewhat shifted towards the transitional forest region of the country. Cross-validation results highlight that the model fit well with a correlation of 0.73. Further efforts to incorporate intervention coverage would be beneficial to understand the impact each intervention has had to the declining prevalence to help infer best intervention mixes to take Ghana to the elimination stage.

1498

IMPROVING DATA QUALITY BY CHECKING THE CONSISTENCY OF DATA ON PREVENTION TREATMENT AND USE OF COMMODITIES AGAINST MALARIA IN THE VALIDATION OF DHIS2 ROUTINE DATA IN SANKURU PROVINCE IN THE DEMOCRATIC REPUBLIC OF CONGO

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In the Democratic Republic of Congo, the National Malaria Control Program and its partners continue to intensify efforts for improving malaria data quality to better inform program implementation. In August 2021, with support from partners, the provincial and health zone (HZ) team in Sankuru reviewed the quality of malaria data and analyzed key performance indicators for the first half of 2021 (January-June 2021) at the HZ level, comparing malaria prevention and case management data from the DHIS2 to commodity consumption data (rapid diagnostic test [RDT], artemisinin-based combination therapy [ACT], injectable artesunate, Sulfadoxine-pyrimethamine, and long-lasting insecticidal nets [LLIN]) from the Logistic Management Information System (LMIS). The team developed an action plan for improving data quality and indicator performance. We performed an analysis to assess improvement after six months of implementation of the action plan, comparing the pre-action plan period (January-June 2021) to the post-action plan period (July-December 2021). The results show a decrease of HZs underreporting commodity consumption data including injectables, RDT, ACT, and artesunate, from 58% (pre-action plan) to 33% (post-action plan). The results also show an increase from 42% to 68% of HZs not reporting commodities losses, including RDTs, ACTs, and injectable artesunate in 42% of HZ, as well as other commodities like LLINs and Sulfadoxine-pyrimethamine. Checking for consistency between morbidity data (prevention and treatment) and consumption of antimalarial products in the Malaria LMIS improves data validation and the quality of logistics data in DHIS2. Thus, improve quantification of antimalarial commodities in Sankuru province that can be replicated throughout the country.

1499

MALARIA HELMINTH COINFECTION IN AN ENDEMIC REGION OF COLOMBIA

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Malaria is a major public health problem worldwide. Biological, socioeconomic and cultural determinants of human populations promoting the mutual development of these infections have been described. The effects of helminth co-infection on malaria in humans remain uncertain. The objective was to assess the prevalence of co-infection with helminths and malaria by Plasmodium vivax and its contribution to anaemia. A descriptive, analytical and cross-sectional study was carried out, involving 33 children with malaria, 39 with helminths, 27 with malaria-helminthiasis co-infection and 31 healthy children, in the Tierra Alta region (Córdoba-Colombia), in a six-month period of 2021. A survey was applied to collect sociodemographic information. Infections with Plasmodium vivax and intestinal helminths were diagnosed by thick droplets, stained with Giemsa and by the Kato-Katz technique, respectively. The hemoglobin concentration was determined from automated blood table 7 of IV generation, total proteins were quantified by a Qubit® protein assay kit and using the Anthro and Anthro Plus software, individuals were characterized according to height and body mass index according to their age group. Out of 130 children who were evaluated, 25.4% had *plasmodium vivax* malaria, 30% helminthiasis and 20.8% showed co-infection. T. trichiura showed a frequency of more than 90% among those infected, children aged 6-15 showed a higher risk

of malaria (P=0.01), those of indigenous origin had a higher probability of malaria and co-infection. The mean hemoglobin concentration in the co-infected by malaria-helminths differed statistically from individuals with only helminthiasis and healthy individuals (p = 0.0006 and p<0.0001 respectively). Total protein plasma concentration showed no significant differences among groups. In conclusion, the indigenous population and children aged 6-15 are usually the most vulnerable to *plasmodium vivax*, while malaria-s helminth co-infection seems to be more related to the development of anemia than to nutrient deficiency.

1500

GENDER AND OTHER DEMOGRAPHIC FACTORS OF IRS PERFORMANCE ON BIOKO, 2010-2021

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The role of gender equality in malaria control and elimination is not well understood. Historically, social norms have prevented women from working in vector control programs. The Bioko Island Malaria Elimination Project (BIMEP) has actively sought to reduce gender inequity in malaria control operations by promoting female participation in IRS for many years, with few other programs implementing similar gender-inclusive policies. This study will investigate the progress of female engagement in the project and quantify spray productivity by gender and other demographic variables from 2010 to 2021. The factors that will be assessed using descriptive and regression analyses include age, attendance, education level, ethnic group, and the number of spraying rounds worked, referred to as longevity. Spray productivity will be measured as the average number of rooms and houses sprayed daily, with a normalized productivity indicator as a ratio of the two measures. Preliminary results found that the percentage of female spray operators fluctuated each year, with an overall increase from 24.6% in 2010 to 38.2% in 2021. Observed differences in spray productivity between men and women were marginal, and those that were statistically significant were not meaningful operationally. This study adds to the growing evidence base that women are well equipped to carry out disease control interventions, and that their participation provides significant contributions and improvement to outcomes. There is still work to be done to achieve and sustain gender equality in vector control programs, including the BIMEP. Gender-intentional approaches in public health are crucial for advancing human rights, strengthening access to health care, promoting sustainability of interventions, and reducing disease burden for women, children, and for all.

1501

QUALITY OF MALARIA CASE MANAGEMENT AND ROUTINE DATA ACROSS SIX PROVINCES IN MOZAMBIQUE

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Health facility surveys (HFS) are powerful tools for evaluating malaria case management practices. A 2018 study in three provinces in Mozambique showed varying quality of case management and gaps in the quality of data reporting. To evaluate the success of interventions enacted since then a new HFS was conducted in 2021 in six provinces, including two of the original ones. This survey had three goals: 1) evaluate the performance of healthcare workers (HCWs); 2) measure case management knowledge of community health workers (CHWs); and 3) conduct a data quality audit to determine consistency of malaria data in facility registers and aggregate data in the routine health information system (HMIS). Performance of HCWs measured through observation of patient consultations, patient exit interviews and re-examination. A total of 3757 patients were included in the study from 240 facilities. At these facilities a total of 592 HCWs and 369 CHWs were interviewed. The percentage of suspected cases tested for malaria ranged from 64-85% in the target provinces, while the percentage of confirmed cases treated appropriately ranged from 50-91%. Compared to 2018, Maputo Province improved in most key indicators, in particular the percentage of all cases treated appropriately (32% from 14%), while Zambezia decreased in various indicators (especially HCWs trained on RDTs, to 51% from 89%). The percentage of CHWs who had sufficient kits during the past year was low across all provinces (22-61%), and more than 50% of CHWs in four provinces reported stockouts of AL. Overall case management knowledge of CHWs and HCW knowledge of microscopy was low in all provinces. Finally, significant differences were found in key malaria indicators, with HMIS reported data consistently higher than register data. Although there are limitations in the comparisons of the results of the two studies, these results still provide key areas of focus for the Mozambique NMCP, as well as a roadmap for improving both case management and data quality in the country through contributing to the upcoming Malaria Program Review.

1502

EVALUATING THE CONTRIBUTION OF INCREASED RAINFALL ON RISING PREVALENCE ON BIOKO ISLAND, EQUATORIAL GUINEA DESPITE SUSTAINED VECTOR CONTROL

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From 2004-2018, sustained intensive vector control on Bioko Island reduced malaria prevalence from over 40% to around 10%, but since 2016 there has been an increasing trend in prevalence despite continued vector control. While pyrethroid resistance has been observed, resistance to the insecticides used in indoor residual spraying campaigns, which have been the primary mode of vector control on Bioko Island, has not. Anecdotally, the increased prevalence since 2016-2021 coincides with a period of increased rainfall compared to previous years. However, the contribution of changing rainfall patterns towards increased prevalence has not been evaluated systematically, partially due to a lack of weather data from Bioko. In recent years, advances have been made in using remote sensing to reliably estimate rainfall at high temporal resolution globally. The BIMEP has leveraged remote sensing rainfall estimates, along with annual malaria indicator surveys and routine entomological monitoring on Bioko Island to evaluate how much of the observed increase in prevalence may be related to precipitation. Broadly, rainfall estimates corroborate anecdotal evidence of increased rains starting in 2016 compared to 2015, though not to unprecedented levels. Functional data analytic techniques were used to assess the relationship between not only the annual precipitation totals, but also the shape of seasonality, to parasite prevalence. Notably, fitted models indicated that much of the increase in prevalence between 2018 and 2019 may be attributable to rainfall, but also that other factors may be more important in explaining why elevated prevalence was maintained through 2021. This pattern held when refitting models to prevalence data among individuals not reporting off-island travel in the most recent two weeks. These findings suggest that while changing rainfall patterns are one factor in the reversal of the prevalence trend, more work identifying other causes could provide alternative strategies to regain reductions in prevalence.

1503

EVALUATING THE MALARIA SURVEILLANCE SYSTEM IN THE DEMOCRATIC REPUBLIC OF CONGO FOR STRENGTHENING SURVEILLANCE AND EFFICIENT MALARIA CONTROL

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A strong malaria surveillance system is the backbone of malaria control. We conducted an assessment of the malaria surveillance system in DRC to evaluate its performance, identify determinants of performance, and develop actionable and prioritized recommendations to support its elevation as a core intervention and to inform strategic planning. The assessment was conducted in 2021 using the WHO Malaria Surveillance System Assessment Toolkit. Key informant interviews were conducted at national and provincial levels, a data quality review of key malaria variables in the health management information system was done for 2018-2020, and a semi-structured survey and data quality audit were conducted in 239 health facilities and 80 health zones in four provinces. Findings show that while the system is operational and data are collected regularly, the various reporting platforms are not fully integrated. Reporting and data element completeness rates are high, and the surveillance system captures essential malaria indicators, yet health personnel have inadequate training, insufficient knowledge of malaria case definitions, and limited access to national case management and surveillance guidelines, resulting in very low accuracy of reported data (39% of audited facilities had an average reporting accuracy of ≥ 80%). We estimate about 36% of individuals with malaria symptoms are diagnosed and reported in the routine surveillance system. Key recommendations developed in consultation with country and partner stakeholders include strengthening access to care through increased community-based case management and surveillance tools; ensuring availability of adequate resources such as equipment, guidelines, and supplies to facilitate surveillance activities; integrating malaria surveillance data from different information systems to strengthen data visualization and analysis; strengthening the capacity of surveillance agents to validate, access, and use data; and improving data quality by applying validation rules at the data recording level, setting up regular data review workshops, and conducting routine data quality audits.

1504

MALARIA TREND IN LIBREVILLE GABON FROM 2000 TO 2020

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Patterns of epidemiologic, biological and clinical characteristics of malaria are valuable at the country level because it support national public health malaria program. Moreover, it can also be useful for health care researchers in identifying malaria risk factors and to understand needs for care in the case to adjust public health policy.Objective : to provide more appropriate trends over time in the prevalence of malaria from 2000 through 2020 using a cross-sectional analysis. Methodology. We used systematic data collected from active malaria hospital-based surveillance system in a sentinel site for malaria survey of Melen in Gabon. ResultsMalaria rate decreased from 2000 to 2007, dropping from 45.4% (95% confidence interval [CI], 40.7% - 50.2%) in 2000 to 11.6% (95% CI, 10.1% - 13.2%) in 2007, a 292.6% (95% CI, 280.2% - 304.6%) decrease. And substantial decrease thereafter. The prevalence of malaria was lower in children less than five year, whileit was higher with children aged between 5 to 9 years old. However, in 2015 the prevalence of malaria have shifted on the top of all curves for children aged between 10 and 15 years old. The median parasite densities (MPD) was 8400 p/µL [1500 p/µL – 39900 p/µL] and did not vary significantly over the study period. Overall, age was independent predictors for parasitemia (P<0.01). A changing seasonality was also observed.Conclusion : Changing patterns of malaria frequency according to age and over the year was observed in Gabon within 20 years. Efforts should be done to improve control strategy coverage.

1505

A DECADE OF MALARIA CONTROL IN INDONESIA (2010-2019): ANALYSIS OF ROUTINE SURVEILLANCE AND BED NETS DISTRIBUTION DATA

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More than a decade after the implementation of mass distribution of long-lasting insecticidal nets (LLINs), the burden and dynamics of malaria remains highly diverse across Indonesia. The diversity involves transmission of five *Plasmodium* species, carried by over 20 *Anopheles* mosquito species, with regions ranging from those near-elimination such as Java to the highly endemic Papua. Understanding the ongoing impact of interventions at the sub-national level is key to designing optimal future control strategies but trends in cases in routine surveillance data may be obscured by recent improvements in case-reporting. We applied Generalised Additive Models (GAMs) to nationwide routine surveillance data between 2010-2019, adjusting for reporting rates by district, to estimate changes in the number of cases appearing at health facilities and the test positivity rate within these individuals, stratifying our estimates by age and species of infection. Our estimates highlight a reduction in cases numbers across all regions and a broadly consistent shift towards older populations and males, though the species distribution within cases show less consistent trends. Using district-level LLIN distribution data, we found largest declines in years immediately following mass distributions. Our findings show the signature of a consistent shift in transmission towards elimination driven by the scale-up and maintenance of control measures over the previous decade. They also highlight the need for future tailored solutions if future progress is to be achieved. This is likely to require incremental measures to tackle community-based transmission in the higher burden districts of Papua, allied to measures to identify and target residual exposure within key populations (e.g., older and male) in areas nearing elimination.

1506

PERFORMANCE OF A QUANTITATIVE SUSPENSION ARRAY TECHNOLOGY (QSAT) ASSAY TO ASSESS SARS-COV2 SEROPREVALENCE IN MALARIA-EXPOSED AFRICAN INDIVIDUALS

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Weak SARS-CoV2 surveillance systems in Africa limits the understanding of the COVID-19 pandemic and the public health response in the continent. Seroepidemiological studies are seen as a way to reinforce SARS-CoV-2 surveillance in Africa. The objective of this study was to assess the performances of three qSAT immunoassays in African samples to measure IgG, IgM and IgA levels against a multiplex panel of 10 SARS-CoV2 and *Plasmodium falciparum* antigens using the MagPIX platform, which included spike (S full length, S2 subunit, and a receptor binding domain [RBD] from the Wuhan and Delta variant) and nucleocapsid (N full length and C-terminus) SARS-CoV-2 proteins and *P. falciparum* proteins (MSP-1, AMA-1, EBA-175 and MSP-3) to monitor exposure to both pathogens, acknowledging a potential reduction in malaria control due to the COVID-19 pandemic. Sensitivities and specificities for each isotype and SARS-CoV-2 antigen were determined using 100 pre-pandemic samples, as negative controls, distinct for IgA and IgG than for IgM assays, and samples from SARS-CoV-2 PCR positive individuals, as positive controls, all from Manhiça (Southern Mozambique). For IgG and IgA, specificities were > 96% for all SARS-CoV2 antigens. For IgG, sensitivities for S2, N fl and N C-term were low (23%, 45% and 6%, respectively). The best performing antigen was S, followed by RBD, with sensitivities of 83% and 81%, respectively, and specificities of 98% and 100%, respectively. For IgA, sensitivities were low for N fl, N C-term, and RBD (25%, 11% and 38%, respectively), and the best performing antigen was RBD delta, with a sensitivity of 67%. S antigen performed with a sensitivity of 36% and a specificity of 98%. For IgM, the global sensitivity was < 5% and the global specificity was 94%. In conclusion, IgM appears not to be useful for SARS-CoV-2 seroepidemiological studies in African settings probably due to its cross-reactivity with *P. falciparum* and other antigens. Overall performance of the qSAT assay only including IgG and IgA was 94% sensitivity and 87% specificity.

1507

DESIGN OF A MULTIPURPOSE AMPLICON SEQUENCING PANEL FOR HIGH RESOLUTION SURVEILLANCE OF *PLASMODIUM FALCIPARUM* RELATEDNESS, GEOGRAPHIC ORIGIN, AND DRUG AND DIAGNOSTIC RESISTANCE

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Plasmodium falciparum genomic data can guide control and elimination strategies. Markers of drug and diagnostic resistance can inform choice of antimalarials and diagnostics. Genetic variation can differentiate infections to estimate key aspects of epidemiology such as transmission intensity, rate of importation, and granular details of local transmission. To maximize programmatic utility, methods should be robust and provide rich information from field samples, which may be low density and polyclonal in endemic areas of sub-Saharan Africa. We developed a multipurpose, modular tool based on Multiplex Amplicons for Drug, Diagnostic, Diversity and Differentiation Haplotypes using Targeted Resequencing (MAD4HatTeR). MAD4HatTeR has 278 targets distributed in two modules: (1) 165 high-diversity and spatial differentiation multiallelic microhaplotypes; and (2) 118 targets that cover 15 drug resistance-associated genes and assess for hrp2/3 deletion, along with vaccine candidate targets and non-falciparum species identification. We evaluated the method on DNA extracted from dried blood spots (DBS) and whole blood from lab strains and field studies, and sequenced products using the Illumina platform. We analyzed sequencing data to obtain allele counts. In control samples we obtained a depth of at least 100 reads per amplicon at or below 100 parasites/µL from DBS and 10 parasites/µL from whole blood in both modules. We captured minor allele frequencies down to 5%, correctly estimated multiplicity of infection up to 7 clones, and identified hrp2 and hrp3 deletions. Analysis of field samples is ongoing, and indicates similar results as controls. Simulations indicate that MAD4HatTeR will provide high resolution estimates of relatedness facilitating ancestry inference, including in polyclonal samples. MAD4HatTeR provides a streamlined and flexible approach to obtain rich data for malaria molecular surveillance, with a broad range of targets and the ability to genotype polyclonal and low-density samples. We are implementing this approach in malaria endemic regions to provide data relevant for public health and research.

1508

COMPARISON OF ANEMIA AND MALARIA PREVALENCE IN PREGNANT VERSUS NON-PREGNANT WOMEN OF REPRODUCTIVE AGE IN WESTERN KENYA, 2015-2019

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In high *Plasmodium falciparum* transmission areas, new or worsening anemia due to malaria contributes to poor fetal outcomes and morbidity and mortality in pregnant women. We describe and compare anemia and malaria profiles among pregnant and non-pregnant women of reproductive age. We conducted a continuous year-round malaria indicator household survey in western Kenya from April 2015 to June 2019. All household members aged ≥1 month were tested for malaria with HRP2-based rapid diagnostic tests and hemoglobin (Hb) was measured using photometers. Anemia was defined using the 2011 WHO Micronutrient Indicator guidelines (Hb <12 in women aged 15-49, Hb <11 in pregnant women). Data from all women aged 15-49 years were analyzed as a complex survey accounting for clustering by compound and household. We conducted log-binomial regression to assess associations with anemia by pregnancy status. Ethical review and approval was obtained from all affiliated institutions. We conducted 3,881 interviews among non-pregnant and 214 among pregnant women. Anemia prevalence was 55.6% (95% CI: 48.2% -62.8%) in pregnant and 45.0% (95% CI: 43.1% -47.0%) in non-pregnant women. Malaria prevalence was 16.4% (95% CI: 11.8% -21.8%) and 18.4% (95% CI: 17.0% -19.9%), respectively. Pregnant women were 1.2 (95% CI: 1.1 -1.4) times more likely to have any anemia and 1.4 (95% CI: 1.2 -1.7) times more likely to have moderate to severe anemia (Hb <10 in pregnant and Hb <11 in non-pregant women). We calculated attributable fractions, and among pregnant and non-pregnant women, 18.4% and 8.3% of anemia prevalence was attributed to malaria infection, respectively. Additionally, 33.1% and 1.3% of moderate to severe anemia was attributed to malaria in pregnant and non-pregnant women, respectively. Malaria in pregnancy is more highly associated with anemia than in non-pregnant women. Efforts, such as screening women of reproductive age for anemia, early screening and treatment of anemia in pregnancy, and intermittent preventive treatment of malaria in pregnancy may reduce the levels of anemia and mitigate associated adverse outcomes in pregnancy.

1509

USING DIGITAL DROPLET (DD) PCR TO BETTER UNDERSTAND *HRP2* DELETION COMPLEXITY OF INFECTION

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The emergence of *Plasmodium falciparum* parasites with *hrp2* deletions threatens malaria control programs reliant on rapid diagnostic tests (RDTs). Current molecular tools used to assess *hrp2* gene deletions depend on conventional techniques such as polymerase chain reaction (PCR) and DNA

sequencing. In addition, *P. falciparum* infections are often polyclonal and co-existing *hrp2*+ and *hrp2*- clones within a single infection can lead to discordant results between RDTs and PCR. Here, we report the first digital droplet (dd)PCR technology implementation to determine the proportion of *hrp2*-deleted parasites within clinical isolates. In doing so, we hope to decipher mixed results by PCR and RDT in relation to infection clonality. We implemented a radial multiplexing triplex assay targeting *hrp2* exon 1 (FAM) *hrp*2 exon 2 (FAM:HEX) and *tRNA synthetase* for reference (HEX) using Biorad QX200 digital droplet PCR system. Clinical samples were collected as part of the Ethiopia Public Health Institute (EPHI) National Malaria Survey. RDT results were recorded, and end-point PCR assessed the *hrp2* deletion profile as per the World Health Organization protocol. The ddPCR radial multiplexing assay had a limit of detection of 1 genome copy/uL of extracted sample. Twenty-two clinical isolates were assessed, of which 3/22 displayed insufficient material, 13/22 agreed with all methods (9 pos. and 4 neg.), 2/22 were RDT+/ddPCR+/PCR-, 3/22 were RDT+/ddPCR-/PCR[DP1] -, and 1/22 was RDT-/ddPCR-/PCR+. The quantification of malaria parasite gene copy for *tRNAsynthetase* and *hrp2* using a threshold of three droplets to call a sample positive was successful in 19/22 samples, of which 8 presented a complete deletion of *hrp2* and 11 were positive for *hrp2*. The majority of the positive samples (10/11) identified> 75% of clones with *hrp2*+[DP2] , while one sample presented < 75% of clones *hrp2*+. [DP3] Since ddPCR is analytically sensitive and allows for accurate gene copy quantification, this project has the potential to determine the true prevalence of *hrp2* deleted parasites and contribute to the public health surveillance of *hrp2* deleted parasites.

1510

STRATIFYING MALARIA CONTROL APPROACHES IN MADAGASCAR: MONITORING SPATIO-TEMPORAL VARIATION AND THE IMPACT OF EXTREME WEATHER EVENTS IN THE COASTAL MANANJARY DISTRICT

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Malaria transmission varies greatly across Madagascar, in terms of seasonality and spatial distribution. In high burden districts, increased knowledge of how local ecology, and in particular extreme weather events, impact burden at the community level may enable new stratified approaches to help meet control goals and account for changing weather patterns. To characterize sub-district variation and the impact of cyclone activity on incidence in Madagascar, a prospective study of 10 cohorts (n = 2485, all ages, 171-292 individuals per site) was launched in 2021 in peri-coastal communities in southeast Madagascar. Mobile clinical teams conduct active surveillance in each community monthly, assessing infection status, providing treatment to infected individuals, and recording prevention and care-seeking behavior at the individual and household level. At baseline, prevalence varied from 15.3% to 60.2% between sites (x=33.5%; n=2485). Over follow-up visits in November 2021-February 2022, before the onset of cyclone season, we observed mean prevalence declined to a range of 1.3% to 30.1% between sites (x=13.9% n=1990). Following two cyclones in February 2022, follow-up surveys in late February-April 2022 did not show a large increase in prevalence (range: 2.6% to 28.2%, x: 9.71%). Data collection efforts are ongoing to monitor for an extended lag effect and the duration of cyclone-driven disruptions to prevention and treatment resources. Our preliminary results suggest that the use of mobile active surveillance teams can be effective in increasing access to treatment in the context of low access to care and bednet usage. We conclude that stratified malaria approaches should be considered in low access and high malaria burden areas as an approach to prepare for and mitigate disruptions due to extreme weather events.

1511

ACTIVE CASE DETECTION FOR MALARIA: SURVEILLANCE OR INTERVENTION?

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Active case detection (ACD) extends testing to find infections among people who are asymptomatic, minimally symptomatic or who have not sought care. ACD may supplement passive case detection (PCD) for malaria, particularly in locations that are underserved by health facilities or in populations encountering barriers to accessing care. In such settings, ACD may serve to improve the coverage and timeliness of the surveillance system. However, if ACD significantly increases case-finding overall or reduces the time to treatment, ACD may also reduce malaria transmission. To determine whether ACD reduces malaria incidence or prevalence at the community-level, systematic literature reviews and meta-analyses were conducted for three ACD approaches: mass testing and treatment (MTaT), targeted testing and treatment (TTaT) among higher-risk groups, and reactive case detection and treatment (RACDT) around confirmed malaria cases. After literature searches and title/abstract screening, 7, 3 and 3 articles were included in meta-analyses for MTaT, TTaT and RACDT, respectively. The certainty of evidence (CoE) was GRADEd for each outcome by strategy. MTaT had little to no impact on parasite prevalence (risk ratio [RR] 0.93; 95% confidence interval [CI] 0.82-1.04; 1 cluster-randomized controlled trial [cRCT]; high CoE) and resulted in a small reduction in the incidence of clinical malaria (RR 0.81, 95% CI 0.70-0.95; 1 cRCT; high CoE). TTaT probably had no effect on incidence of malaria infection (RR 1.13; 95% CI 0.82-1.55; 1 cRCT; moderate CoE). The only cRCTs that assessed RACDT used it as the comparator to reactive chemoprevention and the evidence was very uncertain about the impact on prevalence (odds ratio [OR] for RACDT: 1.85, 95% CI 0.96 - 3.57; 1 cRCT; very low CoE) or incidence of clinical malaria (RR for RACDT: 1.30, 95% CI 0.94-1.79; 3 cRCT; very low CoE). The few robust studies of ACD strategies that were identified have not shown evidence of reduction in malaria transmission. However, ACD still plays an important role in extending surveillance to underserved areas and populations and in supporting claims of malaria elimination.

1512

THE CHANGES IN MALARIA EPIDEMIOLOGY AS WE APPROACH MALARIA ELIMINATION: IDENTIFICATION OF *PLASMODIUM CYNOMOLGI* AND *P. KNOWLESI* AND *P. MALARIA* IN SOUTHEAST ASIA

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Although cases remain infrequent, simian malaria in humans is being reported at an increasing rate in malaria-endemic areas that are approaching malaria elimination. In collaboration with National Center for Parasitology, Entomology, and Malaria Control (CNM), Thai MoPH, the Royal Thai Army (RTA), Armed Forces Research Institute of Medical Sciences (AFRIMS) continues to monitor the epidemiology of malaria in Southeast Asia with a focus on hard to reach populations, to include surveillance sites in the areas in Thailand near conflict zone in Yala, and Steung Treng Province in Cambodia, bordering Laos. From 2019 through 2021, there were 321 cases of malaria enrolled at participating field sites in Cambodia and Thailand, 9 of which were confirmed by multiplex real-time polymerase chain reaction (PCR) to be *Plasmodium cynomolgi* (n=3)*, P. knowlesi* (n=4)*, and P. malariae* (n=2). All 9 subjects presented to the field sites with fever and were initially diagnosed as having vivax malaria. The co-infections with vivax were common in this study, similar to previous reports. The clinical presentation in a human host was consistent with mild symptomatic malaria, uncomplicated clinical course, and the following most common symptoms: fever, chills, and headaches. The detected *P. cynomolgi*, *P.knowlesi*, and *P. malariae* had low parasitemia levels, and were separated by time and distance, suggesting unrelated history of exposure. Future plans include whole-genome sequencing to assess relatedness to other cases of simian malaria reported in neighboring countries. The morphological characteristics of reported cases overlapped with vivax malaria which can lead to misdiagnoses even by skilled microscopists. Parasite morphology of simian malaria in Giemsa-stained blood smears will be described in human host, to include challenges with diagnosis using available diagnostics. The significance and epidemiology of *P. cynomolgi*, *P. knowlesi, and P. malariae,* will be presented, as well as the morphological features that can aid in diagnosis, based on latest field data from Cambodia and Thailand.

1513

ENVIRONMENTAL PREDICTORS OF MALARIA INFECTION IN SUSSUNDENGA, MOZAMBIQUE

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Currently, Mozambique has 5th highest malaria incidence in sub-Saharan Africa. The central corridor of Mozambique is already experiencing the impacts of climate change through, which is expected to influence malaria transmission and risk throughout the country. Malaria is highly sensitive to environmental conditions, including climate variability and land use practices. Ecologically, Sussundenga District, Mozambique has a significantly lower elevation compared to the Zimbabwe border and a more tropical climate compared to southern and northern Mozambique due to high seasonal rainfall. We aim to evaluate the effects of climate and environmental factors at the household level on malaria risk. We are using data collected during a cross-sectional community survey in Sussundenga village from December 2019 - February 2020. A random sample of 98 households with 302 residents completed the study. *P.* falciparum infection was determined using a rapid diagnostic test (RDT). For environmental and climate data, we have collected publicly available USGS satellite data on elevation, vegetation, and land use cover. Additionally, we collected satellite data on day and night land surface temperatures and evapotranspiration which we will assess at 1- and 2-week lags. We have spatially and temporally joined these data with malaria infection data at the household level. Using this database, we will assess how these environmental factors are associated with malaria risk using spatio-temporal models that account for the underlying correlation structure. Risk factor surveillance is an important tool for controlling the spread of infectious diseases. The results from modeling of the ecological predictors of malaria infection and spatial maps provided in this study will aid in developing frameworks to spatially and temporally predict malaria risk in relation to changing climate factors in this region. Understanding how environmental changes impacts malaria transmission and infection at the household level will have important implications for vector control and disease surveillance strategies utilized by the District.

1514

MALARIA VACCINE AVERTED HEALTH BURDEN IN AFRICA: MODELING CASES, RESISTANT CASES, AND DEATHS AVERTED BY 2030

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Malaria caused an estimated 627,000 deaths in 2020, 96% of which occurred in Africa with 80% among children under five. Gains towards the 2030 targets set by the World Health Organization and the United Nations have stalled in recent years, with many countries in sub-Saharan Africa making no progress or seeing increases in malaria mortality. Drug resistance poses a major threat to the effectiveness of pharmaceutical treatments and will likely lead to devastating health and economic consequences without action. Vaccines, such as the RTS,S vaccine against *Plasmodium falciparum*, effectively prevent infections, reducing pathogen-associated antibiotic use and selection pressure for resistance. To explore this dynamic, we built a Susceptible-Infected-Susceptible (SIS) model to project cases, drug-resistant cases, and deaths averted in 42 African countries over the 10-year period 2021-2030. We first modeled a baseline scenario and then a scenario in which a vaccine against *P. falciparum* was administered yearly to infants. We assumed 40% efficacy, 70% coverage, and four years' immunity waning time to mimic a routine vaccination schedule with an RTS,S-like vaccine. Because resistance to one or more Artemisinin-based Combination Therapies (ACTs) could develop rapidly, as was the case with chloroquine, we modeled an additional resistance scenario in which treatment failure rates increased incrementally to 80% by 2030. With the hypothetical vaccine, a total of 76.9 million cases, 805,000 resistant cases, and 209,000 deaths could be averted, corresponding to a reduction of ~18% for all outcomes. Countries with the most cases averted per capita included Niger, Burkina Faso, and Benin. Countries with the most resistant cases averted per capita included Burkina Faso, Burundi, and Niger, while Sierra Leone, Burkina Faso, and Niger had the most deaths averted per capita. If treatment failure rates increased to 80% by 2030, nearly 20 million drug-resistant cases could be averted with the proposed vaccine. Swift and widespread deployment of the RTS,S vaccine could substantially reduce the health and economic burden caused by malaria in Africa.

1515

CHEMOGENOMIC PROFILING OF A *PLASMODIUM FALCIPARUM* MUTANT LIBRARY REVEALS SHARED EFFECTS OF DIHYDROARTEMISININ (DHA) AND BORTEZOMIB (BTZ) ON LIPID METABOLISM AND EXPORTED PROTEINS

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Antimalarial drug therapies have enabled significant progress in malaria control and yet recurrent emergence of drug resistant parasites makes it clear that there is a critical need to optimize the use of current drugs

and continue to development new drugs against novel target. The complexity of the malaria parasite phenotype involved in the artemisinin (ART) mechanism of action requires more systematic approach to understanding of ART sensitivity and resistance. Functional genomics offers an alternate unbiased experimental approach to identify and characterize drugs and antimalarial inhibitors on a broader phenotypic level. Specifically, phenotype selection screens can be used to define genotype-phenotype relationships. This study uses functional genomics of *Plasmodium falciparum* to elucidate drug-gene interactions and potential gene functions related to ART mechanism of action. We used *piggyBac* transposon-mediated insertional mutagenesis to generate random mutations and create a mutant library for forward-genetic screens. The phenotypic screen of *P. falciparum* ~600 *pB-mutant*s identified genes linked to altered sensitivity to the antimalarial drug dihydroartemisinin and the proteasome inhibitor bortezomib. The major results of the phenotype selections linked *P. falciparum* sensitivity to these compounds to fatty acid metabolism and PTEX/exportome complex components, unfolded protein response, isoprenoid element, and splicing machinery. Our findings give insight into the complex array of molecular mechanism that regulates *P. falciparum* response to this critical antimalarial drug.

1516

USE OF TRAVEL HISTORY AND PARASITE GENOMIC DATA WITH STANDARD SURVEILLANCE TO TRACK MALARIA TRANSMISSION DYNAMICS AND IDENTIFY RESERVOIRS OF TRANSMISSION IN THE LOW-ENDEMIC SETTING OF ZANZIBAR

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To eliminate malaria, it is vital to determine whether sustained local transmission or importation drives malaria transmission. Detailed travel histories along with parasite genetic data from incident cases may address these challenges in malaria surveillance. We analyzed genetic (26 microsatellites), travel history and epidemiological data for all confirmed malaria cases (N = 1980) identified within 46 health facilities in a geographically contiguous area of Unguja Island, Zanzibar between May 2010 and June 2011. We estimated relatedness between all samples via identity by descent (IBD, indicating shared ancestry) using *Dcifer* which incorporates multiallelic data from polyclonal samples. We estimated the proportion of samples related between shehias (the smallest administrative unit) and across the two transmission seasons within this low transmission setting. We found that 20% (N = 177/1018) of samples observed in the second transmission season were related (lower bound of 95% confidence interval for relatedness by IBD > 0.1, adjusted p-value < 0.05) to samples observed in the first transmission season, suggesting that reservoirs of local transmission remained across transmission seasons. Using estimates of genetic relatedness, we identified highly connected geographic areas between North B, Central and West districts of Unguja island which were not captured within the travel history data. We also combined these results with estimates of incidence based on the timing and location of symptom onset and travel history to map potential sources and sinks of transmission. While the data analyzed are historical, this work in demonstrates how genetic analysis from densely captured malaria cases can identify sustained malaria transmission across transmission seasons, and patterns of connectivity between geographic regions which provides substantially more detail than information obtained by travel history data.

1517

EPIDEMIOLOGY OF *PLASMODIUM VIVAX* ACROSS DUFFY PHENOTYPES BY HIGHLY MULTIPLEXED AMPLICON DEEP SEQUENCING TO ASSESS MICROHAPLOTYPES

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Despite being the most common malarial species worldwide, *Plasmodium vivax* is relatively rare in Sub-Saharan Africa. Merozoites must bind to the Duffy antigen receptor during erythrocyte invasion, and it is well understood that Duffy negativity confers resistance to blood stage *P. vivax* infection. Populations in Sub-Saharan Africa are nearly entirely Duffy negative, and this has long explained the general lack of *P. vivax* infection on the continent. Recently, however, several studies have unearthed evidence of *P. vivax* infections in Duffy negative individuals. We seek to examine the relatedness of these *P. vivax* infections from varying Duffy phenotypes using a novel microhaplotype (highly multiplexed amplicon deep sequencing) assay; and to explore if these rare cases of *P. vivax* infections in Duffy negatives exhibit evidence of selective evolution toward strains capable of evading Duffy based infection resistance. Dried blood spots were collected from hospitals and mass blood surveys in southwest Ethiopia, an area with low *P. vivax* transmission and high Duffy heterogeneity; Duffy phenotype distribution is 54.1% positive, and 48.8% negative. Of the 14,142 DBS processed, 341 (2.4%) were positive for *P. vivax*, and of those just 9 (0.06% of total) were confirmed as phenotypically Duffy negative. Given the rarity of these infections we sought to utilize a highly novel microhaplotype sequencing assay to gain maximum population genetics inference power. This method has been shown to yield significantly higher resolution for discriminating related and unrelated polyclonal infections compared to standard SNP barcodes and microsatellite analyses for *P. falciparum*. We developed a panel of 146 *P. vivax* targets, including highly polymorphic sections linked to potential alternate invasion mechanisms. Preliminary results indicate that our panel is well adept at assessing geographic population structuring and use of this panel to determine population genetics of *P. vivax* malaria across Duffy phenotypes will likely yield significant insight into the nature of these infections and their potential future impact on *P. vivax* endemicity in Africa.

1518

DYNAMICS OF COMPLEXITY OF *PLASMODIUM FALCIPARUM* INFECTION AND GENETIC DIVERSITY OF *PFAMA1* AND *PFCSP* BETWEEN BOUGOULA-HAMEAU AND FALADJE IN MALI

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The fight against malaria is a multicomponent approach comprising, prevention, early diagnosis and rapid case management of confirmed malaria cases by treatment with effective antimalarials. Artemisinin-based combination therapies are used as first-line treatments for uncomplicated malaria in endemic areas. Cases of resistance to artemisinin have already been described in South-East Asia resulting in prolonged parasite clearance time after treatment. In Mali, in the absence of mutations in the K13 gene associated with clearance delay in Asia, a significant difference in parasite clearance time was observed between Bougoula-Hameau and Faladje in Mali after treatment with artesunate. The complexity of *Plasmodium falciparum* infection may influence the response to antimalarial treatments. This work therefore aimed to assess the complexity of infection and genetic diversity of *P. falciparum* in two villages Bougoula-Hameau and Faladje in Mali. Thirty patients per village were randomly selected from

221 patients enrolled in a prospective artesunate monotherapy study conducted in Faladje and Bougoula-Hameau in 2016. All positive samples up to the last positive slide were retained for this work. DNA was extracted with the Qiagen kit and Pfcsp and *Pfama1* used for strain typing and genetic diversity were amplified by PCR and then sequenced using the Illumina platform. Data were analyzed with R. The median number of parasite clones genetically distinct at enrollment in Faladje was 7 with an IQR [5-9] while it was 6 with an IQR [4-10] in Bougoula-Hameau (p-value = 0.1). One day after initiation of treatment the complexity of the infection was higher in Faladje (6[4-8]) than in Bougoula-Hameau (4[4-6]) with a p-value =0.02. Parasites were more similar between the two villages at the start of treatment, compared to 24 hours after initiation of treatment. Genetic diversity of Pfama1 and Pfcsp between the two villages was high. This study demonstrated that the difference observed between the two villages could be due to the genetic diversity of the parasites.

1519

VARIABILITY OF PLASMODIUM FALCIPARUM ASEXUAL AND SEXUAL PARASITE CARRIAGE AMONGST INDIVIDUALS WITH SYMPTOMATIC AND ASYMPTOMATIC INFECTIONS IN KOMBEWA, KISUMU COUNTY KENYA

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Malaria prevalence continues to decline across sub-Saharan Africa as a result of various intervention strategies but still poses a public health concern in the region. The burden is based on convenient screening of symptomatic cases only. Asymptomatic infections are becoming highly prevalent hence increasingly an important target for interrupting transmission. This study aimed at describing *Plasmodium falciparum* asexual and sexual parasite carriage as well as *P. falciparum* multidrug resistance (*Pfmdr1*) and *P. falciparum* chloroquine resistance transporter (*Pfcrt*) genotypes associated with antimalarial drug resistance among individuals with symptomatic and asymptomatic infections. 739 samples obtained from 339 symptomatic and 400 asymptomatic individuals in Kombewa Western Kenya between 2018 and 2021 were characterized for *P. falciparum* prevalence and gametocyte carriage by using reverse transcription-quantitative PCR (RT-qPCR). Genotyping of *Pfcrt* and *Pfmdr1* was carried out on the iPLEX MassARRAY platform. *Plasmodium falciparum* prevalence was 71% and 56% in symptomatic and asymptomatic cases respectively (p=0.002). Gametocyte prevalence was higher in symptomatic 78% than in asymptomatic individuals 33%, (p<0.001). A total of 4.4% symptomatic infections harbored *Pfmdr1* 86Y mutations while none of the asymptomatic cases were observed with this allele (p=0.037). The prevalence of *Pfmdr1* 184F mutation in symptomatic individuals was 38% compared to 54% among asymptomatic. In addition, *Pfmdr* 1246Y mutations present in symptomatic was 7% and asymptomatic had 3%(p=0.8). For *Pfcrt* 76, both symptomatic and asymptomatic did not have any mutations. Correlation of gametocyte carriage with the SNPs indicated 88% having both Pf16 and Pf25 lifecycle stage had mutant *Pfmdr1* 184F, (p=0.025). The marginally high *Pfmdr1* 184F mutation observed in asymptomatic individuals and the differences in parasite carriage suggests an association with virulence and distinct prevalence according to clinical status. Increased gametocyte carriage with mutations implies an important factor driving resistance of *P. falciparum.*

1520

POPULATION GENETICS OF *PLASMODIUM FALCIPARUM* CIRCUMSPOROZOITE PROTEIN IN FOUR REGIONS WITH DIFFERENT MALARIA ENDEMICITY IN TANZANIA

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In 2021, the World Health Organization approved RTS, S/AS01 as the first malaria vaccine to be used among children. The vaccine comprises of a *Plasmodium falciparum* 3D7 strain circumsporozoite protein (*Pfcsp*) and the hepatitis B virus surface antigen. Studies have shown limited efficacy of the vaccine which has been attributed to polymorphisms in the *Pfcsp* gene. To establish baseline data before deployment and to estimate the vaccine's future performance, we analyzed *Pfcsp* for genetic diversity, population structure, and signatures of selection in four districts in Tanzania (Muheza – a low transmission area, and Muleba, Nachingwea, and Ujiji – all high transmission areas). DNA was extracted from dried blood spot samples collected from patients of all age groups between May 2014 and January 2015. Whole-genome sequences were generated from 647 samples as part of the MalariaGEN Community Project at Sanger Institute (UK) using Illumina platform. The sequences were mapped to the *P. falciparum* 3D7 reference genome. After quality checks, 577 sequences were retained for analysis. The allele frequency distribution within *Pfcsp* was slightly higher in Muheza (0.45) than Muleba (0.38), Nachingwea (0.39), and Ujiji (0.38). Polyclonal infections were less frequent in Muheza (25.6%) and Ujiji (30.6%) compared to Muleba (88.5%) and Nachingwea (82.3). Based on F_{ST} (mean=0.0068) and principal component analysis, no population structure was detected. Nucleotide diversity was similar among all sites (Muleba ϖ =0.00039; Muheza ϖ = 0.00035, Nachingwe ϖ = 0.00031, Ujiji ϖ= 0.00024). Tajima's D was higher in Muleba (0.78) compared to Muheza (0.265), Nachingwea (0.122), and Ujiji (0.21), suggesting existence of potential slight balancing selection in all districts. Despite limited population differentiation and structure in the *Pfcsp* gene, high genetic diversity and polyclonality especially in high transmission areas (Muleba and Nachingwea) could potentially cause expansion of none-vaccine haplotypes hence reduce vaccine efficacy and needs to be monitored.

1521

TRACKING ANTIMALARIAL RESISTANCE IN MOSQUITO POPULATIONS

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Artemisinin-based combination therapies (ACTs) are the only drugs approved to treat malaria in sub-Saharan Africa (SSA). Yet reports of decreased susceptibility to both artemisinin and ACT partner drugs have been increasing in SSA. Despite the urgency, the coverage of surveillance efforts remain spatially and temporally limited. We hypothesized that the analysis of mosquito blood meals may be an efficient, informative method to monitor molecular markers of resistance. We conducted a series of cross-sectional surveys in Bama, Burkina Faso over two rainy seasons (10/2018, 09/2019) and one dry season (03/2019), sampling an average of 209 households per survey. Overall, we collected 1,483 dried blood spots (DBS) from humans and 2,151 DBS from blood-fed *Anopheles* mosquitos collected in the same households on the same day. We used an ultrasensitive qPCR to detect *P. falciparum* (*Pf)* infections and amplicon-based deep sequencing to determine multiplicity of infection (MOI). We genotyped *Pf*+ samples for two alleles associated with partner drug susceptibility, *pfmdr1* N86Y and *pfcrt* K76T, using high resolution melting. In total, we identified 551 *Pf*+ humans and 346 *Pf*+ mosquito blood meals:

infection rates fluctuated in humans over time but remained consistent in mosquitos. After adjusting for MOI, the frequency of *pfmdr1* 86Y was statistically equivalent in humans and mosquitos for all surveys (p<0.0001, p<0.0001, and p=0.045). The frequency of *pfcrt* 76T was statistically equivalent in the final survey (p=0.0019), whereas the mutation was significantly more frequent in mosquitos compared to humans for the first two surveys. This disparity likely reflects preferential and multiple feeding behavior in mosquitos as well as fitness costs related to *pfcrt* 76T. Finally, we found that mosquito aspiration was acceptable in the community and easily deployable within existing entomology infrastructure, supporting synergies in malaria surveillance. Our results support the novel usage of blood-fed mosquitos to track markers of drug resistance, particularly those circulating at low frequencies e.g. emergent markers of artemisinin resistance.

1522

LONGITUDINAL GENOMIC ANALYSIS OF *PLASMODIUM FALCIPARUM* TRACKS ADAPTATION DURING A PERIOD OF INTENSIVE INTERVENTION

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Whole genome sequencing has vastly improved our understanding of how *Plasmodium* parasites adapt to novel environments, hosts, and drugs. Most studies infer past selection events from single-timepoint data, however, the parasite's short generation time also enables direct tracking of evolution via longitudinal sampling. We analyzed 202 *P. falciparum* parasite genomes sampled in French Guiana over a 17-year period of intensive public health intervention (1998-2015). During this timeframe, multiple public health measures, including the introduction of new drugs and expanded rapid diagnostic testing, were implemented. These measures reduced infection prevalence by an order of magnitude and likely imposed strong selection pressures on the local parasite population. Consistent with the large reduction in prevalence, we saw a dramatic increase in the relatedness among parasites, but we found that no single clonal background grew to dominate the population. We therefore analyzed these genomic data for evidence of both hard and soft selective sweeps using two distinct methods: calculating individual allele frequency trajectories and measuring reductions in haplotype diversity. As expected, we identified genes implicated in drug resistance but also found other novel candidates including transcription factors involved in the conversion to *Plasmodium*'s vector-transmissible form, gametocytes. This highlights not only the power of longitudinal sampling but also how public health interventions impose wide-ranging selection pressures that affect phenotypes beyond canonical drug resistance.

1523

GENOMIC VARIATION OF RELAPSING *PLASMODIUM VIVAX* IN CAMBODIA

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Plasmodium vivax, now the predominant malaria species in Cambodia, causes latent liver infection, helping it to evade malaria control efforts designed to eliminate *P. falciparum*. It is believed that a substantial proportion of the *P. vivax* burden in Cambodia is due to relapses arising from hypnozoites, as opposed to mosquito-borne infection. If this is the case, genomic characterization of relapsed parasites should resemble that of the "background" *P. vivax* parasite population. We have sequenced the parasite genomes from 33 patients with relapsing *P. vivax* - including 20 that developed *P. vivax* a median of 28 days after being treated for *P. falciparum* (Anlong Veng and Kratie, 2015), 7 with multiple vivax recurrences and amplicon sequencing data showing a high degree of variant overlap between episodes (Anlong Veng, 2011), and 6 who developed vivax recurrence after being relocated to a non-malaria endemic setting (Rattanakiri, 2014-15) - and processed them in parallel with 250 publicly available whole genome sequences of Cambodian *P. vivax*, many collected from the same locations. In both cases, we aligned genomes to the PvP01 genome assembly and performed variant calling using bcftools mpileup, followed by hard filtering ultimately leading to a database of 1,270,991 high-quality biallelic SNPs with 99.9% having a read depth greater than 500. We plan to investigate whether these two parasite populations - relapsing and "background" - differ in genetic complexity (Fws) or in their population structure and genetic relatedness (principal component analysis). We will examine signatures of selection within and between populations, as we previously found evidence of strong directional selection in processes involved in transcriptional control in Cambodian vivax. Finally, we will determine whether pairs of relapsed infections exhibit greater identity by descent (IBD) between relapse episodes within persons than between persons. The genomic variation uncovered in relapsing *P. vivax* may contribute to an understanding of how crucially malaria elimination in Cambodia hinges on tackling the hypnozoite reservoir.

1524

TRACKING *PLASMODIUM FALCIPARUM* ANTIGENIC DIVERSITY IN A LONGITUDINAL COHORT

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In malaria-endemic settings, humans do not develop sterilizing immunity to *P. falciparum* infection; instead, naturally acquired immunity (NAI) builds with age, driving antigenic diversity. Most of the *P. falciparum* genome has low diversity, except for these specific antigenic regions. For this diversity to be maintained in parasite populations, it must offer some level of fitness advantage. To better understand this, we have used the 4CAST amplicon sequencing panel to deeply profile DNA sequences from four antigens (*csp, ama1, sera2, trap*) in the *P. falciparum* genome. These targeted regions are highly diverse, with haplotypic diversity ranging from 0.84 to 0.92 in *P. falciparum* samples from Mali. We have used 4CAST to sequence 6127 samples from 464 subjects, originating from a longitudinal cohort in Kalifabougou, Mali. In this study, participants ranged in age from 3 months to 25 years, and they contributed blood samples every 2 weeks during the 6-month period of active malaria transmission in 2011, as well as during any clinical malaria cases. Sequencing these samples at diverse antigens allowed us to estimate the complexity of infection (COI; the number of distinct parasites within a single infection), which ranged from 1 to 16 in these samples, as well as longitudinally track individual haplotypes within a subject across the transmission season. We also explored the range of antigenic diversity observed within the data when stratified by age (a proxy for NAI development) or time of year. We observed no strong instances of *ama1* allele stratification by age, suggesting that NAI does not generally develop in a temporal progression beginning with more common alleles. These data have motivated functional experiments examining the potential effects of the observed antigenic diversity on *P. falciparum* fitness deriving from invasion efficiency, providing a clearer understanding of the tradeoffs between immune evasion and parasite fitness.

1525

TRACKING ACTIVE SELECTIVE SWEEPS IN *PLASMODIUM FALCIPARUM* IN SENEGAL THROUGH SHARED HAPLOTYPES

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Drug resistance presents a major, recurring obstacle to the success of malaria control efforts. Detecting the signals of positive natural selection at resistance-associated loci has been an effective approach to identifying the causal mutations that underlie resistance. In order to identify sites currently under active selection, including novel sites that are only beginning to respond to changing drug environments, we have adopted a novel approach of looking for evidence of selection specifically in closely related parasites, since they should be enriched for rapidly spreading resistance alleles. Adapting previously used haplotype-based metrics for detecting selection, we have searched for chromosome segments that show unexpectedly high sharing among related parasites, using genome-wide sequence data from 340 parasites sampled from across Senegal in 2019. We find multiple candidate loci that show evidence for a selective sweep in the broader population, and for which the signal is stronger among relatives. These include the well-characterized *pfcrt* locus on chromosome 7, a 200 kb region near the 3′ end of chromosome 6 containing *aat1* that has been previously identified as the location of a selective sweep, a 90 kb region on chromosome 12 containing the *gch1* gene (implicated in antifolate susceptibility in Plasmodium falciparum), and a previously unreported 70 kb region near the 3′ end of chromosome 9. We also find one 200 kb region on chromosome 11 which shows evidence for selection only among related parasites, which could represent either a statistical fluctuation or a very early sweep. Analysis of haplotype structure at each locus reveals patterns that range from simple (the well-known causal haplotype on chromosome 7) to complex (multiple shared haplotypes on chromosome 6, seemingly clustering at more than locus within the region). Application of population genetics strategies to identify and track drug resistance loci has value toward informing drug use policy and threats to drug efficacy.

1526

IS THE *PLASMODIUM FALCIPARUM* POPULATION ON BIOKO ISLAND, EQUATORIAL GUINEA, DISTINCT FROM THOSE IN NEARBY CONTINENTAL AFRICA?

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Since 2004, the Bioko Island Malaria Elimination Project (BIMEP) has been conducting annual malaria indicator surveys (MIS) on Bioko Island (BI), Equatorial Guinea. BIMEP has decreased malaria burden by implementing effective control interventions, but a stagnation in the decline of malaria prevalence hampers elimination prospects. Despite efforts to monitor the prevalence *Plasmodium falciparum*, the dominant malaria species on the BI, it remains unclear the degree of genetic diversity, panmixia and isolation on BI from continental Africa. During the 2019 MIS, dried blood spot (DBS) samples were collected by finger prick and preserved on filter papers. We selected samples containing the highest levels of asexual blood stage parasitemia as measured by 18S qPCR (n=90; mean Cq = 33.6), to generate whole genome sequence (WGS) data following selective whole genome amplification. Initial Principal Component Analysis using genome-wide single nucleotide polymorphisms (SNPs) demonstrate BI strains are most similar to those from Central and West Africa. As expected, there is little differentiation between BI *P. falciparum* population and Cameroon, the country geographically closest to BI (Wright's fixation index, F_{ST} = 0.01). Curiously among BI samples, several strains appeared distinct from the rest. To determine if this is due to population structure within BI and/or to the importation of *P. falciparum* strains from continental Africa we are using a variety of population genetics analyses and metrics of genetic diversity, similarity, and differentiation, including nucleotide diversity (ϖ), F_{ST}, identity-by-descent and Admixture analysis. Results from our investigation will characterize for the first time the *P. falciparum* population on BI and its relationship to other African malaria populations. Epidemiological metadata for BI samples will be utilized in conjunction with population genetic results to establish possible sources of infection, both local and imported transmission. Results will further our understanding of *P. falciparum* transmission dynamics and identify potential restraints to malaria elimination on BI.

1527

INFLUENCE OF DRUG PRESSURE ON GENETIC DIVERSITY OF *PLASMODIUM FALCIPARUM* FOLLOWING THE ADMINISTRATION OF ARTEMISININ-BASED COMBINATION THERAPIES AMONG CHILDREN INFECTED WITH UNCOMPLICATED MALARIA IN YAOUNDÉ, CAMEROON

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The genome of *Plasmodium falciparum* contains highly polymorphic regions that may account for the genetic diversity observed in key surface-expressed antigens. However, the impact of drug pressure on malaria parasite genetic diversity is not completely understood. Hence, this study aimed to determine the influence of drug pressure on the genetic diversity of *P. falciparum* following the administration of artemisinin-based combination therapies among children infected with uncomplicated malaria in Yaoundé, Cameroon. Samples were obtained from a pharmacovigilance study conducted in Yaoundé, Cameroon from 2019 to 2020. The *P. falciparum* merozoite surface protein 1 (*Pfmsp1*), merozoite surface protein 2 (*Pfmsp2*) and glutamate-rich protein (*Pfglurp*) genes were genotyped to assess genetic diversity. The genotyping was done using allele-specific nested polymerase chain reaction followed by gel electrophoresis for fragment size analysis. The analyses involved the family types of *Pfmsp1* (K1, MAD20 and R033), *Pfmsp2* (3D7/IC and FC27) and *Pfglurp*. In *Pfmsp1*, the K1 allelic family was the most dominant with 75.4% (178/236). In *Pfmsp2*, the 3D7/IC allelic family predominated with 67.4% (159/236), In the *Pfglurp* allelic family, the frequency was 78.4% (185/236). A total of 74 genotypes and 1,457 distinct alleles were reported in all the polymorphic genes of *P. falciparum*. The overall mean expected heterozygosity and mean multiplicity of infection were: *Pfmsp1* (0.084 versus 1.21), *Pfmsp2* (0.158 versus 1.68) and *Pfglurp* (0.143 versus 1.69). There was a significant association between *Pfglurp* gene clonal infections and artemether-lumefantrine treatment outcome (P=0.018). Moreover,

it was also reported that drug pressure had no influence on genetic diversity. In conclusion, this study documented a low genetic diversity of *P. falciparum* in Yaoundé. This may imply that the malaria parasites circulating in Yaoundé and its environs are highly homogeneous.

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FIRST COMPLETE GENOME OF THE SIMIAN MALARIA PARASITE *PLASMODIUM BRASILIANUM*

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There are over 100 species of the *Plasmodium* parasite but only 5 are known to cause malaria in humans, *P. falciparum, P. vivax, P. malaria, P. ovale*, and *P. knowlesi* (zoonotic parasite). Recent evidence shows that *P. brasilianum* can cause human malaria in the Amazon basin region in South America. *P. brasilianum* is a simian malaria parasite found to infect 13 genera and 36 species of New World monkeys across Central and South America. Previous studies have shown strong similarities in the morphology and 18s rRNA, mtDNA, and several surface protein gene sequences between *P. brasilianum* and *P. malariae*. These similarities have led to the suggestion that the two species are the same species, with P. brasilianum originating from a spillback of *P. malariae* into nonhuman primates. Here we report the first complete reference genome of *P. brasilianum* by expanding on our previously generated draft genome for *P. brasilianum* by using a combination of optical mapping, longer read PacBio sequencing, and Illumina short-read sequencing. The genome is 31.4 Mb in size and comprises 14 chromosomes, the mitochondrial genome, the apicoplast genome, and 29 unplaced contigs. We compared 81 orthologous genes among 17 *Plasmodium* species, which demonstrates that *P. malariae* is the closest related species to *P. brasilianum*. Comparing the *P. brasilianum* genome with the *P. malariae* reference genome, we found 98.4% identical nucleotides, 97.3% pairwise identity, and 41,125 nonsynonymous mutations (0.072% of genome) between the two genomes. We also found a variation in tetrapeptide repeat lengths of the circumsporozoite protein (CSP) between the two genomes, which may be driven by the different hosts the parasites were isolated from. Overall, our results demonstrate the close evolutionary relationship between *P. malariae* and *P. brasilianum*. Our data supports the hypothesis that *P. brasilianum* is a variant of *P. malariae* that has adapted to infect New World monkeys in the Amazon basin and may be easily exchanged between humans and monkeys. This complete genome will benefit future investigations into *P. brasilianum* evolution and its ability to infect humans.

1529

INFANTS BORN FROM MOTHERS UNDER DP OR SP IPTP HAVE SIMILAR SEROLOGICAL RESPONSES AGAINST PFEMP1 PROTEINS

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Intermittent preventive treatment of malaria during pregnancy (IPTp) decreases malaria burden in pregnant women and mitigates its adverse effects among mothers and newborns. While sulfadoxine-pyrimethamine (SP) has been the primary IPTp drug due to its slow elimination from the body, dihydroartemisinin-piperaquine (DP) is currently used as a substitute due to the high prevalence of malaria parasite resistance to SP. Given this high level of resistance, we hypothesized that the natural humoral immune response of infants born to mothers who received IPTp-SP would differ from those infants born to mothers who received IPTp-DP. To measure the impact of IPTp drug combinations on humoral immune response, we developed a custom protein microarray with 250 large protein fragments specifically targeting PfEMP1s, which comprise a family of variant surface antigens associated with severe malaria pathogenesis. In total, 192 infants born to pregnant women randomized and treated either with DP or SP were followed actively from birth to up to twelve months. Reactivity to PfEMP1s at birth was measured by probing the microarray with with cord blood serum. For each protein fragment, median fluorescent intensities (MFIs) were calculated and used to assess seroreactivity, defined as the magnitude of microarray fluorescence intensity, and serorecognition, defined as proteins with MFIs greater than the median plus two standard deviations of the seroreactivity of naïve North American controls. There was no statistical difference in the number of serorecognized antigens by children born to mother under SP or DP chemoprophylaxis (2.3% *vs* 2.7%; p=0.98), and neither group of children uniquely recognized a particular PfEMP1. Both treatment arms recognized 56% of protein fragments, whereas 38% of protein fragments were not recognized by either group (Kappa score = 0.78, 95% CI: 0.71 - 0.86), indicating an excellent agreement in protein recognition. The similar humoral immune responses are consistent with the lack of difference in malaria risk in babies born in both treatment arms.

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DEVELOPMENT OF AN IN VITRO MODEL TO INVESTIGATE THE CONTRIBUTION OF IMMUNE DYSREGULATION TO CEREBRAL MALARIA DEVELOPMENT

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Malaria kills approximately 430,000 people every year, mostly children under 5 years old in sub-Saharan Africa. Many of these lethal cases are due to cerebral malaria (CM), a condition caused by Plasmodium falciparum and characterized by cerebral inflammation, blood-brain barrier (BBB) breakdown, brain swelling and death. The exact mechanisms that lead to CM are unknown. The endothelium likely plays a key role, as it comprises the BBB and can initiate inflammatory responses. P. falciparum-infected red blood cells (iRBCs) bind to the endothelium via P. falciparum erythrocyte membrane protein 1 (PfEMP1). This, along with a dysregulated immune response, is thought to induce endothelial activation and loss of interendothelial junctions (loss of the BBB) which correlates with disease development. Innate immune cells such as neutrophils, platelets, and monocytes have all been investigated for contributions to CM on an individual basis in past studies. Platelets and monocytes accumulate at sites of parasite sequestration in the brain where they can induce further inflammation and attract more innate immune cells resulting in a positive feedback loop. Additionally, monocytes and platelets are capable of binding to iRBC and participate in aggregation. Also, our prior studies show that neutrophil activation and NETs are associated with CM. To our knowledge, the contribution of these cells has not been studied synergistically in an in vitro system. We are developing an in vitro model to characterize platelet and leukocyte roles in endothelial activation, immune dysfunction and BBB breakdown in the presence of parasitized red blood cells (iRBC). We will also examine synergistic effects that occur from combinations of these innate immune cells. Using this model, we have initiated studies investigating the role of the Wnt/β-catenin pathway in CM, loss of BBB integrity, and gene expression changes in the endothelial cells.

1531

SEROLOGICAL RESPONSES TO MALARIA VARIANT SURFACE ANTIGENS AT BIRTH AND RISK OF MALARIA DURING INFANCY

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Plasmodium falciparum is the deadliest and most prevalent malarial species in Africa, largely affecting infants and young children. During the blood phase of its life cycle, the parasite expresses variable surface antigens (VSA), predominantly the highly diverse *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), on the surface of infected red blood cells allowing it to bind to host endothelium and evade host immunity. Maternal antibodies present in infants at birth are thought to be protective against malaria in the first six months of life. We hypothesized that serological responses to PfEMP1 in cord blood at birth, measured as the intensity of the responses (seroreactivity) and number of variants recognized (serorecognition), would correlate with subsequent risk of malaria. We analyzed results from 197 infants in Liwonde, Malawi with a mean follow up time of 5.4 months (range 10 weeks - 24 months) and 74 episodes of malaria infection. We collected serum from cord blood at delivery and collected specimens at quarterly visits and any time a participant was ill for up to 2 years. Malaria infection was defined as a positive PCR from dried blood spots or a positive rapid diagnostic test. Serum samples were probed for serological response using a protein microarray spotted with 259 diverse fragments of PfEMP1 from reference strains and clinical isolates as well as select VSAs. Odds ratios of seroreactivity were calculated for each PfEMP1 fragment. Results suggest that infants with high antibody levels to fragments of PfEMP1 at birth have lower odds of developing malaria infection within the first 6 months of life, which may inform future malaria vaccine development.

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RNA-SEQ REVEALS ALTERATION OF TRANSCRIPTS FOR GLUTAMINE TRANSPORTERS IN KENYAN CHILDREN WITH SEVERE MALARIAL ANEMIA

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Severe malarial anemia (SMA: Hb<5.0 g/dL, with any density parasitemia), a common clinical manifestation of severe malaria in children under five in holoendemic *Plasmodium falciparum* transmission areas such as Siaya county of western Kenya, persists as the major cause of malaria-related morbidity and mortality in the region. Our previous studies showed that circulating glutamine (GLN) levels were significantly lower in pediatric patients with SMA, compared to those with non-SMA. Reduced GLN was linked to reduced mRNA and protein levels of HSP70, resulting in dysregulation of nuclear factor-kappa B (NF-κB) signaling and production of proinflammatory cytokines (*e.g.*, IL-1β, IL-6 and TNF-α) known to be important in SMA pathogenesis. However, the underlying mechanisms for lower circulating GLN levels in SMA patients remain undefined. As such, we performed transcriptomic analyses on leukocytes collected from immune-naive children (3-36 months) with non-SMA (Hb>5.0 g/dL, n=41) and SMA (n=25) who presented at Siaya County Referral Hospital with acute malaria (pretreatment). Next Generation Sequencing was conducted to a depth of >20 million high-quality mappable reads using the Illumina platforms, and sequence reads were mapped to the human genome (GRCh38.p13) using the STAR software, followed by differentially expressed gene (DEG) analysis between the two clinical groups (*P*adj<0.05) using the EdgeR package. The results revealed 3,420 up-regulated genes in SMA, which includes 53 genes for *solute carrier* (SLC) group of membrane transport proteins, and 3,442 down-regulated genes in SMA (including 40 SLC protein genes). Specifically, six of these DEGs encode transporters for GLN: SLC6A19 (~18-fold increase, *P*adj=$3.96x10^{-29}$), SLC7A5 (~5.8-fold increase, *P*adj=$9.92x10^{-20}$), SLC1A5 (~5.6-fold increase, *P*adj=$3.19x10^{-19}$), SLC38A1 (1.28-fold increase, *P*adj=0.004), SLC38A2 (log_2 fold-change at -0.28, *P*adj=0.007), and SLC38A3 (log_2 fold-change at -1.38, *P*adj=0.015). Collectively, these results open new avenues for exploring the contribution of dysregulation in GLN transporter genes in the pathogenesis of SMA.

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IMPLICATIONS OF THE INNATE IMMUNE RESPONSE TO *PLASMODIUM FALCIPARUM FOR* MODELING: A LITERATURE REVIEW AND MODELING ANALYSIS

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Agent-based models of malaria are increasingly used to support decision-making in malaria-endemic settings and rely on data to inform detailed parameters for human hosts, vectors, and *Plasmodium* parasites to adequately simulate malaria transmission dynamics. Parameter misspecification affects output credibility and regular review of model inputs is critical. Innate immune response parameters are especially uncertain due to difficulty measuring in the field and can have significant impact on modeled outcomes, such as incidence of fever, uncomplicated malaria, severe malaria, and mortality. It is thus vital that these parameters reflect nature. We conducted a literature review to compile experimental and field data to better inform future model calibration. We identified studies with data on cytokine killing of infected red blood cells, pyrogenic thresholds, and first wave parasitemia after *P. falciparum* infection, as well as modeling approaches to innate immune response. We found substantial variation in estimates of parasite densities and pyrogenic thresholds, with some studies highlighting age-dependent variation. Using EMOD, a mathematical model of malaria transmission, we explored how different approaches to modeling innate immunity impact clinical incidence and prevalence in different transmission settings and intervention scenarios. We found notable differences in both incidence and prevalence outcomes when comparing modeled scenarios with and without variation in pyrogenic threshold and across different types of variation in innate immune response. This exercise presents an opportunity to improve model parameterization to better reflect within-host dynamics of *P. falciparum*. Adjusting these parameters' ability to capture within-host dynamics more accurately will lead to more reliable model predictions on clinical burden and intervention impacts.

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HUMAN ANTIBODY RESPONSES TO ANOPHELINE SALIVARY ANTIGENS AFTER MOSQUITO SKIN FEEDING IN A MALARIA ENDEMIC SETTING

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Malaria remains a major global health challenge and is caused by the transmission of *Plasmodium spp* by *Anopheles* mosquitoes. Human antibody responses to Anopheline salivary proteins have the potential to be used as biomarkers of exposure to infective mosquito bites, but interpreting responses in malaria endemic settings where exposure is prevalent may prove challenging. Leveraging sera from a cohort of Tanzanian children and adults with asymptomatic *P. falciparum* parasitemia who underwent direct mosquito skin feeding assays (DFAs) as part of a malaria transmission study, we investigated the humoral response to three sporozoite related saliva proteins - AgSAP, SAMSP1, and mosGILT - and the salivary gland protein SG6-P1. 76 participants undergoing DFAs were exposed to bites from 50 female *A. gambiae* for 15 minutes, leading to engorgement of the majority of mosquitoes. Sera collected at baseline prior to DFA, and 2 and 4 weeks later, were diluted 1:50 or 1:200 to measure IgG responses to purified proteins via ELISA. Baseline anti-SG6 and anti-AgSAP IgG OD were higher in participants with submicroscopic parasitemia compared to malaria-negative controls from the same villages ($p<0.01$), but this was not the case for SAMSP1 and mosGILT, which showed strongly correlated values ($r = 0.80$). Two weeks after DFA, there was a detectable IgG response to SG6-PI and AgSAP, with boosting in 33-35/50 individuals that was more likely to occur during the wet season. At four weeks, a weak but detectable response to SAMPS1 and mosGILT was present, with boosting in 16/26 individuals, while anti-SG6-P1 declined below baseline in 21/26 individuals. In summary, the investigated salivary proteins induced correlated IgG responses 2 and 4 weeks after an artificial 50-mosquito-bite inoculum, with anti-SG6-PI showing more promise as a marker of recent anopheline exposure. Ongoing analyses will continue to explore the kinetics of anti-salivary antibody responses in this malaria endemic population, including after consecutive inoculation (50 bites 2 weeks apart), as well as whether such responses influence an individual's ability to transmit malaria to biting mosquitoes.

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MACAQUE MONKEYS (*MACACA MULATTA*) DIFFER IN THEIR GENE EXPRESSION RESPONSE TO TWO *PLASMODIUM* SPECIES

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Malaria imparts an immense selection pressure on primates that may be infected with various parasite species that differ in severity and symptomatology. For example, when macaques are infected with *Plasmodium coatneyi* (comparable to the human *P. falciparum*), they experience a ~35% mortality rate if antimalarial drug treatment is not given, however, when infected with *P. cynomolgi* (comparable to the human *P. vivax*), they have a much milder reaction. Here, we compare gene expression response to the two parasite species using data from experimental infections of an important primate model of human malaria. First, we validate a proxy of parasite load calculated using RNA sequencing read counts against a standard microscopic measure of parasite load. Then we use this metric to compare the transcriptomic response of rhesus macaques (*Macaca mulatta*) that have been experimentally infected with the two *Plasmodium* species. We find that our inferred measure of parasite load was tightly and significantly correlated with the microscopy measure and captured similarly informative differentially expressed genes (R^2=0.85, P<<0.05). Furthermore, we find that the uniquely differentially expressed genes in macaques infected with *P. coatneyi* include *ELOVL1* (adj. P=2.65e-10), *OCEL1* (adj. P=5.22e-8), and *ARL16* (adj. P=1.59e-7), which are associated with neurological disorder, adult brainstem neuroglial tumor, underdeveloped connective tissue of the brain, and childhood onset schizophrenia, respectively. Uniquely differentially expressed genes in macaques infected with *P. cynomolgi* had no such neurological functions. In this study, we discovered that these macaque populations are both immunologically distinct in their reaction between *P. coatneyi* and *P. cynomolgi* yet immunologically similar to the human-infecting *P. falciparum* and *P. vivax*, respectively. By exploring such infection responses in macaques, we not only provide support to the use of macaque models in human studies of malaria infection but we also elucidate the molecular mechanism involved in Plasmodium-species specific infection.

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PREVALENCE OF STUNTING AND ITS ASSOCIATION WITH COGNITIVE IMPAIRMENT IN CHILDREN IN UGANDA WITH OR WITHOUT SEVERE MALARIA

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Uganda has a high prevalence of childhood undernutrition and severe malaria (SM). To assess the impact of acute and chronic undernutrition in children <5 years hospitalized with SM compared to community controls (CC) in two socio-demographically distinct sites in Uganda (Kampala and Jinja), we compared growth indicators of undernutrition in a prospective SM cohort study conducted from 2014-2018. Undernutrition was defined as z-scores two standard deviations below the median for weight-for-age (underweight), height-for-age (stunting), and weight-for-height (wasting). We evaluated prevalence of undernutrition at enrollment and 12-month follow-up, and the association between enrollment growth parameters with cognitive z-scores at 12-months using linear regression adjusted for age, sex, SM complication, socioeconomic status, and education. At enrollment, wasting was more common in SM than CC in Kampala (12 vs. 3%) and Jinja (13 vs. 2%) (all p≤0.03). Being underweight at enrollment was comparable in SM vs. CC in both Kampala (19 vs. 8%) and Jinja (18 vs. 8%) (all p≤0.07). All returned to CC levels by 12 months. Prevalence of stunting was generally high among all children in the study; at enrollment it was comparably high in SM and CC in Kampala (22 vs 25%) and Jinja (24 vs 36%, p=0.51 and 0.06, respectively) and remained high at 12 months. Stunting and being underweight at enrollment were associated with lower cognitive z-scores at 12 months in SM (beta coef. [95% CI], -0.42 [-0.62, -0.22], p<0.001 and -0.33 [-0.55, -0.11], p=0.004, respectively), but not wasting (-0.10 [-0.36, 0.17], p=0.46). In CC, only stunting at enrollment was associated with lower cognition at 12-months (-0.72 [-1.11, -0.33], p<0.001). These associations with cognitive outcomes were site independent. In summary, we did not observe significant differences in prevalence of undernutrition by site. Prevalence and persistence of stunting and the association with cognitive impairment at 12-month follow-up was observed irrespective of SM, indicating a need to target national levels of chronic childhood undernutrition in Uganda.

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EFFECT OF HOST RESPONSE ON BLOOD STAGE *PLASMODIUM FALCIPARUM* EXPORTOME

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Plasmodium falciparum extensively modifies infected red blood cells (RBC) by exporting over 300 proteins into the host cell. Many of the exported proteins are implicated in the parasite cytoadhesion virulence determinant, but to date there has been no systematic investigation of the parasite "exportome" in disease severity. Recent work indicates that the age of circulating parasites differs between mild and severe malaria infections and that febrile temperature and hyperlactemia modify gene transcription of parasite exported proteins. To investigate the role of exported parasite proteins in parasite virulence, we designed a nanoString codeset of 50 targets chosen mostly from the parasite exportome, excluding the highly polymorphic *var* and *rifin* gene families. In initial studies, we determined conditions for febrile and hyperlactemia *in-vitro* by measuring the expression of glycophorin binding protein (GBP) and knob-associated histidine-rich protein (KAHRP) for hyperlactemia, and *Pf*AP2-HS for febrile conditions. These conditions are being used to study the effect of febrile temperature and hyperlactemia on the expression of the selected 50 exported parasite proteins in lab-adapted parasite lines representing the placental binding and cerebral binding phenotypes. We will follow-up these studies in a pediatric cerebral malaria cohort versus mild malaria cases. This will determine the effect of host response on parasite exported proteins that modify the cytoadhesion virulence determinant and hence malaria disease severity.

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ANALYSIS OF THE STRUCTURE AND EPITOPE CHARACTERISTICS OF NOVEL *PLASMODIUM FALCIPARUM* ANTIGENS

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In 2020, *Plasmodium falciparum* (Pf), the most virulent agent of human malaria, caused an estimated 241 million human infections and 627,000 deaths. The immense burden exerted by Pf highlights the need for new, effective interventions, including highly efficacious vaccines. To date, no malaria vaccine has achieved consistently high efficacy in endemic regions, in part due to allele-specific efficacy. The design of new, highly efficacious vaccines would be facilitated by novel Pf vaccine candidates and a better understanding of the characteristics of functional Pf epitopes associated with protection. In a separate abstract, our group reports leveraging allele-specific efficacy in clinical trials of a whole-organism, sporozoite-based malaria vaccine tested in an endemic area to identify Pf antigens associated with protection, using genome-wide sieve analyses. These analyses revealed hundreds putative protective antigens in each of two trials, including well-established pre-erythrocytic vaccine candidates. We hypothesized that, if most of these candidates are in fact protective antigens, then at the Pf genomic sites significantly differentiated between vaccinees and controls (or "target sites"), (*i*) the vaccine allele should be underrepresented in infections from vaccinees relative to controls, and (*ii*) target sites should fall preferentially in epitopes. Our analyses show that, consistent with (*i*), in ~70% of target sites, the vaccine allele is significantly depleted among Pf infections in vaccinees ($p<0.05$). We are currently analyzing the distribution of target sites relative to predicted epitopes. T-cell epitopes were predicted using the netMHCpan suite and predominant HLA types at the clinical trial sites. Continuous B-cell epitopes will be predicted with BEPIPRED and discontinuous B-cell using DISCOTOPE, based on 3D structural predictions generated using AlphaFold2. Target sites that fall in epitopes or structural motifs will be further analyzed to characterize the properties of the amino acid residue changes associated with differences in immunogenicity and that contribute to vaccine evasion.

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EVALUATION OF THE PROTECTIVE ROLE OF TGF-B1 AND IL-10 DURING HEMATOLOGICAL COMPLICATIONS IN VIVAX MALARIA

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The host immune response during *Plasmodium spp* infections in malaria is complex. Studies have suggested that during *Plasmodium vivax* infections there is an uncontrolled increase of proinflammatory molecules in the host, which has been associated with complicated malaria. The circulation of molecules with an anti-inflammatory effect such as TGF-β and IL-10 improve the clinical prognosis of the disease. The aim of this study is to evaluate regulatory molecules of the immune response and their role during hematological complications in vivax malaria. Cross-sectional analytical research (Study Zone: Tierralta, south of Córdoba, Colombia). Nine proinflammatory molecules (IP-10, MCP-1, IL-6, INFγ, IL-12p70, IL-2, IL-1β, TNFα, IL-17A) and 4 anti-inflammatory molecules (IL-10, TGF-β, IL-4 and IL-8) were quantified in the plasma of 165 individuals with malaria and 60 healthy subjects. Flow cytometry in a bead-based multiplex assay was performed. Malaria patients were divided into 4 groups: i) Malaria and anemia (MA); ii) Malaria and thrombocytopenia (TM); iii) Malaria anemia and thrombocytopenia (MAT); iv) Malaria without hematological alteration (M). Statistic analysis were performed with non-parametric statistical tests in the GraphPad Prism version 7.0 software. This project was approved by the ethics committee of the University of Córdoba. Concomitant anemia and thrombocytopenia was the most frequent finding (49%), followed by thrombocytopenia (28%) and anemia (13.9%). 9% of the patients did not develop any hematological alteration. No differences were observed between groups for IL-8 and IL-4, contrary to IL-10 and TGF-β1 which exhibited statistical differences between study groups ($p<0.05$), was observed that TGF-b1 was 4 times increased in the M group compared to the groups with hematological alterations (AM, MAT, MT). IL-10 was found to be 4 times lower in the M group versus MAT and MT; the MT group had 10 times more concentration of IL-10 than the M group. TGF-β1 exhibited a protective effect against malaria-associated thrombocytopenia and anemia, suggesting a more effective regulatory effect compared to IL- 10.

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ALTERED GENE EXPRESSION IN GAMMA DELTA T CELLS IN CHILDREN WITH MALARIA AND SCHISTOSOMIASIS CO-INFECTION RELATIVE TO CHILDREN INFECTED WITH MALARIA ALONE

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Malaria and schistosomiasis are the two most prevalent parasitic infectious diseases in sub-Saharan Africa, and often co-occur in the same patient. Schistosomiasis, a neglected tropical disease, is thought

to impact the acquisition of a secondary malaria infection in young children. Evidence suggests that the presence of a helminthic infection can influence the maintenance of malaria-specific memory response, but the mechanisms remain to be elucidated. Our group demonstrated enhanced multifunctional responses over a transmission season and differential antigen-specific cytokine production in memory populations in children co-infected with *Schistosoma haematobium* and *Plasmodium falciparum* (*Sh-Pf*) when compared to children infected only with *Pf*. We hypothesized that the expression of genes and cell receptors that promote sustained memory populations will be pre-dominantly expressed in PBMCs acquired from children with *Sh-Pf* co-infections when compared to PBMCs from children infected with *Pf* alone. To address our hypothesis, we used CITEseq to characterize immune cell populations and gene expression patterns in peripheral blood mononuclear cells (PBMCs) from a malaria-schistosomiasis co-infection cohort from Mali. We performed cell clustering based on gene expression patterns using Seurat and identified fourteen distinct clusters. For each cluster, we compared gene expression between cells from *Sh-Pf* and *Pf* individuals. We find evidence of differential gene expression in eight of the clusters, including those formed by gamma delta T (gdT) cells and B cells. We observed up-regulated expression of TRDV2, TRDC, and GZMH genes in gdT cells and CXCR4 and RRAS2 in memory B cells from *Sh-Pf* children relative to age-matched *Pf* children. Taken together, our preliminary results suggest differential behavior of immune cell populations in these two sets of children and begin to elucidate a mechanistic explanation of the role of chronic *Sh* infection on ameliorating acquisition of Pf malaria.

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SPECIFIC MEROZOITE-STAGE AND VARIANT SURFACE ANTIGENS ARE TARGETS OF PROTECTIVE IMMUNITY UNDER DIFFERENT CLINICAL MALARIA STATUS

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Sustaining the significant gains on reductions of the global burden on malaria will require critical re-thinking of the control tools as well as designing new ones. Second-generation tools such as vaccines may be key in this direction. Studies have suggested that broadly reactive antibodies against variable surface antigens and merozoites stage antigens are targets of naturally acquired protective immunity, making these proteins important candidates for anti-malaria therapeutics and vaccines. However, predicting the relationship between the antigen-specific antibodies and protection from clinical malaria remains unresolved. Here, we used multiple data analysis approaches of new and published data to examine the multi-dimensional relationship between antibody responses and symptomatic malaria outcomes in a malaria exposed population. We identified 22 proteins composed of blood-stage and variable surface antigens that associated with reduced risk to clinical malaria under three different clinical malaria definitions (1,000/2,500/5,000 parasites/µl plus fever). Of these, 17 were PfEMP1 domains, 3 RIFIN family members, merozoite surface protein 3 (PF3D7_1035400), and merozoites-associated armadillo repeats protein (PF3D7_1035900). In addition, Principal Components Analysis (PCA) indicated that the first three components (Dim1, Dim2 and Dim3 with eigenvalues of 306, 48, and 29, respectively) accounted for 66.1 % of the total variations seen. Specifically, Dim1, Dim2 and Dim3 explained 52.8 %, 8.2 % and 5% of variability, respectively. We also observed a significant relationship between the first component scores and age with antibodies to PfEMP1s being the key contributing variables. This is consistent with a recent observations suggesting that there exists an ordered acquisition of antibodies targeting PfEMP1 proteins. Thus, although further work on the significance of the selected antigens will be required, these approaches may provide insights for identification of drivers of naturally acquired protective immunity as well as guide development of additional tools for malaria elimination and eradication.

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IMPROVING ACCESS TO ESSENTIAL TREATMENT SERVICES FOR CHILDREN UNDER-FIVE YEARS OF AGE BY USING THE MALARIA INTEGRATED COMMUNITY CASE MANAGEMENT PACKAGE IN TWO U.S. PMI IMPACT MALARIA SUPPORTED DISTRICTS, RWANDA

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Rwanda has implemented integrated community case management (iCCM), a strategy to improve access to essential treatment services for children under five years of age with community health workers (CHWs), since 2005. Each village has 4 CHWs, including a male-female pair providing basic care and the iCCM package. Data from two consecutive national malaria annual reports 2019/2020 - 2020/2021 highlighted that in all villages of the country, 95% of children under five years of age are seeking treatment within 24 hours of the onset of symptoms, resulting in a decrease in severe malaria cases from 4,358 to 2,592 cases. A baseline assessment conducted in 2 iCCM districts supported by the U.S. PMI Impact Malaria project (IM) in October 2020 revealed that 18% of CHWs could not provide any iCCM services, only 62.5% had received supportive supervision (SS) visit in 2020, and the health facilities did not have a plan for refresher training for newly elected CHWs. To address these challenges, the Ministry of Health (MOH), in collaboration with IM, implemented the following interventions in supported districts: training of 426 new CHWs on iCCM package, conducting quarterly SS visits of 2360 CHWs in Rusizi and Nyamasheke districts, and quarterly coordination meetings of health leaders and administrative local leaders. To determine the impact of the interventions, we extracted data from the country's Health Management Information System related to malaria diagnosis and treatment for the period October 2020 - December 2021. It showed the percentage of children treated among all febrile children who sought care in both iCCM supported districts increased from 83% to 93% (Nyamasheke) and 73% to 91% (Rusizi), compared to the national average which increased from 57% to 64%. Also, the findings showed that the knowledge score of CHWs after training was 93% at the third SS visit compared to 78% at the first visit. With the collaboration between IM, MOH, and local administrative leaders to access essential services, iCCM strategy implementation was strengthened; CHWs skills and service provision improved, and the number of children under five years of age treated increased.

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A RANDOMIZED TRIAL OF TEXT MESSAGES TO PROMOTE INSECTICIDE-TREATED NET (ITN) USAGE USING BEHAVIORAL ECONOMIC PRINCIPLES AND THE SMARTNET INITIATIVE MOBILE PHONE NETWORK

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Malaria control efforts require accurate data collection and community engagement. Mobile technology use in Malawi has increased to around 52.3 mobile phone subscriptions per 100 people in 2020. The Malawi SmartNet Initiative leverages mobile technology to reach ITN users. In March 2020, 300,000 ITNs with a shortcode were distributed Malawi-wide via antenatal clinics. In August 2021, the initial 53,900 SmartNet Initiative respondents who had dialed the shortcode were randomized into 7 groups. Each group received a baseline survey with 11 sociodemographic and net usage questions. In September 2021, six of the groups received a specific behavioral economic influenced health message designed to increase ITN usage. One group did not receive any messages. In October 2021, a follow-up survey was sent with the same 11 questions. Of the 11,840 (19%) respondents to both surveys, there was an average reported increase in net usage of 8.3% from the 59% pooled average (range +5-10%). The top three health messages associated with an increase in reported net usage are 1. Normal message: "Mosquito nets fight malaria, use them regularly" (+10%), 2. Control group: no message (+10%), and 3. Bandwagon effect: "Join the fight. Use your mosquito net daily to help Malawi be the first country in Southern Africa to eliminate malaria" (+10%). Multivariate analyses regarding individual responses are ongoing and may confirm the null hypothesis that the type of message did not affect reported net usage. Limitations included potential lack of representativity of this sentinel sampling approach and lack of measurement of outside factors affecting ITN usage; potential biases include a greater likelihood of participation by those who are literate, urban dwellers and own mobile phones. It is feasible to deliver different messages and compare changes in self-reported malaria prevention behaviors, however, the generalizability and utility of this data remain to be determined. Given the clear limitations, further research is needed to determine whether there may be a role for a mobile technology-based network to rapidly evaluate and deliver targeted malaria health messaging.

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COMPARING MALARIA DISABILITY ADJUSTED LIFE YEARS VS TOTAL FUNDING, 2000-2017

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Since 2000, substantial progress has been made in decreasing the global burden of malaria, while total global funding for malaria has reached an all-time high. Here, we compare changes in total funding and malaria burden between 2000-2017 and compare trends across endemicity categorizations. We used preliminary estimates of malaria burden from the 2020 Global Burden of Disease (GBD) study and estimates of malaria spending from the Financing Global Health study to compare total malaria spending against malaria Disability Adjusted Life Years (DALYs), globally and by country. Change in malaria DALYs per capita were calculated and compared against estimates of total spending per capita, along with estimates of malaria dollars spent per DALY. We aggregated to three-year averages and assigned endemicity status in 2000 using GBD malaria *Plasmodium falciparum* parasite rate (PfPR) estimates. We present preliminary GBD 2020 results here. Global malaria DALYs were estimated to be 69.9 million (95% UI 40.3-107 million) in 2000-2002 and 54.6 million (95% UI 27.6-89.6million) in 2015-2017, a decline of 21.9% (95% UI 16.5%-31.5%). Meanwhile global total spending on malaria increased by 240% from 2000-2002 to 2015-2017 [1.48 million (95% UI 1.37-1.62 million) to 5.05 million (95% UI 4.84-5.32 million)]. These trends were observed in almost all countries, though a subset showed both reductions in DALYs and total spending since 2000-2002. Regardless of endemicity status in 2000, most countries showed an increase in malaria dollars spent per DALY in 2015-2017 vs 2000-2002. Hypo-endemic countries overall showed more dollars per DALY being spent than either meso- or hyper-endemic countries. As decreases in burden are achieved, our results illustrate that hypo-endemic countries spend more dollars per DALY than their meso-and hyper-endemic country counterparts. It is therefore increasingly imperative that funding is tailored to country-specific needs.

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IMPROVING DELIVERY OF SEASONAL MALARIA CHEMOPREVENTION IN MINING AREAS IN GUINEA: FINDINGS OF IMPLEMENTATION RESEARCH

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Uptake of SMC in Guinea is monitored by the National Malaria Control Programme through coverage surveys undertaken at the end of each year. In 2020, 82% of eligible children received SMC at least once and 71% received four treatments, but SMC uptake was lower in the largest prefecture, Siguiri, where only 47% of eligible children received SMC. In 2020, the NMCP undertook qualitative research to understand community attitudes to SMC, barriers to uptake, and facilitating factors, through 12 focus groups which were held with caregivers, fathers, and drug distributors, 8 in-depth interviews with SMC supervisors at local and national level, and direct observation of SMC delivery. Strategies to address

the barriers were then developed through a participatory approach and piloted in 2021. Key barriers were a mistrust of medicines provided free, and of drug distributors who were often from outside the community; health expenditure for the treatment of malaria in children was a smaller proportion of income of families in mining areas in Siguiri than was the case in agricultural communities; and distributors and supervisors lived far from distribution areas, distributors had insufficient time, lacked adequate training, and found families often away from home. Strategies to improve delivery included reducing workload by increasing the number of distributors, selecting those who would be available throughout the season, ensuring each distributor pair includes one from the local community and one who is literate, strengthening community mobilisation by recruiting an advocate for SMC resident in each community, and starting mobilisation 5 days in advance of each cycle. These strategies were piloted in two communities during the 4th SMC cycle of 2021. Local advocates were found to be highly effective in strengthening social mobilization, and were the primary source of caregivers' information about SMC. Increasing the number of distributors increased costs, but made it possible to reach areas that could not be covered previously. It was recommended to apply this strategy in areas with low SMC uptake identified through coverage surveys.

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3D MICROFLUIDICS-ASSISTED MODELING OF NUTRIENT TRANSPORT IN PLACENTAL MALARIA

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The human placenta is a critical organ, mediating the exchange of nutrients, oxygen, and waste products between fetus and mother. Placental malaria (PM) resulted from Plasmodium falciparum infections causes up to 200 thousand newborn deaths annually, mainly due to low birth weight, as well as 10 thousand mother deaths. In this work, a placenta-on-a-chip model is developed to mimic the nutrient exchange between the fetus and mother under the influence of PM. In this model, trophoblasts cells (facing "maternal" blood therefore called "maternal" side) and human umbilical vein endothelial cells (facing "fetal" blood therefore called "fetal" side) are cultured on the opposite sides of an extracellular matrix gel in a compartmental microfluidic system, forming a physiological barrier between the co-flow tubular structure to mimic a simplified placental interface. The influences of infected erythrocytes (IEs) sequestration through cytoadhesion to chondroitin sulfate A (CSA) expressed on the surface of trophoblast cells (maternal side), a critical feature of PM, on glucose transfer efficiency across the placental barrier was studied. To create glucose gradients across the barrier, uninfected erythrocyte or IE suspension with a higher glucose concentration was introduced into the "maternal" channel and a culture medium with lower glucose concentration was introduced into the "fetal" channel. The glucose level in the fetal channel in response to CSA-adherent erythrocytes infected with CS2 line of parasites under flow conditions was monitored. Uninfected erythrocytes served as a negative control. The results demonstrated that CSA-binding IEs added resistance to the placental barrier for glucose perfusion and decreased the glucose transfer across the placental barrier. The results of this study can be used for better understanding of PM pathology and development of models useful in studying potential treatment of PM.

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RECALIBRATION OF A MATHEMATICAL MODEL OF MALARIA TRANSMISSION WITH PARASITE AND INFECTIVITY DATA FROM BURKINA FASO

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A major barrier to malaria elimination in endemic areas is the abundance of chronic infections with asexual parasite densities low enough to avoid symptoms - and thus treatment - but gametocyte densities high enough to perpetuate transmission. Screening, testing, and treatment (STT) interventions detect and treat asymptomatic gametocyte carriers, interrupting the chain of transmission. Various forms of STT have been evaluated through clinical trials, and mathematical models of malaria transmission have been used to further predict the impact of permutations of STT and extrapolate STT impact to new settings. To make accurate predictions, models must reproduce key quantitative relationships between parasites, symptoms, gametocytes, and infectiousness within modeled human hosts. We leveraged detailed parasite, gametocyte, and infectivity data from a trial of STT in Burkina Faso (INDIE trial), to recalibrate the within-host component of the established malaria transmission model, EMOD. We constructed a grid model of the INDIE study area with spatially heterogeneous transmission rates based on mosquito counts and surveys on the use of bed nets and antimalarial drugs. We simulated standard-of-care interventions (passive case management, bed nets, seasonal chemoprevention) and tuned model parameters related to fever, antigenic variation, immunity, and gametocyte development to fit parasitemia, gametocytemia, and infectivity measurements from the control arm of INDIE. Our recalibration yielded a new set of internally consistent within-host parameters in EMOD, suitable for modeling the impact on malaria transmission if STT were implemented on a larger scale or in a different setting than in existing clinical trials. A major change from previous versions of EMOD was an increase in the modeled infectivity of chronic infections. In addition to producing a set of within-host parameters suitable across high-transmission settings, this work also generated a detailed spatial site-specific model of malaria transmission in a highly seasonal and endemic West African setting, providing a platform to explore other interventions.

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EPIDEMIOLOGICAL AND GENETIC MODELING OF MALARIA TRANSMISSION TO INTERROGATE THE RELATIONSHIP BETWEEN GENETIC FEATURES AND TRANSMISSION PROPERTIES

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The use of malaria parasite genetic data for control, surveillance, and elimination efforts is growing. Features derived from malaria parasite genetic data have been shown to correlate with measures of transmission intensity. However, cross-sectional characterization of the population cannot fully reconstruct the underlying epidemiology and the resulting genetic structure of a population. To understand the relationship between epidemiology, genetic features, and transmission informativeness of features, we leverage a layered mathematical modeling approach. Combining EMOD, an epidemiological model of malaria transmission which accounts for transmission history, GENEPI, a malaria parasite genetic model that simulates genomic evolution on a transmission network accounting for co-transmission and superinfection, and an observational component to recreate sampling and sequencing uncertainty, we can interrogate the effect of the parameters in each portion of the model on genetic features. Our findings suggest that the model can be used to

identify the limits of different variant panel sizes and allele frequencies to derive common metrics, such as the complexity of infection, across different transmission scenarios. Additionally, the model can guide thresholds of polygenomic infection relatedness by co-transmission or superinfection to distinguish between modes of transmission based on population allele frequencies and intensity. Broadly, the model could highlight the best use cases for genetic data and robust genetic features to support the interpretation of field data by malaria control programs.

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FACTORS INFLUENCING UPTAKE OF INTERMITTENT PREVENTATIVE TREATMENT OF MALARIA IN PREGNANCY AT THE REDEMPTION HOSPITAL SEPTEMBER 2021

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Malaria infection in pregnancy poses a high burden on the health of the public, with significant threats for the mother, the unborn child and eventually the newborn. However, malaria effect in pregnancy such as mortality and morbidity is most prominent in areas of sub-Saharan Africa where there is widespread transmission. This study aimed to ascertain factors that influence the uptake of Intermittent Preventive Treatment (IPTp) of Malaria among pregnant women in the Redemption Hospital. A cross-sectional, facility-based study was conducted with 250 pregnant women, who answered items from a structured questionnaire during their wait times for antenatal care visits. Data was analyzed using Microsoft Office Excel and R Statistical Software. Data was summarized using descriptive statistics. The results of study found that 82.8% of participants (n=207) were knowledgeable on the prevention of malaria during pregnancy. However, resource constraints at the health facility challenged the uptake of IPTp. A total of 121 (65%) were found to have received the minimum required number of IPTp doses. The unavailability of SP affected 117(52.5%) of participants. Furthermore, most participants (n=133, 53.2%) said that they carry or buy their own water when they come to the clinic in order to take the SP that is given them. Furthermore, most participants (n=133, 53.2%) said that they carry or buy their own water when they come to the clinic in order to take the SP that is given them. Despite resource constraints, quality of care was not perceived as an issue. Majority of the pregnant women (n=208, 83.2%) indicated that healthcare workers' attitudes were positive during their ANC visits. To promote higher uptake of IPTp during ANC visits, a regular monitoring and evaluation of services should be instituted to promote continuous availability of drugs, clean water and clean cups for proper IPT management. Furthermore, the benefits of SP should be taught during ANC health education sections to guarantee that antenatal women know the correct number of doses that are required of them.

1550

MALARIA PREVENTION IN SOUTHERN ANGOLA: A POST INDOOR RESIDUAL SPRAY STUDY TO ASSESS POPULATION KNOWLEDGE, ATTITUDES, AND PRACTICES IN FIVE TARGETED DISTRICTS

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The Angolan National Malaria Control Program, in close collaboration with SADC Malaria Elimination 8 secretariat has been implementing an aggressive agenda to reduce malaria in southern Angola and significantly contribute to malaria elimination in the bordering districts of Namibia. Since 2017, several strategies have contributed to reduce the malaria burden namely community case management, indoor residual spraying (IRS), long-lasting insecticidal nets (LLIN) distribution, and active surveillance approaches. Since 2018, nearly 145,000 houses have been sprayed in southern Angola. To independently assess IRS coverage, post IRS measures and malaria knowledge, attitudes and practices, a survey was implemented between February and March 2022 in Calai, Cuangar, Dirico, Menongue and Rivungo districts in Cuando Cubango province. A two-stage sampling strategy was used stratifying the number of households to be surveyed proportionally to the population in the five targeted districts and then using probability proportional to the size to select villages. Once in the villages, the EPI walk method was used to select households to be sampled. Interviews were conducted to each head of household using a structured questionnaire. 647 interviews were conducted, of which 51% were females. 64% of respondents reported their household has been sprayed in the past campaign. In total, 89% of respondents were able to identify at least one action to conduct after the IRS, with proportions varying from district to district. Overall, 92% considered IRS and LLIN safe prevention method against malaria. In total, 75% of people were able to identify at least three signs and symptoms of malaria and 99% were able to recognize at least one method of preventing this disease. This study showcased IRS is a widely accepted intervention and that those who received IRS know what measures to take after the campaign. Malaria adequate KAP is widespread in targeted areas, likely due to the intense operational and communication efforts made to control malaria in these.

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COMMUNITY PERCEPTIONS AND PRACTICES IN MALARIA AND DEVELOPMENT OF AN EDUCATIONAL INTERVENTION CONDUCTED IN AN ENDEMIC AREA OF COLOMBIA

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Malaria prevention and control programs are mainly oriented to the *Anopheles* vector. Considering that malaria disease encompasses not only biological components but social aspects, the design of prevention and control strategies should consider the community's beliefs and practices. This study aimed to determine the knowledge, attitudes and practices (KAP) towards malaria in a community of a Colombian endemic area in order to develop an educational intervention. Data were collected through a KAP survey. Of 75 people in the community, 43 answered the KAP survey. In addition, a dialogue was held within a focus group. Survey results showed that participants recognized that a mosquito is the disease vector (72.09%), and identified some of the main symptoms of the disease. Regarding attitudes, most of the people agreed with performing indoor residual spraying (IRS), and less than half of the participants would seek healthcare assistance in the presence of symptoms. People recognized the use of mosquito nets (65.12%) as the most common practice of disease prevention; however, information from the focus group revealed a lack of access to the nets or possessing very deteriorated mosquito nets. The educational intervention was focused on strengthening community knowledge related to the mechanism of disease transmission, attitude towards seeking healthcare assistance and prevention practices. These results highlight the importance of the development of locally contextualized prevention and control strategies.

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COMMUNITY HEALTH SERVICE READINESS THROUGH THE INTEGRATED COMMUNITY CASE MANAGEMENT (ICCM) PROGRAM IN UGANDA

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The World Health Organization (WHO) recommends Integrated Community Case Management(iCCM) program since 2012 to increase access to health and reduce health access inequity. iCCM is implemented

in over 30 countries globally including Uganda and contributes towards the achievement of the global target of reducing under-5 mortality to at least 25 per 1,000 live births. The intervention strategy is the use of trained Community Health Workers (CHWs) to manage malaria, pneumonia and diarrhea cases among children under five years. The success of this program is hedged on the service readiness of the CHWs. Between June to July 2019, we conducted a cross sectional study in Uganda among 360 CHWs to assess service readiness against the Uganda national iCCM implementation guidelines as a standard. This standard is defined as completion of the standard iCCM training and possession of the necessary diagnostic (Malaria Rapid Diagnostic kits (RDTs) and Respiratory timers) and treatment commodities (Artemisinin Based Combination Therapy drugs (ACTs), Amoxicillin, Zinc and Oral Rehydration Solution (ORS). The CHWs were sampled through multistage cluster sampling technique from 15 districts, each representing a health region based on the Uganda Demographic Health Survey regional stratification. We administered a structured questionnaire and observed for the presence of functional and non-expired diagnostic and case management / treatment commodities and drugs for malaria, pneumonia and diarrhea. Data was analyzed using STATA version 14. Results showed that out of the 360 CHWs, 99% [95% CI 98% - 100%] were trained while 30% [95% CI 25% - 35%], 29% [95% CI 24% - 34%] and 45% [95% CI 40% - 50%] had the required diagnostic and treatment commodities for malaria, pneumonia and Diarrhea respectively. Overall,9% [95% CI 6% - 12%] had the required diagnostic and treatment commodities for all the three iCCM targeted childhood illnesses. In conclusion, almost all the iCCM CHWs and they just need to be equipped with diagnostic and treatment commodities to be fully ready to provide iCCM services in the communities.

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INTERPERSONAL COMMUNICATION: AN EFFECTIVE APPROACH IN BOOSTING AND SUSTAINING UPTAKE OF MALARIA SERVICES AND PRODUCTS IN KANCHIBIYA DISTRICT, ZAMBIA

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Recent studies show that although information, education, and communication (IEC) is effective in increasing malaria prevention knowledge, it does not translate into adoption of desired behaviors required for malaria elimination. The 2018 Malaria Indicator Survey (MIS) revealed low uptake of three or more doses of intermittent preventive treatment during pregnancy (IPTp)— 67.0% for rural populations and only 60% in Muchinga Province. The National Malaria Elimination Program (NMEP) supported by the United States President's Malaria Initiative (PMI)-funded project PAMO Plus, is shifting away from primarily IEC to social and behavior change (SBC) to overcome barriers that hinder uptake of malaria interventions. One such intervention is empowering community change agents (CCAs) to utilize interpersonal communication (IPC) approaches. In 2021, in Kanchibiya District of Muchinga Province in Zambia, the NMEP introduced IPC and trained 220 community volunteers. CCAs, through regular household visits, build a relationship of trust among community members. They engage individuals and communities, using community dialogues, peer education, and counseling, to identify behavioral barriers (e.g., belief that ITNs cause infertility among men), facilitate two-way discussions on the identified barriers, and encourage adoption of proven malaria prevention behaviors. There has been noted improvement after the introduction of IPC in Kanchibiya. Indoor residual spraying (IRS) coverage increased from 64% in 2020 to 74% in 2021. Uptake of the first dose of IPTp within the 1st trimester increased from 54.2% in 2020 to 68.5% in 2021 and IPTp 3 coverage increased from 26.9% in 2020 to 40% in 2021. These changes have been partly attributed to IPC and efforts by CCAs and effective community engagement. IPC is a promising approach to increase uptake of proven malaria interventions. There is therefore a need for the malaria program to invest in this approach and take it to scale to accelerate targeted malaria elimination efforts in Zambia.

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STRENGTHENING FEVER CASE MANAGEMENT IN NIGERIA THROUGH BEHAVIORAL ECONOMICS AND HUMAN CENTERED DESIGN

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Provider adherence to malaria case management guidelines is a challenge in Nigeria. Studies have shown that many public (51%) and private (95%) providers prescribe artemisinin-combination treatment (ACTs) to patients with negative malaria test results (Obi 2019; Bamiselu 2016). This suggests that limited stocks of malaria treatment are dispensed to patients who do not need them, and appropriate treatment for other causes of fever may be delayed or overlooked. Breakthrough ACTION (BA) and the President's Malaria Initiative for States (PMI-S) projects used behavioral economics and human-centered design to understand the factors driving provider adherence and designed prototypes targeting them. Ninety-two (92) provider interviews, 56 client interviews, and 29 facility observations were conducted. Identified factors included high caseloads and misconceptions leading to distrust of malaria rapid diagnostic tests (mRDTs), among others. A participatory design process resulted in a package with five prototypes: (1) a group discussion tool to address distrust of malaria RDTs; (2) streamlined testing procedures; (3) provider job aids to support differential diagnoses for fever; (4) a counseling tool to support clients along the continuum of care; and (5) supportive supervision with data validation and feedback processes. All prototypes were tested in 12 facilities (9 primary and 3 secondary) from three states. Prototypes were revised and scaled up to 778 facilities in four states between July 2020 and 2021. This analysis used routine health information system data from 669 facilities with complete data in the 6 months before and after the scale-up. There was variation across and within facilities over time, but the trend shows convergence towards 100% adherence over the period, as was desired (ex: in Oyo state, the range fell from 168 percentage points to 35 and in Cross River, from 197 to 77). Fever testing rates rose from 93.2% to 99.9%. Future steps include clarifying which prototypes best suit which types of facilities and which ones are most impactful; these insights will inform how the prototypes complement existing interventions.

1555

EVALUATING FUNCTIONAL ACTIVITY OF HUMAN MONOCLONAL ANTIBODIES TO PLASMODIUM VIVAX DUFFY BINDING PROTEIN USING THE *PLASMODIUM KNOWLESI* TRANSGENIC MODEL EXPRESSING PVDBP

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Plasmodium vivax (Pv), induces blood-stage infections by invading reticulocytes, using the Duffy (Fy) blood group antigen and its endogenous Fy binding protein (PvDBP). Limited in vitro growth of Pv has made evaluating human monoclonal antibodies (humAbs) targeting PvDBP and serum from individuals vaccinated with PvDBP difficult. To address this

limitation, the closely related, easily cultured malaria parasite *P. knowlesi* (Pk) with a 27-hour blood stage life cycle serves as a model for Pv due to its similar requirement of Fy for invasion into human erythrocytes. Here we demonstrate the utility of PvDBP specific human monoclonal antibodies (humAbs) to inhibit transgenic Pk (CRISPR-Cas9 modified to express PvDBP; PkPvDBP) invasion of human erythrocytes. We show that the concentrations of humAbs to PvDBP that inhibit Pv invasion of human reticulocytes in vitro using clinical isolates are comparable to that observed for PkPvDBP, and that growth inhibition is greater at 24h, rather than at 6h. Of the 10 humAbs to PvDBP tested, 8 showed 70-100% inhibition of PkPvDBP invasion with IC50 values ranging from 27 to 300ug/mL. Notable was that concentrations of humAbs that blocked binding of recombinant PvDBP to erythrocytes by flow cytometry failed to consistently predict the levels of invasion inhibition observed with PkPvDBP parasites demonstrating the importance of parasite invasion inhibition assays. Lastly, preliminary combinatorial experiments testing two mAbs at once indicate potential synergistic effects of humAbs on growth inhibition. This PkPvDBP transgenic model will allow evaluation of strain variation of PvDBPII and pvdbp gene amplification on humAb efficacy and can identify optimal combinations of humAbs for future adoptive transfer studies in non-human primate models and humans.

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AN ANTHROPOLOGICAL STUDY OF HEALTH SYSTEM, INDIVIDUAL AND SOCIO-CULTURAL FACTORS THAT INFLUENCE PREGNANT WOMEN'S DECISION TO SEEK TESTING AND TREATMENT SERVICES FOR MALARIA CARE IN HEALTH FACILITIES IN EIGHT GHANAIAN DISTRICTS

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Malaria in pregnancy (MiP) is an important public health problem across sub-Saharan Africa. In the last 20 years Ghana has controlled MiP through regular use of longlasting insecticidetreated bednets (LLINs), directly observed administration (DOT) of intermittent preventive treatment with sulfadoxinepyrimethamine (IPTpSP) and prompt testing and treatment of MiP. Yet, Ghana still experiences the debilitating effects of MIP such as still births, low birth weight and maternal anemia. We explored how health system and socio-cultural factors influence pregnant women's decisions to seek testing and treatment services in eight districts. The study design was ethnographic, employing non-participant observation, case studies and in-depth interviews in 8 health facilities and 8 communities from April 2018 to March 2019. Recommended ethical procedures were observed. At the health system level health facility arrangements, policy change resulting in charges for testing for malaria influenced pregnant women's decision to treat malaria in pregnancy. Trust and reliance on alternative treatment such as traditional remedies, visiting prayer camps and poverty influenced pregnant women's decision not to seek care for testing and treatment for malaria. Also, community beliefs that malaria is caused by standing in the sun or being cursed affected decision to seek health care. Incidence of pregnant women suffering from malaria attacks and consequent negative effects were interpretated as curses from enemies. The possible effects of malaria in pregnancy such as miscarriages, low birth weight and anemia were not linked to malaria, thus, there was no urgency to visit health facilities to treat malaria during pregnancy. Testing and treating malaria is influenced by both health system and socio-cultural factors. It is important that intensive health education is carried out in communities in order to encourage pregnant women to utilize such services in health facilities. Additionally, government and health facilities need to enforce free maternal health care to promote utilization of malaria in Mip services in health facilities.

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THE BIOKO ISLAND MALARIA ELIMINATION PROJECT (BIMEP) EXPERIENCE: BUILDING CAPACITY AND TRANSITIONING TECHNICAL LEADERSHIP TO NATIONAL STAFF FROM 2004-2022

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Since 2004, Medical Care Development International (MCDI) has implemented the Bioko Island Malaria Elimination Project (BIMEP) in Equatorial Guinea. The BIMEP is an integrated malaria control project supporting the National Malaria Control Program (NMCP) at the Ministry of Health and Social Welfare (MOHSW) aiming to eliminate malaria from Bioko Island. A core objective of the project is to strengthen the MOHSW and build local capacity to lead the implementation of malaria control activities on Bioko and the rest of the country. Initially, capacity building focused on improving specific technical skills and on the job training for the immediate needs of project implementation. As a result, field implementation staff gained the skills necessary to assume technical management roles. However, the capacity building objectives evolved to ensure national staff had the skills to effectively plan, monitor, evaluate and manage control program efforts. In particular, the BIMEP focused on providing advanced academic training to national staff in international programs for Master's and PhD degrees. This has led to numerous local staff achieving advanced degrees abroad and returning to lead malaria control activities in Equatorial Guinea. Additionally, national staff in charge of vector control activities has been trained in the use of spatial decision support systems for data-driven planning, implementing, monitoring, and adaptive management of field interventions. The BIMEP has created a competency framework for all key technical positions of the project and the NMCP to identify gaps and weaknesses of the staff to guide future professional development. The BIMEP has demonstrated the value of sustained engagement with the NMCP to develop the future leaders of malaria control activities in Equatorial Guinea.

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IMPROVING HEALTH SYSTEM PERFORMANCE THROUGH MUTUALIZATION OF SMC ACTIVITIES WITH CATCH-UP IMMUNIZATION IN LABÉ, GUINEA

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The performance of the health system in Guinea is threatened by the interference of activities. The pooling of activities therefore appears to be a solution. In a context of scarcity of resources, the National Malaria Control Program and the Extended Immunization Program supported by their partners StopPalu+/USAID and GAVI have agreed to pool their activities. This work aims to share the results and innovative measures applied during the 4th round of the SMC campaign to improve immunization coverage in the Labé region in 2021. We conducted a descriptive study between September 1 and 8, 2021 in the Labé region with three phases. A 1st preparatory phase consisting of the organization of meetings of stakeholders, the identification of strategies, needs and the design of tools. The implementation phase included the distribution of SMC drugs, the identification of children and women to be caught up

and the immunization. The last phase was a synthesis of achievements, sharing of results and lessons learned. The preparatory phase identified 3,218 outstanding records of the expanded program of immunization (EPI) and 1,763 outstanding antenatal care (ANC) records of pregnant women for the entire region. During the implementation of the SMC, the overall administrative coverage of the 4th round was 101% for a target of 251,450 children. For the implementation of catch-up immunization, 3,218 EPI cards were identified at the health center level and 4,290 children were found in the community by the SMC distribution agents. Ninety-two percent of the children found in the community were vaccinated and 784 of them were not registered in the health centers. For pregnant women, 1,763 ANC cards were identified at the health centers and 2,058 pregnant women were found in the community by the SMC distribution agents. Among the pregnant women identified, 83% received ANC services. In conclusion, we have demonstrated that the implementation of the mutualization of SMC activities with catch-up immunization has contributed to improving immunization coverage. This example should be replicated in all districts eligible for SMC in Guinea.

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PLASMODIUM VIVAX AMA1 DERIVED HUMAN MONOCLONAL ANTIBODY BLOCKS *P. KNOWLESI* ERYTHROCYTE INVASION

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Apical membrane antigen 1 (AMA1) is a leading blood-stage vaccine candidate or target for therapeutic mAbs. AMA1 is an essential protein involved in the moving junction during the red blood cell invasion, where it forms a tight interaction with another parasite-derived protein that integrates into the host red cell membrane called RON2. To identify *Plasmodium vivax (*Pv) specific human monoclonal antibodies (humAbs) directed against PvAMA1 we isolated PvAMA1 specific IgG+ B cells from a Cambodian with antibodies that block recombinant (r)PvAMA1 binding to rPvRON2L. cDNA was synthesized from single B cells and IgG heavy and light chains variable regions were amplified, cloned and IgG1 expressed in HEK293H cells. Single humAbs were affinity purified, concentrated, and tested for their ability to block *P. falciparum* or transgenic *P. knowlesi*/ PvDBP invasion of erythrocytes *in vitro* since the sequence identity of PvAMA1 to PfAMA1 is 60 % and 85 % to PkAMA1 spanning 562 residues. In preliminary studies we tested six humAbs to PvAMA1 and two control humAbs; a non-relevant epitope (mAb043038) as a negative control and previously described humAb to Duffy binding protein of *P. vivax* (mAb099100) which inhibits the *P. knowlesi* transgenic but not *P. falciparum* invasion. Our preliminary data show that both controls worked as expected with no inhibition with 043038 in both parasites and only inhibition in *P. knowlesi* with 099100 by 46% (P=0.005). From 1 of 6 humAb to PvAMA1 tested, 826827 blocked *P. knowlesi* invasion of erythrocytes at 100 µg/ml by 67 % (P<0.0001); control mAbs were used at 100 µg/ml as well. None of the humAbs inhibited *P. falciparum* invasion of erythrocytes. These preliminary studies suggest the possibility of a species and strain transcending epitopes recognized by human mAbs to PvAMA1.

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DEGREE OF ANEMIA IN PATIENTS WITH *PLASMODIUM VIVAX* IN A NON-AMAZONIAN ENDEMIC AREA, CÓRDOBA-COLOMBIA

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Anemia is one of the most frequent hematological findings in malaria. The objective of this study was to determine the degrees of anemia in patients with Plasmodium vivax in an endemic area of the department of Córdoba. A demonstration of 168 patients with P. vivax monoinfection was carried out, confirmed by diagnostic PCR, IV generation hemogram and parasite count in thick smear were performed. The degree of anemia in each patient was determined according to the WHO classification, mild anemia (Grade 1: 10-13 g/dL), moderate anemia (Grade 2: 9.9-8 g/dL) and severe anemia (Grade 3: 7.9-6g/dL and Grade 4: <6 g/dL). 81.5% (n=138) of the patients presented some degree of anemia. It was found that 75% (n=103) had mild anemia, 24% (n=33 patients) had moderate anemia, and 1% (n=2 patients) had severe anemia. Of the 138 patients, 20% (n=27) were hospitalized. When comparing hemoglobin between hospitalized and non-hospitalized patients, no significant difference was found (p<0.0001). No significant difference was found in the parasite concentration between the mild anemia group (mean: 11487.5p/uL) and the moderate anemia group (mean: 7025.7p/uL). When relating the parasitemia with the hemoglobin concentration in the mild anemia group, a slight indirect association was found in men (r=-0.3281), with a significant difference of (p=0.017), in women no connections were observed. No conclusions were found between parasitemia and hemoglobin in the Moderate Anemia (MA) group neither for men nor for women. In conclusion, parasitemia does not seem to be a predisposing factor for generating anemia in patients with vivax malaria.

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EXPANDED ROLES OF COMMUNITY HEALTH WORKERS BEYOND MALARIA SERVICES IN THE ASIA-PACIFIC: A SYSTEMATIC REVIEW

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In the Asia Pacific, community health workers (CHWs) are a key component of malaria elimination strategies. However, there may be decreasing support for, and uptake of, malaria services as malaria declines. To sustain malaria CHW services, expanding their roles beyond malaria has been proposed. A systematic review was conducted to identify and characterize CHW programmes in the Asia-Pacific region which provide services in addition to those for malaria. The aims were to describe the expanded roles, identify evidence of impact or success of the programmes, and explore strategies to ensure sustainability and factors for effective implementation to inform the design and implementation of CHW programmes for malaria elimination. Searches were conducted in six academic databases, of grey literature, and in bibliographies of retrieved articles. Data were extracted from 24 published articles, 12 programme reports, and 4 programme briefs. Thematic coding and descriptive analysis were adopted to identify and synthesize the data and findings on three main outcomes. 24 programmes were identified in which CHWs perform both malaria and non-malaria roles. There was evidence of impact on malaria incidence in 4 of these, none on malaria mortality and 4 on other diseases. Monitoring and evaluation mechanisms, multi-sectoral stakeholder collaborations, and adequate training and consistent supervision of CHWs were key to effective programme implementation. Integration of programmes into broader health services, ongoing political and funding support, and engagement with local communities were found to contribute to sustaining provision of health services by CHWs. Expanding the roles of CHWs depends largely on programme management and strengthening linkages with the local health system. To maintain CHW services, countries need adequate policies and financing, and sufficiently strong health systems to deliver basic health services, together with adaptation to respond to the current health needs of the community in order to sustain these services.

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KNOWLEDGE, ATTITUDES, AND PRACTICES ON MALARIA IN VENEZUELA: PRELIMINARY DATA

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Venezuela remains the country with the highest morbidity and mortality from malaria in Latin America, representing the main obstacle for malaria elimination in the region. Understanding knowledge, attitudes, and practices (KAPs) on malaria in the main endemic regions of Venezuela could provide tools for the development of new intervention strategies. A national cross-sectional survey was conducted between 2020-2022 to assess KAPs among patients with malaria seen at the three main malaria diagnostic centers in Venezuela. Out of 429 patients surveyed, 364 (84.4%) had *P. vivax*, 39 (9.1%) had *P. falciparum*, and 26 (6.1%) had mixed malaria (*P. vivax*/*P. falciparum*) infections. Patients' mean age was 34 years (SD 14), mostly men (59.9%), with a high school education (39.6%) and previous malaria infection (71.8%). Main occupations were housewife (18.9%) and mining worker (16.8%). Most of the patients knew malaria is transmitted mainly by an infected mosquito bite (90.2%) and they should go to a microscopist or other healthcare worker when they have malaria symptoms (90.4%). Positive attitudes regarding malaria transmission, diagnosis, treatment, and prevention were observed in most patients; however, almost a third consider it normal to get sick with malaria, and worryingly more than 20% said they found it uncomfortable to use the mosquito net. Lack of appropriate practices were identified in most patients. Only 52.2% of respondents use a mosquito net and 49.2% monitor the presence of stagnant water. At the time of symptom onset, patients mainly went to the microscopist (42.7%) and to other healthcare workers (38.5%). Mean days between symptom onset and performing the thick blood drop was 5 (SD 6) days. Finally, 24% of the patients with a previous history of malaria admitted that they had not completed malaria treatment in at least one of their previous episodes. The identification of knowledge gaps, negative attitudes, and inappropriate practices in the context of the geographic, ethnic, and cultural diversity of each endemic region of Venezuela could contribute to the optimization and redirection of malaria control programs in the country.

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EVALUATION OF THE IMPLEMENTATION OF THE SEASONAL MALARIA CHEMOPREVENTION (SMC) THROUGH INDEPENDENT MONITORING IN BURKINA FASO

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In Burkina Faso, malaria in children under 5 years accounted for 40% of severe malaria and 72% of malaria deaths in 2020. Seasonal Malaria Chemoprevention (SMC) has been implemented in Burkina Faso since 2014. SMC consists of three days by month doses of amodiaquine plus sulfadoxine-pyrimethamine to all eligible children (3-59 months) during the season of high malaria transmission. To ensure the quality of the intervention and that good coverage is achieved, two independent monitoring surveys were conducted after the first (C1) and fourth (C4) cycles in 2021. Teachers were recruited to conduct this independent survey and were trained and supervised during the implementation of the survey. Monitoring was conducted in 43 of 70 districts. In the project area (19 districts), 838,000 children received SMC treatment. The number of children assessed in the houses visited was 6,752 at C1 and 6,608 at C4 (10 houses per selected village per cycle). The results show that 98% and 98.2% of the targeted children received treatment at C1 and C4, respectively; 78.8% presented evidence of treatment (cards or empty drug packs) at C1 and 78.3% at C4. Of the 2% of children who did not receive treatment in C4, 65% were not eligible (due to fever, illness, etc.). During C4, only 57% had SMC cards and of those 75% were correctly filled in on Day 2 and Day 3 by the parents. Parents reported that 97.4% of the children took the treatment on Day 2 and Day 3 during C1 and 97.1% during C4. Also, 1.1% of the parents did not give the medication on Day 2 or Day 3 by forgetting at C1 and 2.4% at C4. Parents reported being satisfied with the SMC at C1 (99.7%), and 99.9% at C4. However, challenges exist with outreach communication, availability and proper storage of treatment cards, and referral of cases that need to be seen by a health care worker. Independent monitoring offers insight into achieved SMC coverage and provides indications on how to improve the implementation of a high-quality SMC campaign.

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ANALYSIS OF ANTIPLASMODIAL EFFECTOR MOLECULES ON THE MIDGUT MICROBIOTA OF *ANOPHELES STEPHENSI* MOSQUITOES

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Malaria is a deadly vector-borne disease caused by parasitic protists in the genus *Plasmodium* that are spread through the bite of infected female *Anopheles* mosquitoes. Despite preventative measures such as bednets and indoor insecticide spraying, there were an estimated 250 million cases of malaria and over 600,000 deaths in 2020. This indicates a need for new strategies to combat malaria. One strategy is paratransgenesis, where the native microbiota of mosquitoes is engineered to secrete antiplasmodial molecules, stopping the mosquito from becoming infectous. *Asaia bogorensis* is a Gram-negative acetic acid bacterium and a major component of the mosquito microbiome. Previously, *A. bogorensis* secreting antiplasmodial effectors was shown to successfully reduce the oocyst prevalence of *An. stephensi* mosquitoes. However, there has been no analysis of the effects of antiplasmodial effector production on the overall midgut microbiota of *An. stephensi* mosquitoes. Commonly, a mix of general antimicrobial and *Plasmodium* specific effectors are used to combat *Plasmodium* expression, and these could have different and significant effect of the microbiota. Here we aim to examine the effects of several antiplasmodial effectors on the *An. stephensi* midgut microbiome and associated fitness costs for the mosquito.

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IMPACT OF SEASONAL MALARIA CHEMOPREVENTION ON MALARIA INFECTION IN CHILDREN UNDER FIVE YEARS OLD LIVING IN MALARIA ENDEMIC RURAL AREA OF SABOU BURKINA FASO

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Seasonal Malaria Chemoprevention (SMC) is a control strategy to reduce malaria burden in young children in seasonal malaria transmission countries. SMC consists of administrating a full treatment courses of sulfadoxine–pyrimethamine plus amodiaquine (SP + AQ) to 3-59 months old children at monthly intervals during the malaria high transmission season (From July to October). This study aimed to address key knowledge gaps in our understanding on how SMC affect malaria infection and host antibodies responses to malaria specific antigens.This study was conducted in Sabou Health District (central western region of Burkina Faso) where malaria is hyperendemic and seasonal. A total of 182 children under 5 years were enrolled in July before the first administration of SMC drug (SP+AQ) and then visited during four cross sectional surveys. Sera, blood spots and smears were obtained from each child at enrollment and during each visit to establish the relationship between parasite densities and prevalence before and after of SMC. We noticed a significant increasing prevalence of *Plasmodium falciparum* infection across SMC from the beginning (16.11% (IC95%: 15.29-16.92)) to the peak of high transmission season (30.46% (IC95%: 29.30-31.61)) and then decrease at low transmission season (19.30% (IC 95%: 18.38 -20.22) p=0.002. Likewise, an increase of parasite density was noticed across SMC from the beginning (8324.622/µl (IC95%: 1287.173 – 17936.42/µl) to the peak of transmission season (9608.747/µl; (CI95%: 1402.546 – 17814.95). However, the value of parasite density decreases from high to low transmission (3299.38/µL (IC 95%:1321.812 – 5276.948 /µl)) p=0.02. Despite, the introduction of SMC, the profile of malaria transmission is maintained. However, we noted a reduction in parasite prevalence and density compared to data published before the introduction of SMC in Burkina Faso.

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BARRIERS AND FACILITATORS TO THE ACCEPTABILITY OF INTERMITTENT PREVENTIVE TREATMENT IN PREGNANCY WITH SULFADOXINE-PYRIMETHAMINE (IPTP-SP)

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Pregnant women are particularly vulnerable to malaria. Since 2004, the World Health Organization recommends the administration of Intermittent Preventive Treatment in pregnancy (IPTp) with Sulfadoxine-Pyrimethamine (SP) as one of the methods for preventing malaria in pregnancy but, in Mozambique, its coverage remains low. The literature shows that community health workers (CHW) can contribute to improve the coverage of malaria prevention strategies. The TIPTOP project has aimed at evaluating the distribution of ITPp through CHW (C-IPTp). A longitudinal qualitative study was carried out to assess the acceptability of C-IPTp in the districts of Nhamatanda, Meconta and Murrupula (Mozambique). We conducted this study in 2021. 36 in-depth interviews, 9 focus group discussions, 42 direct observations, and 35 informal conversations were performed Pregnant women, health workers, traditional healers, and community leaders participated in the study. Data were coded in an Excel matrix for content analysis. Factors facilitating pregnant women's acceptability of the intervention were the familiarity with the benefits of SP; their willingness to preserve the health of the fetuses; the fact that women can avoid consuming SP on an empty stomach, reducing the risk of experiencing unpleasant after effects; and trust in the members of the community involved in the intervention, especially traditional birth attendants recruited as CHW. Barriers to the acceptability of the intervention consisted of: unpleasant experiences with the drug; the negative influence of women's peers and relatives; perceptions that SP causes large fetuses and leads to complicated deliveries; and preference to take SP at the health center where they can complete their antenatal care visit. Despite the reported barriers, C-IPTp tends to be accepted. However, to maximize acceptability, greater involvement of community leaders, traditional birth attendants, and female community health workers is needed, as well as strengthening strengthening the promotion of IPTp-SP at the community level. Keywords: Acceptability, barrier, malaria, drug, and community health workers

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THE IMPACT OF DELAYED ACCESS TO TREATMENT ON MALARIA TRANSMISSION FOR *PLASMODIUM VIVAX* AND *P. FALCIPARUM* MALARIA: AN EVALUATION USING MATHEMATICAL MODELS

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Adequate case management is a crucial tool to reduce malaria burden. One of its components, the time it takes infected individuals to access treatment after the onset of symptoms, impacts malaria severity. However, its effect on malaria transmission is still under-investigated**.** We used two deterministic compartmental models that include case management, one for *P. vivax* and one for *P. falciparum* malaria, to explore how delaying the access to antimalarial treatment influences onward transmission under varying scenarios. A scenario consists in a unique endemic situation with an intervention that targets delays (i.e. time until start of treatment) and effective treatment coverage of blood stage parasite and liver stage parasite (for *P. vivax* parasite only). Various baseline case management levels were assumed. Malaria transmission was evaluated in each scenario by computing the reproductive number under control (Rc), i.e. the reproduction number in presence of effective case management. The effect of delays in accessing treatment on transmission is modelled by extending the infectious period of treated individuals. This delay must be large enough to overcome the pre-infectious period. For both models, we performed an uncertainty analysis and a sensitivity analysis, computing Sobol indices, in order to explore the variability in Rc values according to varying scenarios. For *P. vivax*, Rc values ranged between 0.1 and 5, with the largest variability in Rc obtained when baseline delays are small and baseline effective treatment coverage is high. In this model, at least 85% of the total variance in Rc is due to effective treatment coverage and 4% to delays with minor changes caused by baseline values. For *P. falciparum*, Rc values ranged between 0.4 and 2.4 and nearly 100% of the total variance observed in Rc is due to effective treatment coverage regardless of baseline values. Regardless of the *Plasmodium* species and baseline epidemiological assumptions, the effective treatment coverage is the most important contributor to outcome variance. For *P. vivax*, treatment delays are an additional factor towards malaria transmission variability.

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ACCEPTABILITY OF THE SEASONAL MALARIA CHEMOPREVENTION (SMC) AS A STRATEGY TO PREVENT MALARIA IN MOZAMBIQUE: A QUALITATIVE STUDY WITH DIFFERENT STAKEHOLDERS AND BENEFICIARIES

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Mozambique is among the six countries accounting for more than half of all malaria cases and deaths worldwide (5% of global cases and deaths). The World Health Organization recommends seasonal malaria chemoprevention (SMC) as a highly effective community-based intervention to prevent malaria infection. SMC involves monthly administration of the antimalarial combination of sulfadoxine-pyrimethamine plus amodiaquine to at-risk populations during the rainy season. In collaboration with the National Malaria Control Programme, Malaria Consortium conducted an implementation study to investigate

the feasibility and impact of SMC in Nampula Province, Mozambique, which involved delivery of four cycles of SMC to around 70,000 children 3-59 months between November 2020 and February 2021. As part of the larger implementation study, a qualitative study aimed to explore views and perceptions about acceptability of SMC among beneficiaries and stakeholders.Two weeks after the end of the annual SMC round, 20 in-depth interviews and 20 focus group discussions were conducted with key stakeholders and caregivers of children receiving SPAQ for SMC. Interviews were conducted in Portuguese and Emamkwa (local language) and audio recorded. Thematic analysis was performed, and themes were identified and categorized following prevalent topics. Participants perceived that the introduction of SMC in the area helped to reduce cases of malaria among children under five. Many caregivers felt that after receiving SMC, their children became healthier, and they expressed the belief that the drug was appropriate for preventing malaria. Stakeholders mentioned that coordination between local authorities and implementing partners, as well as engagement of community and religious leaders were crucial for the success of SMC. Some caregivers expressed fear and mistrust of the intervention and the absence of male partners' permission to allow children to receive SMC was given as a potential challenge. An additionally process evaluation will be done on the phase 2 to understand the process and acceptability outcomes of the SMC intervention

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COMMUNITY HEALTH WORKERS DELIVERED QUALITY DOOR-TO-DOOR SEASONAL MALARIA CHEMOPREVENTION TREATMENTS TO CHILDREN UNDER FIVE YEARS: RESULTS FROM A HYBRID TYPE 1 EFFECTIVENESS-IMPLEMENTATION PILOT IN NORTH-EASTERN UGANDA

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Few studies have documented quality of seasonal malaria chemoprevention (SMC). We assessed quality of SMC delivered door-to-door by village health teams (VHTs), and identified areas for improvement in Moroto and Kotido districts, north-eastern Uganda. A parallel mixed methods study was conducted in October 2021. Two standardized checklists containing 29 and 17 indicators for health workers (HWs) and VHTs respectively were used to observe and assess performance in each of 5 SMC cycles. Review of filled checklists, supervision reports and SMC distribution meetings notes were conducted. A structured end of cycle assessment tool administered to ministry of health, district and facility level supervisors and implementers of SMC, selected through stratified purposive sampling was used to assess overall quality. Ratings of VHTs and HWs performance were computed for each cycle as proportions. Performance quality indicators were categorised into those on track and off-track. Textual data and open comments were synthesised and coded to identify what worked well and what needed improvement. A total of 13 (76.5%) indicators of VHT performance had an overall score above the 85% cut-score. Four indicators had scores below the cut-score. A total of 25 (86%) indicators of HWs performance had scores equal to 98% cut-score or above. Four indicators had scores below 98% cut-score. Overall 62 (90%) of end of round quality indicators were met. These had scores rating above the 2.5 cut-score. A total of seven indicators had mean score ratings of 2.5 or below. Enumeration of children, SMC commodities storage, determination of age eligibility, and translation of SMC training tools were identified as areas for improvement. Use of VHTs as community distributors and active engagement of all stakeholders, including beneficiaries and local leaders were outstanding factors for high quality implementation. SMC delivery was of high and acceptable quality. Active engagement of stakeholders were critical to achieving quality SMC delivery and performance.

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OPTIMIZING THE IMPACT OF SEASONAL MALARIA CHEMOPREVENTION IN SOUTHERN SENEGAL: CHOOSING THE OPTIMAL NUMBER AND TIMING OF SMC CYCLES IN EACH REGION

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Updated WHO guidelines recognize that more than 4 SMC cycles per year may be required in some areas. We investigated the optimal number of cycles in southern Senegal, where SMC was introduced for children under 10 in 2014 with 4 SMC cycles per year in Kedougou and 3 in the regions of Tambacounda, Kolda and Sedhiou. In 2018, no SMC was delivered due to a health worker strike, and SMC was discontinued in Sedhiou from 2020. Suspension of SMC allowed impact to be assessed by comparing malaria incidence in years with and without SMC. Individual outpatient data for all patients tested or treated for malaria in the period from 1 Jan 2017 to 31 Dec 2020 were collected from a sample of 32 health posts. SMC impact was estimated by fitting Poisson regression models to the daily number of confirmed cases. Optimal timing was defined as 28-day periods during which the fraction of annual burden was maximized. Optimal allocation of SMC treatment cycles to regions was determined by ranking optimal 28-day periods in each region according to estimates of the malaria incidence in each period. SMC was associated with a reduction in the incidence of 61.1% (95%CI 52.5%,68.2%), within 21 days of treatment, and 54.0% (95%CI 45.6%,61.1%) during the period from the first day of the cycle until 28 days after the last day. Estimates of the number of outpatient cases averted per 1000 SMC treatments in each intervention year ranged from 41 to 70 per 1000 in Kedougou, 11 to 27 per 1000 in Kolda, 6 to 7 per 1000 in Tambacounda, and 1 to 2 per 1000 in Sedhiou. The 5-9 age group accounting for 58% of the cases averted. The optimal strategy for a given number of treatments is to deliver SMC in the months and regions with the greatest malaria burden. Plotting the cumulative incidence if cycles are added in optimal order, showed that 5 cycles should be implemented in Kedougou before considering other regions. Kolda and Tambacounda follow in order of priority, with a 5th cycle in Kolda and a 4th in Tambacounda being prioritized before any SMC in Sedhiou. The current implementation of SMC in Senegal could be substantially improved by optimising the timing and number of cycles.

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COMBINED IMPACT OF PERENNIAL MALARIA CHEMOPREVENTION AND RTS,S TO REDUCE MALARIA IN YOUNG CHILDREN: A MODELING ANALYSIS

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Malaria chemoprevention in perennial transmission settings (PMC), formerly known as intermittent preventive treatment in infants (IPTi), is receiving renewed attention to decrease malaria burden in young children. At the same time, the malaria vaccine RTS,S was also recommended by the WHO for pediatric malaria prevention. However, the combined impact of PMC and RTS,S on incidence remains unclear and concerns exist about delayed malaria. We used EMOD, a mathematical model of malaria transmission, to investigate the impact of PMC and RTS,S in southern Nigeria and across a range of transmission intensities. We simulated PMC (varying 3, 5, 6, or 7 doses before 1 or 2 years of age) and RTS,S (4 doses) alone and in combination. We assessed the number of clinical and severe cases averted in children under the age of 1, 2, 5, or 10 years, compared to no PMC and no RTS,S. In children under 1 year of age, PMC with 3 doses averted more clinical and severe cases than did RTS,S, while in children under 2, cases averted were substantially higher for RTS,S. PMC with 5 doses in the first year of life averted a similar number of cases in children under 2 years as did RTS,S. The combination of PMC and RTS,S averted more cases than either intervention alone until an age of around 2 years, after which averted cases were mainly due to RTS,S. Hence, when combined with RTS,S, additional doses of PMC during the second year provided only a marginal impact. Despite a rebound in children older than 5 years, the cumulative cases averted in children under the age of 10 years were higher with either single intervention than without. Model results showed that cases averted depended on schedule, transmission intensity, and age group monitored. Thus, understanding which age groups are at greatest risk for malaria morbidity is crucial for determining whether an extension of PMC or a potential combination with RTS,S would be most appropriate in a given setting. Our modeling results provide expected impact predictions that address pressing questions in the planning of deployment strategies and priorities of PMC and RTS,S.

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FACILITATORS AND BARRIERS TO UPTAKE OF SEASONAL MALARIA CHEMOPREVENTION IN NIGERIA

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Nigeria introduced SMC in 2014, scaling up to 18 states by 2021. To understand community attitudes to SMC, barriers to uptake and facilitating factors, the National Malaria Elimination Programme conducted a qualitative research project in five states: Kano, Kwara, Nasarawa, Yobe and Kebbi, soon after the 2021 SMC campaign. In each state, Local Government Areas (LGAs) were ranked based on administrative coverage of SMC in 2021, and one LGA with high coverage and one with low coverage selected. Focus group discussions (FGDs) with caregivers, in-depth interviews (IDIs) with community leaders, community drug distributors and state-level and LGA malaria focal persons, and key-informant interviews (KIIS) with representatives of the international partners working on malaria in Nigeria, were conducted in each study area. Interviews were recorded, transcribed, and then translated into English from the local language of interview, and analysed using NVivo software. A total of 190 FGDs, KIIs and IDIs were carried out. In all study areas malaria was seen as a major health concern and SMC was widely accepted as a key preventive measure. Community drug distributors (CDDs) were trusted and their work appreciated by most caregivers. Most caregivers preferred SMC delivered door-to-door than visiting distribution points, in addition to allowing them to continue daily tasks, there was more time for the CDD to explain how to administer the treatments and advise about adverse reactions. Barriers identified included perceived side effects, lack of understanding of the purpose of SMC, unfriendly attitudes of some CDDs, and a perception by some caregivers that the drugs were ineffective. Key informants and caregivers reported SMC distributions limited by drug shortages, supplies running out before all children in the community had been treated. Overall, there was widespread acceptance of SMC, but strategies need to be developed to overcome specific barriers to improve delivery and uptake.

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EVALUATION OF ADAPTATION AND IMPLEMENTATION FIDELITY OF THE SEASONAL MALARIA CHEMOPREVENTION INTERVENTION IN THE CONTEXT OF COVID 19 IN KARAMOJA REGION WITH PREDOMINANTLY NOMADIC PASTORALIST POPULATION

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In 2021, Ministry of Health (MOH), Uganda collaborated with Malaria Consortium to conduct a 5 months' phase 1 implementation-research to assess seasonal malaria chemoprevention (SMC) with sulphadoxine-pyrimethamine (SP) and amodiaquine (SPAQ) as a supplementary malaria intervention in two districts of Karamoja region, where malaria transmission is highly seasonal. The implementation was at the peak of COVID19 pandemic and lockdown. This study component evaluated the adaptation of Sahel's SMC implementation model to the Uganda context as well as its implementation fidelity in a predominantly nomadic pastoralist community. A case series study using observational and cross-sectional descriptive design was conducted between May-October 2021 in the 2 districts. Data was collected using qualitative and quantitative methods at the end of each of the 5 SMC cycles. Review of documents on SMC from the Sahel and WHO guidelines, individual interview with key informants from study districts and MOH, Focus group discussions with caregivers were conducted. The medical research council process evaluation framework for complex Interventions was adopted to evaluate the adaptation process of SMC into Ugandan context while Carroll's conceptual framework was used to evaluate implementation fidelity. All (100%) SMC implementation component of the Sahel's region were successfully adapted to Uganda context. SMC was successfully delivered according to schedule and coverage was consistently high across the five cycles comparable to the rates in Sahel. In total 409,495 SMC medicines were administered over the 5 months' period to 71,425/73,464 (97%) in cycle 1, 83,700/73,464 (114%) in cycle 2, 84,030/73,464 (114%) in cycle 3, 82,307/73,464 (112%) in cycle 4, and 88,033/73,464 (120%) in cycle 5. Payment of health workers increased from 0% (cycle 1) to 100% (cycle 5). SMC implementation model of Sahel Region was successfully adapted to Uganda context during COVID19 pandemic and proved that cashless payment is feasible with recommendation for rollout to all districts in the region.

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INSECTICIDE-TREATED NETS COVERAGE, USE AND MALARIA INFECTION IN CENTRAL-SOUTH BURKINA FASO: A CROSS-SECTIONAL COMPOUND SURVEY

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Despite the large distribution of the insecticide-treated nets (ITNs) through national malaria control program, the appropriate coverage and usage by the population remains questionable and can impact malaria morbidity. Adults are known to contribute significantly to the infectious reservoir of malaria. This study examined ITNs utilization and related factors as well as the effect on malaria parasite prevalence in rural populations living in Burkina Faso. Two cross-sectional surveys were conducted at the end of malaria transmission season between September and November 2019 in Sapone health district, central-south Burkina Faso, a few months following the 2019 mass campaign. Data were collected on individual, compound and community characteristics, and malaria parasitemia was determined on capillary blood by qPCR. Logistic regression was used to assess determinants of ITNs usage, while multivariable, mixed effect analysis assessed the impact of ITN usage on malaria parasite prevalence. All compounds owned at least an ITN from which almost three-fourth (73.3%) had at least one ITN for every two people. 88.2% participants reported using an ITN every night throughout the year, and 65.6% took down their ITN at any time during the year whatever the reason. Participants who took down their ITN were less likely to use an ITN frequently (aOR=0.32 95%CI 0.12, 0.82). Washing, moving, being too hot, and no mosquitoes were reasons for taking down nets. Parasite prevalence was 87.7%. There was no statistically significant association between ITN usage and malaria parasite prevalence (aOR=1.90, 95%CI 0.49, 7.36). ITN coverage and usage were high in our study population, but there was no significant effect of ITN usage on malaria parasite prevalence among adults. Behavior change communication and additional targeted control strategies are needed to impact the reservoir of transmission.

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MICROBIOTA COMPOSITION IN *ANOPHELES* MOSQUITOES AFTER AMOXICILLIN TREATMENT VIA THE BLOOD MEAL

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The *Anopheles* mosquito's microbiota influences malaria transmission. Antibiotics ingested during a blood meal impact the mosquito microbiome and malaria transmission, with substantial differences between drugs. In this study, we assessed if amoxicillin affects the mosquito microbiota. We collected *Anopheles* larvae in Burkina Faso, kept them in semi-field conditions and offered a blood meal to adult females. We tested the impact of blood supplementation with two alternative amoxicillin preparations on microbiota composition, determined by high-throughput sequencing in individual gut samples. Our analysis detected four main genera, *Elizabethkingia*, *Wigglesworthia*, *Asaia* and *Serratia*. The antibiotic treatment significantly affected overall microbiota composition, with a specific decrease in the relative abundance of *Elizabethkingia* and *Asaia* during blood digestion. Besides its interest on the influence of amoxicillin on the mosquito microbiota, our study proposes a thorough approach to report negative-control data of high-throughput sequencing studies on samples with a reduced microbial load. *Keywords: Mosquito, Microbiota, Malaria*

1576

A QUASI-EXPERIMENTAL EVALUATION OF A LARGE HEALTH SYSTEMS STRENGTHENING PROJECT ON INTERMITTENT PREVENTIVE TREATMENT UPTAKE AT ANTENATAL CARE VISITS AMONG PREGNANT WOMEN IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Malaria in pregnancy cause maternal and neonatal poor outcomes. The Democratic Republic of the Congo (DRC) coverage of receiving at least two doses of intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP) improved from 5% to 21%, to drop to 14% between 2007 till 2014. Over five years, the Access to Primary Health Care (ASSP) project worked to improve maternal, and child health-centered outcomes through health systems strengthening interventions in the DRC. This study investigates ASSP project impact on increasing IPTp-SP uptake of one or more (IPTp1+), two or more (IPTp2+), and three or more (IPTp3+) SP doses among pregnant women at antenatal care (ANC) visits by comparing ASSP to non-ASSP assisted health zones in 2014 and 2017 across four provinces. A Quasi-experimental community-level panel study design with intervention and matched control health areas was conducted. Villages were the unit of randomization, with one village selected for each health area, and women were the unit of analysis. Cross-sectional household survey data were collected in 2014 and 2017. Difference-in-differences (DID) approach was used to measure the project's impact on IPTp-SP uptake of (IPTp1+, 2+, and 3+). 1,004 women reported receiving SP at an ANC. ASSP areas' IPTp 2+ uptake was the only one significantly increased from 29.9% to 48.2% at the end-line compared to baseline [absolute change: -18.22; P-value: > 0.0001]. No significant impact was found for the ASSP interventions on IPTp-SP uptake of any specified doses at ANC visits. Plotted predictive probability of all specified doses increased over time, with IPTp2+ showing the steepest slope increase. Overall, tight 95% confidence intervals observed around the ASSP areas estimates suggesting its precision and the plausible attribution of observed changes to the project. ASSP project impact evaluation research is the first to rigorously evaluate similar projects within the DRC context. Findings of this study could inform the development of future strategies enhancing ANC access, IPTp-SP coverage, and uptake within the DRC and low-income countries with comparable contexts.

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EFFECTIVENESS, SAFETY AND ADHERENCE OF DOXYCYCLINE IN PROPHYLAXIS OF MALARIA AMONG TRAVELERS GOING TO MALARIA-ENDEMIC AREAS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Doxycycline is one of the recommended malaria chemoprophylaxis for travelers going to the malaria-endemic areas. This study aimed to compare the effectiveness, safety, and adherence of doxycycline in malaria

prevention to other proposed prophylactic drugs among people who traveled from the non-endemic areas to the malaria-endemic areas. A systematic search using PubMed, Embase, Web of Science, and CENTRAL was done. Selection criteria included experimental and observational studies relevant to malaria and doxycycline prophylaxis among travelers in the English language up to February 19, 2022. Meta-analyses were conducted using a random-effects model to evaluate the summary outcomes of effectiveness, adverse events, and adherence. Of 3,766 potential studies, 21 were included in the meta-analysis (22,974 travelers). Nine studies (2,349 travelers) reported effectiveness data, while 11 studies (15,842 travelers) and 12 studies (17,969 travelers) had adverse events and adherence data, respectively. The effectiveness of doxycycline in malaria prophylaxis was significantly lower than other chemoprophylaxis (RR = 1.78, 95% CI 1.09-2.90). The number of adverse events among travelers who took doxycycline was also significantly higher than those taking other chemoprophylaxis (RR = 1.19, 95%CI 1.02-1.38), whereas there was no significant difference in adherence (RR= 0.93, 95%CI 0.86-1.01). Doxycycline has lower effectiveness and more adverse events with similar adherence in prophylaxis against malaria among travelers from nonendemic areas going to the endemic areas compared to other chemoprophylaxis.

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ADDITION OF AZITHROMYCIN TO SEASONAL MALARIA CHEMOPREVENTION (SMC+AZ) DOES NOT SIGNIFICANTLY AFFECT THE RELATIONSHIP BETWEEN GASTROENTERITIS AND UNDERNUTRITION

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Seasonal malaria chemoprevention (SMC) aims to reduce the burden of malaria in under five children during the period at high risk of malaria in the Sahel. During the rainy season severe bacterial infections such as gastroenteritis also contribute at worsening the life expectancy of under-five children. The addition of an antibiotic with large spectrum as azithromycin to SMC drugs showed positive effect on reducing the incidence of gastroenteritis in children during the malaria transmission season. But how this effect impacts on the prevalence of undernutrition at the end of malaria transmission season in children who received SMC drugs combined or not with azithromycin, is not well known? We carried out 3 consecutive cross-sectional studies in Burkina Faso and Mali a month after the end of SMC delivery with or without azithromycin in 2014, 2015 and 2016, respectively as part of the SMC+ Azithromycin project. At each survey, mothers of around 2000 randomly selected children were interviewed, then children were examined with anthropometric measurements performed. Data were pooled and malnutrition status determined as stunting, underweight and wasting. Bivariate analysis and multivariate logistic regression were used to estimate the relationship between episodes of gastroenteritis and types of undernutrition. The prevalence of stunting in Burkina Faso was 27.02% versus 30.94% in Mali, p<0.001, that of underweight was 21.32% versus 23.12%, respectively (p=0.02). The prevalence of wasting was similar in both countries with 15.01% in Burkina Faso and 15.90% in Mali. In Burkina Faso, the proportion of children with one or more episodes of gastroenteritis was lower in the azithromycin group, p=0.001. In Mali, the same proportion was similar between study arms (p=0.08). At the end of malaria transmission season, children with one or more episodes of gastroenteritis were 30% more at risk of being stunted in Mali and 47% more at risk of being wasted in Burkina Faso. No significant relationship was found between episode of gastroenteritis and underweight at the end of malaria transmission season in both countries.

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ACCEPTABILITY AND UPTAKE OF RTS,S/AS01 MALARIA VACCINE 18 MONTHS AFTER PILOT INTRODUCTION IN WESTERN KENYA

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The World Health Organization recommended pilot implementation of the RTS,S/AS01 (RTS,S) malaria vaccine to evaluate the safety, impact, and feasibility of integrating the 4-dose schedule (at ages 6, 7, 9, and 24 months in Kenya) in the Expanded Program on Immunization (EPI). A population-representative household survey was conducted in 46 sub-counties participating in the pilot in western Kenya in May-July 2021, 18 months after the vaccine launch, to assess the uptake of the first 3 doses of RTS,S in 3,074 children aged 12-23 months. Home-based vaccination records (HBR) were present for 88% of children; caregiver recall was obtained for the remaining 12%. By HBR or recall, among 1,438 children residing in implementing areas coverage was 78.6% (95%CI 73.7-82.8), 71.4% (95%CI 66.2-76.0), and 62.3% (95%CI 57.1-67.3) for RTS,S doses 1, 2 and 3, respectively; resulting in 9.2% dropout rate from dose 1 to dose 2; and 20.7% from dose 1 to dose 3. Median age at dose 1, 2, and 3 was 6 months (mean 8.7; SD 5.0), 8 months (10.2; 4.9), and 10 months (12.2; 4.4), respectively. No differences in RTS,S uptake were noted by sex, caregiver's age or parity, residence (urban vs. rural), or malaria prevalence level. Children of caregivers with secondary or higher education were 1.3 times (95%CI 1.1-1.7) more likely to return for each subsequent dose than those with primary education only. Uptake was lower among children not sleeping under a bednet the night before, compared to those who did (dose 1: 69.1% vs. 79.4%; dose 2: 63.1% vs 72.0%; dose 3: 51.4% vs. 63.2%; p<0.05); and in areas with indoor residual spraying (IRS), than areas without IRS (dose 1: 68.4% vs. 82.2%; dose 2: 60.3% vs. 75.3%; dose 3: 48.2% vs. 67.4%; p<0.05). Caregivers thought the vaccine was beneficial (96.4%), safe (92.6%), and provided some protection against malaria (93.9%). Beliefs that RTS,S prevents malaria (77.5%), feeling positive about RTS,S (61.6%), and the ability to take children for vaccination (39.9%) were main drivers of caregiver acceptability. With some dropout at the 2nd and 3rd dose, our study found high acceptability and uptake of RTS,S vaccine in Kenya, 18 months after its integration into EPI.

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IMMUNOGENICITY OF THE R21/MATRIX-M VACCINE IN MALARIA-NAÏVE AND ENDEMIC POPULATIONS

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Malaria is a leading cause of childhood mortality; an effective vaccine is needed. R21 is a virus-like particle based vaccine displaying the NANP and C Terminus (CT) region of the circumsporozoite protein (CSP) of *Plasmodium falciparum* (*Pf*) and fused to the Hepatitis B surface antigen

(HBsAg). Immunogenicity of R21 in combination with saponin-based Matrix-M™ (R21/MM) adjuvant is investigated. A Phase I/IIa trial in malaria-naïve (UK) adults compared immunogenicity of the standard dose regimen (10,10,10µg) with a delayed third dose (at 6 months). A delayed fractional dose regimen with a lower final dose given at 6 months (10,10,2µg) and a higher delayed fractional dose regimen (50,50,10µg) were also investigated. A significant 2-fold increase was observed in anti-IgG specific antibodies to the NANP repeat region of CSP in the delayed 3rd dose group. Irrespective of dose, volunteers with an antibody response >1100 ELISA units were significantly more likely to be protected when challenged with *Pf*, suggesting a potential correlate of protection for R21/MM in malaria-naïve adults. A randomized phase IIb efficacy trial in 450 infants in Burkina Faso with R21 using low dose R21 (5ug) with either 25µg or 50µg of MM adjuvant is ongoing. Infants receiving 50µg MM had 2-fold higher antibody titre compared with infants receiving 25µg MM 1 month post third vaccination. Antibody titres decline 12 months after vaccination, however with the addition of a booster dose 1 year later, antibody levels return to levels seen at the previous peak. Both UK adult and Burkinabe infants antibody titres to NANP and CT display similar characteristics. However avidity towards the CT region remains significantly higher across all groups compared with NANP. Nevertheless avidity to CT, as with NANP avidity, does not correlate with protection, suggesting further immune correlates are to be identified. Data presented supports vaccine dose-sparing, with implications for access and the economic impact on vaccine delivery. Additional assessment including antibody isotype and subclass, as well as cellular responses to other vaccine components such as HBsAg, will be presented.

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FIRST-IN-HUMAN EVALUATION OF A PFS48/45-BASED *PLASMODIUM FALCIPARUM* TRANSMISSION-BLOCKING VACCINE

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The stalling global progress in malaria control highlights the need for novel tools for malaria elimination, including transmission-blocking vaccines (TBV). TBVs target functionally important proteins expressed during parasite fertilisation or development in the mosquito midgut, thereby preventing onward transmission. The Pfs48/45 protein is a leading *Plasmodium falciparum* TBV candidate, but its complex structure has long hampered recombinant expression of correctly folded protein. In 2016, the R0.6C fusion protein, consisting of the 6-cysteine C-terminal domain of Pfs48/45 (6C) coupled to the N-terminal region of *P. falciparum* Glutamate Rich Protein (R0), was successfully produced in *Lactococcus lactis*. Preclinical studies demonstrated that R0.6C adsorbed to Alhydrogel was able to induce functional antibody responses in rodents, which was further improved by addition of Matrix-M™ as a second adjuvant. Here, we evaluate the safety and transmission reducing efficacy of R0.6C adsorbed to Alhydrogel, with and without Matrix-M™ adjuvant in a phase I, open label, first-in-human clinical trial. Thirty-two healthy malaria-naïve adults were allocated to receive four intramuscular vaccinations on days 0, 28, 56 and 168 with either 30 µg or 100 µg of R0.6C adjuvanted with Alhydrogel alone, or combined with 15 or 50 µg Matrix-M™, respective to the R0.6C dose. Adverse events are recorded from baseline until 84 days after the fourth vaccination. Anti-6C and anti-R0.6C antibody quantities were measured by enzyme-linked immunosorbent assay, and transmission reducing activity in participants' serum was assessed by standard membrane feeding assays using laboratory-reared *Anopheles stephensi* mosquitoes and cultured *P. falciparum* gametocytes. At the time of abstract submission, all participants have just received their final (fourth) R0.6C vaccination. Administration of the first three vaccinations was safe and well tolerated, with no serious or grade 3 adverse events. Final follow-up is scheduled for June 2022. We anticipate presentation of complete safety, antibody kinetics and transmission reducing activity data at ASTMH 2022.

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PLASMODIUM SPECIES COMPOSITION IN INDIVIDUALS ENROLLED FOR RTS, S/AS01E AT BASELINE AND DURING THE SUBSEQUENT FOLLOW-UP PERIOD IN MALARIA ENDEMIC REGIONS OF WESTERN KENYA

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RTS,S is a recombinant protein-based malaria vaccine that elicit the proliferation of ABs against the *Pf* circumsporozoites, therefore, blocking the establishment of the infection in the liver . In 2014, a phase 3 trial established that RTS,S had high efficacy in infants the basis on which the WHO recommended the vaccine for pilot implementation in selected regions of Africa. However, Information on the potential of the vaccine to protect against the acquisition of non-*Pf* species *ae Pm*, *PoC* and *PoW* is scanty despite the rising frequency of non-*Pf* species infections accounting for 25% of imported malaria . 272 samples were collected from adults aged between 18-45yrs the year 2020-2021 in a study assessing vaccine efficacy in *Pf* infections in adults with sub-clinical PCR positive parasitemia and treated to clear the parasites before RTS, S, administration to determine the rate of re-infection of malaria species among patients who have been vaccinated. Concurrently, 153 samples were obtained from symptomatic individuals visiting KCH within the same catchment of the vaccine trial. Species composition of the infections were established using rtPCR at enrolment as well as upon subsequent infection detection. *Pm* was the most prevalent species at enrolment 30.70% of the asymptomatic individuals and at subsequent visits, five 38.89% and eleven 19.23% followed by *Pf*, *PoC,* and *PoW* Single species infections were present at frequencies of *Pm* 18.86%, *Pf* 7.4%, *PoC* 3.51% and *PoW* 4.8%. On the other hand, infections containing *Pf* 76.19% were most frequent among the symptomatic individuals enrolled from the same catchment followed by *Pm* 27.38%, *PoW* 17.86%, and *PoC* 10.0%. Single species infections were present at frequencies of *Pm* 0%, *Pf* 49.4%, *PoC* 0% and *PoW* 0%. Preliminary results show that the frequency of non-*Pf* single species or multiple species infections was significantly higher in asymptomatic otherwise healthy individuals at enrolment than the symptomatic. This trend was sustained in the asymptomatic group across the subsequent follow-up period. Analysis of the response of species composition to the vaccine intervention is pending completion of the study.

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CHARACTERIZATION OF THE SPOROZOITE-SURFACE PHOSPHOLIPID SCRAMBLASE AS A LIGAND FOR *PLASMODIUM* SPOROZOITE LIVER HEPATOCYTE INFECTION

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Malaria mammalian infection begins with the release into the skin of ~50 *Plasmodium* sporozoites by an infected mosquito. Some of these sporozoites enter the blood circulation and a few of them invade the liver hepatocytes to produce over twenty thousand merozoites and these infect and propagate in red blood cells causing malaria symptoms. Sporozoite hepatocyte infection is an obligatory step for malaria infection and serves as a prime target for vaccine development as this constitutes a dramatic bottleneck in the proliferation of the parasite in its mammalian host. Using screening of a phage peptide display library, we recently determined that sporozoite-surface phospholipid scramblase (PLS) interacts with hepatocyte carbamoyl-phosphate synthase 1 (CPS1) to infect hepatocytes, making PLS a new vaccine antigen candidate. Here we report that the C-terminal end of the PLS protein is important for hepatocyte infection and are exploring the use of this epitope as a malaria vaccine antigen.

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IMMUNOLOGICAL CORRELATES OF PROTECTION FOR R21/ MATRIXMTM , A MALARIA VACCINE WITH HIGH-LEVEL EFFICACY

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Malaria remains a major cause of mortality in young children in sub-Saharan Africa and global progress in malaria control has stalled with cases and deaths increasing in recent years. A Phase 2b clinical trial of the candidate malaria vaccine R21/Matrix-M™ demonstrated a favourable safety profile and high-level efficacy of 77% at 1 year after vaccination and 78% in the second year of follow up following a booster dose given at 12 months. We analysed total IgG responses to the NANP repeat region of the CSP antigen to determine association with VE and identify putative immune correlates. Antibody levels peaked one month after the primary series, and booster doses given 1 and 2 years later restored antibody titres to the level observed after the primary vaccination series. Higher antibody levels were detected when higher doses of Matrix-M™ adjuvant were used (50µg compared with 25µg) and this was associated with sustained VE of 80% at 12 months after the first boost. VE correlated strongly with NANP antibody levels and time to first episode of malaria over the first 12 months of follow up (HR 0.38, 95% CI 0.21-0.7, p=0.002), irrespective of adjuvant dose. We identified a threshold of antibody response that correlates with VE, demonstrating that levels greater than 5,191 EU/ml are associated with a 74% reduction in the risk of clinical malaria. Using a Spearman's test, we demonstrated a negative correlation between NANP response and the number of malaria episodes (p=0.0001). Following a booster dose, the correlation remained significant (p<0.0001) and antibodies were significantly higher in participants with no malaria compared with those who had at least one episode (p<0.006). In the higher adjuvant dose group, the threshold of protection for 80% VE was 6130 EU/ml. Further work to evaluate this correlate is underway in a larger Phase 3 trial as are studies to determine the functional mechanism for the protective efficacy of R21. Immunological correlates of protection are important in vaccine development to facilitate rapid evaluation of VE in different populations, mitigating the time and costs associated with large-scale efficacy trials.

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FULLY SYNTHETIC NUCLEIC ACID PRIME-AND-TRAP VACCINATION IN A RODENT MALARIA MODEL

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Highly effective and durable prevention methods are urgently needed to stop the yet-again rising burden of malaria. A pre-erythrocytic (PE) *Plasmodium* vaccine has the potential to significantly improve the portfolio of malaria interventions. If successful, such a vaccine would prevent parasite progression to the blood stage and prevent transmission to mosquitoes. "Prime-and-trap" vaccination is a potent vaccine strategy which achieves sterile protection against *P. yoelii* rodent malaria challenge by inducing high frequency, parasite-specific, liver resident memory CD8$^+$ T (Trm) cells. In its first generation, prime-and-trap consisted of gene gun *P. yoelii* circumsporozoite protein (CSP) plasmid DNA priming followed by a later trapping dose of radiation-attenuated sporozoites (RAS). To advance this concept, efforts are underway to replace attenuated sporozoites with a liver-targeted wholly synthetic vaccine, ideally with favorable manufacturing and administration characteristics. To demonstrate proof-of-concept, RAS trapping was first replaced with hydrodynamic transfection (HDT) of PyCSP DNA, which showed that HDT induced CSP-specific CD8$^+$ liver Trm cells and achieved sterile protection against *P. yoelii* challenge. However, because HDT cannot be performed in humans, extensive optimization studies were conducted to screen and refine DNA lipid nanoparticles (LNPs) capable of safely and efficiently transfecting hepatocytes with DNA to serve as a trapping vaccine. Two of the best liver targeting DNA LNP formulations were advanced to immunogenicity and protection studies. Gene gun PyCSP priming and DNA LNP trapping generated CSP-specific CD8$^+$ liver Trm cells and induced sterile protection against *P. yoelii* sporozoites in mice. Additional studies investigated dose ranging and administration route optimization. This next-generation strategy of prime-and-trap vaccination holds pre-clinical promise for accelerating the path to a highly effective and durable pre-erythrocytic vaccine that could greatly reduce the burden of malaria worldwide.

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ENHANCING IMMUNOGENICITY OF PRIME-AND-TRAP VACCINATION IN A RODENT MALARIA MODEL

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To combat the yet-again rising burden of malaria worldwide, a highly effective and durable vaccine against disease-causing *Plasmodium* parasites is urgently needed. The pre-erythrocytic "prime-and-trap" vaccine is a heterologous vaccination strategy shown to induce sterile protection in mouse models of malaria through the production of protective liver-resident memory CD8+ T (Trm) cells. This vaccine strategy consists of priming via gene gun-administered *P. yoelii* circumsporozoite protein (CSP) plasmid DNA and later trapping with a single dose of *P. yoelii* radiation-attenuated sporozoites (PyRAS). CSP-specific CD8+ T cells are generated during priming and directed toward the liver by PyRAS to produce Trm cells. While this is a potent vaccine strategy that reproducibly confers sterile protection in mice, it must be optimized to ultimately advance it into humans. With a focus on priming, there are many avenues that could enhance immunogenicity and lead to a more robust vaccine including but not limited to: vaccine schedule, dose, adjuvants, and antigens. Increasing the intensity of DNA priming by dosing on Days 0 and 2 ("cluster priming") significantly increased immunogenicity compared to a single prime on Day 0. Since cluster priming is not ideal for human use due to schedule considerations, genetically-encoded adjuvants and tags are being actively explored to obviate the need for the cluster priming approach. Candidate genetic adjuvants include a plasmid encoding the *Escherichia coli* heat-labile toxin (LT) and modification to the antigen-expressing plasmid to add a mouse chemokine XCL1 as an N-terminal fusion protein tag to CSP or other candidate antigens. The LT adjuvant did not significantly influence the frequency of CSP-specific, interferon-gamma producing CD8+ T splenocytes after priming with and without the LT-expressing plasmid. In contrast, N-terminal XCL1 tagging significantly increased the number of these cells. This data highlights the many ways that nucleic acid vaccination is amenable to different modifications that may accelerate the path to a highly effective malaria vaccine.

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TRANSGENIC *PLASMODIUM BERGHEI* AS A TOOL TO STUDY THE PROTECTIVE EFFICACY OF *P. FALCIPARUM* AND *P. VIVAX* PRE-ERYTHROCYTIC ANTIGENS

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The development of an efficacious vaccine against *Plasmodium falciparum* and *P. vivax* malaria remains a top priority for global health. Anopheline mosquitoes inject sporozoites into the dermis when probing for a blood meal and eventually the parasites reach the liver through blood stream to infect the liver and upon completing development initiate clinical blood-stage infection. Therefore, targeting antigens expressed during the pre-erythrocytic (PE) stages offers the potential to prevent clinical malaria from being initiated. While circumsporozoite protein (CSP) remains the leading vaccine candidate, there is an urgent need to explore additional PE antigen targets to develop a more effective malaria vaccine. To evaluate PE antigens for a multivalent *P. vivax* vaccine we selected *P. vivax* targets that are functionally important and whose upregulation in activated sporozoites correlated with infectivity. Since clinical evaluation of protective efficacy of PE antigens is technically challenging and access to *P. vivax* sporozoites is limited, we pursued an alternate strategy creating transgenic *P. berghei* that expresses SSP3 and SPECT1, complementing existing transgenic lines for *P. vivax* CSPs and CelTOS. The protective efficacy of these PE vaccine candidates are being evaluated by well-established *in vitro* functional assays for their potential efficacy as part of a multistage multivalent vaccine against vivax malaria.

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DEVELOPMENT OF NOVEL PRE-ERYTHROCYTIC *PLASMODIUM FALCIPARUM* ANTIGENS AS HUMAN VACCINE CANDIDATES

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Pre-erythrocytic vaccines prevent malaria by targeting the parasite in the liver stage (LS) and preventing progression to the blood stage. Currently, the leading pre-erythrocytic vaccine RTS,S is a circumsporozoite protein (CSP) based vaccine, however, efficacy and durability suggest CSP vaccines could be improved. Previous work identified highly expressed LS proteins that that act in combination with CSP to improve its activity. Combining *Plasmodium yoelii* (*Py*) CSP with 4 *Py*PEVA (pre-erythrocytic vaccine antigens) achieved enhanced sterile protection in a mouse challenge model. To advance PEVAs as a viable addition to a CSP based vaccine, we generated the *Plasmodium falciparum* (*Pf)* variants and produced the proteins in a cost effective and scalable manner. Two of our top candidates, *Pf* serine hydroxymethyltransferase (SHMT) and TATA-box-binding protein (TBP), were advanced to production in *E. coli*. Full-length *Pf*SHMT was expressed as insoluble protein in *E. coli*. Refolding conditions were screened and further optimized to promote stability and suppress aggregation. Production of *Pf*SHMT was scaled up and refolded material was further purified using by size-exclusion chromatography (SEC). The purified *Pf*SHMT had a SEC elution profile consistent with a monomeric and soluble protein. According to immunogenicity studies conducted in Balb/c mice, PfSHMT is highly immunogenic. We employed *in silico* and structural prediction to design a construct that improves recombinant expression and may focus B cell responses. *Pf*TBP was produced in *E. coli* and purified to a high level using mixed mode chromatography. Our results suggest that multiple *Pf*PEVA candidates can be made in *E. coli*, a platform that is amenable to manufacturing. Immunogenicity and protection studies using a combination of *Pf*PEVA and *Pf*CSP are ongoing in mice that will be challenged with *Pb-Pf*CSP transgenic parasites. These results will inform about the effectiveness of co-immunization with vaccines representing unique stage of pre-erythrocytic Plasmodium development.

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A NOVEL NON-HUMAN PRIMATE MODEL FOR VACCINATION IN THE CONTEXT OF ASYMPTOMATIC BLOOD STAGE MALARIA OR PREVIOUS CHRONIC MALARIA EXPOSURE

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Recent malaria clinical trials have demonstrated that vaccines show decreased immunogenicity and efficacy in malaria-endemic populations compared to naïve populations. Significant effort is now being focused on defining the immunological mechanisms of malaria vaccine hyporesponsiveness in endemic settings. While these mechanisms are likely complex, two clear trends have emerged - first, that vaccination during ongoing asymptomatic infection leads to poor vaccine responses, and second that even if infections are drug-cured, previous malaria exposure has lasting immunological effects that are detrimental to vaccine outcomes. Non-human primates are ideal models to study complex immunological mechanisms because they permit sampling of relevant tissues such as the spleen, lymph nodes, bone marrow, and liver. However, the commonly used rhesus macaque/*Plasmodium knowlesi* malaria model is characterized by acute symptomatic hyperparasitemia, and is thus not ideal for studying asymptomatic malaria or previous chronic malaria exposure. Here we report a novel pig-tailed macaque/*P. knowlesi* malaria model that is characterized by chronic asymptomatic infection that can be sustained for many weeks. In two cohorts, animals were challenged intravenously with 2,500 purified, cryopreserved, wild-type *P. knowlesi* sporozoites (PkSPZ) and monitored for blood stage parasite kinetics by Giemsa-stained thin smear and quantitative 18S rRNA reverse transcription PCR. All animals showed similar kinetics of infection, but strikingly, no outward clinical signs. The novel pig-tailed macaque/*P. knowlesi* model thus offers a unique opportunity to investigate tissue mechanisms of vaccine hyporesponsiveness in the context of either asymptomatic infection or prior chronic malaria. Using funding from a recently awarded NIAID U01 Cooperative Research Agreement, this model will now be used to perform systems immunology studies in naïve versus previously-exposed pig-tailed macaques following PkSPZ vaccination to define tissue mechanisms of vaccine hyporesponsiveness in the context of prior chronic malaria.

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PFSPZ VACCINES: THE POTENTIAL ROLE OF CD8+ CELLS IN FC AND COMPLEMENT MEDIATED KILLING OF PARASITES?

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Plasmodium falciparum (Pf) sporozoite (SPZ) vaccines protected 100% of non-immune recipients against CHMI with heterologous Pf parasites at 12 weeks after last vaccine dose and protected semi-immune Africans against heterogeneous Pf infection for 18 months. Our goal is to identify an assay

that predicts an individual will be protected. For >30 yrs, CD8+ T cells have been considered the mediators of attenuated SPZ vaccine protection. However, passive transfer of antibodies to the CSP are also protective. Thus, we have assessed cellular and antibody immune responses in the blood in our clinical trials. Cellular immunity assay results have been inconsistent and non-predictive. The antibody studies have included IgG, IgM, and IgA antibodies to PfCSP and other Pf proteins by ELISA, IgG antibodies to PfSPZ by IFA and inhibition of sporozoite invasion assays, and recently systems serology assays. In multiple clinical trials in African adults and children, and non-immune adults, protected subjects had significantly higher median antibody responses by the standard assays than did non-protected subjects. Recently, systems serology identified associations between FC receptor and complement binding and protection. These associations between antibodies and protection raise the question of whether antibodies to PfSPZ are minor mediators of protection and primarily markers for protective tissue resident cellular immune responses, or are significantly involved in mediating protection? Could interpretation of CD8+ cell depletion studies during the past 30 years, which focused on CD8+ T cells, have been incomplete or wrong, and missed the fact that depletion of CD8+ NK and dendritic cells participating in FC receptor-mediated antibody effector functions were the cause of elimination SPZ vaccine-induced protection? We will present the results of antibody studies from > 25 clinical trials of PfSPZ vaccines in 5 month to 61 year olds in 5 countries in Africa, Germany, and the US, the associations between antibody responses and protection, the correlations between the different antibody assays, and our results with systems serology.

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ASSAYS FOR LONG TERM STABILITY OF CRYOPRESERVED *PLASMODIUM FALCIPARUM* SPOROZOITES

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Sanaria's *Plasmodium falciparum* sporozoite (PfSPZ) products are all cryopreserved and stored in liquid nitrogen vapor phase (LNVP). Here we examine data over a four year stability period for multiple lots of Sanaria® PfSPZ Vaccine (irradiated PfSPZ) and Sanaria® PfSPZ Challenge (infective PfSPZ) produced under Good Manufacturing Practices for clinical studies in the US and multiple countries in Africa and Europe. A sporozoite membrane integrity assay (SMIA) is performed on all lots of PfSPZ products prior to cryopreservation, at the time of release and at several time points during the stability period; this assay is used as a surrogate for PfSPZ viability. A 3-day hepatocyte infectivity assay is also performed at the same time points on all lots of PfSPZ Vaccine as an indicator of vaccine potency as it measures the capacity of PfSPZ to invade liver cells *in vitro* then round up and express liver stage antigen 1 (PfLSA-1). Within lots, the trends in results for both assays were remarkably similar. The SMIA data showed a decline in viability associated with cryopreservation but thereafter, the results were stable showing almost no decline over the subsequent 4 years. Conversely, there was no dramatic decline in 3-day assay results associated with cryopreservation, but there was a significant but minimal decline in potency. Based on clinical data with PfSPZ Challenge, which shows 100% infectivity and stable pre-patent periods in controlled human malaria infection over 4 years , these results reflect the sustained viability and potency of PfSPZ when stored in LNVP. Cryopreservation followed by thawing and re-cryopreservation, and an accelerated stability storage at -80 °C both emphasize the utility of these assays in identifying decline in PfSPZ quality under suboptimal storage conditions.

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BRINGING PFSPZ VACCINE IN LNVP TO THE END USER - STUDIES IN TWO CIVILIAN AND TWO MILITARY TRAVEL AND IMMUNIZATION CLINICS

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Prior to the arrival of vaccines against SARS-CoV-2 it was accepted opinion that vaccines requiring ultra-low or cryogenic temperature storage could not be implemented for widespread use. Recently, vaccine distribution using a -80 °C cold chain, despite the requirement for specialized equipment for storage and transport, has proven successful for delivery to destinations on all continents. Maintaining a cryogenic cold chain at -150 °C is simpler and more robust than maintaining a -80 °C cold chain and is accomplished using liquid nitrogen vapor phase (LNVP) cryoshippers that operate without the need for electricity and use a convenient 7-14 day liquid nitrogen (LN2) re-charging schedule. We conducted sequential 28-day pilot studies to evaluate the feasibility of shipping, storing, maintaining and accessing PfSPZ vaccine in two DoD and two civilian travel health/immunization clinics. Members in each clinic were trained in use of the equipment, and procuring and handling LN2. All sites quickly assimilated the requisite expertise. Sites identified sources for LN2 and recharged the cryoshippers from LN2 delivered every one or two weeks. Vaccine ordering, receipt, storage and inventory control were established at each site. Vaccine cryovial retrieval from the cryoshippers for thawing and dose administration was conducted under different conditions to simulate vaccine preparation and administration in travel clinic settings or large-scale group immunization clinics at 10 immunizations/hour. Continuous temperature monitoring at each site was maintained and the data showed no temperature excursions above -150 °C, the maximum allowable threshold for cryopreserved injectable human products during shipping, use and reverse shipping. Staff were debriefed at the end of the 28-day period to assess feasibility and challenges and provided feedback that has been incorporated into our models for LNVP cryogenic distribution logistics to travel and military medicine immunization clinics. These studies indicate that PfSPZ vaccine delivery to and administration at these clinics both practical and acceptable to the end user.

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MAGNITUDE AND AVIDITY OF ANTIBODY RESPONSES TO PLASMODIUM FALCIPARUM CIRCUMSPOROZOITE PROTEIN ANTIGENS INDUCED BY A NEXT GENERATION VIRUS LIKE PARTICLE VACCINE CANDIDATE R21 ASSOCIATE WITH PROTECTION AGAINST SPOROZOITE INFECTION

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R21 is a next generation vaccine candidate that presents a higher proportion of *Plasmodium falciparum* (*Pf*) circumporozoite protein (CSP) on the virus like particle surface than the malaria vaccine RTS,S. R21 in a phase 2 trial involving children living in a malaria endemic area showed 74% to 77% vaccine efficacy at 6 months primary analysis that was retained at 12 months. A controlled human malaria infection (CHMI) study to assess the efficacy of R21 against sporozoites challenge has been concluded. To investigate whether the R21 induced antibody magnitude and/or avidity correlate with protection against *Pf* sporozoite challenge, the specific binding responses (magnitude) and dissociation

rates (avidity) of vaccinees' serum antibodies interaction with the vaccine antigen R21, a recombinant *Pf* CSP and peptides corresponding to the central repeat region (NANP6 and NPNA3) were measured using a Biolayer Interferometry (BLI) assay. On the day before *Pf* sporozoite challenge, all groups of vaccinees that received different doses of R21 adjuvanted with Matrix M showed higher antibody binding responses to R21, CSP, NANP6 and NPNA3 than the infectivity control group. There was no significant inter-group differences in the vaccinees either in binding responses or in dissociation rates for any of the antigens tested. However, compared with the not-protected vaccinees, the protected vaccinees from all vaccinated groups combined exhibited significantly higher median R21, CSP and NPNA3 responses (p values 0.04, 0.018 and 0.017 respectively), and trended to have higher median NANP6 responses (p = 0.095). The protected vaccinees also showed significantly slower median NANP6 and NPNA3 dissociation rates (p values 0.007 and 0.002 respectively), and a trend of slower median CSP dissociation rates (p = 0.086) than the not-protected vaccinees. These BLI measurements of antibody dynamics reveal that the R21 vaccine-induced protection against CHMI is associated or trended with higher antibody magnitude and avidity for CSP antigens. Such immune correlate analyses would help understand protective immunity in future malaria vaccine trials.

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OPTIMIZATION OF A SURROGATE ASSAY FOR EFFICACY OF A MALARIA TRANSMISSION BLOCKING VACCINE

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An estimated 241 million malaria cases and 627,000 malaria deaths occurred worldwide in 2020. Efforts to develop a higher efficacy malaria vaccine are a global priority, but parasites pose a complex biological puzzle for vaccine development. Thus, innovative vaccine strategies are necessary to better combat the complexity of the parasite. Among these, transmission blocking vaccines (TBV) target the mosquito stages of parasite development to inhibit parasite transmission and thereby pursue regional elimination and ultimately eradication of malaria across the globe. The current leading TBV called Pfs230D1-EPA targets Pfs230, a Plasmodium falciparum gamete surface protein that mediates binding of microgametes to red blood cells. Antibodies against Pfs230 bind and lyse gametes in a complement-dependent manner blocking transmission. Here, we are exploiting a panel of human monoclonal antibodies (hmAb) generated from human volunteers who received Pfs230D1-EPA formulated in Alhydrogel or AS01 adjuvants, to develop a competitive ELISA platform. This assay will quantify epitope-specific serum antibodies along with their features and effector functions, expanding the conventionally used functional assay of standard membrane feeding (SMFA). The competitive ELISA is being developed with single-chain variable fragments (ScFv) to define epitope-specific binding of antibodies in sera from vaccinated individuals. Sera of human volunteers from trials in Mali, Africa will be assayed to assess epitope-specific serum antibody binding that is competed off in the presence of saturating levels of ScFv. Preliminary optimization of the competitive assay has shown concentration-dependent epitope-specific competition between ScFv and hmAbs and confirmation of ScFv binding to Pfs230D1 antigen. Further optimization of this efficacy assay will characterize the complement-binding and isotype/subclass-specific features of epitope-specific antibodies. These efforts will lay the foundations for standardized assays that can assess correlates of vaccine efficacy and durability of this leading TBV.

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REMOTE BEDNET USE MONITORING TO DESCRIBE PATTERNS OF USE AND EXPOSURE TO FEMALE *ANOPHELES* MOSQUITOES IN AN UGANDAN COHORT

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Long lasting insecticide-treated bednets (LLINs) are the most widely used tool for preventing malaria. There are urgent questions about the effectiveness of LLINs in many African countries. In this study, remote LLIN use monitors were deployed in a cohort in Eastern Uganda to explore how LLIN use interacts with mosquito exposure. The SmartNet study included 20 households from May to October 2019. SmartNet devices recorded, every 15 minutes, whether an LLIN was unfurled or folded up. Unannounced visits were used to assess SmartNet accuracy. Risk factors associated with poor LLIN use were assessed using generalized linear equations. Female Anopheles exposure was estimated by combining hourly probabilities of exposure from human landing catches and measures of density from biweekly CDC light traps in participants rooms. Mosquito exposure averted by LLINs was quantified using SmartNet measurements and age-related differences were estimated using generalized linear equations, adjusting for relevant covariates and household clustering. Ninety-six individuals contributed 5,640 SmartNet observation nights. In 126 unannounced visits, SmartNet had an area under the curve of 0.869 in classifying whether the LLIN was up or down. The rate of non-use was 13.5% of nights (95% CI: 12.6 to 14.3%). Compared to children under 5, non-use was 1.8 times higher (95% CI: 1.6 to 2.1; p<0.001) in children 5-15 years and 2.6 times higher (95% CI: 2.2 to 3.1; p<0.001) in participants aged 15-<30years. There was no difference between children under 5 years and adults >30 years. LLIN use averted 50.3% of female Anopheles mosquito exposure (95% CI: 40.0% to 60.0%), with decreasing efficacy across age groups: from 61.7% (95% CI: 42.6% to 80.7%) in children under 5 years to 48.0% (95% CI: 29.1% to 66.8%) in adults over 30. Objective monitors are accurate and can feasibly be deployed to obtain data about LLIN use. LLINs provided protection from only 50% of female Anopheles mosquito exposure in this cohort and protection was dependent upon age. In assessing the role of LLINs in malaria prevention it is crucial to consider the dynamics between mosquito exposure and LLIN use behaviors.

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MALARIA VECTOR COMPOSITION, SPATIO-TEMPORAL VARIATION AND INSECTICIDE RESISTANCE IN MANICA, MOZAMBIQUE

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Malaria is a major public health concern in Mozambique, especially in Manica Province, which records the third highest annual incidence in the country. The study sought to determine the malaria vectors, their specific composition and density, the susceptibility and level of resistance to insecticides and the variation of species along the year in Manica Province. Surveillance sites were selected in each district and georeferenced using hand-held GPS. Larvae were collected in breeding sites and reared to adulthood. Insecticide susceptibility bioassays on adult anopheless female mosquitoes was carried out using standard WHO procedures. Proportions of each identified species was determined. Mortality rate was calculated and resistance was obtained using WHO criteria. Chimoio presented the

highest number (9) of larvae per ladle followed by Sussundenga and Gondola districts with 4 each. *Anopheles gambiae* was susceptible to all insecticides tested (Deltamethrin, Phirimpho-methyl, Bendiocarb, DDT and lambdacyhalothri) with 98 to 100% mortality. *Anopheles gambiae* and *funestus* proportion was 3.3:1 in Sussundenga and 1.1:1 in Chimoio. Most *An. gambiae* catches in Sussundenga were in August while *An. funestus* are throughout the year peaking in September. The findings demonstrate no resistance to insecticides currently used, species proportion difference per districts and, species occurrence variation along the year. The findings can be used by policy and project programmers to enhance malaria control activities.

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EFFECT OF SEASONAL MALARIA CHEMOPREVENTION PLUS AZITHROMYCIN ON *PLASMODIUM FALCIPARUM* TRANSMISSION: GAMETOCYTE INFECTIVITY AND MOSQUITO FITNESS

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Seasonal malaria Chemoprevention (SMC), strategy recommended by the WHO, aims to prevent malaria in children under 5 children by administration of sulfadoxine-pyrimethamine /amodiaquine (SPAQ) in areas with seasonal transmission such as the Burkina Faso. Thus, the combination of AZ, an antibiotic whose effectiveness has already been proved, would further reduce infant mortality. However, a wide variety of drugs, including antimalarials and antibiotics can influence the transmission of malaria parasites. We conducted a study on the effect of adding AZ to SPAQ on the transmission of *P. falciparum* in the human host and in the vector. This is an add-on study to the project of SMC+AZ conducted in Mali and Burkina Faso.Blood collections from children who were administered SPAQ or SPAQ+AZ and from a control group were carried out between 2015 and 2016 in western Burkina Faso. Thick blood smears have made it to estimate gametocytes carriage in humans; the Direct membrane feeding assay (DMFA) has been made to evaluate the infectivity of gametocytes as well as the effect of drugs on the life history traits of *An gambiae*. The results indicate that the drugs significantly reduced the prevalence of the asexual forms, but also of the gametocytes of *P falciparum*, 1.6% (3/183) for the SPAQ group, 4.7% (9/190) for the SPAQ +AZ group versus 27% (48/177) for the control group.In treated children, a significant reduction in the proportion of infectious blood meals was observed with 12.1% (23/190) for the SPAQ + AZ group, 5.5% (10/182) for the SPAQ group against32.16% (55/171) for the control group. The addition of AZ to SPAQ was associated with a higher proportion of infectious blood meals, suggesting a significant effect of AZ on gametocyte infectivity. There was a negative effect of SPAQ and SPAQ+AZ on mosquito survival (LRT X^2_2=330, P<0.0001).Our study showed a potential blocking effect of SP/AQ and AZ on the transmission of *P. falciparum* to mosquito. Additional studies should be conducted to better explain the effect of AZ on gametocyte infectivity.

1598

ANOPHELES GAMBIAE REEMERGENCE AND RESURGENT MALARIA TRANSMISSION IN EASTERN RWANDA, 2010 - 2020

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Rwanda achieved unprecedented gains in malaria control from 2000 to 2010, but cases increased 20-fold after 2011. Despite this alarming increase, no scientific studies have investigated the root causes of the resurgence. Furthermore, the relative importance of the two primary malaria vectors in Rwanda, *Anopheles gambiae* and *Anopheles arabiensis*, has not been well studied. This information is critical for informing malaria control measures and preventing future epidemics in Rwanda and the region. We conducted a retrospective study in four sentinel sites in eastern Rwanda which perform monthly entomological surveillance and provide outpatient malaria care. We compared sporozoite rates, human blood index (HBI), and relative abundance of *An. gambiae* and *An. arabiensis* using monthly laboratory data from 2017 to 2020. We then assessed the effects of insecticide resistance, vector control coverage, and monthly air temperature on species composition and reported malaria incidence from 2010 to 2020 using log-binomial and Poisson models. Sporozoite rates were 28 times higher (11.6% vs. 0.4%) and HBI was four times higher (80% vs. 20%) in *An. gambiae* compared to *An. arabiensis*. *An. gambiae* was controlled following universal insecticide treated net coverage in 2010, but rapid increases in pyrethroid resistance were associated with increased *An. gambiae* relative abundance and malaria incidence. Major outbreaks corresponded to periods of *An. gambiae* reemergence. A 2.3°C increase in observed maximum temperatures from 2010 to 2016 was associated with an additional 61% increase in malaria incidence. However, non-pyrethroid indoor residual spraying (IRS) reduced sporozoite rates and relative abundance of *An. gambiae* by > 90%, and malaria incidence by 79%. In conclusion, insecticide resistance and regional warming drove the reemergence of *An. gambiae* and resurgence of malaria transmission in eastern Rwanda from 2010 to 2020. However, the success of non-pyrethroid IRS suggests that existing control measures can mitigate vector reemergence and climate-related malaria increases, providing insecticide resistance is adequately managed.

1599

PLANNING AND IMPLEMENTING LARVAL SOURCE MANAGEMENT USING TRANSMISSION HOT-SPOTS TO SUPPORT MALARIA CONTROL ON BIOKO ISLAND

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Malaria control was initiated on Bioko Island in 2004, resulting in a drastic reduction of the disease until 2016. However, despite the continuous implementation of control efforts, including indoor residual spraying (IRS) and long-lasting insecticidal bed nets (LLIN), malaria prevalence stalled from 2016 to 2018 and has risen since 2019. In response to this rise, the BIMEP proposed an integrated vector control approach in 2022 to deliver IRS to the entire Island, distribute LLINs, and conduct larval source management (LSM) in malaria hot spots. Transmission hot spots were identified using a three-year (2019-2021) Plasmodium falciparum Prevalence (*Pf*PR) change from the malaria indicators survey (MIS). As a result, 1027 map sectors (100 x 100m high-resolution grids) with increased *Pf*PR by at least 5% in the last three years were targeted for LSM. Trained fieldworkers will conduct a larval survey in the selected map sectors, identifying, characterizing, and geo-referencing potential mosquito breeding sites. The team will collect samples for larval identification, speciation, and count. Positive breeding sites will be treated with *Bacillus thuringiensis israelensis (Bti)* with call-back visits every seven to ten days. Impact will be measured by calculating early and late stage (late stage and Pupae) larval density weekly and adult mosquito density monthly, and measuring *Pf*PR change between using the 2022 MIS data.

1601

EXAMINING THE RANGE OF SPATIAL EFFECTS OF NEW CLASSES OF LONG-LASTING INSECTICIDAL NETS (LLINS) ON MALARIA INFECTION AND VECTOR DENSITY: AN ANISOTROPIC SEMIVARIANCE ANALYSIS IN THE CONTEXT OF A PHASE III CLUSTER RANDOMIZED MALARIA VECTOR CONTROL TRIAL OF DUAL ACTIVE INGREDIENT LLINS

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At high levels of population coverage with long-lasting insecticidal nets (LLINs), the mass killing of malaria vector populations can create a community effect, protecting individuals in a community who do not sleep under a net themselves. In cluster randomized trials evaluating new LLINs, spatially localized reductions in malaria transmission may contaminate proximal intervention arms unless carefully designed; impacting vector density and malaria infection prevalence in households adjacent to nearby intervention clusters and biasing results. Unsampled buffer areas are commonly used to mitigate contamination, but no consensus on optimal buffer size exists. Knowledge of the spatial range of LLIN effects on malaria transmission is needed to inform trial design and optimal buffer size between trial clusters. Using data from a phase III cluster randomized trial in northern Tanzania assessing three dual active ingredient LLINs against standard LLINs, our study aims to determine the spatial form of LLIN intervention effects on malaria infection and vector density. We measured malaria infection in 1,550 children and vector density from 830 households across four geographically contiguous areas, each with a common LLIN allocation, using a cross-sectional study in July 2020. Spatially lagged models for malaria infection and vector density are being computed to evaluate LLIN effects in the quasi-absence of spatial trends. Model results will be presented, and residual estimates will be used to compute variograms of localized effects for malaria infection and vector density. Variograms will be evaluated by structural form and range to determine an absolute distance of LLIN effects for each net type. We expect semivariance range estimates to exceed commonly used buffer sizes, indicating a potential for contamination between study arms. A previously study conducted in a similar context found median estimates greater than one kilometer. Results will be discussed in the context of trial design and the implications for a more defined policy recommendations on buffer sizes in cluster randomized malaria vector control trials.

1602

ASSESSMENT OF KEY MALARIA VECTOR CONTROL ACTIVITIES WITHIN PROGRAM AREAS OF THE TRANS KUNENE MALARIA INITIATIVE (TKMI) / ISDELL: FLOWERS CROSS BORDER MALARIA INITIATIVE (IFCBMI) IN FOUR BORDER MUNICIPALITIES OF CUANDO CUBANGO PROVINCE, ANGOLA

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Angola continues to prioritize insecticide treated nets (ITNs) and indoor residual spraying (IRS) in its efforts to reduce the impact of malaria. TKMI/IFCBMI supports community-based implementation of malaria control activities within four of Cuando Cubango Province's border municipalities: Calai, Cuangar, Dirico, and Rivungo. Their strategic border positioning has made them priority areas for malaria elimination efforts, including as indicated by previous funding requests of the SADC Elimination 8 Secretariat to The Global Fund and the Bill & Melinda Gates Foundation. These municipalities, classified nationally as "moderate risk" (300-500 annual cases per 1000 people), are some of Angola's few targeted areas for annual universal IRS campaigns. Mass ITN distribution last occurred there in 2018. This study assessed reported access to and use of ITNs and coverage of IRS within IFCBMI program areas though a yearly cross-sectional household survey of 2805 (2020) and 2249 (2021) households. Across all program areas, the proportion of people with appropriate access to an ITN the night before the survey (defined as one ITN per two people) decreased significantly, from 71% in 2020 to 67% in 2021, while people using an ITN was nonetheless constant (75% in 2020 and 74% in 2021). Relatedly, the average household ratio of ITN use to ITN access increased significantly from 1.10 in 2020 to 1.16 in 2021 (ratios over 1.0 indicate that, on average, more than two people slept under each ITN), showing that ITN use is high when there is access. Between 2020-2021, the proportion of households that received IRS in the prior 12 months increased significantly in Rivungo program areas (from 47% to 85%); non-significant changes were observed among program areas in Calai (80% to 81%), Cuangar (89% to 89%), and Dirico (79% to 80%). In 2021, among households without IRS, the most common reason for not receiving IRS was "no one was home at the time of spraying" in Calai (56% of those not sprayed), Cuangar (58%), and Rivungo (64%); and "household is ineligible for spraying" in Dirico (53%).

1603

EVALUATING THE IMPACT OF INDOOR RESIDUAL SPRAYING ON MALARIA TRANSMISSION IN MADAGASCAR USING EXISTING DATA SOURCES

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Indoor residual spraying (IRS) and insecticide-treated bed nets (ITNs) are cornerstone malaria prevention and control methods in Madagascar. From 2016 to 2020, non-pyrethroid IRS was deployed to complement standard pyrethroid ITNs in 14 districts with high malaria burden, targeting 5 to 9 districts each year. Districts received IRS for 1 to 3 consecutive years during the study period. This retrospective observational study uses routine data to evaluate the impacts of IRS overall, sustained IRS over multiple years, and achieving high (≥85%) IRS coverage (structures sprayed/found). We fit a multilevel mixed effects model to data from all 114 districts of Madagascar from July 2016 to June 2021. We estimated the effect of IRS exposure, consecutive years of IRS, and high IRS coverage on monthly population-adjusted RDT-confirmed malaria cases at health facility level. Facilities missing data, and communes missing geolocations were excluded, leaving 84% of records included. The model controlled for ITN survivorship, mass drug administration (MDA), precipitation, enhanced

vegetation index (EVI), month, year, and district. Using the fitted model we predicted malaria cases under observed and *no IRS* scenarios and estimated the number of cases averted by IRS. IRS was associated with reduced case incidence and an estimated 196,075 (79,879-316,809) cases were averted in targeted districts (~15% of the 1.3m reported cases). The effect varied by district and was associated with ITN survivorship, MDA, precipitation, EVI, month and year. One year of IRS was associated with higher incidence versus two (IRR = 1.15, 95%CI = 1.03-1.29) or three (IRR = 1.16, 95%CI = 1.01-1.33). High coverage (achieved in 94% of IRS areas) was associated with a 12% lower incidence rate (IRR=0.88, CI=0.82-0.95) compared to areas with lower coverage. This study suggests that IRS together with ITNs may substantially reduce malaria incidence over ITNs alone, and high spray coverage and >1 year of IRS may confer additional benefits. This work highlights the value of routine data to evaluate the impact of intervention combinations and to inform future targeting decisions in Madagascar.

1604

COUNTING MOSQUITOS TO COUNTER MALARIA: HOW MUCH DOES ENTOMOLOGICAL SURVEILLANCE IMPROVE MALARIA CONTROL DECISIONS?

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Strategic malaria control relies on using surveillance data to inform decision making; every aspect of malaria transmission— human, parasite, vector— can potentially inform decisions on where limited resources should be deployed. Entomological data on vector species abundance and seasonality contains a great deal of information about transmission dynamics. Unfortunately, the challenging and resource-intensive demands of entomological data collection mean that this detailed information is very often unavailable and malaria control decisions must be made primarily from reported incidence of clinical malaria cases coupled with infrequent cross-sectional surveys of parasite prevalence. Entomological data is clearly of great scientific value, but quantitatively how much does this information improve malaria control decision-making? To answer this question, we use a mathematical model of malaria transmission fit to successive levels of data from Magude, Mozambique where entomological data was gathered monthly over multiple sentinel sites for several years. First, we use a Bayesian history-matching algorithm to fit the model purely to clinical incidence and cross-sectional prevalence surveys, identifying the posterior set of potential transmission scenarios that could plausibly have produced that data. Next, we include the entomological data into the model fitting process and quantify how much this additional information constricts the posterior plausible transmission scenarios. Finally, we explore the impact of ITNs, IRS, and MDA across the transmission scenarios that are plausible with and without entomological data to explore how much uncertainty is reduced in the inferred intervention effect sizes. Our results may be used to help control programs and funding partners decide on when it makes sense to invest limited resources into improving entomological surveillance and data collection.

1605

MOLECULAR CHARACTERIZATION OF EXTENDED-SPECTRUM BETA-LACTAMASE (ESBL) PRODUCING *ESCHERICHIA COLI* ISOLATED FROM HOSPITAL ENVIRONMENTS AND PATIENT SAMPLES IN BANGLADESH

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The presence of ESBL producing *E. coli* is a major concern for various hospital and community healthcare settings, often being linked to an increased incidence of nosocomial infections. In this study, we investigated the molecular characteristics of ESBL forming *E. coli* in hospital and healthcare environments in Bangladesh. In total, 117 ESBL producing *E. coli* were isolated from environmental and patient samples between March and May 2019. The isolates were subjected to molecular typing using ERIC PCR, antibiotic susceptibility and PCR analysis for the presence of resistance and virulence genes, and lastly quantitative adherence assay. All the isolates were found ESBL producers and 107 of these isolates were found to be KPC-producing. Out of 117 isolates, 67.5% were positive for bla_{CTX-M} gene, 39.3% were positive for bla_{TEM} gene, 1.7% were positive for bla_{SHV} gene and 30.77% were positive for the bla_{NDM-1} gene. At a temperature of 25ºC, 17 isolates exhibited strong biofilm formation with 25 and 33 isolates showing moderate and weak biofilm formation respectively, whereas 42 isolates were non-biofilm formers. At another temperature of 37ºC, 3 isolates exhibited strong biofilm formation with 4 and 37 isolates showing moderate and weak biofilm formation respectively, whereas, 73 isolates were non-biofilm formers. Among the ExPEC virulence factors, 7.6%, 11%, 5.9%, 4.3% and 21.2% isolates harbored the *focG*, *kpsMII*, *sfaS*, *afa* and *iutA* genes, respectively. In regard to antibiotic susceptibility testing, all the isolates were found to be multi-drug resistant (MDR) and 15 isolates were found to be extensively drug resistant (XDR). ERIC-PCR resulted in 52 clusters, with cluster number 50 containing the maximum number of isolates. This study suggests that the ESBL producing *E. coli* is prevalent in the healthcare settings of Bangladesh, acting as a potential reservoir for AMR bacteria. The information may have a profound effect on treatment, and improvements in public healthcare policies are a necessity to combat the spread and increased incidences of hospital-acquired infections in the country.

1606

ORGANIZATION AND IMPLEMENTATION OF ORAL CHOLERA VACCINATION CAMPAIGNS IN A HUMANITARIAN CRISIS AMONG THE FORCIBLY DISPLACED MYANMAR NATIONALS (FDMN) POPULATION IN COX'S BAZAR, BANGLADESH

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Over 700,000 Myanmar Nationals known as 'Rohingya' fled into Cox's Bazar, the southern district of Bangladesh. As this vast number of displaced people were living in densely populated unhygienic areas, they were vulnerable to numerous communicable diseases, especially cholera. Assessing the risk conditions, the Government of Bangladesh (GoB) with the help of the icddr,b, and other international partners (WHO, UNICEF, IOM, MSF, Red Cross), decided to take preventive measures and conducted OCV campaigns. This presentation aims to describe the organization and implementation of oral cholera vaccination

campaigns in the humanitarian crisis in Bangladesh. There were seven rounds of OCV campaigns conducted between 2017 to 2021, and different strategies were followed during these campaigns. Based on the campaigns, experience reveals that OCV delivery is feasible in complex refugee settings. Around 900,000 FDMNs were vaccinated in seven campaigns. In addition, 528,297 beneficiaries from the host community also received OCV. A total of 4,661,187 doses of OCV were delivered. Among them, 3,765,499 doses were used for FDMN and 895,688 doses were used for the host community people living near the FDMNs. These OCV campaigns were carried out applying different strategies. In the first three rounds of the OCV campaign, the fixed-site strategy was used while a routine immunization platform was used in the fourth round. House to house strategy was adopted in the fifth and sixth rounds and camp by camp rolling approach strategy in the seventh round. The vaccine was well accepted, as a result, a high level of coverage was achieved which ranges from 87% to 108% in different campaigns. After the successful pre-emptive campaigns in Cox's Bazar humanitarian camps, no cholera outbreak was detected either in the FDMN or in the host communities. In addition to vaccination, the WASH intervention, sustainable surveillance system, and proper case management system were needed to be established through a multisectoral approach to prevent cholera outbreaks in the humanitarian crisis refugee camps and surrounding host communities.

1607

HIGH FREQUENCY OF AMR IN BACTERIA CAUSING DIARRHEAL DISEASES AT THE COMMUNITY HEALTH CENTER OF YIRIMADJIO, MALI

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Diarrhea is a public health problem especially in developing countries where, it is the second leading cause of child mortality. In Mali, because of the scarcity of complementary diagnostic systems and self-medication, antibiotics are used to treat any type of diarrhea which may result in multidrug-resistant bacteria development. The objective of this work was to determine the microorganisms responsible for diarrhea in children less than 15 years and to characterize their susceptibility to a panel of antibiotic used in Mali. This was a prospective study conducted from December 2021 to March 2022 including children under the age of 15 at the Yirimadjio Community Health Center. These samples were analyzed by conventional coproculture and antibiotic susceptibility was determined by Müller Hilton's agar diffusion method. Our preliminary results showed that: of the 200 children included in this study, the mean age was 17.26 months and the standard deviation was 21.65. Children under 2 years of age were the most prevalent with (87%), The bacteria responsible for gastroenteritis were *E. coli* (21.5%) and *Salmonella* (1%). In our samples, 25.6% of the *E. coli* were producer of Extended-spectrum beta-lactamase. All the E. coli tested to date were resistant to amoxicillin (43 samples) and co-trimoxazole (43 samples).This study showed that E. coli is the most frequent bacteria implicated in diarrhea in children under 15 years of age in Mali, which are resistant to amoxicillin and co-trimoxazole, two antibiotics commonly prescribed in this setting.

1608

TYPHOID CONJUGATE VACCINE EFFECTIVENESS IN MALAWI - AN EVALUATION OF THE TEST-NEGATIVE DESIGN

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The test-negative design (TND) is commonly used to estimate influenza vaccine effectiveness (VE) and has been applied to COVID-19 vaccines. Despite increasing popularity, TND has not been evaluated for typhoid conjugate vaccine (TCV) effectiveness. We aim to verify the core assumption of TND that TCV has no effect on non-typhoid fever, and compare VE derived by TND to the gold standard per-protocol analysis of a randomized controlled trial (RCT) of TCV in Malawi. In the RCT, children were randomized 1:1 to receive a single dose of TCV or meningococcal capsular group A conjugate vaccine from 2/2018 to 9/2018 and were followed for blood culture (BC) confirmed *Salmonella* Typhi illness until 9/2021.A total of 27,882 Malawian children aged 9 months to 12 years were included in the RCT with 8,161 BC specimens collected from 6,218 children between 2/2018 and 9/2021, including 101 *S.* Typhi BC positive specimens from 97 children (cases). Three approaches were used for the TND analysis: 1) participant-based analysis without censoring for typhoid where controls were participants with febrile illness and BC negative for *S.* Typhi; 2) participant-based analysis with censoring for typhoid where controls excluded participants who ever tested positive for *S.* Typhi; and 3) specimen-based analysis where cases were *S.* Typhi positive specimens and controls were *S.* Typhi negative specimens, rather than individuals.Vaccine efficacy against *S.* Typhi in the RCT through 9/21 was 80.4% (95% CI 66.4%, 88.5%). For all three TND approaches, VE estimates and their confidence intervals (80.3% [66.2%, 88.5%] vs. 80.5% [66.5%, 88.6%] vs. 80.4% [66.9%, 88.4%]) were virtually identical to the RCT results. Receipt of TCV did not affect the risk of non-typhoid fever (-0.4% [-4.9%, 3.9%] vs. -1% [-5.6%, 3.3%] vs. -2.5% [-6.4%, 1.3%]). This study validates the core assumption of the TND approach for the estimation of TCV VE and confirms the accuracy and precision of its estimates compared to RCT. These results suggest TND can be a suitable design for post-introduction VE evaluations for typhoid, assuming the correct classification of vaccination status.

1609

SAFETY AND IMMUNOGENICITY OF LIVE ORAL CHOLERA VACCINE CVD 103-HGR (PXVX0200) IN CHILDREN AND ADOLESCENTS 2 TO 17 YEARS OF AGE

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The attenuated recombinant *Vibrio cholerae* O1 strain CVD 103-HgR, redeveloped as PVXV0200 [Vaxchora® (Cholera Vaccine, Live, Oral)], elicits a rapid serum vibriocidal antibody (SVA) response in adults as soon as 7 days after vaccination, and protected against cholera-induced diarrhea in volunteer challenge trials. This was a Phase 4, placebo-controlled, double-blind multicenter study to assess the safety, immunogenicity and tolerability of a single, oral dose of PXVX0200 in children and adolescents 2-17 years of age and bridge immunogenicity to adults 18-45 years of age from a separate lot consistency study. Volunteers were randomized 6:1 to receive a single dose of 1 x 10^9 colony forming units (CFU) of PXVX0200 or 0.9% saline placebo. Immunogenicity endpoints included SVA levels on days 1, 11 and 29 in volunteers 2-17 years of age, on days 91 and 181 in volunteers 12-17 years of age, and on days 365, 547 and 730 in a subset of volunteers 12-17 years of age. Safety was assessed by comparing solicited adverse events (AEs) through day 8, unsolicited AEs through day 29 and serious adverse events (SAEs) through day 181. The primary immunogenicity endpoint was the SVA seroconversion rate (>4-fold rise over baseline) on day 11. At 9 study sites in the United States, 550 subjects were enrolled into three cohorts: cohort 1, aged 12-17 years (N=189); cohort 2, aged 6-11 years (N=185) and cohort 3, aged 2-5 years (N=176). SVA seroconversion at day 11 occurred in 99.4%, 97.8% and 98.1% of vaccine recipients in cohorts 1, 2 and 3, respectively, and was non-inferior to the 93.5% seroconversion rate in adults. In the long-term immunogenicity subset of cohort 1, seroconversion persisted in 64.5%

of vaccine recipients at day 730. There were no differences in the rates of solicited and unsolicited AEs between vaccine and placebo recipients and no vaccine-related SAEs. The study vaccine was well accepted, with 99.4%, 91.0% and 82.7% of cohort 1, 2 and 3 recipients, respectively, taking at least 80% of the dose. CVD 103-HgR is safe, immunogenic and well-tolerated in children and adolescents 2-17 years of age, and SVAs persist for at least 2 years in a majority of adolescents.

1610

ACCEPTANCE OF TYPHOID CONJUGATE VACCINE AMONG PARENTS OF CHILDREN AGED 6 MONTHS TO 15 YEARS IN THE CONTEXT OF EXTENSIVELY DRUG RESISTANT OUTBREAK IN LYARI TOWN KARACHI, PAKISTAN

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Parental decision-making about childhood vaccination is complex and multidimensional. This study was conducted in the urban slum settlement of Lyari Town, Karachi to evaluate the parental acceptance of the newly introduced Typhoid Conjugate Vaccine (TCV) in the context of extensively drug-resistant typhoid outbreak. A cross-sectional survey using the WHO-recommended rapid vaccine coverage assessment technique (30 clusters X 7 households) was conducted from 8th November 2019 to 18th November 2019 in Lyari Town, Karachi. Sampling was powered at the Town level. Four union councils (lowest level of administrative unit in Sindh) in Lyari town were randomly selected among the total 11 and the survey was conducted in those randomly selected union councils. A total of 210 households per union council from the selected union councils were included to have union council level specific information on coverage rates and parental acceptance with sufficient power for statistical calculations. Parents of the children aged 6 months to 15 years old, living in the selected union council were invited to participate in the survey. A total of 230 households were approached and 2325 children were analyzed for vaccination status, 50% were male. Results of the multivariate analysis showed that the parents who knew the time of vaccination services offered had strong intention to get their child vaccinated (OR: 1.988; 95% Confidence Interval (CI): 1.657,2.386). Parents who thought that vaccination had side effects among children including fever (OR:0.614; 95% CI: 0.49,0.771), irritability (aOR:0.632; 95% CI: 0.489,0.816) , disturbed sleep (aOR:0.692; 95% CI: 0.505,0.95) and inappropriate feeding behavior (OR: 0.432; 95% CI: 0.211,0.884) had no, low or moderate intention to get their child vaccinated. A multi-pronged strategy is recommended to address community awareness, existing myths, and enhance physician-patient communication to increase the parental acceptance of childhood vaccines.

1611

DIFFERENCES IN ROTAVIRUS SHEDDING BY INFANT ORAL ROTAVIRUS VACCINATION STATUS IN DHAKA, BANGLADESH

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Oral rotavirus vaccines are less effective in low-income compared to high-income settings. In settings with lower vaccine efficacy, breakthrough rotavirus disease among vaccinated children is common. However, it is unknown how much these breakthrough cases contribute to transmission. We used data from the Performance of Rotavirus and Oral Polio Vaccines in Developing Countries (PROVIDE) randomized controlled trial to examine the relationship between Rotarix® (RV1) vaccination and quantity of rotavirus shed in stool during episodes of rotavirus gastroenteritis (RVGE). 700 healthy infants from PROVIDE were randomized to receive two doses of RV1 at 10 and 17 weeks of age or randomized to the non-placebo control arm. We used multivariable linear regression to analyze 184 episodes of rotavirus diarrhea testing positive by ELISA occurring in children 10 weeks to 1 year of age. The primary outcome of interest was quantity of rotavirus shed in stool by qPCR testing. Vaccinated children had significantly lower levels of fecal viral shedding compared to unvaccinated children after controlling for age, WAZ, HAZ, exclusive breastfeeding at time of episode, and time in days since symptom onset (mean difference = -0.59 log copies per gram of stool, 95% CI: -0.99, -0.19). We found no evidence of interaction by child age or disease severity (modified Vesikari score). In a sensitivity analysis, we found no significant interaction by time when comparing effect estimates between children 10 to 19 weeks of age (after receipt of first dose) to children 19 weeks to one year of age (2 weeks after receipt of second dose). These results suggest that RV1 vaccination reduces shedding burden among breakthrough cases of RVGE, in addition to preventing RVGE cases entirely. Our results also suggest that breakthrough cases among vaccinated children may have lower transmission potential than cases among unvaccinated children, though further study is needed.

1612

BREASTFEEDING AND SECRETOR STATUS MEDIATE SUSCEPTIBILITY TO *CAMPYLOBACTER JEJUNI* GASTROENTERITIS IN A NICARAGUAN BIRTH COHORT

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Campylobacter spp., causes an estimated of 400 - 500 million cases of acute gastroenteritis (AGE) annually. Previous studies have shown that *Campylobacter jejuni* attaches to host fucose residues in enterocytes when establishing the infection. Thus, susceptibility to *C. jejuni/coli* infection may be mediated by the expression of histo-blood group antigens (HBGA). Also, human milk oligosaccharides (HMO), which vary by maternal HBGA status, may mediate protection against *C. jejuni* AGE. Yet, the role of HBGA, breastfeeding practices and HMO on the burden of *C. jejuni/coli* AGE in children have not been well documented. We aimed to examine the role of child and maternal secretor status and breastfeeding practices (at least once per day two weeks before the AGE episode), on children's susceptibility to *C. jejuni/coli* AGE in the first year of life. *C. jejuni/coli* AGE and breastfeeding was assessed in 241 Nicaraguan children. Stool samples were tested for *C. jejuni/coli* by qPCR, and secretor status was done by phenotyping of saliva. Of 424 AGE episodes experienced by children, 68 (16.0%) tested positive for *C. jejuni/coli* with an overall incidence of 32/100 child-years. In secretor children, *C. jejuni/coli* was detected as early as the first month of life and tended to have a higher incidence compared to non-secretor children (34 vs 25/100 child-years). Stratification by maternal and child secretor status and breastfeeding showed among breastfed (BF) $Se^{+}_{m}Se^{-}_{c}$ pairs, 25% had *C. jejuni/coli* detection compared to 100% of non-breastfed children (NBF). In BF and NBF of $Se^{-}_{m}Se^{+}_{c}$ pairs, *C. jejuni/coli* was detected in 17.6% and 12.5%, respectively. $Se^{-}_{m}Se^{-}_{c}$ pairs independent of breastfeeding status, no *C. jejuni/coli* was detected. Surprisingly, in BF and NBF of $Se^{+}_{m}Se^{+}_{c}$ pairs, *C. jejuni/coli* was detected in 34.3% and 41.2%, respectively. Layering these group by ages 0-6 and 7-12 months, and BF and NBF, *C. jejuni/coli* was detected in 33.8% and 58.3%, and 34.8% and 32.0%, respectively. These preliminary finding suggest that child and maternal secretor status, breastfeeding practice, and likely HMO composition may influence the incidence of *C. jejuni/coli* AGE.

1613

ASYMPTOMATIC ENTERIC PATHOGENS RELATIONSHIP WITH HISTOLOGY IN UNDERNOURISHED CHILDREN WITH ENVIRONMENTAL ENTERIC DYSFUNCTION (EED)

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Environmental Enteric Dysfunction (EED) is an acquired syndrome of subclinically altered gut function, the etiology of which is unknown. EED is postulated to be a major contributor to growth faltering in early childhood. Few studies have interrogated the critical organ (the upper small bowel), and the potential role(s) of enteric pathogens in the pathophysiology of EED remains poorly defined. The aim of this study was to assess if colonization of the gut with enteropathogens could predict subsequent EED histology severity. Stool was obtained from undernourished children without diarrhea who failed nutritional intervention and subsequently underwent endoscopy to determine the lesion associated with their poor growth. Biopsies from 246 (Bangladesh n=119 Pakistan n=57, Zambia n=70), such children were scored using a histologic grading protocol by a group of pathologists blinded to the metadata from each participant. Enteric pathogens were identified in stool using TaqMan Array Cards (TAC) (Bangladesh and Pakistan) and the Luminex (Zambia) platform. Multivariable linear regressions adjusting for site, age at stool collection, and stool to biopsy interval demonstrated: 1) Norovirus and *Shigella* presence predicted increased enterocyte injury 2) *Campylobacter* and enterotoxigenic *E. coli* predicted higher summative EED scores (comprised of the five most informative histology parameters). Analyses of TAC only data (Bangladesh, Pakistan) are underway. These novel findings offer a basis for future studies to measure contributions of enteric pathogens on EED prevalence and severity.

1614

WHOLE GENOME SEQUENCING OF *VIBRIO CHOLERAE* REVEAL SUB-CONTINENTAL TRANSMISSION PATTERN IN EAST AFRICA

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Whole genome sequencing (WGS) has recently been used to understand and identify introductions of seventh pandemic *Vibrio cholerae* El Tor O1 strains into Africa from Southeast Asia. Thirteen introduction events have been identified by previous studies, deemed the T1-T13 sub-lineages of the seventh pandemic lineage. Although these introductions can be used to understand cholera dynamics on a continent-wide scale, regional and local transmission patterns are still not well understood. In particular, although WGS has been used to explore cholera transmission across West Africa, much remains unknown about the regional dynamics of *Vibrio cholerae* in East and Southeastern Africa. We generated whole genome sequences from 65 *Vibrio cholerae* isolates collected from suspected cholera patients in Kenya, Tanzania, Uganda and Malawi from 2007 to 2019. We performed phylogenetic analysis of these sequences alongside 1391 published sequences to understand the lineages circulating in East Africa from 2007 to 2019. We observed the T13 lineage in Kenya in isolates collected in 2007-2009, several years earlier than the previously estimated introduction date of this lineage (2013-2014). We also evidence of multiple co-circulating lineages in Malawi. Both of these findings highlight the need for additional genomic surveillance of *Vibrio cholerae* in Southeastern Africa. The 65 new cholera samples included in this analysis included different sample types, including stool spotted filter paper, isolate spotted filter paper, boil extracted isolates, and column extracted isolates. As part of our analysis, we explored sequencing success rates across the different isolate types and found promising evidence that even low-cost specimen preservation systems, such as stool spotted filter paper, have potential to be useful in WGS studies. Further development of laboratory sequencing techniques for these types of samples will be crucial to continued genomic surveillance in the Southeast African region.

1615

PREVALENCE AND RISK FACTORS OF *SHIGELLA* SPP INFECTION AMONG SCHOOL-AGED CHILDREN FROM A RURAL AND URBAN COMMUNITY IN CAJAMARCA, PERU

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Shigella spp. is a gram-negative bacilli that belongs to the Enterobacteriaceae family. It is one of the leading causes of diarrhea worldwide, causing around 164 million infections every year. Clinical symptoms range from asymptomatic infection to gastroenteritis and severe dysentery. Diarrheal diseases are still an important cause of morbidity and mortality in Peruvian children and data of the epidemiology of *Shigella spp.* is still scarce. The objective of the present study was to evaluate the prevalence of *Shigella spp*. and to determine the associated factors in school-aged children from an urban and rural community in the department of Cajamarca in Peru. We performed a cross-sectional, descriptive study with non-probabilistic convenience sampling. The study was conducted on children aged 4 through 14 years old who attended a local school. The diagnosis of *Shigella spp.* was attained using real-time polymerase chain reaction (RT-PCR). A total of 243 children were enrolled, 111 from an urban community and 132 from a rural community. The prevalence of *Shigella spp.* was 9.1% in the rural community and 3.6% in the urban community. Raw salad ingestion (p=0.24) and lack of handwashing before eating (p=0.008) were found to be associated factors for *Shigella spp* infection. The most common symptoms were abdominal pain (72.4%) and weigh loss (42.4%). Diarrhea was reported only in 28.8% of the patients. No cases of dysentery, fever, nausea, or vomiting were reported. Our study found a high prevalence of *Shigella spp*. in school-aged children from a rural community. Symptoms such as diarrhea, fever or dysentery may not always be present. We suggest implementing interventions, such as molecular diagnosis, to promptly diagnose infections by this gastrointestinal bacterium.

1616

ACUTE SYMMETRICAL POLYARTHRITIS - AN ATYPICAL PRESENTATION OF REACTIVE ARTHRITIS

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Reactive arthritis is classically regarded as a form of spondyloarthropathy following an antecedent gastrointestinal or urogenital infection. The infrequency with which it is encountered makes it a rare disease even among rheumatology practices. It usually presents with asymmetric oligo or monoarthritis involving lower extremities. A 52-year-old woman presented with complaints of multiple symmetrical joint swelling along with pain and prolonged morning stiffness (more than one hour) two weeks after an episode of gastroenteritis. She didn't have any extra-articular manifestations. Examination revealed signs of inflammatory arthritis symmetrically involving multiple large joints (including both knees, ankles). She had ankle enthesitis too. Baseline investigations were suggestive of leucocytosis and high procalcitonin levels with negative HLA B-27. Plain radiographs of knee joints were non-contributory. Cultures were negative. Abdominal imaging showed the presence of gross pyo-hydroureteronephrosis. However, she didnot have any urinary symptoms. Antibiotics, drainage, and analgesic therapy were initiated. With treatment, the pattern of joint involvement became asymmetrical polyarticular in a two weeks' time. She was discharged and had dramatic clinical improvement on a follow up visit. Reactive arthritis largely remains a clinical diagnosis and can unusually present as acute symmetrical polyarthritis involving the large joints with associated coexisting urogenital and gastrointestinal infections. At times identifying the correct causative or triggering infection may be elusive.

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DEVELOPMENT AND EFFICACY OF ORAL THERAPEUTICS TO PREVENT AND TREAT ENTERIC BACTERIAL INFECTIONS

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There remains an unmet need for affordable, non-antibiotic-based therapeutics to treat enteric bacterial infections, particularly in developing countries. Protein-based therapeutics present an opportunity to meet this need, but traditional biologics are often limited by high cost, complicated manufacturing, and cold-chain requirements. We have developed spirulina (*A. platensis*) as a new platform for the manufacturing of orally delivered biologics therapeutics. Spirulina-based oral therapeutics can be produced cost-effectively, do not require purification, and are stable for long periods at ambient temperature. A combination of single-domain antibodies and bacteriolytic enzymes expressed in a spirulina have been used to develop therapeutics to prevent and treat enteric infection by *C. jejuni* and *C. difficil*e. These treatments were designed to confer passive immunity by preventing colonization or reducing bacterial load. We have shown that the therapeutic proteins are expressed at a high level in spirulina, retain bioactivity, and have efficacy in pre-clinical animal models of infection. Clinical trials evaluating the safety and efficacy of both therapeutics are currently underway

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A MOUSE MODEL OF *SALMONELLA* RELAPSING INFECTIONS

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Salmonella infections can cause relapse in a significant proportion of treated patients, and for which novel interventions are needed. Therefore, a murine model of *Salmonella* relapse for Drug Discovery is paramount. We developed a mouse model of *Salmonella* relapse in mice using *S. enterica* Typhimurium 14028 strain. C57BL/6 mice were pre-treated with streptomycin and infected by oral gavage. Bacterial burden was measured by colonies counting in XLD plates, while bodyweight and spleen size were used as markers of disease and inflammation. Infection enabled progression of robust bacterial burdens in spleen, mesenteric lymph nodes and feces. Weight loss and increased spleen were significantly observed after a week of infection, and some infected mice may survive for up to 20 days post-infection. Antibiotic treatment with enrofloxacin treated infected mice, improving bodyweight trajectory, recovering spleen size and clearing bacterial burden in all tested tissues. Removal of antibiotic treatment enabled relapse of infection with robust bacterial burden and disease outcomes within two weeks post-removal of antibiotic therapy. In addition, further establishment of initial infection before antibiotic treatment led to following faster and robust relapsing infection. In conclusion, infection inoculum size, antibiotic treatment duration and antibiotic treatment starting time are major modulators of *Salmonella* relapse in mice. This model will enable screening for novel interventions to prevent or reduce *Salmonella* relapsing infections. All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

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INTERLEUKIN-10 AS A POSSIBLE BIOMARKER OF SEVERITY IN SEPSIS

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Sepsis is complex immune response and is accompanied with considerable derangements of both the innate and adaptive immune systems. Invasive infection triggers a pro-inflammatory and anti-inflammatory response, the magnitude of which depends on multiple factors, including pathogen site of infection, virulence, host genetics, and comorbidities.IL-10 is a molecule with immune-regulatory properties. Secretion of IL-10 in sepsis could limit and ultimately terminate inflammatory responses, which called as anti-inflammation cytokine. Besides, high levels of IL-10 could induce a state of functional immunoparalysis, leading to an incontrollable infection.The objective of this study was to measure the plasma levels of IL-10 and correlate them with the severity of sepsis in patients with this clinical condition, admitted to the Intensive Care Unit (ICU) of a Hospital in Montería, Córdoba-Colombia. A descriptive study was designed, in which 50 ICU patients who met the inclusion criteria were evaluated. The Human IL-10 Biolegend commercial kit (San Diego, CA) was used to determine the plasma levels of IL-10, and the results were analyzed with the SPSS statistical software, applying the Mann Whitney U test for non-parametric data. A statistically significant difference in IL-10 levels was found between septic and non-septic participants, being higher in the sepsis group. Regarding its levels according to the generating focus, a higher value of IL-10 was found in the pulmonary focus. Of particular relevance among the findings is the positive relationship between IL-10 levels, the severity of the disease and the outcome of the clinical picture, taking into account that it is classified as an anti-inflammatory cytokine. Overall, these preliminary results add to our understanding of the global increase in IL-10 production induced by septic shock. More research is required to determine the pathophysiological mechanisms that lead to such increased IL-10 production and its role as a potential biomarker of sepsis severity.

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PREVALENCE OF CARBAPENEM-PRODUCING *KLEBSIELLA PNEUMONIAE* IN PATIENTS WITH SEPSIS IN A HOSPITAL IN NORTHWESTERN COLOMBIA, 2017-2019

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Carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) has been established as important nosocomial pathogen worldwide. A high prevalence of CP-Kp is now observed in many countries causing serious infections that are associated with prolonged hospitalization and increased morbidity and mortality. In healthcare facilities with inadequate infection control practices, these organisms spread from patient to patient very efficiently. The objective of this study was to determine the prevalence of CP-Kp as a cause of sepsis in patients hospitalized in the adult ICU of a health care institution in Montería, Córdoba-Colombia. All data from patients hospitalized in the ICU who developed septic shock due to CP-Kp from November 2017 to December 2019 were retrospectively analysed. Patients who fulfilled the following criteria were enrolled into the study: age 18 years or over, and septic shock due to CP-Kp infection. 120 patients met the inclusion criteria during the study period. The production of Extended Spectrum Betalactamases (ESBL) was confirmed in 23.5% of the isolates, as well as the production of CP-Kp in 11.76%. CP-Kp-producing microorganisms must be subject to compulsory and permanent surveillance by Microbiology laboratories and medical personnel to avoid an increase in therapeutic failures.

1621

ISOLATION OF PATHOGENIC LEPTOSPIRA FROM THE URINE OF SLAUGHTER HOUSE WORKERS, RODENTS AND CATTLE SLAUGHTERED AT THE YANGANDA SLAUGHTER SLAB, JOS NORTH, PLATEAU STATE, NIGERIA

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Leptospirosis is a zoonotic disease of public health importance and listed by WHO as neglected. This research was carried out to determine the prevalence and genetically characterized *Leptospira species among the* slaughter house workers, rodents and the cattle slaughtered at the yanganda slaughter slab, Jos North, plateau state, Nigeria. Urine samples were obtained from 125 slaughtered cattle, 120 trapped rat bladders and 149 Abattoir workers, accompanied structured interviewer-administered questionnaire were collected and inoculated into Ellingausen McCullough-Johnson Harrison (EMJH) medium containing 5-fluorouracil and further subcultured into EMJH medium containing 8-azaguanine and incubated at 13^{o}C for the isolation of pathogenic *Leptospire* according to Johnson and Harris, (1967) and Mgode (2006) respectively. Nested polymerase chain reaction was used to detect the isolates belonging to genus Leptospira, pathogenic Leptospira specific sequence and 16SrRNA Sequence were used to determine the genomospecies of the isolates. The study reveals that out of the 149, 125 and 120 urine and bladder samples from human, cattle and rat examined, 55 (39.6%) , 25(20%) and 53(36.9%) were found to be *Leptospira* positive by PCR. Factors found to be associated with leptospirosis among slaughtered cattle were breed of cattle(x^2 = 15.163; P<0.000) and source of cattle (x^2 = 17.746. P<0.000), while for the abattoir workers are; Age group 26-45year ((x^2 = 9.418; P< 0.024), Educational level ((x^2 = 15.071; P< 0.002), and work duration ((x^2 =8.918; P< 0.012). Also the attitude and practices of the workers were significantly associated with leptospirosis among the workers at P<0.05. This study showed the presence of pathogenic leptospires belonging to *Leptospiraborgpetersenii, Leptospirainterrogans, Leptospirasantarosai and Leptospirakmetyi* in the yanganda slaughter slab, Jos North, plateau state, Nigeria.**Keywords:** Leptospira; cattle, rodents, urine, isolation, PCR, phylogeny; associated risk

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HIGH RATES OF ANTIMICROBIAL RESISTANCE IN CLINICAL ISOLATES FROM CHILDREN WITH BACTEREMIA AND MALARIA IN A HOLOENDEMIC *PLASMODIUM FALCIPARUM* TRASMISSION REGION OF WESTERN KENYA

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Children in holoendemic *Plasmodium falciparum* transmission regions, such as western Kenya, commonly have malaria and bacteremia co-infections leading to increased morbidity and mortality. High rates of suspected antimicrobial resistance (AMR) challenge clinical management. We present AMR patterns for 131 clinical isolates from children with bacteremia and malaria who presented with acute febrile illness at Siaya County Referral Hospital, western Kenya. Prior to treatment, venous blood was collected and incubated in a BD BACTEC 9050 automated system. Positive cultures were Gram-stained, sub-cultured, and incubated for 18-24 hours to obtain pure colonies for identification. AMR resistance patterns were identified using disk diffusion method for commonly used antibiotics including ciprofloxacin (CIP), ampicillin/sulbactam (SAM), gentamycin (GM), ampicillin (AM), imipenem (IMP), amoxy-clavulinic acid (AMC), ceftriaxone (CRO), chloramphenicol (CHLO), tetracycline (TE), nalidixic acid (NA), kanamycin (K), vancomycin (VA), and trimethoprim/sulfamethoxazole (SxT). The most prevalent Gram (-) clinical isolate (52.6%) was *non-Typhoidal Salmonella (NTS)* and was susceptible to K (100%), IMP (100%), and GM (96%) with resistance to CIP (12%), NA (20%), CRO (15%), and TE (13%). *Staphylococcus aureus* was the most common Gram (+) clinical isolate (14.5%) and was susceptible to SAM (100%) AMC, (100%), and CIP (100%). However, there was resistance for GM (33%), SxT (35%), and CHLO (18%). *E. coli*, *Acinetobacter spp*., *Pseudomonas aeruginosa*, *Salmonella enterica serovar enteritidis*, *Enterococcus faecalis*, *Haemophilus influenza*, and *Klebsiella pneumoniae* had high susceptibility to most of the commonly used antibiotics. However, *Enterobactereeacea* was 100% resistant to SAM, GM, AMC, SxT, and CHLO, while *Haemophilus influenza*, *Klebsiella pnuemoniae*, *Pseudomonas putida*, *Salmonella typhi*, *Shigella Spp*, and *Streptococcus group D* were 100% resistant to SxT. Taken together, these data suggest bacteremia-causing pathogens in the region have high rates of AMR with resistance to at least one of the commonly used antimicrobials.

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CHARACTERIZATION OF *KLEBSIELLA PNEUMONIAE* STRAINS FROM HOSPITALIZED PATIENTS IN BANGLADESH

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The prevalence of multi drug resistant bacteria is increasing worldwide owing to overuse of antibiotics, particularly in developing countries. *Klebsiella pneumoniae* (Kpn), highly resistant to antibiotics, has emerged as a leading cause of neonatal sepsis. In addition, information on the immune targets of Kpn, is critical for the development of effective vaccine candidates. In this study, we aimed to characterize a collection of Kpn isolates to determine: 1) the extent of antibiotic resistance of the isolates, 2) the dominant lineages found in Bangladesh, and 3) major K and O antigens expressed by these strains in Bangladesh. Isolates are collected from individuals with invasive Kpn infection being treated at a tertiary care hospital. The resistance pattern was determined by Kirby-Bauer disc diffusion test and confirmed by Vitek-2 in case of ambiguity. Whole genome sequencing (WGS) is ongoing to determine the dominant

lineages, common capsular (K) and O-polysaccharide (O) antigen types, AMR and virulence genes. The study so far shows that the Kpn isolates identified from patients ranging in age from 14 days to 75 years. Most (27.6%) of the isolates were collected from the surgical ward, outpatient department (20.7%), and intensive care unit (13.8%). The isolates were obtained from various clinical samples: wound swab/pus (41.4%), sputum (24.1%), urine (20.7%), tracheal aspirate (10.3%), and blood (3.4%). The cases were diagnosed accordingly: wound infection (41.4%), pneumonia (31%), urinary tract infection (20.7%), and sepsis (3.4%). Antimicrobial sensitivity tests were performed using 14 antibiotics. More than 50% of isolates were resistant to 6 antibiotics: Tigecycline, Ceftriaxone, Ceftazidime, Cefepime, Ciprofloxacin and Doxycycline. Notably, 31.8% of the isolates showed resistance to carbapenems (meropenem and imipenem) and gentamicin. In this study, the plan is also to compare the community acquired and hospital acquired Kpn isolates. While the study is ongoing, including WGS for all isolates, initial clinical and phenotypic findings suggest further analysis which can be useful for future approach of vaccine development.

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THE GEOGRAPHICAL DISTRIBUTION OF SCRUB TYPHUS IN INDONESIA: EVIDENCE MAPPING

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Scrub typhus is a potentially fatal febrile illness caused by the obligate intracellular bacteria *Orientia tsutsugamushi*. Although scrub typhus cases have been documented in Indonesia, definitive knowledge concerning the distribution and risk of scrub typhus in Indonesia is scant. This study aimed to confirm the presence and distributions of *O. tsutsugamushi* and its vector, *Leptotrombidium* mites, at certain locales in Indonesia. We executed a mapping effort employing two-pronged approach, i.e. geographic placement of reported evidence on *O. tsutsugamushi* transmission and its vector presence, and a serosurvey of archived febrile illness samples collected at Jambi, Denpasar, and Tabanan using in-house enzyme-linked immunosorbent assay (ELISA). The subnational units were assigned scores and ranked based on the certainty for the presence of human infection risk by *O. tsutsugamushi*. Literature searches were performed in electronic databases to locate existing evidence, along with searches of the grey literature. Data from 1908 to 2018 were extracted, yielding 354 data points across 25 out of 77 (32%) subnational units. Though data points were documented across the five major islands (Borneo, Java, Sumatra, Sulawesi, and Papua), this still highlighted the lack of evidence in the other two thirds of subnational units. We found one confirmed acute scrub typhus case with unknown infection location. There were 2,780 probable human cases documented. All animal hosts infected were rodents. *Leptotrombidium deliense* was the most commonly documented vector species. South Sumatra and Biak had the best evidence of sustaining infective vector. We can conclude that *O. tsutsugamushi* exists in Indonesia. Although the presence of infective vectors was well documented, this study also highlighted areas of knowledge gaps. A great deal more work in Indonesia remains to be done to inform even the most basic understanding of the distribution and burden of this infection, and our efforts begin to fill those many wide gaps in understanding.

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THE CHARACTERISTICS OF BACTEREMIA AMONG PATIENTS WITH ACUTE FEBRILE ILLNESS REQUIRING HOSPITALIZATION IN INDONESIA

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Blood culturing remains the "gold standard" for bloodstream infection (BSI) diagnosis, but the method is inaccessible to many developing countries due to high costs and insufficient resources. To better understand the utility of blood cultures among patients in Indonesia, a country where blood cultures are not routinely performed, we evaluated data from a previous cohort study that included blood cultures for all participants. An acute febrile illness study was conducted from July 2013 to June 2016 at eight major hospitals in seven provincial capitals in Indonesia. All participants presented with a fever, and two-sided aerobic blood cultures were performed within 48 hours of hospital admission. Positive cultures were further assessed for antimicrobial resistance (AMR) patterns. Specimens from participants with negative culture results were screened by advanced molecular and serological methods for evidence of causal pathogens. Blood cultures were performed for 1,459 of 1,464 participants, and the 1,030 (70.6%) participants that were negative by dengue NS1 antigen test were included in further analysis. Bacteremia was observed in 92 (8.9%) participants, with the most frequent pathogens being *Salmonella spp.* (51), *Escherichia coli* (14), and *Staphylococcus aureus* (10). Two *Salmonella spp.* cases had evidence of AMR, and several *E. coli* cases were multidrug resistant (6/14, 42.9%) or monoresistant (2/14, 14.3%). Culture contamination was observed in 37 (3.6%) cases. Advanced laboratory assays identified culturable pathogens in participants having negative cultures, with 23.1% to 90% of cases being missed by blood cultures. Blood cultures are a valuable diagnostic tool for hospitalized patients presenting with fever. In Indonesia, pre-screening patients for the most common viral infections, such as dengue, influenza, and chikungunya viruses, would maximize the benefit to the patient while also conserving resources. Blood cultures should also be supplemented with advanced laboratory tests when available.

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THE IMPACT OF THE COMMUNITY AND PUBLIC HEALTH RESPONSE TO COVID-19 ON PEDIATRIC TYPHOID SURVEILLANCE AND DETECTION IN MALAWI

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Typhoid is an important cause of morbidity and mortality. Disease estimates depend on blood culture confirmation; however, this is dependent on health-seeking behaviour and access to health facilities with blood culture services. The COVID-19 pandemic has affected healthcare attendance, and may affect accurate estimates of typhoid burden. We investigated the impact of COVID-19 on patient attendance, blood culture surveillance and typhoid detection in Malawi, using segmented negative binomial regression, with both 'step' and 'slope' changes post-COVID (01/04/2020-31/12/2022) and harmonic terms to account for seasonal peaks. We utilised data from: 1. routine paediatric blood cultures collected at Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi, and enhanced community surveillance within the Typhoid Vaccine Acceleration Consortium (TyVAC) phase 3 TCV clinical trial 2. Paediatric in- and out-patient (OP) healthcare attendance data from patient registers at QECH, and two community health centres 3. Malawi National censuses. COVID-19 substantially impacted paediatric typhoid case detection rates in Blantyre, with an estimated fall of 63% (95% CI 60 -65%), resulting in an estimated 263 (235-291) missed typhoid cases. There was a concordant fall in paediatric blood culture collection rates of 62% (61-64%), with a predicted 21,381 (20,349—22,413) being missed. Similarly, QECH paediatric OP attendances declined by 29% (26-32%) and ward admissions by 48% (45-51%). There was a 69% (67-71%) decline in paediatric attendances at the health centres. During the study period, healthcare attendance, blood culture collection, and typhoid detection did not recover to pre-COVID levels, except OP attendances at QECH. Paediatric typhoid case detection fell substantially post-COVID, driven predominantly by reduced health facility attendance and did not recover within the study period. The proportion of febrile presentations and blood culture positivity did not change, suggesting a substantial burden of typhoid was being missed in the community, potentially leading to increased morbidity, mortality or typhoid transmission.

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SERO-EPIDEMIOLOGY IN AFRICA OF INVASIVE NON-TYPHOIDAL SALMONELLOSIS (SAINTS STUDY); STUDY AIMS, DESIGN AND EARLY FINDINGS

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Non-typhoidal Salmonella (NTS) are a major cause of paediatric bloodstream infections in sub-Saharan Africa. Understanding the seroepidemiology and correlates of protection (COP) for invasive NTS (iNTS) in relation to risk factors (malaria, anaemia, malnutrition) among children is needed to inform vaccine implementation. SAiNTS aims to: understand the epidemiology of enteric NTS and subsequent acquisition of immunity in children; the impacts of gut health, risk factors and geographic setting; identify a population antibody COP; compare acquired immunity between invasive and asymptomatic NTS disease. SAINTS is a prospective community cohort study collecting 3-monthly paired serology samples from 2500 children 0-5 years to measure age-stratified acquisition of lipopolysaccharide O-antigen antibody and serum bactericidal activity to the main serovars causing iNTS (*Salmonella Typhimurium* and *Enteritidis*). Children are selected from censused randomly selected households in Chikwawa, Malawi, covering areas with contrasting malaria burden. Data on risk factors, socioeconomic status, water and sanitation, is collected via rapid diagnostic tests (RDT), anthropometry, and electronic reporting. Stool samples are processed for NTS culture and pan-Salmonella PCR. Cases of iNTS disease are followed for longitudinal immunity. Gut health will be assessed through a multiplexed serum assay for enteric environmental dysfunction, and stool myeloperoxidase. To date, 2295 children have been enrolled. *Salmonella* stool positivity rate in healthy children is 6% (n=116): *S. Typhimurium* 13.8% (16), *S. Enteritidis* 11.2% (13), *S.* species 73.3% (85), S. Typhi 1.7% (2) and shows a seasonal pattern. Malaria RDT positivity at enrollment is 11% (261); 17% (209) in high and 5% (52) in low malaria transmission areas. Severe-acute malnutrition was present in 1.2% (28) by weight-for-height z-scores (<-3 SD) and 2.9% (67) by mid-upper arm circumference <12.5cm. We will assess NTS immunity in relation to these epidemiological risk data to derive COP; identify windows of immune susceptibility; and inform vaccine implementation.

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GENOMIC CHARACTERIZATION OF BACTERIA ISOLATED FROM FEBRILE PATIENTS IN GHANA

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Invasive bacteria like typhoidal, non-typhoidal *Salmonella* spp. and nosocomial bacteria like *Bacillus* spp. have been implicated in severe sepsis. In this study, we used whole genome sequencing (WGS) to better understand the genomic epidemiology and antimicrobial resistance (AMR) patterns of these pathogens isolated from the blood of febrile patients in Ghana. Five bacteria (3 *Salmonella enterica* serovar Typhi, 1 *Salmonella enterica* serovar Typhimurium and 1 *Bacillus cereus*) were isolated from blood cultures of acutely febrile patients from selected health centres. Whole genome sequencing (WGS) was performed on the Illumina Miseq Platform. Assembled genomes were used to query PubMLST.org, the Comprehensive Antimicrobial Resistance Database (CARD) for genomic epidemiology and AMR genes information. The four *Salmonella* spp. were identified as *S.* Typhi (3/4) and *S.* Typhimurium (1/4). The *S.* Typhi and *S.* Typhimurium were determined to have sequence types (STs) ST-2 and ST-313, respectively. These STs have emerged as multidrug resistant strains known to cause severe *Salmonella* infection in sub-Saharan Africa. They are also known to have increased pathogenicity. All *Salmonella* isolates encoded different virulence genes such as *beaR*, *Mdtk* and *CRP.* These isolates also contained multidrug resistance genes like *AAC(6)-Laa* (4/4), *tet(B) and tetR* (1/4), *dfrA15* (2/4), *TEM-1* (2/4) and *gyrA(D87Y)* (1/4), which confer resistance to aminoglycosides, tetracyclines, chloramphenicol, ß-lactams, and fluoroquinolones, respectively. The *B. cereus* strain carried a resistant gene for fosfomycin, *fosB.* The ST for *B. cereus* could not be determined, indicating a probable novel ST. Despite the limited sample size of bacterial isolates recovered, this study demonstrates evidence of emerging multidrug resistance in *S.* Typhi to the current first-line antibiotics used in Ghana. This study highlights the need for prospective genomic surveillance and molecular characterization of bacteria isolated to further improve local antibiograms.

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COST AND COMMUNITY ACCEPTABILITY OF ENHANCED ANTIBIOTIC APPROACHES FOR TRACHOMA IN THE REPUBLIC OF SOUTH SUDAN: ENHANCING THE A IN SAFE (ETAS) STUDY PROTOCOL

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The World Health Organization (WHO) has targeted trachoma for global elimination as a public health problem by 2030. Reaching elimination thresholds by the year 2030 in South Sudan will be a considerable challenge as the country currently has many counties considered highly endemic. Evidence from randomized trials, mathematical modeling, and population-based surveys suggest that enhancements may be needed to the standard-of-care mass drug administration (MDA) trachoma intervention to reach elimination thresholds in a timely manner. Here we describe a study protocol to determine the cost and community acceptability of enhanced antibiotic strategies for trachoma in South Sudan. The Enhancing the A in SAFE (ETAS) study is a community randomized intervention costing and community acceptability study. Following a population-based trachoma prevalence survey in one county, 30 communities will be randomized 1:1 to receive 1 of 2 enhanced MDA interventions, with the remaining communities receiving standard-of-care MDA. The first intervention strategy will consist of a community-wide MDA followed by 2 rounds of targeted treatment to children ages 6 months to 9 years approximately 2 weeks and 4 weeks after the community MDA. The second strategy will consist of a community-wide biannual MDA approximately 6 to 8 months apart. The costing analysis will use a payer perspective and identify the total cost of the interventions and annual MDA. Community acceptability will be assessed through MDA coverage monitoring and mixed-methods research involving community stakeholders. A second prevalence survey will be conducted approximately 12 months after the original survey. ETAS has received ethical approval from Emory University and the Ministry of Health of South Sudan. The study began in March 2022. The results of this study will provide key information to trachoma programs on the affordability and acceptability of enhanced antibiotic interventions. These results will further aid in the design of trachoma-specific antibiotic efficacy trials. Enhanced MDA approaches could help countries reach trachoma elimination as a public health problem by 2030.

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ADVANCING IN THE ELIMINATION OF TRACHOMA AS A CAUSE OF BLINDNESS: THE CASE OF SÃO PAULO METROPOLITAN AREA, BRAZIL

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Brazil is still considered an endemic country for trachoma. However, surveys carried out in the last decade have shown a consistent drop in the prevalence of inflammatory trachoma in children aged 1 to 9 years. Most surveys have been carried out in poor rural populations with a history of trachoma. In Brazil, in the past decades, there was an intense migration of the rural population to the periphery of large cities, constituting a belt of poverty in their surroundings. The question we sought to answer was whether the migration of poor populations from rural areas had brought trachoma with it. A household survey on the prevalence of trachoma was carried out in a representative sample of the population aged 1 to 9 years in two of the poorest municipalities in the metropolitan region of São Paulo, Brazil's largest city. These municipalities have experienced large population growth in the last two decades (an average population growth of 40% between 2000 and 2021). The municipalities, and within them the census sectors sampled, were selected among those with the worst income and sanitation indicators. A visit was made to the selected households, in which the study was presented and the invitation to participate was made. Those who accepted provided written consent. All household members were examined for signs of trachoma by standardized examiners. The prevalence of TF in children aged 1 to 9 years was 1.5% (79/5393). Among their siblings aged between 10 and 19, the prevalence was 2.4% (67/2809), being significantly higher among girls (3.2%) than among boys (1.5%). Among adults (>20 years) the prevalence of TF was 0.5% (33/7073). No cases of TS, TT or CO were diagnosed. The results suggest that the urbanization of trachoma did not occur, and reinforce the hypothesis of the elimination of trachoma as a cause of blindness in Brazil. The decline in the prevalence and severity of trachoma and the maintenance of a low prevalence level highlight the need for new approaches to disease surveillance and control in the post-elimination period.

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PREDICTORS OF PERSISTENT AND RECRUDESCENT TRACHOMA: FINDINGS FROM A QUALITATIVE INVESTIGATION IN KALAMBO DC, MPWAPWA DC AND MONDULI DC IN TANZANIA

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In 2014, 71 evaluation units (EU) had ≥5% trachomatous inflammation-follicular (TF) prevalence, thereby requiring mass drug administration (MDA). By 2022, only 10 EUs need MDA, with 3 still experiencing persistent TF. This study analyzed the challenges from the latest MDA conducted in these EUs. Key informant interviews (KII) were done at the district level with District Medical Officer, District Neglected Tropical Disease (NTD) officer, Water Sanitation and Hygiene (WASH) and Veterinary officers. Factors such as timing of MDA, mobile migrant populations, hard-to-reach areas were explored. Two sites from each district were selected based on their TF prevalence. One frontline health care worker and 2 community drug distributors (CDD) were interviewed. 2 focus group discussions (FGD) were conducted among community members divided by sex. From the FGDs, participants were aware and had basic knowledge of trachoma disease and MDAs. However, many of them were not reached by the CDDs especially in Monduli DC and Mpwapwa North due to most of them being out of their residence areas. Interviews with CDDs also coincided with the findings from the FGDs that they mostly couldn't reach remote areas especially rainy seasons such as Winza in Mpwapwa DC. Also, due to insufficient number of CDDs it was hard to attend all households, especially in Monduli DC where one hamlet consists of up to 100 households. In Monduli DC, findings revealed that timing of MDA sometimes conflicts with the annual migration of the pastoralists. Recommendations for strengthening MDA include 1) district officers be part of MDA planning from onset 2) disburse funds for MDAs on time through early planning with districts 3) Leverage for additional resources to strengthen logistics, supplies and human resources, and 4) enhanced daily supervision especially in hard-to-reach areas.

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CHLAMYDIA TRACHOMATIS TRANSMISSION DYNAMICS IN AN AREA OF PERSISTENT AND RECRUDESCENT TRACHOMA IN KAJIADO COUNTY, KENYA

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Kajiado County in southern Kenya is an area of persistent and recrudescent trachoma. Kajiado West sub-county has conducted multiple rounds of azithromycin MDA since 2007 (as part of the full SAFE strategy) but has failed to achieve elimination thresholds as expected. Whilst in Kajiado South, East and West sub-counties, trachomatous inflammation-follicular (TF) elimination thresholds were achieved in 2017 but surveillance surveys in 2020 reported an increase in TF, resulting in a resumption of mass drug administration. The International Trachoma Initiative has recently produced guidance to countries where persistent and recrudescent TF has been identified, highlighting the need for an in-depth data review and support to alternative treatment strategies. Sightsavers in partnership with the Kenyan MoH have implemented an operational research study to review reasons for the persistent or resurgent TF in Kajiado County, including an assessment of the contribution of various programmatic, epidemiological and survey sampling issues. This will inform necessary programmatic adaptations, including enhanced treatment strategies. A key step in this research is to better understand the *Chlamydia trachomatis* (*Ct*) transmission dynamics, to evaluate if the reported TF is a result of *Ct* infection and evaluate the evidence of on-going or potential increases in recent transmission. In September 2021 a survey comprising of four evaluation units (sub-counties) were conducted where clinical, *Ct* infection and anti-*Ct* antibody data was collected from children aged 1-9 years, through a two-stage population-based survey. This was conducted before the next round of MDA planned for the end of 2021. A follow-up survey will also be conducted six months after the MDA in 2022. This presentation will outline the results of the pre-MDA survey. The clinical data highlights that three of the four sub-counties had TF prevalence of over 5% (ranging from 8.1% to 18.0%) in children aged 1-9 years, with only Kajiado East reporting a TF prevalence below the 5% elimination threshold. The infection and antibody data are currently being compiled and will also be presented.

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EXPERIENCE FROM JOINT MASS DRUG ADMINISTRATION FOR TRACHOMA TARGETING MIGRANT POPULATIONS IN UGANDA AND KENYA

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Uganda launched the surgery, antibiotics, facial cleanliness and environmental improvements (SAFE) strategy for trachoma elimination in 2006. Thus far, Uganda has stopped mass drug administration (MDA) in 46 out of 51 endemic districts. However, trachoma remains persistent or recrudescent in five districts (Moroto, Nakapiripirit, Nabilatuk, Amudat and Buliisa); thus we investigated the underlying reasons. The investigation showed that MDA was systematically missing hard-to-reach populations such as nomadic pastoralists, mine-workers, and mobile cultivators that migrate across the border into Kenya. To target the cross-border mobile populations, a joint MDA activity with Kenya was recommended. A meeting of senior Ministry of Health (MoH) officials and partners from both countries was held to: review findings from investigations; discuss strategies to target MDA to previously unreached populations; and identify areas for collaboration. A joint committee of MoH official and partners was formed to oversee planning, budgeting, mobilisation of political leaders and communities, and allocation of resources. The first ever cross-border Uganda / Kenya MDA for trachoma was launched on 21st October 2021 by respective ministers, local government leaders and senior MoH officials in both countries. After the MDA, Amudat and Moroto districts, which neighbours Kenya, reported program coverage of 83.6% and 84.7%, respectively. Coverage evaluation survey (CES) results from Amudat showed that 82.6.% of population was offered treatment while 84.3% of those offered treatment swallowed the medicine (compliance). In a sub-sample of populations in pastoralist kraals CES revealed that 89.3% of eligible population was reached and compliance was 97.9%. The Joint MDA approach enabled effective coverage among the hard-to-reach populations. This Joint MDA approach contributed to meeting the WHO recommended MDA coverage target of 80% and above in Moroto and Amudat. Cross-border coordination, proper planning and commitment from both countries were key to achieving a successful joint MDA and should be sustained in future activities.

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POST-ELIMINATION TRACHOMA SURVEILLANCE: THE *SURVEILLANCE POST-ENDÉMIQUE DU TRACHOME* (SPET) STUDY NIGER

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Niger has observed considerable reductions in trachoma since the start of SAFE (surgery, antibiotics, facial cleanliness, and environmental improvement) interventions in 2002. With only 12 districts remaining to demonstrate achievement of the trachomatous inflammation-follicular (TF) threshold, the country is expecting to eliminate trachoma as a public health problem by 2025. While this will be a monumental achievement, recrudescence of trachoma after elimination is reached is a concern for Niger and the global program. The aim of the *Surveillance Post-Endémique du Trachome* (SPET) study was to determine the long-term threat of recrudescence in areas historically hyperendemic for trachoma using standard and enhanced indicators. The 3 SPET districts, which were highly trachoma endemic (TF >30% among children ages 1 to 9 years) at baseline in 1999, had achieved the TF elimination threshold (<5%) between 2010 and 2014 and had further stayed below threshold as determined by a surveillance survey in 2018. Within each district, a population-based cluster-randomized survey was conducted. Certified graders assessed trachoma signs among children ages 6 months to 15 years using the WHO simplified system. Conjunctival photographs were taken, and conjunctival swabs and dried blood spots were collected to test for Chlamydial infection and serological responses, respectively. During the 2022 SPET study, 3,690 children (ages 1 to 9 years) were examined for trachoma. All 3 districts, Bagaroua (1.2%, 95% Confidence Interval (CI): 0.6-2.2), Ilela (3.1%, 95% CI:1.4-6.8), and Malbaza (2.4%, 95% CI:1.2-4.5) remained below the 5% TF threshold after up to 12 years without antibiotic intervention. Trachomatous inflammation-intense prevalence in this age group was <1.5% for all districts. Once available, photographic, infection, and serology data will help characterize and confirm this low trachoma prevalence. Trachoma recrudescence was not observed after 12 years post-antibiotic cessation within formerly hyperendemic districts. Further work remains to develop programmatic strategies for long-term post-elimination surveillance.

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SEROLOGIC RESPONSES WITHIN DISTRICTS EXPERIENCING PERSISTENT TRACHOMA, AMHARA, ETHIOPIA

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Persistent trachoma occurs when endemic districts do not reach the elimination as a public health problem (EPHP) threshold of <5% trachomatous inflammation—follicular [TF] among children ages 1–9 years after more than the recommended number of years of SAFE (surgery, antibiotics, facial cleanliness, environmental improvement) strategy interventions based on the baseline TF prevalence. Persistent trachoma is increasingly recognized as a serious concern for the global trachoma program. This study investigated if enhanced monitoring of trachoma transmission intensity using infection and serologic markers could elucidate long-term transmission patterns within 4 districts in Amhara, Ethiopia, with persistent trachoma. During population-based surveys conducted in 2019, certified graders examined 3,065 children ages 1–9 years for clinical signs of trachoma using the WHO simplified grading system, a conjunctival swab was taken from children ages 1–5 years to monitor for *Chlamydia trachomatis (Ct)* infection, and finger-prick blood was taken from children ages 1–9 years to measure antibodies to the *Ct* antigen Pgp3 using a bead-based immunoassay. Seroconversion rates (SCR) were estimated using a generalized linear model and robust standard errors to estimate the force of ocular *Ct* infection among children ages 1–9 years. Ebinat district remained hyperendemic, with a TF prevalence of 42.5% and infection prevalence of 7.1%. These indicators were lower in the other 3 districts, ranging from 10.7% to 17.9% TF prevalence and 0% to 1.7% infection prevalence. The SCR in Ebinat was 0.108 seroconversions/child/year (95% confidence interval [CI]: 0.082, 0.144); by comparison, the SCR was much lower in the other 3 districts, ranging from 0.011-0.039. This study demonstrated that, while slow, the SAFE strategy can push hyperendemic districts towards the elimination threshold and that other markers of ocular *Ct* transmission support continued transmission in Ebinat. Districts with persistent trachoma may require more intensive antibiotic, water, and sanitation interventions to reach EPHP by 2030.

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TACKLING TRACHOMA END GAME CHALLENGES AND FAST-TRACKING TRACHOMA ELIMINATION IN TANZANIA: LEVERAGING NEW APPROACHES TO SCALE UP SAFE INTERVENTIONS

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Between 2004 and 2012, 71 trachoma endemic districts were identified. The mean prevalence of active trachoma inflammation follicular (TF) was 25.4%. The highest prevalence of TF among children 1-9 years was 69%. Mean Trachomatous Trichiasis (TT) was 2.7% with an estimated 12.5 million people at risk for trachoma. Implementation of Mass drug Administration (MDA) was initiated in a few districts and by 2015, 71 were covered. Despite several MDA rounds (5 in Arusha to over 8 in Dodoma) recrudescent and persistent TF ranged from 14.5% in Longido to 5.8% in Kalambo. In pursuit of the World Health Organization (WHO) 2030 roadmap for Neglected Tropical Diseases (NTDs) Tanzania has updated its MDA strategy for trachoma elimination. 9 districts with persistent and recrudescent TF were analyzed and identified to form a geographical link known as the trachoma belt. 5/9 districts are inhabited by Maasai nomadic pastoralist with routine cross-border movement alongside Kenya. The timing of MDA, inadequate behavioral change communication (BCC), delayed access to funds, drug stock out, and misconceptions of MDA contributed to poor drug uptake. Access to improved toilet was 25% in Kiteto while access to hand and face washing facilities was 14% in Monduli. Given the limited coverage of WASH, MDA still remains important against trachoma. We revised our approach by substituting impact surveys with enhanced MDAs in 4 districts which will increase the antibiotic pressure and result in more increased TF burden reduction. We will strengthen MDA among Maasai population across the Tanzania-Kenya border by conducting joint MDA between neighboring trachoma endemic districts. We will strengthen drug uptake through Microplanning and in-depth community sensitization to assure high level community engagement in areas with the highest TF prevalence, and hard to reach characteristics. We have adjusted MDA timing to June each year and lengthened MDA duration to 7 days that will guarantee high uptake and coverage. Daily data capture will be conducted that will help to identify low performing villages in real time and intervene accordingly.

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ADDRESSING TRICHIASIS SURGICAL DATA CHALLENGES FOR DOSSIER VALIDATION IN THE TRACHOMA ELIMINATION ENDGAME: EXPERIENCE FROM TANZANIA

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Trachomatous trichiasis (TT) was endemic in 87 districts where TT prevalence was ≥0.2% from 2004 -2017. Recently, 61 districts still had TT prevalence ≥0.2%. For elimination of trachoma as a public health problem, the World Health Organization (WHO) recommends evidence of TT prevalence of <0.2% and a system to identify and manage incident cases. This study presentsresults of an assessment to gather data for prioritizing TT surgery services and to collate evidence for districts where TT elimination had been attained. We conducted a desk review of TT data for 184 districts in Tanzania. Districts were grouped into three categories: non-endemic districts(with?) no baseline survey; formerly endemic districts at baseline with TT prevalence <0.2% at most recent survey; and current endemic districts. The latter was further subdivided into 3 groups: 1) planned upcoming survey; 2) completed the TT surgery program but had unsatisfactory data; and 3) ongoing TT surgical program. In the evaluation 80 districts were non-endemic, 45 districts were endemic at baseline but currently had low TT prevalence at the most recent survey and 59 districts are currently endemic. Among the currently endemic districts: 10 had upcoming surveys; 10 had completed the TT surgery program but had unsatisfactory data; and 39 had on-going TT surgical interventions. This grouping allowed detailed plans for each category and the procedures of verifying documentation of attainment of TT elimination. Three key strategies were proposed: 1) to mobilize the existing TT surgery data in districts with previous TT surgery program and make sure the records were archived; 2) to conduct TT-only surveys in districts which had completed TT surgical program but no satisfactory records of data available; and 3) to conduct data audit and collate reports for all endemic districts with no or poor historical data. Verifying the existence of TT surgery records to evidence full geographical coverage in all TT endemic districts and proper archiving of existing data/ documents is important to support Tanzania archive evidence for future application to WHO for validation of elimination of trachoma.

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REACHING THE TRACHOMATOUS INFLAMMATION—FOLLICULAR TARGET AND STOPPING MDA IN ALL TRACHOMA ENDEMIC HEALTH DISTRICTS OF GUINEA

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Mapping of trachoma conducted between 2011 and 2016 identified 18 health districts (HDs) endemic with trachoma: 9 with trachomatous inflammation – follicular (TF) prevalence of 5-9.9%, 4 with TF prevalence of 10-29,9% and 5 with TF prevalence ≥30%. One to five rounds of mass drug administration (MDA) for all at-risk populations were needed to reach the TF elimination target in these HDs. Between 2014 and 2020, 16 HDs received the recommended number of rounds of MDA with azithromycin and tetracycline ointment, with support from the United States Agency for International Development (USAID) through the ENVISION Project and Act to End NTDs | West program. 15 HDs successfully passed trachoma impact survey (TIS) during 2017-2019 (TF prevalence <5%) and stopped MDA, while 2 HDs did not conduct MDA based on re-mapping results from 2017 and 2018 that showed TF prevalence had since decreased to <5%. A TIS (Trachoma Impact Survey) in the last HD (Dinguiraye) was conducted in 2021, six months after its last round of MDA. A cross-sectional survey using a cluster sampling method of 20 villages and 30 households randomly selected was conducted to assess the prevalence of TF in children aged 1-9 years and the prevalence of TT in adults aged 15 years and above. TF and TT were diagnosed by clinical examination using the World Health Organization (WHO) simplified grading system. A total of 1,551 children and 1,164 adults from 502 households were screened for clinical signs of TF and TT, respectively. The results showed a significant reduction from the baseline: TF prevalence decreased from 37.19% to 0.32% and TT prevalence from 4.50% to 0.08%. Therefore, one to five rounds of annual trachoma MDA with sufficient program coverage has significantly reduced TF prevalence to below 5% in all endemic HDs, reaching the criteria to stop MDA in Guinea. The persistently elevated TT prevalence in some districts highlights the need of systematic TT surgical intervention in Guinea.

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MASS DRUG ADMINISTRATION IN INSECURE CONTEXTS: CHALLENGES AND SOLUTIONS FOR CAMPAIGN IMPLEMENTATION IN BOSSO AND DIFFA DISTRICTS IN DIFFA REGION, NIGER

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Despite progress in Niger to eliminate trachoma as a public health problem, insecurity is a challenge to achieve the elimination targets. Since 2015, the health districts (HDs) of Diffa and Bosso (both in Diffa region) have experienced growing insecurity due to terrorist groups such as Boko Haram in the border area between Niger and Nigeria, impacting the Diffa region of Niger and the Yobe and Borno states in Nigeria. These two HDs failed a recent trachoma impact assessment (TIS) in 2019, with trachomatous inflammation – follicular (TF) >11.5%, requiring three more rounds of MDA. This ongoing insecurity, since 2015, has resulted in internal and external population displacement, leading to challenges in mass drug administration (MDA) implementation. Population displacement makes it difficult to know the true target population for treatment, leading to insufficient quantities of Zithromax requested for MDA. In addition, MDA implementation is difficult due to restrictions placed on community drug distributors: motorcycles are prohibited, working hours are restricted, and access to certain areas is limited. With support from USAID's Act | West program, several strategies have been adapted to improve MDA coverage and quality. These include mapping the villages and towns with displaced populations, redeploying , redeploying distributor teams, increasing the number of days for the MDA,MDA, and using rented vehicles as part of a mobile strategy to improve distribution quality in these areas. Supervision strategies include the recruitment of local supervisors, the use of the supervisors coverage tool by all supervisors, and the creation of a WhatsApp group to conduct daily debriefings and facilitate communication between supervisors. Since the implementation of these new strategies, MDA coverage has increased in Diffa and Bosso HDs from 59.3% and 50.5% in 2018, to 91% and 71% in 2020, and 100.2% and 99.8% in 2021. Additional work is planned to account for the internally displaced population living among targeted communities to better understand the true population magnitude and ensure all targeted populations are reached in future MDA campaigns.

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EXPERIENCES OF FAMILIES BENEFITING FROM COMMUNITY FUNDS FOR TRANSPORTATION STRATEGY IN MANHIÇA (MOZAMBIQUE)

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Access to health services is fundamental for good health. In rural areas of low- and middle-income countries (LMICs), there are still several barriers to accessing health services such as transport to the health facility. Within the Child Health and Mortality Prevention Surveillance (CHAMPS) framework, a community transport strategy was developed within the community to support critically ill to move from the remote community to the health facilities. This strategy consists of identifying and providing local transport to support the needs of the community. The strategy has been implemented in 6 neighborhoods of the Manhiça district, south rural Mozambique. Qualitative approach was conducted to evaluate and monitor the on-going implementation of the strategy, two monitoring rounds were conducted through community meetings and 10 individual semi-structured interviews with the beneficiaries of the strategy. The data extracted in the meetings and interviews were summarized in an MS Excel matrix, submitted to content analysis and thereafter synthetized. Based on the evidence and lessons learned between June 2019 to May 2021, the transport strategy had been implemented for transport of the seriously ill to the health facility and also being used to support other emergencies in the community. As such, several community members benefited from this strategy, among which seven were related to transportation of seriously ill, two related to supporting funeral expenses including transportation and finally for displacement and purchase of medication. The beneficiaries explained that the transportation system created in the community was useful and it is a worth to keep. The availability and readiness of transportation for critically ill has helped prevent the deaths in the community and offered advantages and gains at the community. Community members understood that through community-based initiatives it is possible to create local and timely first response solutions without necessarily having to wait for third party action.

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SNAKEBITES AND ENVENOMATION IN RURAL AREA IN MALI, WEST AFRICA

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Ophidian envenomation is a major health problem in Africa, particularly in Mali. Annually, snakebite kills around 20,000 people in Africa. This mortality reflects the dangerousness of the snake species involved and the difficulties of managing severe cases including hemorrhagic complications. A retrospective and prospective study was conducted between October 2019 and January 2021 in the village of Faladjè, a rural area located 60 km from Bamako, the capital city of Mali. We aimed to describe the epidemiological and diagnostic characteristics of snakebites and to identify the species of snake involved. Patients seeking care at the community health center after a snakebite and willing to participate in the study were included. Clinical and epidemiological data were collected. The snakes were captured and identified through zoological characteristics. A total of 86 cases of snakebite were recorded from which 89.5% were cases of envenomation. The age group over 18-year-old was the most affected (52.3%) with a predominance of males (65.1%). The frequency of bites was higher during the rainy season (July to November) and occurred during intense farm work where population is predominantly agropastoral. No cases of death were recorded. 84.5% of snakebite were caused by vipers and most frequently the pieces *Echis jogeri* in this area. Snakebites and envenomation's are an important health problem in rural areas in Mali. *Echis jogeri* of the viper group was mainly involved in Faladjè. Further investigations are needed to determine the nature of the venom to support efficient management of cases in remote areas.

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UNEARTHING SPOTTED FEVER GROUP RICKETTSIOSES FOCI IN CENTRAL AMERICA

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Spotted Fever Group Rickettsioses (SFGR) are tick-borne rickettsial pathogens capable of causing significant morbidity and mortality in humans. Most rickettsial diseases are widely unrecognized and underreported epidemiologically, despite being easily treatable, and as such, have been classified as neglected bacterial pathogens. Populations at most risk for severe disease are those in poverty, children, and those in rural areas or who work in agricultural jobs. Countries in Central America with high poverty, low human development index score, and limited health infrastructure lack necessary surveillance for SFGR and other tick-borne pathogens. This paucity of baseline information on SFGR infection prevalence leaves vulnerable populations at risk to remaining undiagnosed. Limited studies exist from El Salvador on antibodies to SFGR with small sample sizes, and none have been published in the last 25 years. To expand the knowledge base on prevalence and potential risk to tick-borne SFGR in El Salvador, our team conducted two different enzyme-linked immunosorbent assays (ELISA) on banked human sera samples from a cohort of approximately 1,000 pediatric participants from a previous study. Commercially available SFGR IgG and IgM kits were utilized following manufacturer recommended protocols. Approximately 2.5% and 1.0% of pediatric participants were positive and equivocal for IgG antibodies to SFGR, respectively, indicating a past lifetime SFGR infection. Additionally, 10.7% and 15.2% of participants were positive and equivocal for IgM antibodies to SFGR, respectively, indicating an acute SFGR infection. Eleven percent of all tested pediatric participants were positive for at least one ELISA assay, and 25% were either positive or equivocal on at least one ELISA assay. The large percentage of acute SFGR infections indicates that SFGR continues to remain an underreported and undiagnosed issue in El Salvador and the Central American region. Public health officials in this region need to consider SFGR as a diagnosis for vulnerable populations to prevent future morbidity and mortality.

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CAT SCRATCH DISEASE (*BARTONELLA HENSELAE* INFECTION) MIMICKING MELIOIDOSIS IN AN IMMUNOSUPPRESSED THAI PATIENT WITH FEVER AND HEPATOSPLENIC LESIONS

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Hepatosplenic cat-scratch disease is a disseminated form of Bartonella henselae infection that is not very common and could be misdiagnosed as melioidosis, particularly in the endemic area. We reported that a 79-year-old Thai patient presented to the hospital with a 1-day history of fever and chills in March 2022. About one year ago, he was diagnosed with the CD5 plus clonal B-cell lymphoproliferative disorder. He received an R-CVP regimen including rituximab, cyclophosphamide, vincristine and prednisolone for five cycles, with the latest one about 30 days prior to this visit. He lives in Rayong with his family and three cats. He had exposure to soil and brackish water, catching fish and crustaceans. On exam, he had a fever up to 39.2 degrees Celsius, blood pressure of 105/57 mmHg, heart rate of 74/min, respiratory rate of 22/min and oxygen saturation of 97% on room air. His liver span was about 12 cm and his spleen of 11 cm. He had tender right groin lymphadenopathy of 3 cm. Laboratory tests were significant for hematocrit of 33%, AST 141 mg/dL, ALT 124 mg/dL, ALP 108 mg/dL and GGT 140 mg/dL. He was empirically treated with piperacillin-tazobactam. Computed tomography of the chest and whole abdomen with contrast showed a few ill-defined hypodense lesions at hepatic segments II, V, VIII and a small, subtle ill-defined splenic lesion; several lymph nodes at left gastric and right inguinal region; multiple lymph nodes at paraaortic, aortocaval, retrocaval, bilateral inguinal and right external iliac regions; 0.3-cm ground-glass nodules at apicoposterior segment of the left upper lobe. A biopsy of a liver nodule showed granulation tissue. Given the history, melioidosis was one of the differential diagnoses given the geographical location, history of exposure to soil, immunosuppression status and several lesions in the liver and spleen. Hemoculture did not grow any organisms. Antibiotic was switched to high-dose meropenem. Despite that, he still had a high-grade fever. Subsequently, 16s DNA from lymph node tissue showed *Bartonella henselae*. Thus, azithromycin and rifampicin were given instead of meropenem with clinical improvement.

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EVALUATING ROUTINE IMMUNIZATION STRENGTHENING ACTIVITIES IN HAUT LOMAMI AND TANGANYIKA

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A large proportion of the global burden of vaccine-preventable diseases (VPDs) occurs in low and middle-income countries (LMICs). In the Democratic Republic of the Congo (DRC), the Expanded Programme for Immunization (EPI) manages the routine immunization (RI) system to vaccinate all children > five years old against selected VPDs. This study aims to evaluate RI strengthening activities in Haut Lomami and Tanganyika provinces. An evaluation plan was developed with two outcome indicators (e.g vaccination coverage) and seven process indicators (e.g: vaccination sessions). The basis of the analysis was to triangulate

quantitative and qualitative data obtained from six routinely collected data sources available by Health Zone (HZ). Data includes annual vaccine coverage surveys, EPI monthly mobile supervision data, administrative data from the District Health Information System (DHIS2) and the District Vaccine Data-Management Tool (DVD-MT), weekly routine surveillance from the Integrated Diseases Surveillance and Response (IDSR) system and polio and measles laboratory confirmed cases (case-based data). Outcomes from specific indicators were ranked to give an overall score for each HZ; HZ were classified as a low, medium or high performing if their overall performance score was below 60%, between 60%-80% or above 80%, respectively. For Haut Lomami with 16 HZ, between January to June 2019, during the 1st review, 31.2% were low performing, 50.0% as medium performing, and 18.7% were high performing. In January to June 2021, 6.2% were low performing, and the remaining HZ were classified as either medium (75.0%) or high (18.7%) performing. In Tanganyika province, out of 11 HZ, 36.4% were low performing between January to June 2019 compared to January to June 2021, when 27.3% were considered low performing. Only Mbulula HZ was considered high performing. In general, Haut Lomami had greater improvements than Tanganyika. The RI evaluation in Haut Lomami and Tanganyika provinces shows improvements in the routine immunization system. Larger scale evaluation models can be used to understand the effects of RI strengthening activities in LMICs.

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PPE ACCESSIBILITY BEFORE AND DURING THE COVID19 PANDEMIC AMONG HEALTHCARE WORKERS IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Healthcare workers (HCW) are among the most at-risk populations for novel coronavirus (SARS-CoV-2) exposure due to direct patient contact. Consistent access to personal protective equipment (PPE) is vital to HCW safety, especially in an outbreak setting. Accessibility to COVID-19-related PPE was studied among HCWs before and during the pandemic in four regions of the Democratic Republic of Congo (DRC). A cohort of 588 HCWs from four locations in DRC, (i.e., Kinshasa, Beni, Kikwit, Mbandaka), were enrolled in a longitudinal phone study. HCWs were surveyed every 2 weeks from August 2020 to August 2021. Due to missing data on key variables, 11 HCWs were excluded from the analysis. Accessibility was defined as always availability of a specific type of PPE within the health facility. Prior to the COVID-19 pandemic, before March 2020, 17.5% HCWs reported access to a face shield, 51.7% to a cloth mask, 42.8% to a surgical mask, and 13.4% to an n95 mask. During the pandemic, the proportion of HCWs with access to face shields decreased from 20.6% (the peak) in August 2020 to 3.6% in August 2021. About two-thirds (68.1%) of respondents reported cloth masks access in August 2020 compared to 39.9% in August 2021. Between August 2020 and August 2021, the proportion of participants with access to n95 masks decreased from 14.4% to 6.0%. Surgical mask access increased from 50.8% in August 2020 to 69.6% in August 2021. The greatest proportion of respondents reported surgical mask access in December 2020, cloth mask access in September 2020, and n95 access in November 2020 (76.6%, 79.8%, and 18.4%, respectively). During the pandemic, an overall downward trend over time of reported accessibility to face shields, cloth masks, and n95 masks was observed while always having access to surgical masks increased. Fluctuation in PPE availability for COVID-19 prevention among this Congolese HCW cohort indicates that PPE stock in the country was likely dynamic throughout the pandemic. Additionally, the relatively low access in general to PPE at times throughout the study reflects a major challenge to HCW protection in a low-resource setting such as the DRC during the COVID-19 pandemic.

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EVALUATION OF ARCHIVED AND CONTRIVED CLINICAL SPECIMENS WITH THE BIOFIRE® GLOBAL FEVER PANEL PLUS

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The BioFire® Global Fever (GF) Panel Plus includes assays to identify 19 viral, bacterial, and protozoan pathogens directly from whole blood including arboviruses, Plasmodium, hemorrhagic fever viruses, and other select agents. A prospective clinical study of the BioFire GF Panel Plus was performed at eleven geographically diverse clinical sites. Archived and contrived specimen testing was necessary to assess all targeted pathogens. Archived specimens with known analyte content or a reasonable likelihood of containing a given analyte were tested using the BioFire GF Panel Plus. Due to the rarity of the targeted analytes, positive specimens were available for only three analytes in sufficient numbers. The BioFire GF Panel Plus showed high negative percent agreement (NPA) for all analytes tested by comparators (≥98.6%). Lassa virus had a positive percent agreement (PPA) of 83.3% with a lower 95% confidence interval bound of 55.2%. PPA for West Nile virus was 90.8% with a lower bound of 81.3%, whereas the PPA for Zika virus was 76.9% with a lower bound of 57.9%. With only three archived specimens obtained, the PPA for Salmonella enterica serovar Typhi was 100% with a lower bound of the 95% confidence interval of 20.7%.Contrived specimens using residual whole blood specimens from patients with signs/symptoms of acute febrile illness and negative for all BioFire GF Panel Plus analytes were spiked at various levels with Bacillus anthracis, Crimean-Congo hemorrhagic fever virus, Ebolavirus, Francisella tularensis, Lassa fever virus, Leishmania spp., Marburgvirus, West Nile virus, yellow fever virus, and Yersinia pestis. A total of 316 contrived specimens spanning clinically relevant concentration ranges were tested. Performance of all analytes met the desired statistical performance goal of at least 95% PPA with 80% PPA as the lower bound of the 95% confidence interval. The NPA for all analytes except West Nile virus (99.6%) was 100%.The ability of the BioFire GF Panel Plus to detect multiple pathogens, even with reduced sensitivity, provides a valuable diagnostic for pathogens with overlapping clinical presentation.

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PREDICTORS OF SEVERITY IN ACUTE DENGUE INFECTION DURING THE 2019 EPIDEMIC IN BRAZIL

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Dengue is the most important arbovirus in terms of morbidity and mortality worldwide. All four serotypes of the virus are capable of causing from mild to severe clinical conditions. The pathogenesis of severe forms is quite complex and involves a series of viral and host interactions. The occurrence of previous infection by a dengue virus (DENV) serotype is classically known as a risk factor for hospitalization and severity. This study aimed to investigate the influence of potential host risk factors for the occurrence of dengue with warning signal (DWS) and severe dengue (SD), by including 1,490 patients confirmed for dengue by RT-PCR positive and/or NS1 detection during the 2019 epidemic in a hyperendemic region for the virus. Among the patients enrolled, 73.8% were adults, and 54.9% female. The main comorbidities reported were systemic arterial hypertension (14.4%) and diabetes mellitus (7.9%). Besides, 78.1% had

history of previous infection by DENV and 20.3% by ZIKV. According with the WHO Clinical Classification (2009), 68.8% of patients presented as dengue without warning signal (DwWS), 29.5% as DWS and 1.61% as SD. Binary logistic regression analysis showed that individuals older than 60 years had a risk 1.9 times higher (95% CI 1.42- 2.55; p< 0.001) for severe forms (DWS + SD) compared to adults. Individuals with diabetes mellitus presented a risk of 6.54 higher for severe forms (95% CI 1.9 - 22.4; p= 0.003). Interestingly, individuals with history of dengue did not present a risk associated with severe forms, contrary to the expected antibody-dependent enhancement theory. Regarding hematimetric patterns at the time of medical care, the occurrence of leukopenia was associated with a risk of 6.64 times with severe forms (95% CI 5.09 - 8.65; p< 0.001), as well as thrombocytopenia, with a risk of 9.98 (95% CI 6.49 - 15.34; p< 0.001). Once the mechanism by which only a few individuals progress to severe forms of dengue is still unclear, the identification of reliable and validated predictors of disease severity is essential to guide the appropriate clinical management already in the early stages of the disease, contributing to favorable outcomes.

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MEASLES SEROPREVALENCE IN PEDIATRIC PATIENTS CARE FOR SUSPECTED ARBOVIROSIS DURING THE 2019 DENGUE EPIDEMIC IN NORTHWEST PAULISTA

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Measles has a high socio-epidemiological impact, especially in the pediatric population. Although the prevention through vaccination is currently possible, outbreaks have occurred in Brazil in recent years, including in 2019 when many cases and deaths occurred in children under 5 years of age. In this study, we carried out a retrospective analysis with the objective of evaluating the seroprevalence of anti-measles IgG antibody in blood samples from patients under 15 years old, treated with suspected Dengue infection during the 2019 epidemic, in a tertiary hospital in Brazil. A total of 302 samples were analyzed, in which 92% were white and 52% male. Anti-measles IgG antibodies were identified in 63.2% (191/302), while 20.2% were non-reactive and 16.6% undetermined. Data from medical records analyzed were ethnicity, sex, age group, presence of comorbidities and immunosuppression, with no statistical significance between them. Seroprevalence was 21.1% (4/19) in children under 1 year old, 69.9% (51/73) between 1 to 4 years old, 67.4% (64/95) between 4 and 9 years old, and 62 .2% (72/115) from 10 to 14 years old. Our data allowed us to identify a low seroprevalence of IgG antibodies against Measles in all age groups, despite the vaccination coverage in the region being above the national target, highlighting the importance of knowing the seroprevalence against Measles in view of the recirculation of the virus in the country, which would allow disease outbreaks if the population were not adequately protected.

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PREVALENCE MAPPING OF MALARIA HELMINTH COINFECTION AMONG PRESCHOOL AND SCHOOL AGE CHILDREN LIVING IN A LOW MALARIA TRANSMISSION SETTING IN SENEGAL

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Malaria, Soil-transmitted helminthiasis and schistosomiasis are co-endemic parasitic infections in many tropical countries, particularly in sub-Saharan Africa. These infections are responsible for a very important morbidity in pre-school and school aged children. However, there is a lack of information on the magnitude of the burden of these co-infections. This information would be important in developing and implementing integrated control programmes targeted at the co-infections. We conducted a population-based survey in Saraya health district among children aged from 1 to 14 years in June 2021. Sociodemographic, clinical and biological data were collected using a pre-tested, semi-structured questionnaire. Blood, urine and stool samples were collected from each participant enrolled into the study. Immunological (POC CCA), microscopy (thick and thin blood smears, urine filtration, kato-katz) and molecular biology techniques were used to examine these samples. Of the 553 children enrolled, 72 participants were infected with *Plasmodium spp*, giving a prevalence of 13.02%. The prevalence of schistosomiasis and soil-transmitted helminthiasis were respectively at 41.77% and 0.36%. Preliminary findings showed that the prevalence of malaria-schistosomiasis co-infection in 34 participants was 6.14%. In Bivariate analysis showed a significant association between Plasmodium infection and age and nutritional status of the child participant (p=0.04). Also, the analysis showed a significant difference in male children co-infected with malaria-schistosomiasis (p=0.03). These prevalence results will be used to design a study to investigate the feasibility and safety of an integrated treatment approach for malaria-helminth co-infection.

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PREVALENCE OF DYSLIPIDEMIA IN PATIENTS WITH TYPE 2 DIABETES IN GANADOUGOU, MALI: A CROSS-SECTIONAL STUDY

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Dyslipidemia is a disorder where abnormally high lipid concentrations circulate in the bloodstream and is highly prevalent among type 2 diabetic patients in West Africa. Dyslipidemia is further characterized by elevated plasma triglyceride and low high-density lipoprotein cholesterol. The condition is associated with numerous comorbidities, including the increased risk of atherosclerosis and associated mortality. There is a lack of awareness of dyslipidemia in rural parts of Africa and, more specifically, in rural Mali, where populations lack adequate resources, health care structure, and qualified staff. This study, therefore, sought to determine the prevalence of dyslipidemia among type 2 diabetic patients in the rural community of Ganadougou, situated in Mali's second-largest province of Sikasso. We conducted a cross-sectional study of 707 participants residing

in Ganadougou between November 2021 and March 2022. Demographic and lipid profile variables were recorded based on using a set of survey questionnaires and standard blood chemistry tests. Among the study participants, 104 subjects were type 2 diabetic patients. Among type 2 diabetic patients, the prevalence of dyslipidemia was 78.8%. Observed dyslipidemia prevalence rates were higher in females than males (82.1% [46/104] versus 75 [36/104], respectively). Abnormal total cholesterol and mixed dyslipidemia were the most observed dyslipidemia subtypes (67.3% and 58.7%, respectively). Dyslipidemia was also associated with increased age and time since the onset of diabetes. In low-resource settings such as rural Mali, there is a crucial need to improve infrastructure for routine dyslipidemia screening as a first step toward guiding its prevention and intervention approaches.

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AN ASSESSMENT OF THE LABORATORY NETWORK IN GHANA: A NATIONAL-LEVEL ATLAS SURVEY, 2019-2020

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Integrated health systems with strong laboratory networks are critical in improving public health. The Global Health Security Agenda (GHSA) requires countries to establish tiered national laboratory systems and determine the diagnostic capability required at each tier from national to district. Since the assessment of the Ghanaian laboratory network in 2006 with focus on HIV diagnostic resources using the Assessment Tool for Laboratory Services (ATLAS), there has not been any publicly available assessment of the laboratory network. The study assessed the Ghanaian laboratory network and its functionality within a wider scope. A national-level ATLAS survey was conducted among stakeholders in the laboratory network in Accra, Ghana through face-to-face interviews from December, 2019 to January, 2020. Follow-up phone interviews were conducted between June and July, 2020. Supporting documents provided by stakeholders were reviewed for supplementary information. Where possible, data obtained from the survey were used to complete the LABNET scorecard to quantify functionality of the laboratory network and overall advancement toward achieving International Health Regulations (IHR;2005) and GHSA targets. The assessment found a collaboration between disease control programmes, clinical and public health laboratories in the forecasting, procurement and distribution of laboratory supplies, and supportive supervision for laboratory testing. No clinical laboratory had yet received ISO accreditation although some had been assessed using the SLIPTA checklist. In terms of functionality, the laboratory information management system advanced the most (74%) toward achieving IHR and GHSA targets whereas the political, legal, regulatory and financial framework rated the least (33%) with the finance component at the least stage of functionality. Stakeholders recommended that the country's funding landscape be reviewed. Considerations should be made to fund laboratory services from internally-generated funds. Also, the laboratory policy should be implemented to ensure an adequate workforce and standardization of laboratories.

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RICKETTSIOSES IDENTIFIED AS A CAUSE OF FEBRILE ILLNESS REQUIRING HOSPITALIZATION AT TWO HOSPITALS IN UGANDA

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Background: Rickettsial illness is suspected to be a common cause of febrile illness in sub-Saharan Africa, but the burden of severe illness is unclear. We describe rickettsial IFA and PCR results from an ongoing acute febrile illness protocol of hospitalized adults from two sites Uganda. Methods: From August 12, 2019, to January 28, 2021, 80 febrile participants admitted to two regional referral hospitals western and central Uganda were enrolled. Serum IFA was performed to measure spotted fever group (SFG) rickettsia, typhus group (TG) rickettsia, and *Orientia* IgG titers with baseline (acute) and one-month (convalescent) samples. Seroprevalent subjects were indicated if there was a ≥ 1:128 titer in either serum sample. A four-fold rise in titer between acute and convalescent samples was considered a seroconversion. RT-PCR was performed using the baseline whole blood sample targeting broad 16S ribosomal RNA (broad-range TG and SFG sequence), and positive results were followed by quantitative PCR targeting 17-kDa DNA PCR TG gene sequence), 56-kDA (*Orientia* gene), and *ompA* (SFG gene). Results: Participants (60.0% female; median 36.3 years of age) presented after a median 4.7 (SD: 2.5) days of symptoms. Seroprevalence was high at 42.5% for SFG, 9.2% for TG, and 25.6% for *Orientia*. Seroconversions were observed due to SFG rickettsia (N=6; 9.0%), TG rickettsia (N=2; 3.0%), and *Orientia* (N=1; 1.5%). There were 2 participants with positive 16S rRNA RT-PCR testing: one typhus group rickettsia by PCR and IFA seroconversion and the other SFG rickettsia by IFA seroconversion but OmpA PCR negative. Both 16s positive and the participant with *Orientia* seroconversion were negative for *Orientia* with PCR. Conclusion: In this cohort in Uganda, SFG and TG rickettsia led to febrile illness requiring hospitalization. Rickettsia seroprevalence was high including *Orientia* IgG. Further research to define the burden of rickettsial illness and *Orientia* circulation are needed in this region.

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DEVELOPING A SUSTAINABLE CARE MODEL FOR NEWLY ARRIVED REFUGEES- A PRIMARY CARE APPROACH

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Between October 2021 and February 2022, Minnesota welcomed 1260 humanitarian parolees from Afghanistan. Due to situations surrounding their evacuation, the parolees did not undergo pre-departure medical examinations prior to coming to the United States. As a result of this need, providers with experience in refugee and global health coordinated a volunteer-led health response. The multi-phased response model sought to triage immediate needs and refer individuals/families to primary care clinics. Over half of the newcomers (53%) who completed a health and safety assessment had at least one referral, and 21% were referred to primary care. To guide referral decisions, clinics provided state officials information on capacity to accept newcomers. The Community University Health Care Center (CUHCC), a federally qualified healthcare center, was identified as the main referral clinic for primary care, COVID vaccinations, obstetrics, and dental care needs. To manage the increase in referrals and

unexpected urgent needs, CUHCC dedicated weekly slots to schedule new arrivals. An Afghan response team consisting of community outreach workers, patient navigators, and Afghan interpreters welcomed newcomers to the clinic. Additionally, clinic providers and learners volunteered at the temporary housing site to establish connections and continuity of care when possible. Community-based clinics play an important role in caring for refugees and other newcomers. In the era of COVID-19 and during virus surges, access to the designated clinics allowed for timely access to health care for newly arrived parolees. This model prevented unnecessary emergency room visits while also meeting their immediate health care needs; several individuals who were identified to have high medical needs were connected to primary care within days of arrival to the state. Although connections to care were established quickly, there remained additional challenges of communicating appointments, interpreter availability, staffing, and transportation. Financial costs of missed appointments for various reasons made it difficult to offer health care for some arrivals.

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A LONGITUDINAL COHORT AND BIOREPOSITORY IN BOSTON, MASSACHUSETTS TO ADDRESS KEY QUESTIONS IN CHAGAS DISEASE

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Chagas disease is a neglected tropical disease estimated to affect nearly 8 million people globally. In the US alone, estimated Chagas disease cases exceed 300,000. Approximately 30% of individuals diagnosed with Chagas disease will develop cardiac or gastrointestinal manifestations. Despite the health implications, several knowledge gaps remain including predicting which patients will develop end organ disease, how the disease manifests differently by discrete typing unit, and how to determine if a treated patient is cured. To address these questions, our team has started to create a longitudinal cohort study and biorepository of well-characterized samples, allowing for biomarker and epidemiologic research. Patients with confirmed Chagas disease are enrolled at Boston Medical Center and we collect data on demographics, medical comorbidities, symptoms, physical examination, Chagas disease testing, and cardiac and gastrointestinal studies. We follow patients during and after treatment;treatment, collecting data and blood samples at baseline, 2 time points during treatment, 3-6 months after treatment, and yearly after that. We draw 7mL of blood at each encounter and retain all remnants available from clinical blood draws. Thus far, we have enrolled 14 patients (4 (28.6%) male; median age 48 years) and have 106 unique aliquots in our biorepository. By creating this biorepository with a large, well-defined set of samples, we will facilitate research to address the gaps in Chagas disease diagnostics and treatment, as well as advance our understanding of the pathogenesis of the disease. Furthermore, we aim to collaborate with other sites caring for patients with Chagas disease, align data and sample collection, address the geographic heterogeneity of the parasite, and facilitate multi-site collaborative studies. While based in the US, we hope these data will ultimately help improve understanding of Chagas disease as well as patient treatment and outcomes on a global scale.

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CLINICAL MARKERS OF POST-CHIKUNGUNYA CHRONIC INFLAMMATORY JOINT DISEASE

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Chikungunya fever (CHIKF) remains a major issue to public health in many countries, including Brazil. Up to 50% of symptomatic patients may evolve to post-Chikungunya Chronic Inflammatory Joint Disease (pCHIKV-CIJD), which strongly impacts their quality of life. Here, we aimed to identify clinical markers of evolution to pCHIKV-CIJD during acute and post-acute phases. Using a prospective cohort of 169 volunteers with CHIKV infection, longitudinal clinical data were collected from symptoms onset up to 90 days. Of 169 patients with confirmed CHIKF, 86 (50.9%) completed the 90-day follow-up, 39 of whom met clinical criteria for pCHIKV-CIJD on day 90 (45.3%). The risk of chronification was 50% higher in women compared to men (RR: 1.52, 95% CI: 1.15 - 1.99). In the first visit, none of the symptoms or signs were predictive of pCHIKV-CIJD, while being symptomatic on 21st-day was a risk factor for chronification. Number of affected joints was greater in those who evolved to pCHIKV-CIJD, as they had a mean of nine affected joints, while non-pCHIKV-CIJD individuals had a mean of four. 29 patients of the pCHIKV-CIJD group had abnormal results by ultrasonography (87.9% of those examined), in whom ankles were the most affected joints (48.3%), followed by knees (31%). The most common sonographic signs were synovitis and joint effusion. In CHIKVF, women, and patients who are symptomatic on the 21st-day of the disease have a higher risk of developing pCHIKV-CIJD. However, clinical signs alone are not enough to define the individual risk of chronification. Further understanding of the disease's pathophysiologic mechanisms, including prognostic biomarkers, are needed to evaluate interventions that, when implemented during the acute or post-acute phases, are potentially capable of modifying the course of the disease.

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THERAPEUTICAL APPLICATION OF A HALLOYSITE-BASED HYBRID HYDROGEL BIONANOCOMPOSITE FOR PARASITIC INFECTIONS

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Infectious diseases are global problem and a leading cause of disability and mortality worldwide. Most parasite diseases and their transmission routes have been identified, and it is widely understood that environmental changes, population migration, and human behavior have a significant impact on parasitic disease transmission, prevalence, distribution, and incidence. Many diseases, such as Malaria, Trypanosomiasis and leishmaniasis, can be caused by parasite organisms, resulting in substantial morbidity and mortality. The most promising technique for eradicating and halting the spread of these infectious illnesses is nanotechnology-based medicine delivery. Hydrogel dressings have recently piqued interest

because they mirror the native extracellular matrix, providing a moist wound environment and effectively deliver the drug. The hydrogels are three-dimensional (3D) cross-linked polymer networks that can absorb and hold massive volumes of water or biological fluids without dissolving. Halloysite-based Hydroxyapatite/Sodium alginate (HNT/HAP/SA) hybrid bionanocomposite hydrogel beads were developed to effectively transport Metronidazole medication. FT-IR spectroscopy, X-ray diffraction analysis, TGA analysis, and microscopy were used to analyze the produced hybrid hydrogel beads. Due to strong biocompatibility between the components, morphological characterization of the hybrid hydrogel revealed excellent filler dispersion and surface smoothing. The results show that experimental parameters such as the polymer/HAP concentration and Halloysite type (modified or unmodified) have a significant impact on entrapment efficiency (EE) and Metronidazole release. The burst release of the loaded medicine was controlled by the tubular structure of HNTs combined with HAP. As a result, the synthesised hydrogel beads were suitable for the topical delivery of parasitic infection treatment.

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PHARMACOKINETIC ANALYSIS OF A SLOW-RELEASE FLUBENDAZOLE FORMULATION FOR THE TREATMENT OF GUINEA WORM INFECTION IN DOMESTIC DOGS

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Recent increases in Guinea worm (*Dracunculus medinensis*) infections in domestic dogs in Chad, Africa have complicated efforts to eradicate this parasite. To address these infections, new intervention strategies have been implemented, including anthelmintic treatments. Previous treatment trials with oral ivermectin and topical moxidectin did not decrease the number of dogs infected or the number of worms per dog. Flubendazole is an anthelmintic compound with macrofilaricidal effects and, in laboratory trials with experimentally-infected ferrets, appeared to impact the reproductive capacity of adult female worms. A high concentration (500 mg/mL), slow-release formulation of this drug was developed to produce a sufficient duration of drug exposure and minimize the volume of drug administered to dogs, but the pharmacokinetics of this formulation have not been investigated. Therefore, the goal of this study was to evaluate the pharmacokinetics of this flubendazole formulation in laboratory dogs, specifically between dogs with normal and thin body condition, the latter being representative of Chadian dogs. A total of 20 dogs were divided into normal (n = 10) and thin (n = 10) body condition groups with males and females equally represented. In each group, eight dogs received a subcutaneous injection of flubendazole (100 mg/kg) and two received a vehicle-only control. Complete blood counts and chemistry panels were performed to evaluate organ function before treatment and every 30 days after treatment; plasma was collected for high-performance liquid chromatography analysis before treatment, every 6 hours for the first 24 hours after treatment, every 24 hours for the first week, weekly for the first month, then monthly for the six-month duration of the study. Pharmacokinetic parameters were calculated overall, for normal vs thin dogs, and for males vs. females. These results will enable us to determine the appropriate treatment interval for flubendazole in domestic dogs to optimize the effectiveness of this potential treatment for Guinea worm infection.

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EFFICACY OF ALBENDAZOLE AND IVERMECTIN BASED REGIMENS FOR THE TREATMENT OF MICROFILAREMIC LOIASIS IN ADULT PATIENTS IN GABON: A RANDOMIZED CONTROLLED ASSESSOR BLINDED CLINICAL TRIAL

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Loiasis is a highly neglected filarial disease caused by *Loa loa* endemic in Central and West Africa. There are currently no control programmes against loiasis in place in endemic regions. Control programmes based on therapeutic interventions need to effectively reduce microfilaremia in patients with loiasis to reduce onward transmission. We assessed the efficacy and safety of three albendazole-based treatment regimens, alone or in association with ivermectin to reduce *L. loa* microfilaremia in adult patients. We conducted an open label, randomized, assessor-blinded, controlled clinical trial in adult patients harbouring *L. loa* microfilaraemia below 50 000 mf/ml in Lambaréné, Gabon, between May 2018 and April 2020. Eligible patients were randomized in either a Control group (receiving loratadine) or one of three intervention groups in a 1:2:2:2 allocation ratio. Intervention groups consisted of three-week twice daily 400mg oral albendazole followed by 1) no treatment (ALB group), 2) two further weeks of twice daily 400mg albendazole (ALB-ALB group), or 3) a single dose of 150µg/kg ivermectin (ALB-IVM group). Patients were followed up for 168 days. The primary outcome was the proportion of participants with *L. loa* microfilaremia ≤ 100 mf/ml at Day 168. 78 participants were screened and 49 were enrolled in the clinical trial. 6 patients were treated in the control group and 40 patients in the intervention groups (n=12 ALB group; n=16 ALB-ALB group; n=12 ALB-IVM group). Median *L. loa* microfilaremia at baseline was 10150mf/ml, 11375mf/ml, 9300 mf/ml and 13125 mf/ml in ALB, ALB-ALB, ALB-IVM and CONTROL groups, respectively. In the per protocol analysis 0 (0%; CONTROL group), 1 (9%; ALB group), 5 (39%; ALB-ALB group) and 2 (22%; ALB-IVM group) participants met the primary outcome of microfilaremia below 100/ml. 33 % of participants in the interventional groups (15/46) reported adverse events possibly related to study therapy All therapeutic regimens were adequately tolerated and safe. A three-week twice daily regimen of 400mg albendazole plus two-week albendazole or plus a single dose of ivermectin were the most effective regimens.

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THE CBC WITH DIFFERENTIAL - A MISSED OPPORTUNITY: WHY PRIMARY CARE PHYSICIANS SHOULD ALWAYS LOOK AT THE DIFFERENTIAL

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In 2009, a 45 -year-old female immigrant from rural Oaxaca with a history of abnormal uterine bleeding presented to a community clinic in Los Angeles. At that visit, a CBC with differential was drawn to investigate for anemia. While the patient's primary care physician focused on her hemoglobin, the differential on her CBC was telling another story. She had an absolute eosinophilia of 688. For the most part, the patient was asymptomatic besides irregular menses, the etiology of which was eventually diagnosed as an endometrial polyp. Over the years, she continued to follow up in the clinic for primary care, and was

eventually diagnosed with difficult to control HTN, T2DM, and HLD. Her PCP also monitored her for iron deficiency anemia - each time a CBC with differential was drawn, and each time her eosinophilia went unnoticed. In 2015 her peripheral count was 563 and rose to 764 in 2016. In 2021, twelve years after the patient's initial presentation, now at age 57, she presented with hypertensive urgency and concern for a previous myocardial infarction with deep inferior Q waves on ECG. A CBC with differential was drawn as part of a comprehensive workup for this new serious condition. Finally, now at a level of 864, the patient's eosinophilia sounded an alarm. The differential diagnosis was broad but included hematologic malignancy, parasitic infection, drug reaction, and autoimmune etiologies. A full laboratory work-up was sent. Stool ova and parasites as well as giardia testing were negative. Serology for Stongyloides stercoralis Ab ultimately resulted as positive. Likely contracted during her rural residency in Oaxaca, the patient's eosinophilia was most likely explained by chronic Strongyloides infection. At her relatively young age, her acute cardiac presentation was concerning for sequelae of eosinophilic myocarditis, hypereosinophilic syndrome, or even disseminated strongyloidiasis. With an easy 1-2 dose course of ivermectin, this patient's strongyloides infection could have been treated years ago at minimal cost. This patient's case should serve as a reminder to clinicians everywhere to always remember to check the differential.

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PHARMACOKINETICS OF MOXIDECTIN AND IVERMECTIN IN COMBINATION TREATMENTS FOR BANCROFTIAN FILARIASIS

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Moxidectin (MOX) is a macrocyclic lactone with a good safety profile, large volume of distribution and a long elimination half-life. The efficacy of MOX for the treatment of lymphatic filariasis (LF) and its potential use in mass drug administration protocols for the elimination of LF has not been established. In the context of a clinical trial, we investigated the pharmacokinetics and drug interactions of a combination of moxidectin (MOX) plus albendazole (ABZ) with or without diethylcarbamazine (DEC) compared to ivermectin (IVM) plus ABZ with or without DEC in the following four different treatment arms: (I) IVM (0.2mg/kg) plus DEC (6 mg/kg) and ABZ (400mg); (II) IVM plus ABZ; (III) MOX (8 mg/kg) plus DEC and ABZ; and (IV) MOX plus ABZ. *Wuchereria bancrofti*-infected adult participants were eligible for study inclusion. Ten plasma samples per participant were collected over 168 hours following drug administration. Drug concentrations were determined using validated liquid chromatography-mass spectrometric methods. Pharmacokinetic parameters were determined using standard non-compartmental analysis methods. Statistical analysis was performed using JMP software. Fifty-eight of 164 study participants (fifty-three men and five women) were included in the pharmacokinetic study. Among these participants, ages ranged from 18 to 63 yrs (mean=37). The mean (range) area under the curve $(AUC)_{0-\infty}$ for MOX, 3406 (742-11376), and IVM 1906 (692-5900), varied over a ~15.3 and ~8.5-fold range, respectively. The geometric mean ratio for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the no drug interaction range of 80 - 125% for all drugs. This indicates that the addition of MOX to ALB or ALB plus DEC for LF therapy did not result in alterations in drug exposure of co-administered drugs.

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POPULATION PHARMACOKINETICS OF MOXIDECTIN IN PATIENTS WITH LYMPHATIC FILARIASIS

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Moxidectin (MOX) is an antiparasitic drug with a broad-spectrum activity against filarial and other helminthic diseases. Although the use of MOX in Lymphatic filariasis (LF) has not been evaluated to date, giving MOX as a part of the LF treatment regimen may be critical in eradicating LF in areas where the disease is co-endemic with onchocerciasis. The pharmacokinetics (PK) of MOX in LF patients has not been described. Population PK modeling of MOX was constructed to evaluate the drug exposure after a single fixed-oral dose (8 mg/kg) and the impact of clinical and demographic factors associated with observed PK variability. A total of 237 plasma samples from 27 *Wuchereria bancrofti*-infected subjects who received MOX as a part of a clinical trial for the treatment of LF were used in the model-building. Plasma samples were collected from 0-168 hours post-administration and analyzed using liquid chromatography-mass spectroscopy. PK analysis was conducted with Phoenix NLME 8.3 software. A two-compartment model with first-order absorption and linear elimination with absorption time-lag function best described MOX disposition. The mean AUC_{0-inf} value obtained from the population Pk model in LF patients was lower than previously reported value in healthy individuals (3134 ng.h/ml vs 4885 ng.h/ml respectively). The mean peak plasma concentration C_{max} was slightly higher in our patient population (87.96 ng/mL) than reported in healthy individuals (79.1 ng/mL). The total apparent clearance (Cl/F) was higher to reported values in healthy individuals, but the apparent volume of distribution (VD/F) was lower in our population (568.4 L vs 1708 L). Tested covariates did not explain MOX PK variability. The MOX population PK model was suitable for predicting drug exposure in LF patients and can be used for future dose-informing studies by simulating different dosing regimens and comparing the drug exposures resulting from those regimens to fixed dosing. Additional studies evaluating covariates that may account for high variability are warranted to better understand MOX PK in LF patients.

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STRATEGIES FOR ADDRESSING PERSISTENT LYMPHATIC FILARIASIS IN HOT SPOT DISTRICTS: LESSONS LEARNED FROM SIERRA LEONE

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Sixteen districts in Sierra Leone were endemic for lymphatic filariasis (LF) and eligible for mass drug administration (MDA). To date, 9 districts (HDs) have stopped LF MDA. Despite good MDA coverage at the HD level, 6 HDs (4 prior to redistricting) failed both pre-transmission assessment

survey (pre-TAS) in 2013 and re-pre-TAS in 2017, with microfilaremia prevalence ≥1% and antigenemia prevalence ≥2%, respectively. The Western Area Rural failed pre-TAS in 2017, with antigenemia prevalence ≥2%. To identify problematic areas for targeted supervision, subdistrict-level MDA data were analyzed and the results showed low coverage in several communities. The social factors uncovered included transitioning for employment, "commuting", trading, and cattle herding; hard-to-reach location; difficult terrain, limited access during the rainy season; semi-pastoralist communities; and language/ethnic group barriers. Starting in 2018, different strategies and new approaches were implemented to increase compliance and MDA coverage. Social mobilization was intensified to target senior leaders of key ethnic groups who are resistant to messaging unless it is channeled through their hierarchy and traditional healer networks through a local NGO (FOCUS1000); findings from the rapid social science assessment to understand social dynamics were incorporated into the social mobilization approach. The MDA reporting template was revised with Act | West support to automatically flag coverage of <65% or >80% at the subdistrict level and trigger contact with health facilities. Intensified efforts were made for in-process support, including provision of stipends to CDDs and using supervisor's coverage tool to inform focused community revisits by CDDs or initiate mop-up where necessary. The 2020 re-pre-TAS surveys found three districts had antigenemia of <2% in all survey sites. Four districts failed for a third time, but with a significant decrease in antigenemia prevalence from 15.6% to 4.4% (p<0.0001). The results of these assessments suggest that novel approaches implemented during the 2020 re-pre-TAS helped reduce transmission to low levels.

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IDENTIFICATION OF POLYMORPHIC MARKERS IN *LOA LOA* TO ASSESS THE MULTIPLICITY OF INFECTION

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This project aimed to identify genetic markers in *L. loa* microfilaria for genotyping the diversity and the multiplicity of the infection in the human host. The extraction of the various viviparous parental worms from the human body is elusive. Thus, this study proposed to deduce the burden of filarial infection and it's genetic diversity by genotyping the worms' offspring, individual microfilariae from human blood using polymorphic markers. The multiplicity of infection of loiasis in the human host is unknown and a comprehensive understanding of the biology of *L. loa* seems essential for the development of adequate elimination strategies. Samples were available from a previously study from Gabon (Veletzky et al. 2020) and ethical approval was available for this genetic analysis. *L. loa* microfilariae were individualized from whole blood and DNA was extracted using a polystyrene bead-based kit. In silico analysis of the *L. loa* genome revealed various regions containing microsatellites/ short-tandem repeats (STRs). The genotyping comprised PCR amplification of STRs and analysis by capillary electrophoresis. During this pilot study, 2 polymorphic STRs were further developed and the analysis of these two STR loci in 15 individualized microfilariae extracted from each of 9 patients showed a number of 39 and 47 alleles, respectively. The results documented a high allelic diversity indicating a good discriminative power of the methodology and the presence of multiple adult filariae in the sampled individuals. So far, no association between microfilariae densities and numbers of alleles per patient was observed. However, this pilot study shows that the evaluation of the genetic diversity of *L. loa* microfilariae is feasible by genotyping of individualized offspring microfilariae using polymorphic STRs. The methodology can be refined by the development of further eligible STRs and applied to larger epidemiological studies.

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SEROLOGICAL RESPONSES TO FILARIAL ANTIGENS FROM POPULATION-BASED SURVEYS IN NORTH DARFUR STATE, SUDAN

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Both river blindness (RB) and lymphatic filariasis (LF) are endemic in Sudan and targeted for elimination. RB transmission is currently limited to two foci, whereas Federal Ministry of Health (FMOH) mapping in 2016 detected LF transmission in 64 localities (districts) distributed across 14 of 18 states. In 2019-2020 the FMOH Trachoma Control Program conducted population-based serosurveys in 3 localities of North Darfur. Thirty clusters of 25 households were selected by multi-stage cluster random sampling in each of three localities not known to be endemic for RB or LF: Seraif, Kotom, and Saraf Omrah. Nurses collected dried blood spots (DBS) from all consenting/assenting individuals 1 year and older. DBS were analyzed by multiplex bead assay (MBA) for serological responses to multiple pathogens, including RB (Ov16) and LF (Bm14, Bm33, and Wb123). MBA results were available for 8,322 of 8,325 surveyed individuals (99.9%), with 2,781 (33.4%) from Kotom, 2,848 (34.2%) from Seraif, and 2,693 (32.4%) from Saraf Omrah. Ov16 seroprevalence was <0.3% in each locality, with an overall adult seroprevalence of 0.14% (95% CI 0.05 – 0.39%). The results for the three LF antigens varied dramatically, with relatively low seroprevalence for Bm14 (0.93% [95% CI 0.69 – 1.3%]) and Wb123 (3.6% [95% CI 3.1 – 4.3%]) and higher seroprevalence for Bm33 (26.04% [95% CI 25.2 – 28.0%]). Seropositivity to Bm33 increased with age and clustered in the southwest near Saraf Omrah; such patterns were less clear for Bm14 and Wb123. Responses to the three LF antigens were discordant: only 3 individuals tested positive to all 3 antigens. RB results were significantly below the current World Health Organization threshold to start mass drug administration (MDA) (>2% Ov16 seroprevalence in adults) and suggest the absence of active RB transmission in these areas. The LF results are more difficult to interpret. FMOH aims to conduct remapping surveys in these localities to determine whether LF MDA is warranted.

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EFFECT OF FILARIAL LYMPHEDEMA TREATMENT WITH DOXYCYCLINE ON IMMUNE ACTIVATION AND EXHAUSTION FREQUENCIES IN BLOOD

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Lymphatic filariasis is a mosquito-transmitted helminth infection caused by *Wuchereria bancrofti* and *Brugia* species. About 30% of the 68 million infected people worldwide suffer from disfiguring pathology (e.g. lymphedema). Current treatment (200 µg/kg ivermectin (IVM) and 400 mg albendazole (ALB)) acts on microfilariae, the larval stage that is also responsible for transmission, but does not affect the adult worm. Prior studies have shown 100-200mg Doxycycline to act not only on the adult worm, but also when taken daily for 6 weeks, to lead to improvement of those with early stages of lymphedema. A double-blinded, randomized, placebo-controlled trial (LEDoxy) was conducted in Ghana and Tanzania in order to confirm the effect of 200 mg Doxycycline treatment and to test the effect of 100 mg Doxycycline per day for 6 weeks on improvement of filarial lymphedema. Patients were characterized at baseline using the Dreyer *et al.* scale, circumference measurements, and the LymphaTech® infrared scanner. Over a 24 month-period, changes in pathology and immunological parameters were measured (end of treatment, 6 and 24 months post treatment). Additionally, a novel flow cytometry based whole blood method developed by us was used to characterize CD4 and CD8 T cells for a number of activation, maturation, and exhaustion markers (CD45, CD27, FoxP3, CD25, CD38, HLADR, Tbet, Eomes). Flow cytometry data from the first 20 Ghanaian and 43 Tanzanian participants who completed treatment has been analyzed. When comparing individual pre- and post-treatment data from Tanzania, we see no significant difference in the frequency between various T cell subgroups (central and effector memory $CD4^+$ T cells). Yet, we observe an overall significant decline in immune activation parameters ($HLADR^+/CD38^+$ on $CD4^+$ T cells) over the course of treatment. Interestingly, the opposite is observed in the Ghanaian samples when examining paired values from pre- and 6 months post-treatment. Clearer conclusions as to the nature of these differing results will be able to be drawn after unblinding of the study participants (anticipated July 2022).

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CYTOKINES RESPONSES TO IVERMECTIN TREATMENT OF LOW-TO-MODERATE *LOA LOA* INFECTIONS DIFFER FROM *WUCHERERIA BANCROFTI* INFECTIONS, SUGGESTING ROLES FOR *WOLBACHIA IN THE* EMERGENCE OF POST-TREATMENT ADVERSE EVENTS IN FILARIAL INFECTIONS

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Post-ivermectin (IVM) adverse events (AEs) constitute a barrier to filariasis control programs. In bancroftian lymphatic filariasis (LF), post-IVM AEs may result from immune responses to antigens released by dying microfilariae (Mf) or its *Wolbachia* endosymbiont. In contrast, post-treatment AEs in loiasis must be unrelated to *Wolbachia* since *Loa loa* is a *Wolbachia*-free parasite. To test the hypothesis that IVM treatment of loiasis generates similar immunologic responses to treatment of LF, we treated 39 patients with daytime *L. loa* Mf counts ranging from 3,720 to 16,020 Mf/mL (median 8,600, IQR: 5,580-11,980) with 150µg/Kg IVM while closely monitoring AEs for seven days. We collected blood samples before treatment and at 8, 16-, 32-, 40-, and 56-hours post-treatment for Mf counts and measurement of serum immune mediators using the Bio-Plex Pro Human Cytokine 27-plex Assay. Median daytime *L. loa* Mf counts decreased ~75% by 56 hours post-treatment and were associated with a concomitant increase in 15 of 27 assayed cytokines (MIP-1β, MIP-1α, Eotaxin, FGF-β, MCP-1, TNF-α, INF-γ, G-CSF, GM-CSF, IP-10, IL-1rα, IL-8, IL-10, IL-13, and IL-17) that was most pronounced at 32 hours. Another group of cytokines (RANTES, PDGF-BB, IL-2, IL-4, and IL-7) increased transiently post-treatment (8 hours), then decreased below baseline levels by 56 hours, while others (IL-1β, IL-9) were lower at all times post-treatment and some (IL-5, IL-6, IL-12p70, IL-15, and VEGF) were not sufficiently detected to determine a pattern. Unlike findings from LF, no significant association was found between the magnitude of cytokine change and baseline Mf counts or Mf clearance. These data suggest that different mechanisms may be involved in the immune response associated with IVM treatment of loiasis and are consistent with a role for *Wolbachia* antigens in initiating treatment-emergent immune-mediated AEs in LF.

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ONCHOCERCIASIS DRUG DISCOVERY - EVALUATION OF FDA-APPROVED DRUGS AGAINST *ONCHOCERCA GUTTUROSA IN VITRO*

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Onchocerciasis treatment and control relies principally on the use of ivermectin, which has high activity against the microfilarial stage of *Onchocerca volvulus,* but with only limited activity against the long-lived tissue dwelling adult worms. This neglected tropical disease has now been targeted for elimination and there remains an urgent need for new drugs to treat onchocerciasis, ideally with macrofilaricidal activity. In this initial study we aimed to identify existing drugs, obtained from an FDA-approved library, for any anti-*Onchocerca* activity. Based on a range of biological activities, 106 drugs were selected from the Pharmakon-1600 library and tested at a concentration of 12.5 uM against *O. gutturosa* adult male worms, using a 5-day standard assay to measure motility levels and viability using MTT-colorimetry. The results demonstrated a strong showing of hits from the antibacterial/anti-infective drugs, but not exclusively so. Overall, 39 drugs were inactive, while 44 drugs produced moderate activity (50-99% motility and/or MTT reductions), including Amitraz, Broxyquinoline, Cefuroxime sodium, Mangafodipir trisodium, Methenamine, Primaquine phosphate, and Rivastigmine tartrate. However 23 drugs produced good activity (100% motility reductions and significant MTT reductions); these drugs included Atovaquone, Gramicidin, Iodoquinol, Isradipine, Losartan, Nitrofurazone, Oxyquinoline hemisulphate, Rifaximin, Cefaclor, and Pyrantel pamoate. Our results warrant further investigations regarding the possible re-purposing of some of the identified drugs. In addition, the identification of these hits may provide a good starting point for searches for related compounds of possible interest, and/or lead to new chemical synthesis.

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BIOMARKER DISCOVERY AND ASSAY DEVELOPMENT TO DETECT ANTIBODIES TO *ONCHOCERCA VOLVULUS* BASED ON OVCOL-1 AND OV7

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The World Health Organization (WHO) neglected tropical diseases road map for 2021-2030 highlighted the need for better diagnostic tests to support control and elimination of onchocerciasis. WHO's target product profiles (TPP) for new onchocerciasis tests set minimum criteria for mapping as a laboratory-based assay to detect exposure to *Onchocerca volvulus* with ≥ 60% sensitivity and ≥ 99.8% specificity. The minimum

criteria for tests to make mass drug administration stopping decisions have the same specificity but higher sensitivity (≥ 89%). The requirement for very high specificity for both program use cases may necessitate the use of multiple biomarkers in combination. We conducted a serum epitope repertoire analysis (SERA) to identify biomarkers to detect IgG total, IgG1, and IgG4 epitopes using sera from 60 *O. volvulus* confirmed positive individuals and 60 *O. volvulus* negative individuals from Guatemala and 60 *Wuchereria bancrofti* positive sera from Haiti to control for cross-reactivity. SERA identified 22 target proteins for IgG total, 18 for IgG1, and 11 for IgG4. Two identified proteins were previously described antigens, OvCol-1 and Ov7. We expressed these two proteins as GST-fused recombinant antigens and developed a multiplex bead assay (MBA). We evaluated the dual antigen MBA using 35 *O. volvulus defined* positive sera from Guatemala, 197 presumed *O. volvulus* negative sera from U.S. non-travelers, and 63 *W. bancrofti* defined positive sera from Haiti. Detection of IgG4 antibody had the best performance for both antigens. The rGST-Ov7 MBA had a sensitivity of 94% and a specificity of 96%; rGST-OvCol1 had a sensitivity of 86% and a specificity of 92%. Combination of these two antigens to detect IgG4 antibodies met minimum TPP criteria for mapping with a sensitivity of 77% and a specificity of 99.8%. We plan to repeat these analyses using samples from Africa where the onchocerciasis program needs are the greatest and there are potential issues with cross reactivity in sera from persons infected with *Loa loa* or *Mansonella* spp.

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CONSIDERATION OF SCALE IN THE APPLICATION OF SPATIAL STATISTICAL MODELS TO IDENTIFY AREAS AND CLUSTERS OF RELATIVE LOW COVERAGE FROM A LYMPHATIC FILARIASIS MASS DRUG ADMINISTRATION CAMPAIGN IN LEOGANE AND GRESSIER, HAITI

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Haiti's Lymphatic Filariasis (LF) Elimination Program delivered mass drug administration (MDA) in the communes of Leogane (17 rounds since 2000) and Gressier (10 rounds since 2008). The most recent MDA campaign in both communes was conducted in December 2020, followed by a coverage survey. Sampling was stratified by commune and topographical zones (mountains and plains). The World Health Organization defines minimum effective treatment coverage as 65% of the total population. Weighted coverage estimates by strata were: Leogane-mountains, 64.7%; Leogane-plains, 57.6%; Gressier-mountains, 59.3%; and Gressier-plains, 45.1%. Heterogeneity in participation was evident, with 37.7% of sampled census enumeration areas having coverage estimates ≥65%. To better understand the heterogeneity, we mapped coverage using varied geographic scales (combined communes, single commune, and strata) to describe and compare the spatial trends of low participation areas. At the household level, clusters of relatively low participation (compared to locations outside the cluster) were identified retrospectively via space-time scan statistics. At the individual level, relative risk (RR) maps of non-participation were created using kernel density estimation with adaptive bandwidth selection. The utility of dual method mapping is illustrated in Gressier-plains, where the maximum RR of non-participation (RR=1.74) is low due to large numbers of survey participants, yet HH-level modeling revealed 11 statistically significant clusters of relatively low-coverage (RR range: 2.0-18.9). Spatial analysis at the strata level identified relatively low-coverage clusters that would have been obscured at the other scales. The combination of cluster and RR maps at varied scales enhances visualization of areas of relatively low levels of participation which may be missed when only using one method. Comprehensive mapping of coverage data is vital to inform MDA implementation strategies and to identify areas in need of additional resources to improve coverage.

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COVERAGE SURVEY OF LYMPHATIC FILARIASIS MASS DRUG ADMINISTRATION IN LEOGANE AND GRESSIER, HAITI, 2021: AN IMPORTANT TOOL TO ASSESS EFFECTIVE EPIDEMIOLOGICAL COVERAGE

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Lymphatic filariasis (LF) remains a public health problem for many countries in the world including Haiti. The country launched mass drug administration (MDA) in Leogane commune in 2000 and progressively reached others until covering the entire country in 2012. The World Health Organization recommends a minimum effective MDA coverage of 65% for at least 5 years. Despite having received 17 and 10 rounds of MDA, respectively, through 2020, Leogane and Gressier have not interrupted LF transmission. After the most recent MDA in December 2020, where a strictly fixed post distribution strategy was used, a coverage survey was conducted. Using probability proportionate to estimated size sampling, census enumeration areas were divided into segments of 50 households (HH); 30 segments were selected in each of 4 strata defined by commune and topographical zones (mountains and plains). HH members aged 2 years and older were eligible to participate; 6848 from 2444 HH consented to participate and 6400 were residents during the December 2020 MDA campaign and were included in analysis. Weighted coverage estimates (percentage of total population who swallowed pills) was 58.9% (95% CI: 54.5-63.3) for Leogane-overall and 53.3% (47.7-58.9) for Gressier-overall. Coverage tended to be higher in the mountains versus the plains. Common reasons cited for not taking medicines included: unaware of MDA (27.8%) and fear of side effects (11.4%). Males were more likely than females to swallow the pills (83.7% vs. 77.7%, $p<0.001$). When the analysis is restricted to those who received the pills, weighted coverage estimates increase to 79.5% (74.9-83.4) for Leogane-overall and 78.9% (72.6-84.1) for Gressier-overall, well-exceeding the minimum effective coverage of 65%. These results suggest that fixed post distribution campaigns may not be sufficient to reach the entire targeted population. Additionally, the importance of directly observed treatment should be emphasized during trainings. LF elimination programs may consider supplementing fixed post with door-to-door distribution in future campaigns as an effort to improve MDA coverage to effective coverage levels.

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MEASURING THE OUTCOME OF THE MASS DRUGS ADMINISTRATION OF LYMPHATIC FILARIASIS THROUGH SENTINEL AND SPOT SITES SURVEYS FROM 2012 - 2021

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The Ministry of Health of Liberia Lymphatic Filariasis (LF) mapping results show that the disease is endemic in 13 of the 15 counties. The programme began implementing the first LF Mass Drugs Administration(MDA), using a community distribution method, in 2012 in all 13 endemic counties. The programme has subsequently treated in 2013, 2015-2019 and 2021 in all endemic counties. Based on WHO guidelines to monitor the progress and impact of MDA, Sentinel sites must be identified in each implementation unit for evaluation after every 3 rounds of MDA. In consideration of this, the program has conducted 3 destined Sentinel and Spot Check Sites Surveys in the Counties. The objective is to showcase the progress of MDA in reducing micro filarial in the communities through monitoring and Evaluation of Sentinel and Spot sites survey at the county level. To showcase results and data indicating a downward trend of the impact of MDA on lymphatic filariasis with the use of Albendazole in Liberia.

To demonstrate the strategies in determining the impact of the Mass Drug Administration in controlling and eliminating Lymphatic Filariasis in Liberia. The Sentinel and Spot Check sites survey were conducted with a cross-sectional approach whereby people ages 5 years and above were sampled. Samples collected from participants were tested with Filarial Test Strips and counting chambers. The NTD programme has conducted three sentinel site surveys; the first, baseline, was conducted in 2012 in 11 sites and the second was conducted in 2016 in 11 sites across the same 11 counties. The second survey was conducted in 4 spot-check sites and 7 sentinel sites. The most recent survey was conducted in 2018 in 23 sites across 9 counties. The sentinel site survey conducted in 11 counties in December 2016/January 2017 after the 3rd MDA (Sept. 2015 - Feb. 2016) showed that the Mf prevalence in Liberia had been reduced in all but one county. The county of River Gee had an increase from 0% to 0.99% Mf. Maryland, the only county with a MF rate over 1% showed a reduction from 11.37% to 8.36%. There is also the concern of cross-border transmission along the border with Cote d'Ivoire.

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PRE-CLINICAL DEVELOPMENT OF CORALLOPYRONIN A - A NOVEL ANTIBIOTIC ACTIVE AGAINST *WOLBACHIA* ENDOSYMBIONTS OF FILARIAL NEMATODES

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The natural compound corallopyronin A (CorA) inhibits the bacterial DNA-dependent RNA polymerase. CorA is active against the essential *Wolbachia* endobacteria of filarial nematodes, preventing development and leading to sterility and death of the worms. Using the *Litomosoides sigmodontis* infection model in Mongolian gerbils, we demonstrated that CorA depletes *Wolbachia* from microfilariae and adult filariae by more than 2-logs and is thus macrofilaricidal. The macrofilaricidal effect can be reached after 2 weeks treatment and can be further reduced to ten days by combining CorA and albendazole, a significant advance over the current 4-week doxycycline regimen. Long-term treatment of insect cells infected with *Wolbachia* with suboptimal doses of CorA have yielded no CorA-resistant *Wolbachia* after 245 days. Non-GLP in-vitro toxicity tests (off-target, AMES, micronucleus, hERG, phototoxicity) demonstrated that CorA is non-toxic and pharmacologically safe. The maximal tolerated dose (MTD) in rats was 1000 mg/kg CorA, and will be used as high dose in the 7-day repeated dose study. In a first PK study in dogs, the animals tolerated the 75 mg/kd single dose well and CorA reached an oral bioavailability of 41%. These results will build the basis for the MTD and 7-day repeated dose toxicity in dogs conducted in 2022. The CorA drug substance is heterologously produced in genetically modified *Myxococcus xanthus*. Bio Base Europe Pilot Plant (BBEPP) has upscaled the fermentation to 15,000L, a major achievement for the project. We have funding to complete the pre-clinical phase and to prepare and submit a clinical trial application for a first-in-human phase 1 study (planned for 2024) to the German regulatory agency BfArM. CorA would be a first-in-class antibiotic with a novel mode of action to treat filarial infections in support of the UN Sustainable Development Goals.

1673

IMPACT OF MASS DRUG ADMINISTRATION FOR ELIMINATION OF LYMPHATIC FILARIASIS IN ABUJA NIGERIA

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filariasis (LF) is a neglected tropical disease caused by threadlike worms (nematodes) that live in the lymphatic vessels of humans. Nigeria is one of over 70 countries endemic for LF with an estimated 134 million people at the risk of infection. The Federal Capital Territory (FCT), an area endemic for LF, commenced mass drug administration (MDA) using ivermectin (IVM) and albendazole (ALB) in 2011. We assessed the impact of MDA on LF prevalence in two area councils that had achieved five effective annual rounds of MDA.Methodology and principal findingsIn 2010, a baseline mapping exercise was conducted in all six area councils of FCT-Abuja. The results revealed that four out of the six area councils were endemic for LF, with prevalence ranging from 1.0%-4.0%.The number of persons treated with IVM and ALB in the four Area Councils was documented during annual MDA and population-based cluster surveys were conducted at least once in each area council during the five years of treatment, to verify the reported geographic and therapeutic MDA coverage. The survey results confirmed that in two area councils (Abaji and Kuje) the programme coverage exceeded the target of 65%, while two other councils did not reach the recommended coverage. A pre-transmission assessment survey (pre-TAS) was conducted in one sentinel site and at least one spot check site in Abaji and Kuje in 2019 and were found to have LF antigenemia (LF Ag) < 2% (range 0.0% to 1.99%). In 2020, transmission assessment surveys (TAS) were conducted in the two area councils that previously passed the pre-TAS. The results showed that the two Evaluation Units (EU) had achieved the LF Ag threshold required to stop MDA. ConclusionAlthough Abuja-FCT has made significant progress towards LF elimination with two Area Councils qualifying to stop treatment, two other area councils still require a further two years of mass drug administration with effective MDA coverage to qualify for impact assessment. This paper provides evidence of the impact of MDA on LF prevalence in Abuja.

1674

BIOMARKER DISCOVERY AND ASSAY DEVELOPMENT TO DETECT ANTIBODIES SPECIFIC FOR *WUCHERERIA BANCROFTI*

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The World Health Organization (WHO) neglected tropical diseases road map for 2021-2030 calls for better diagnostic tests that would allow greater precision in program delivery. To support national programs working to eliminate lymphatic filariasis (LF) as a public health problem, new diagnostics are urgently needed to make appropriate stopping decisions on triple-drug mass drug administration (MDA) as current WHO-recommended tests cannot confirm active infection. In addition, new diagnostics capable of discriminating low levels of filarial transmission or detecting pre-patent infections are needed for post-MDA surveillance. Antigens specific for the main filarial species causing LF (*Wuchereria bancrofti* and *Brugia* spp.) are needed. To address this, we sought to identify new biomarkers that are sensitive and specific for bancroftian LF and compared their immunoglobulin (Ig) patterns. We conducted in 2020 a serum epitope repertoire analysis (SERA) using existing sera from countries with LF or onchocerciasis. From Haiti, we assessed sera from 60 people, 30 with confirmed bancroftian LF and 30 who were exposed but not infected. From Guatemala, we used sera from 120 people, 60

with confirmed onchocerciasis and 60 with neither LF nor onchocerciasis. SERA analyses were conducted to identify reactivities with total IgG, IgG1, and IgG4. For LF infected persons, SERA identified 49 LF-specific epitopes recognized by total IgG, 93 epitopes for IgG1, and 28 epitopes for IgG4. Using sera from LF exposed but not infected persons, SERA identified 8 specific epitopes for total IgG, 5 epitopes for IgG1, and 96 epitopes for IgG4. These epitopes were further screened using peptide arrays in 2021 on sera from persons with confirmed LF infection; peptides with signal-to-noise ratios ≥ 10 (n =99) were synthesized and re-screened using ELISA. There were 2 peptides recognized by IgG1 and 3 peptides recognized by IgG4 that had > 80% sensitivity and specificity for LF. Efforts are being made to produce chimeric, multi-epitope peptides that will be evaluated for LF programmatic use.

1675

TAS EVALUATIONS IN MALI: STRATEGIC INNOVATIONS IN INSECURE AREAS

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In 2004, mapping showed all the 75 health districts (HDs) in Mali were endemic for lymphatic filariasis (LF). Since 2012, Mali has experienced insecurity in the regions of Mopti, the northern regions, and recently in Sikasso and Segou regions. Nevertheless, with support from USAID's programs, all HDs achieved the criteria to stop MDA in 2020. Mali has committed to submitting its LF elimination dossier by 2025 and the completion of all transmission assessment surveys (TAS) is critical. Starting in 2020, the national LF program (PNEFL) developed special strategies using local staff to perform TAS in insecure areas, as national staff could not safely travel to survey sites. Only remote assistance, monitoring and supervision were provided by the national team. This strategy was used to successfully conduct TAS1 and TAS2 in 8 EUs in Mopti and the northern regions, led by regional staff with TAS experience who could safely travel between villages in these areas. Due to the worsening security situation and the nature of attacks in the central and southern regions, the PNEFL adapted the above strategy for TAS3 in 2021/2022 (Yorosso, Macina-Markala and Niono EUs). Only Technical Directors of Health Centers (TDHCs) implemented the survey, as they were known in the targeted communities and allowed to move between villages without threats from terrorists. In both approaches, surveyors were trained on TAS methodology in safer, neighboring districts, and practiced the use of FTS, including interpretation of results. Supervision was conducted remotely using WhatsApp, and FTS positives were remotely confirmed by supervisors. For the TAS1 and TAS2 surveys, the required samples were met in all EUs except Kidal EU (1514/1524) and no positive cases were reported. For the TAS3 surveys, the required samples were also met, with 1 positive case each for Yorosso and Niono EUs for a threshold of 18 in both. The development of these new strategies has allowed for the implementation of TAS in otherwise inaccessible areas, accounting for about 33 HDs. With these innovative strategies, the program will likely be able to eliminate LF despite the challenging security situation.

1676

THE FIRST PROSPECTION FOR VECTOR BREEDING SITES OF ONCHOCERCIASIS IN LIBERIA: IDENTIFYING PRODUCTIVE SITES OF *SIMULIUM DAMNOSUM* S.L. SPECIES IN 2018

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Onchocerciasis has been earmarked as one of the five neglected tropical diseases (Onchocerciasis, Lymphatic Filariasis, Trachoma, Schistosomiasis and STH) amenable to preventive chemotherapy targeted for elimination. Unlike the other diseases where the target is elimination as a public health problem, onchocerciasis has a goal to eliminate transmission. Towards this goal, the World Health Organization (WHO) has come out with a verification of onchocerciasis elimination guideline. During the mapping, which is based mainly on epidemiological parameters of infection, the selection of communities to examine requires the knowledge of vector breeding sites. Liberia began treatment for onchocerciasis in 2000, however, due to the civil unrest (2001-2003) and the Ebola outbreak (2014-2015), the program experience interruption in the treatment round. After 12 rounds of Mass Drug Administration (MDA), the country along with experts decided to identified vector productive breeding sites, vector *Simulium* species, first line communities and the development of a breeding sites map for Liberia. The survey was completed in 10 counties constituting two regions (northwest & southwest) showing possible transmission zones in Liberia. The research was undertaken in the dry season when most rivers especially the smaller ones were dry while larvae collected were processed involving an initial sorting of the samples into members of the *S. damnosum* complex. During the research, 17 breeding sites were identified, 4 different species seen, 204 samples (larvae) collected and the percent of forest cytospecies predominate with only a few sites having savannah species. Simulium yahense was observed to be the most widespread species in Liberia. The research results have generated valuable data to support the onchocerciasis control and elimination programme in Liberia. It shows the classification of species found in Liberia and have guided the program to the next step of conducting impact assessment for communities' dwellers living within 5km of a productive breeding site.

1677

NON-COMMUNICABLE DISEASE CO-MORBIDITY AND ASSOCIATED FACTORS IN TUBERCULOSIS PATIENTS: A CROSS-SECTIONAL STUDY IN GABON

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Low- and middle-income countries (LMICs) are experiencing an increasing double burden of communicable and non-communicable diseases (NCDs) such as tuberculosis and NCDs comorbidities. In many LMICs, there is not yet a clear strategy to control this new public health issue. The situation is worsened by the absence of lack of contextualized epidemiolocal data. This study investigated non-communicable disease co-morbidity in tuberculosis patients from Moyen Ogooué Province, Gabon. All patients aged 18 years or older consulting for tuberculosis (TB) symptoms in Gabon's Moyen Ogooué province and neighboring provinces from November 2018 to November 2020 were screened for diabetes mellitus, hypertension, and risk factors thereof (obesity, dyslipidemia, smoking, and alcohol consumption). Logistic regression was performed to identify factors associated with TB-diabetes and TB-hypertension co-morbidities. Of

the 583 patients included, 227 (39%) were diagnosed with tuberculosis. In tuberculosis-confirmed patients, the prevalences of hypertension and diabetes were 16·3% and 12·8%, respectively. The prevalence of diabetes was twice as high in tuberculosis patients compared to non-tuberculosis patients. Factors independently associated with hypertension-tuberculosis co-morbidity were age >55 years (aOR=8·5, 95% CI 2·43, 32·6), age 45-54 years (aOR=4.9, 95%CI 1.3-19.8), and moderate alcohol consumption (aOR=2·4; 95% CI 1·02- 5·9), respectively. For diabetes-tuberculosis co-morbidity, age >55 years was positively (aOR=9·13; 95% CI 2·4-39·15), and moderate alcohol consumption was inversely associated (aOR=0·26, 95% CI 0·08- 0·73). One-hundred-and-four (46%) of the tuberculosis patients had at least either dyslipidemia, hypertension, diabetes, or obesity with a majority of newly-diagnosed hypertension and diabetes. Integration of screening of non-communicable diseases and their risk factors during TB assessment for early diagnosis, treatment initiation, and chronic care management for better health outcomes should be implemented in all tuberculosis healthcare facilities.

1678

IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES (PCVS) ON COMMUNITY PNEUMOCOCCAL CARRIAGE PRE AND POST PCV VACCINE IMPLEMENTATION IN RURAL GAMBIA

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Nasopharyngeal carriage of *Streptococcus pneumoniae* which precedes disease is an importance measurement of effect, impact and herd effect of pneumococcal conjugate vaccines (PCVs). Our objective is to assess the impact of childhood PCV13 on pneumococcal nasopharyngeal carriage in the community. We recruited healthy Gambians across all age groups from the rural Gambia community before and post PCV vaccine introduction. Nasopharyngeal swabs were collected from the community during three Pneumococcal Cross-sectional Carriage surveys (PCS); baseline survey in 2009 and two impact surveys in 2015 and 2017 time period. Pneumococci were isolated and serotyped following standardized microbiological methods. A total of 8859 NPS samples were collected in all the three surveys: 2988 (2009**),** 3162 (2015) and 2709 samples (2017). Overall, prevalence of pneumococcal carriage was stable (68.9-72.5) in 0-4 years children but a carriage prevalence increases with age; 26% in 5-17years; 80% in 18-44 years and almost100% in 45 years and above. The risk of Vaccine type (VT) carriage in 0-4 years children reduces significantly by 63% [RR 0.37 (95%CI: 0.28-0.48)] in 2015 and 57% reduction [RR 0.43 (95%CI: 0.33-0.56)] in 2017. Similarly, risk of VT carriage in 5-17yrs marginally reduces in both 2017 [RR 0.86 (95%CI: 0.70-1.07)] and in 2017 [RR 0.99 (95%CI: 0.77-1.25)]. No significant risk changes is observed in adults 18 years and above. Conversely, the risk of NVT carriage in 0-4 years increases significantly [RR 2.22 [95% CI 1.83-2.69]) in 2015 and [RR 2.22 [95% CI 1.80-2.73]) 2017. Similar but slightly reduced risk pattern is also observed amongst all other age group. Non-type-able pneumococci (NT) carriage prevalence remain unchanged across all age groups except in 45+ years of age category [0% to 1.59% (in 2015) and 2.9% in 2017]. PCV vaccination in children decreases the risk of nasopharyngeal colonization in children (0-4 years of age) and in adults. An inverse NVT relationship is observed in all other age groups suggesting vaccine driven selective pressure.

1679

COVID-19 EXPOSURE, TESTING, AND QUARANTINE BEHAVIORS AMONG HEALTHCARE PROVIDERS SUPPORTING HIV SERVICES IN FOUR NIGERIA MILITARY HEALTH FACILITIES

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Background: During the COVID-19 pandemic, PEPFAR endeavored to protect the HIV workforce in supported countries. Following reports of high COVID-19 transmission in Nigerian health care staff, the Nigeria Ministry of Defense-Health Implementation Program and the U.S. Military HIV Research Program implemented an infection prevention and control intervention in supported military health facilities. We report COVID-19 screening responses, quarantine, and testing behavior, of staff in HIV and related departments. **Methods:** The facilities deployed a daily COVID-19 self-screening checklist from January to April 2021. The checklist included yes/no questions about recent exposures to confirmed or presumptive cases & biological material known to contain COVID-19, travel, signs & symptoms, COVID-19 testing in the prior 14 days, & current quarantine. Staff responding 'yes' to any question were prompted to test for COVID-19. Frequencies and proportions were calculated by cadre in Excel. **Results:** Of 254 staff that were screened, 83 (32.7%) were frontline staff (nurses, doctors), 171 (67.3%) were administrative, lab, environmental, and other staff. Frontline providers (61, 73.5%) answered yes to any question more often than other screened cadres combined (68, 39.8%) with the frequent report of symptoms (42, 50.6%), recent exposure to a confirmed or presumptive COVID-19 case (38, 45.8%), or exposure to biological material known to contain COVID-19 (24, 28.9%). Fourteen (23.0%) and 19 (31.1%) frontline staff who were prompted to test at least once reported currently quarantining or testing for COVID-19 in the 14 days prior, respectively. Self-reported quarantine (6, 8.8%) and testing (9, 13.2%) were similarly low for all other cadres. **Conclusion:** Frontline cadres were exposed to COVID-19 and/or reported symptoms more often than other cadres, although all cadres infrequently tested or quarantined. Further work is needed to understand how to best protect the health workforce to reduce COVID-19 risk for staff and people with HIV, especially while vaccination coverage remains low and as new COVID-19 variants emerge.

1680

INVASIVE ASPERGILLOSIS MIMICKING PULMONARY TUBERCULOSIS

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Pulmonary tuberculosis (PTB) remains a major health problem worldwide, it is commonly associated with secondary aspergillosis. The reason for an increased prevalence of fungal disease in PTB is the inefficiency of the immune system and the use of antituberculosis treatment which promotes the growth and reproduction of fungal flora and in turn aggravates the underlying pathology. PTB and invasive aspergillosis are both progressive lung parenchymal disease with similar risk factors, clinical profile, and radiological findings that often becomes cumbersome for a physician in search of a diagnosis. Chest imaging findings of cavitation and fibrosis are common in both diseases. Infarct-shaped consolidations and smooth bronchial wall thickening are more frequent in invasive aspergillosis whereas mass-shaped consolidations and centrilobular nodules are more frequently seen in tuberculosis. In this report, we present a 65-year-old woman with a history of chronic exposure to a construction site around the Ganga River who presented to a tertiary care center with a history of shortness of breath associated with non-productive cough for 14 days. The initial chest imaging showed the presence of a thick-walled cavitary lesion with surrounding areas of consolidation with peripheral ground-glass opacities (halo sign). The patient was started on a loading dose of injection voriconazole 6mg/kg at 12 hours interval followed by a 4mg/kg maintenance dose at 12 hours interval. The serum galactomannan antigen testing was within the normal range. Bronchoalveolar lavage revealed negative KOH mount and fungal culture. However, PTB was detected

in CBNAAT with rifampicin sensitivity and she was started on a weight-based Antitubercular drug regimen. In due course, she was deteriorated and died due to type 1 respiratory failure and septic shock. Hence every clinical-radiological invasive aspergillosis case is not what it looks like, PTB is still the masquerade. Timely recognition rewards but delay in suspicion/diagnosis paves towards death.

1681

MONITORING THE PEDIATRICIANS' CLINICAL DECISION FOR THE DIAGNOSIS OF PULMONARY TUBERCULOSIS AMONG CHILDREN WITH 'XPERT MTB/RIF ULTRA - TRACE DETECTED' IN STOOL SAMPLE

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Diagnosis of childhood tuberculosis (TB) remains challenging for difficulty in sputum collection. Recently, the World Health Organization has suggested stool for testing by Xpert MTB/RIF Ultra (Ultra) for childhood pulmonary TB (PTB) diagnosis. Still, children with "trace detected" results on Ultra (Ultra-trace) in stool need further clinical evaluation by pediatricians to confirm PTB diagnosis. In this study, we monitored the clinical decision of pediatricians for diagnosis of PTB in children with "Ultra-trace" in stool. Children (<15 years old) admitted in 16 hospitals in Dhaka between November'20-December'21 with clinical features suggestive of PTB (pulmonary presumptive) were enrolled, and their respiratory samples (induced sputum/gastric lavage) and stool were tested by Ultra. We also collected socio-demographic and clinical data from their care-givers, after informed written consent/assent. Children with "Ultra-detected" in any samples and "Ultra-trace" in respiratory samples were diagnosed as TB. However, children with only "Ultra-trace" in stool were further assessed by treating pediatricians using an algorithm to confirm TB diagnosis. We analyzed data using statistical software STATA (version 17). Descriptive statistics were used to report demographic, clinical and laboratory profiles. We enrolled 2221 child pulmonary presumptives [median age (IQR): 2.7 (1.0,6.9) years] and tested their respiratory and stool samples by Ultra. In respiratory samples, 76 (3.4%) were "Ultra-detected" and 38 "Ultra-trace" (50%) whereas 222 (10%) stool were "Ultra-detected" and 190 "Ultra-trace" (85.6%). Of children with "Ultra-trace" in stool, 120 (63.2%) were advised for anti-TB treatment. Rests (70, 36.8%) were followed-up monthly till study ended. Of them, 22 (31.4%) were re-tested by Ultra (stool) and one (4.5%) was "Ultra-trace". The child was prescribed for anti-TB treatment. Pediatricians' decision was found appropriate for PTB diagnosis in children having "Ultra-trace" in stool. Still, regular follow-up for at least six months is preferred to monitor outcome. We recommend future study to validate this finding.

1682

CONNAISSANCES, ATTITUDES, PRATIQUES, SENSIBILISATION DE LA POPULATION GÉNÉRALE FACE AU COVID19 ET À LA PRÉVALENCE DES PORTEURS DE COMORBIDITÉS DANS LE GRAND LIBREVILLE AU GABON

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Control measures deployment to fight against Covid19 is hampered by the lack of knowledge and the population attitudes. The aim of the study was to assess the knowledge, attitudes and practices of populations and identify behavioral and risk factors of the severity of Covid 19 in order to better target them of prevention and care strategies. A prospective, cross-sectional on the knowledge, attitudes and practices survey was carried out in Gabon, in Libreville the capital city between november 2020 and May 2021. Demographic, socio-professional and history clinical data such as comorbidities have been recorded. All subjects who gave their consent to participate in the study were interviewed using a standardized questionnaire. 1022 people were interviewed: 54.7%(559/1022) from Libreville, 35%; (358/1022) from Owendo. 55% of the population knew all the preventive measures decreed by the Covid19 scientific committee. Moreover more 56% (n = 487) of the population aged 20 to 45 had a good knowledge of preventive measures against Covid 19 and 54% had good pratical face to Covid 19. More than 38% of the population had reported having comorbidities. Most of them were over 45 years old, and 42% did not know their clinical status and nearly 75% of the population knew of the preventive measures decreed by the Covid 19 scientific committee. However, more than half (65%) did not believe in the disease and therefore did not comply with all preventive measures. In conclusion, these results highlight the need of developping communication strategies based on proximity in the neighborhoods. Also, it will allow a better implementation of prevention and care measures.

1683

IMPROVING COVID-19 VACCINE UPTAKE THROUGH INTEGRATED COMMUNITY OUTREACH SERVICES IN NIGERIA

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Slow uptake of the COVID-19 vaccine is well documented in Nigeria. Access to the vaccine is affected by multiple factors, including vaccine hesitancy fueled by mistrust of the government, concerns about the safety of vaccines, and low risk perception for COVID-19 infection. Breakthrough ACTION Nigeria implements social behavior change for Tuberculosis and active community case finding. Increasing access to medical services through community outreach and motorized campaigns yielded great gains during the pandemic. Offering diagnostic services together with community SBC activities considerably increased the number of TB cases notified and patients placed on treatment. The project added COVID-19 messages, testing and vaccination to TB community outreach following the receipt COVID-19 funding. The 2022 World Tuberculosis Day activities in Kano, Bauchi and Akwa Ibom States provided an opportunity to plan and implement the integration with the state governments and other stakeholders including implementing partners. Community engagement prior to the motorized campaign assured community acceptance of the activities. Use of loud music including TB/COVID-19 jingles and spots in the communities drew crowds. Trained community volunteers facilitated discussions with community members and referred them to the service stand where they were offered screening for TB using mobile chest x-ray, COVID-19 testing, and COVID-19 vaccination. Results for COVID-19 vaccination conducted showed a 35-600% increase in daily vaccination rate in the same districts across the 3 states, and COVID-19 testing for non-travelers recorded a 200-275% increase. Use of interpersonal communication while waiting for services may increase uptake of additional services. Multiple service points may have improved ease of access and a feeling of vaccination being a community norm, and in turn encouraged uptake of the COVID-19 vaccine. Integrating service outreaches may address vaccine uptake in Nigeria.

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DIAGNOSTIC PERFORMANCE OF SARS COV2 ANTIGEN BASED RAPID TEST FOR TRIAGE USE OF COVID-19 SYMPTOMATIC PATIENTS IN INDONESIA

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During the coronavirus disease 2019 (COVID-19) pandemic peak, real time (RT)-PCR, an expensive and time-consuming method was used for diagnosing COVID-19. A low-cost rapid antigen detecting test (Ag-RDT) will be useful to screen triage patients in countries with limited resources. We evaluated an Ag-RDT for the detection of the SARS-CoV2 in respiratory swabs of patients at triage with probable symptoms of COVID-19. The study was conducted in three health facilities in Jakarta, Indonesia. The COVIOS®Ag test (Global Access Diagnostics, Mologic Ltd, UK) was used on nasal samples. Diagnostic performance was determined with reference to RT-PCR (Applied Biosystems™ 7500) performed on samples collected in parallel. We collected 445 samples between September 2021 and January 2022 in patients above one year of age; 50 (11.2%) were positive by Ag-RDT, 58 (13%) were positive by RT-PCR and 81% were ≤ Ct 30. The mean (SD) age in years was 47 (18) and 2% of RT-PCR positive patients were > 7 days post symptom onset . The Ag-RDT sensitivity was 82.8% (95% CI 71.1-90.4%) and specificity 99.5% (98.1-99.9%). The sensitivities at ≤ Ct 30 and >Ct 30 were 95.7% (85.8-98.8%) and 27.3% (9.7-56.6%) respectively. The sensitivity ranged from 87.0% (74.3-93.9%) within two days post symptom onset, to 84.2% (72.6-91.5%) within seven days of symptom onset. The overall diagnostic performance of the COVIOS® Ag test meets WHO recommended values with sensitivity (≥ 80%) and specificity (≥ 97%). As anticipated, the RDT performed better at higher viral load and during early onset of symptoms. The COVIOS® Ag RDT therefore has potential for use at triage for the diagnosis of COVID-19 in health facilities in low-and middle-income in countries like Indonesia.

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SPATIAL AND TEMPORAL TRENDS OF PNEUMONIA DUE TO METHICILLIN-SUSCEPTIBLE AND RESISTANT STAPHYLOCOCCUS AUREUS IN TEXAS

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According to the Centers for Disease Control and Prevention (CDC), each year 2.8 million people in the U.S. are infected with antibiotic-resistant microorganisms and approximately 1 in 100 of these individuals die of infection. In the latest report on antibiotic resistance threats, the CDC listed MRSA organisms as serious threats, because they are common bacteria that can spread in healthcare facilities and the community. National trends of MRSA infections are reported at state and national levels through the Emerging Infections Program (EIP) Healthcare-Associated Infections (HAI) program. However, Texas is not part of the surveillance catchment areas. Texas has limited MRSA surveillance through the Texas Healthcare Safety Network, and reported 44.33 percent (out of 710) SA isolates susceptible to oxacillin/methicillin in 2014. National trends provide useful information on MSSA and MRSA they may not reflect state trends. In this study, we identified temporal and spatial trends of hospital discharges with pneumonia due to methicillin-susceptible (MSSA) and resistant Staphylococcus aureus (MRSA) in Texas from 2006 to 2020. Our main goal is to describe demographics (age, sex, race, ethnicity) and healthcare characteristics at admission (type of admission), healthcare outcomes (length of stay and specific patient status at discharge) and areas with frequent high incidence of infection. Results provide knowledge of hospital-admitted populations with high rates of MSSA and MRSA infection and adverse healthcare outcomes that could potentially be used to reduce incidence of this type of infection.

1686

INCIDENCE AND SOCIAL DETERMINANTS OF TUBERCULOSIS IN PATIENTS FROM THE COHORT OF 100 MILLION BRAZILIANS: A POPULATION-BASED STUDY (2004 TO 2018)

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Antimicrobial resistance has been a hot topic in the last decade, deserving attention from international organizations, multilateral agencies and the Brazilian Ministry of Health. In the case of tuberculosis (TB), knowledge of the epidemiological panorama and the identification of population groups that are at increased risk of disease transmission can inform actions focused on preventing the emergence of resistance to drugs that fight the disease. This study aimed to estimate the incidence and social determinants of tuberculosis in patients from the 'Cohort of 100 Million Brazilians', from 2004 to 2018. Using TB notification data collected between 2004-2018 and linked in the 100 Million Brazilian Cohort, we investigated TB new case detection rates (NCDR) among diagnosed TB patients and within variables exposure categories (e.g., by sex, age, ethnicity, migration, cash transfer benefit, household conditions, urbanicity and Brazilian region). We calculated odds ratios of TB detections by using logistic regressions to assess the associations with potential risk factors for becoming a TB case, including the sociodemographic, household and geographic characteristics. Among 258,239 TB cases, the NCDR of TB was 31.2/100,000 person-years (95%CI 31.1-31.3). Male patients had higher odds of becoming TB cases female (ORadj 1.79, 95%CI 1.77-1.81); and the odds increased among patients aged ≥50 years (ORadj 10.45, 95%CI 10.13-10.77), black (ORadj 1.81, 95%CI 1.78-1.84), with limited education (illiteracy/pre-school [ORadj 1.62, 95%CI 1.20-2.42]), unemployed (ORadj 1.32, 95%CI 1.30-1.34), lived in crowding households (>2 inhabitants/room) (ORadj 1.68, 95%CI 1.65-1.70), and in urban area (ORadj 1.92, 95%CI 1.88-1.95). TB detection varied across Brazilian regions with higher odds at South and Southeast (ORadj 1.88, 95%CI 1.83-1.93; ORadj 1.76, 95%CI 1.72-1.80, respectively). The high TB rates found those patients highlight the urgent need for public health interventions specifically targeting this uniquely vulnerable population. Our findings emphasise the need to prioritise to social development as a means of preventing TB.

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ELEVATED SARS-COV-2 VIRAL LOADS IN A DIVERSE COHORT OF HOSPITALIZED PATIENTS IN NEW MEXICO PREDICTS SEVERE COVID-19 AND MORTALITY

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Defining factors that predict which patients with COVID-19 will develop severe disease and mortality can help improve clinical care options. Studies from our group and others illustrate that certain racial/ethnic groups have disproportionately higher COVID-19 disease severity and mortality. To better understand the pathogenesis of COVID-19 for the identification of therapeutic targets and improving clinical outcomes, we are conducting a prospective study on hospitalized patients at the University of New Mexico Hospital. SARS-CoV-2 viral load (VL) dynamics were investigated in the upper respiratory tract (URT) and peripheral blood (PB) on days 0, 1, 2, 3, 6, 9, 14. VLs were determined by RT-qPCR using the CDC-recommended panel of N1 and RNase P primers and probes. Results presented here are in a diverse cohort of patients (n=469): [American Indian/Alaska Native

(AI/AN) n=148; Hispanic/Latino n=217; Non-Hispanic White n=84; and Other n=20]. Severe COVID-19 (n=187) was defined as admission to the ICU and/or death, while non-severe patients (n=282) did not require ICU support. Time symptomatic prior to hospital admission and time since the first PCR(+) test for COVID-19 were similar (P=0.261 and P=0.159, respectively). Patients with severe disease had significantly higher URT and PB VLs on each of the sampling days and cumulatively across two weeks. Predictors of severe disease included: male [Odds Ratio (OR)=2.88, P=1.88x10^{-5}], older age (OR=1.03, P=2.00x10^{-3}), higher URT mean VL (OR=1.10, P=3.50x10^{-2}), higher PB mean VL (OR=1.63, P=9.11x10^{-10}), and AN/AN ancestry (OR=3.91, P=1.47x10^{-4}). Mortality across hospitalization was associated with being male (OR=2.45, P=6.00x10^{-3}), higher URT mean VL (OR=1.20, P=2.00x10^{-2}), higher PB mean VL (OR=1.62, P=2.58x10^{-8}), and AI/AN ancestry (OR=2.47, P=4.30x10^{-2}). These results identify viral load, particularly in the peripheral blood, and ancestry as important predictors of severe COVID-19 and mortality. Therapeutic interventions that prevent and/or lower SARS-CoV-2 levels in peripheral blood may offer an important intervention to improve patient outcomes.

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DISPROPORTIONALITY ELEVATED SEVERE COVID-19 AND MORTALITY IN HOSPITALIZED AMERICAN INDIAN/ALASKA NATIVE PATIENTS

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Epidemiological data across the USA show health disparities in COVID-19 infection, hospitalization, and mortality by race/ethnicity. However, data on disease severity measures and mortality are largely unreported in diverse cohorts of hospitalized patients. Identifying patient risk factors is essential for improving clinical outcomes. As such, we are conducting a prospective observational study on COVID-19 patients (n=469) admitted to the University of New Mexico Hospital (4/23/2020 to date). Self-reported race/ethnicity, comorbidities, clinical and laboratory measures, and clinical events during hospitalization were documented. Patients were stratified by self-reported ancestry: AI/AN (n=148), Hispanic/Latino (n=217), non-Hispanic White (n=84), and Other (n=20; not included in statistical analyses based on sample size). Severe disease was defined as admission to the intensive care unit (ICU) and/or death, while non-severe disease was defined as not requiring ICU support. Patients were symptomatic for an average 6.6±4.8 days prior to hospitalization with no difference between groups (P=0.955). Mean age in the overall cohort was 53.8±14.6 years. The AI/AN group was younger (P=0.020) with a larger distribution in the 18-44 age category (P=0.013). Established risk factors for severe COVID-19 (e.g., being male and elevated BMI) were comparable across the groups. However, the AI/AN group had an increased requirement for ventilation (P=1.57x10^{-4}), longer stay in hospital (P=4.66x10^{-5}), and a higher rate of severe COVID-19 (P=2.93x10^{-4}). Multivariate modeling revealed that AI/AN ancestry was a predictor of severe COVID-19 (OR=3.44, CI=1.829-6.472, P=1.27x10^{-4}). Although mortality did not differ in univariate analysis, logistic regression modeling showed that AI/AN ancestry was associated with higher mortality (OR=2.45, CI=1.113-5.145, P=0.022). Collectively, these findings in hospitalized patients in New Mexico demonstrate that the AI/AN group had increased COVID-19 severity and mortality relative to the Hispanic and non-Hispanic White groups.

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STRUCTURAL RISK FACTORS FOR SARS-COV-2 INFECTION IN AN URBAN SLUM SETTING

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The structural environment of urban slums, including physical, demographic and socioeconomic attributes (e.g., population density, poor infrastructure and access to services) renders inhabitants more vulnerable to SARS-CoV-2 infection, yet little is known about the specific determinants that contribute to high transmission within these settings. To examine the socioeconomic and structural factors that influence SARS-CoV-2 infection in urban slums and characterize the risk gradients in these communities, we performed a serosurvey in a cohort of 2,035 residents from Salvador, Brazil, from November 2020 to February 2021, after the first COVID-19 epidemic wave. We identified high SARS-CoV-2 seroprevalence (46.4%, 95% CI 44.3-48.6%), mainly among female residents (48.7% [95% CI 45.9-51.6%] vs. 43.2% [95% CI 39.8-46.6%] among male residents), and among children and adolescents (56.5% [95% CI 52.3-60.5%] vs. 42.4% [95% CI 39.9-45.0%] among adults). In multivariable models accounting for household-level clustering, the odds ratio for SARS-CoV-2 seropositivity among children and adolescents was 1.96 (95% CI 1.42-2.72) compared to adults 30-44 years old. Adults residing in households with children were more likely to be seropositive; this effect was more prominent among individuals aged 30-44 and 60 years or more. Women living below the poverty threshold (daily per capita household income <$1.25) and those who were unemployed were more likely to be seropositive. During a single, initial wave of the COVID-19 pandemic, the cumulative incidence of infection approached 50% in this urban slum population in Brazil. In contrast to observations from industrialized countries, SARS-CoV-2 incidence was highest among children, and women living in extreme poverty. Although the study community had an overall high level of poverty, our study identified granular gradients of risk within the urban slum population. These findings emphasize the need for targeted interventions that provide safe environments for children and mitigate the structural risks posed by crowding and poverty for the most vulnerable inhabitants of these informal settlements.

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VARIATIONS OF THE NASOPHARYNGEAL MICROBIOTA ACCORDING TO SEVERITY STATES OF COVID-19

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Different factors influence the severity of the COVID-19, caused by the SARS-CoV-2 virus. This study aimed to compare the nasopharyngeal microbiota of patients with different disease severity. A total of 26 patients were recruited. group 1 (G1): patients with SARS-CoV-2 (+) and

hospitalized in the ICU. Group 2 (G2) patients (+) and hospitalized. Group 3 (G3) patients (+) and not hospitalized. Group 4 (G4) healthy patients with a negative result. All patients underwent SARS-CoV-2 testing by RT-PCR. The nasopharyngeal microbiota was characterized using PCR targeting 13 representative bacteria genus. The analysis of the frequency of detection of the bacteria genus in each group was evaluated. Some bacteria were significantly more frequent in hospitalized patients (ICU and non-ICU) compared to the non-hospitalized patients (asymptomatic and healthy controls). This is the case of *Lactobacillus* with 96.15% in G1, 96.15% in G2, 23.08% in G3 and 15.38% in G4. Similarly, Prevotella presented 96.15% in G1, 80.77 in G2, 0.00% in G3 and 19.23% in G4. In the same way, Veilonella, Bacteroidetes and Firmicutes presented a similar distribution. On the other hand, the detection of some bacteria was more frequent among asymptomatic and healthy subjects, such as Eubacterium with 3.85% in G1, 19.23% in G2, 50.00% in G3 and 30.77% in G4. The relative abundance of the bacteria was evaluated: Lactobacillus and Veilonella were predominant in both hospitalized groups compared to asymptomatic and healthy subjects. Actinobacteria and Eubacterium were predominant in the asymptomatic and healthy groups. In conclusion, the unique nasopharyngeal microbiota profile was found in COVID-19 patients with different disease severity. The presence of Lactobacillus, Prevotella, Veilonella, Bacteroidetes and Firmicutes were higher in critical and hospitalized patients, compared to asymptomatic and healthy subjects. On the other hand. Eubacterium and Actinobacteria were predominant in the groups of asymptomatic and healthy subjects. The nasopharyngeal microbiota should be studied in the future as a therapeutic, diagnostic, and prognostic tool in COVID-19.

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CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH COVID 19 IN PANAMA: A RETROSPECTIVE OBSERVATIONAL STUDY

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged from Wuhan, China, in December 2019 and has raised serious concerns worldwide. This novel and extremely contagious virus causes severe respiratory syndrome and is transmitted through respiratory droplets and physical contact. Not surprisingly, SARS-CoV-2 was transmitted across Panama in a short time followed by the declaration of the first imported case on March 8th, 2020. This study aims to describe the clinical and laboratory findings of patients in Panama with SARS-CoV-2, hospitalized in the main hospital of Panama City, Hospital Santo Tomás. Demographic, clinical, and laboratory characteristics, treatment, and outcomes of adult patients hospitalized in the Hospital Santo Tomás of Panama City were included in the study. 1,586 patients (mean age 54.67 ± 16.74) were identified to be SARS-CoV-2 positive and 60% of the cases were male. All patients were classified as moderate and severe cases, and the most common signs and symptoms at admission were dyspnea (74.5%), fever (64.6%), cough (58.4%), fatigue/malaise (35.7%), cephalea (27%) and anosmia (14.3%). Hypertension (40.3%) and Diabetes mellitus-DM (27.4%) were the most frequent comorbidities. Laboratory indicators such as lymphocyte counts, procalcitonin, IL-6, D-Dimer, and lactate dehydrogenase (LDH) were significantly higher in severe cases. Our results indicate that potential risk factors are older age, multiple comorbidities, and high levels of lymphocyte counts, procalcitonin, IL-6, D-Dimer, and lactate dehydrogenase (LDH). This study provides an understanding of the clinical features that are more common in Panamanian patients. Further collaborative studies are needed to validate our data nationwide.

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LAG ASSOCIATIONS OF EXPOSURE TO AIR POLLUTANTS AND SYMPTOMS OF ACUTE RESPIRATORY INFECTIONS IN CHILDREN IN SOUTH AFRICA 2016

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Short-term exposures to air pollutants such as fine particulate matter (PM2.5) and NOx have been associated with increased risk for symptoms of acute respiratory infections (ARIs) in children. Less well understood is how long-term exposures to these pollutants might increase risk of ARIs and their symptoms. This research uses georeferenced Demographic Health Survey (DHS) data from South Africa (2016) and a remote sensing based rasters of PM2.5 concentrations and NOx to test associations between exposure air pollutants and ARI symptoms in children for up to 12 monthly lags. Predicted PM2.5 and NO2 concentrations were extracted from raster for latitude/longitude locations of survey clusters for up to 12 months previous to the date of survey. These data and other environmental and demographic data were used in a logistic regression model of ARI symptoms within a distributed lag nonlinear modeling framework (DLNM) to test lag associations of PM2.5 exposure with binary presence/absence of fever and ARI symptoms such as cough, cough with rapid breaths and blockage/runny nose and in the previous two weeks. The dataset comprised data from 3,548 children ranging in age from 6 months to 5 years. Average exposure to PM2.5 as 23 micrograms per cubic meter, far in excess of guidelines set by the World Health Organization. Models indicated that there were significant interaction effects of air pollution and fever and symptoms of ARI, with effects of air pollution being significantly elevated in urban areas (OR 1.68, [95% CI 1.05, 2.58]). Relationships held even when controlling for individual and household factors. Conclusions, exposure to air pollutants in a low middle income economy such as South Africa is a serious problem, even in rural areas. Long term exposure to ambient air pollution in this context may intensify risk for acute respiratory infections, compromising long term health.

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RELIABLE ESTIMATION OF SARS-COV-2 ANTI-SPIKE PROTEIN IGG TITERS FROM SINGLE DILUTION ELISA OPTICAL DENSITY VALUES IN SEROEPIDEMIOLOGICAL SURVEYS

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Surveillance of the COVID-19 pandemic requires reliable and scalable seroepidemiology methods to estimate incidence, monitor the dynamics of population-level immunity, and guide mitigation and immunization policies. Our aim was to evaluate the reliability of ELISA optical density values (OD) at a single dilution as a predictor of SARS-CoV-2 immunoglobulin titers derived from serial dilutions. We conducted two serial serological surveys in a community-based cohort in an urban informal settlement of Salvador, Brazil after the first (November 2020 to February 2021) and second (July to October 2022) COVID-19 epidemic waves in Brazil. Anti-SARS-CoV-2 spike protein immunoglobulin G (anti-S IgG) ELISA (Euroimmun AG) was performed with serial 3-fold dilutions of sera from 54 of the 1,101 cohort participants. We used parametric models to fit the relationship between OD at a single 1:100 dilution and

interpolated titers from serial dilutions of each serum sample and assessed the correlation between change in OD and change in interpolated titers between serum samples obtained from each participant during sequential surveys. Single-dilution ELISA OD reliably predicted increases and decreases in interpolated titer with 98.1% agreement (κ = 95.9%). We found a high correlation between changes in OD and changes in interpolated titers between samples from the same individuals in the two sequential surveys (Pearson correlation r = 0.836, Spearman rank correlation rho = 0.873). The area under the receiver operating characteristic curve for the detection of a four-fold increase or decrease in interpolated titer was 0.994 (95% CI 98.4-100.0%). A 1.48-fold change in OD predicted a 4-fold rise in interpolated titer between sequential surveys with 100% sensitivity and 92% specificity. Our findings demonstrate that single nOD can reliably estimate SARS-CoV-2 antibody titers, greatly reducing the time, human and financial resources needed to carry out large-scale serosurveys for surveillance or research purposes. This approach provides a less resource-intensive alternative for settings where financial resources and specialized labor are scarce.

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UNDERESTIMATION OF TUBERCULOSIS MORTALITY IN RESEARCH PARTICIPANTS CAUSED BY CONSENT BIAS

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Reducing mortality caused by tuberculosis (TB) is prioritized by the World Health Organization (WHO) "End TB" strategy and the Sustainable Development Goals (SDGs). Research projects are generally only permitted to analyze data from research participants and not from non-participants. We aimed to compare survival during and after TB disease for participants versus non-participants in a TB cohort. We hypothesized that survival would be worse for non-participants than participants causing important consent bias. To achieve this we obtained research ethics committee approval to specifically study anonymized linked survival data for non-participants (n=73) as well as participants (n=1027) in the PREVENT TB cohort (http://www.isrctn.com/ISRCTN17820976) from July 2016 to July 2017. Reasons for non-participation were declining to give informed consent (n=30), or logistical inability to invite participation (n=43). Mortality/survival data were characterized using WHO definitions: patients who died from any cause whilst awaiting or receiving TB treatment; these data were obtained collaboratively from national records, which in Peru are accurate and comprehensive. After a 15 months follow-up, 3.1% (95% confidence intervals (CI):2.0-4.7% 32/954) had died. Mortality was significantly greater for non-participants, 25% (95%CI:15-36%, 18/73, p<0.001). Patients with TB were significantly more likely to die if they were non-participants than research participants (adjusted relative risk (aRR)=4.2, 95%CI:2.1-8.3, p<0.001). This finding was explained by increased mortality in patients with TB who could not be located, 40% (95%CI:25-56%, 17/43), whereas patients who declined to consent did not have elevated mortality (3.3%, 95%CI:0.8-17%, 1/30). In conclusion, mortality was underestimated in recruited research participants with TB, potentially because gravely ill patients with high risk of mortality may have been too unwell to be invited to participate. This subgroup must be a priority among researchers to avoid bias in research supporting ending TB and achieving the SDG target.

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THE BURDEN OF UROGENITAL SCHISTOSOMIASIS AMONG PATIENTS PRESENTING WITH SIGNS AND SYMPTOMS OF SEXUAL TRANSMITTED DISEASES

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Urogenital schistosomiasis is a public health problem in endemic areas of Tanzania, which include areas along Lake Victoria. The disease is prevalent in communities with low socio economic status and inadequate water and hygiene infrastructure. Signs and symptoms of urogenital schistosomiasis mimics signs and symptoms of sexual transmitted infections (STIs) making it difficult to diagnose in communities co infected with both diseases. This study aimed at determining the burden of urogenital schistosomiasis among patients presenting with signs and symptoms of STIs at Itilima district hospital.Around 311 patients presenting with signs and symptoms of STIs were enrolled in the study. A single urine sample was obtained for parasitological screening of *S. haematobium* ova. A questionnaire was administered to collect sociodemographic characteristics and knowledge about urogenital schistosomiasis among participants. Out of 311 participants, 53.3% were female, 80.4% aged between 18-30 years of age. The prevalence of urogenital schistosomiasis was 22.4%. The prevalence was higher in males 26.9%. Prominent feature of urogenital schistosomiasis was hematuria. About 43.4% of participants have never heard of urogenital schistosomiasis. Only 40.8% knew the signs and symptoms of urogenital schistosomiasis. Majority (67.2%) did not know the correct method of schistosomiasis prevention. Occupation (OR=3.567, p=0.016) and not receiving praziquantel during mass drug administration (OR=2.311, p=0.0173) were associated with urogenital schistosomiasis. Therefore in *S. haematobium* endemic areas where it is not possible to do laboratory diagnosis of urogenital schistosomiasis it is rational to prescribe praziquantel with the combination of existing STI treatment regimen in the management of patients presenting with signs and symptoms of STIs. Also provision of health education to community members on urogenital schistosomiasis in schools, community and health facilities.

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INSIGHTS INTO ENVIRONMENTAL DETERMINANTS OF SOIL-TRANSMITTED HELMINTHS TRANSMISSION USING GPS TRACKING TECHNOLOGY

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Soil-Transmitted Helminthiasis (STH) is targeted for elimination by year 2030 and there are concerns about achieving this target in Ghana due to reports of persistent low albendazole cure rates following treatment with a single dose. Kawampe a rural community in the Brong-Ahafo Region, Ghana recorded 23% prevalence of hookworm in 2015 and has consistently remained high despite interventions in cohort studies. To investigate the persisting high prevalence in this community, this study aimed to identify human and environmental determinants of transmission. A cross-sectional study was carried out involving 59 consenting participants. They were first screened for hookworm infection to enable grouping into positive and negative cases. Each participant was made to wear a GPS tracking device for 10 consecutive days and the movement data was captured in real-time, recorded, plotted and put in clusters. Soil samples were also collected from these clusters where participants spent

most of their time. Soil physical and chemical properties were measured using standard methods and helminth eggs were hatched using the Baermann technique. Determinants of larvae counts were estimated with the Multivariate Negative Binomial Regression (MNBR) model. The MNBR analysis revealed that the soil pH was positively associated with the number of larvae (P<0.001). Carbon and sandy-loamy textures were also significantly associated with high larvae counts (P<0.001) whilst high nitrogen and clay contents were significantly associated with low larvae counts (P<0.001). The larvae counts of six each of soil samples frequented most by infected (n=93) and non-infected (n=192) were not significantly different (Mann Witney U=14400, P=0.59). Our preliminary metagenomics analysis of larval DNA has identified *Parastrongyloides trichosuri* a nematode parasite of small mammals as dominant larvae in soil samples, which was expected. These are preliminary findings and therefore further studies are being conducted to increase sample sizes to enable firm conclusions to be drawn.

1697

UNDERSTANDING THE SOCIO-CULTURAL DETERMINANTS OF HEALTH-SEEKING BEHAVIORS AND HEALTH INFORMATION TRUST AMONG WOMEN AT-RISK FOR FEMALE GENITAL SCHISTOSOMIASIS IN GHANA: A MIXED-METHOD STUDY

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Female genital schistosomiasis (FGS) is a manifestation of schistosomiasis, a waterborne parasitic infection, that is estimated to impact 56 million women primarily in Sub-Saharan Africa. Despite its burden, there is a lack of awareness among community members and health professionals about FGS. Currently, there is scarce literature on FGS and related health-seeking behaviour (HSB) trust among at-risk women. The objective of this study is to understand the socio-cultural determinants of HSB and the health information trust for women at-risk of FGS in Ghana. A community survey and 12 focus group discussions (FGDs) were conducted in the North Tongu and Weija Districts. These districts were selected due to their high prevalence of schistosomiasis. Eight hundred and sixty-nine (869) community members between the ages of 18-59 years in both districts were surveyed. The FGDs consisted of separate groups of women and men from the two districts. There was a lack of awareness surrounding FGS among women in the FGDs with 38.8% reporting hearing about FGS in the surveys, given they were aware of schistosomiasis. Schistosomiasis, or "blood in urine", was perceived to be a boy's disease by women in the communities. Only 48.8% of women reported HSB from the 86 women choosing to talk about their FGS/schistosomiasis-related symptoms. The trust in health professionals (78.5%) illustrated by women in the survey was validated by FGDs. HSB was significantly associated with level of education (p-value: 0.015, 0.024) and monthly steady income (p-value: 0.036), after controlling for age, and source of health information, among women at-risk for FGS. The emerging determining themes for HSB included: environmental and systemic context, shared perceptions, apprehensions, and conflict in roles. The lack of awareness of FGS indicates the need for tailored health information campaigns in endemic communities and increasing communication on susceptibility to the disease. The impact of environmental and systemic context on seeking treatment illustrates a need to improve the accessibility and availability of care addressing women's reproductive health.

1698

ASSOCIATION BETWEEN SERUM LIPID PROFILE AND LIVER FIBROSIS IN PATIENTS WITH SCHISTOSOMIASIS JAPONICUM

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Liver fibrosis is closely related to lipid profile. The possible association between lipids and liver fibrosis caused by different etiologies has been widely explored. However, their association in patients with schistosomiasis japonicum remains unclear. The present study aimed to preliminarily explore the association between lipid profile and liver fibrosis in schistosomiasis japonicum infected patients. This retrospective study enrolled 1,503 patients diagnosed with schistosomiasis japonicum from January 2019 to June 2021 in Xiangyue Hospital, China. Patients were divided into two groups with or without liver fibrosis by two experienced schistosomiasis specialists according to the results of liver ultrasound examination. The demographic, clinical and laboratory variables were collected. Multivariable logistic models were used to estimate the independent associations between lipid profiles and liver fibrosis. Receiver operating characteristic (ROC) curves were used to assess the discriminative ability of the new index in predicting liver fibrosis in patients with schistosomiasis japonicum. Logistic regression analysis showed that HDL (OR, 95% CI=7.334, 5.051-10.649; *P*<0.001), LDL (OR, 95% CI=0.434, 0.370-0.509; *P*<0.001), HB (OR, 95% CI=0.979, 0.971-0.987; *P*<0.001) and PLT (OR, 95% CI=0.996, 0.994-0.999; *P*<0.001) were independently associated with liver fibrosis in schistosomiasis japonicum patients. ROC analysis indicated that the combination of HDL, LDL and HB levels [(HDL*100)/(LDL*HB)] had a higher area under the curve (AUC=0.773), which could enhance the predictive performance of liver fibrosis than APRI (AUC=0.608) and FIB-4 (AUC=0.624). The present study was the first to find that the levels of HDL, LDL, HB and PLT were independently associated with liver fibrosis in schistosomiasis japonicum patients. The combination of (HDL*100)/(LDL*HB) outperformed APRI and FIB-4 in terms of ROC and could be a new predictive index for liver fibrosis. The findings could help clinicians more easily and effectively to identify liver fibrosis in schistosomiasis japonicum patients.

1699

MIXED METHODS EVALUATION OF THE TRANSITION TO GOVERNMENT OWNERSHIP OF SCHISTOSOMIASIS AND SOIL TRANSMITTED HELMINTH CONTROL PROGRAMS ACROSS FOUR STATES IN NIGERIA: BASELINE RESULTS

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The Carter Center has assisted the Federal Ministry of Health (FMOH) to conduct mass drug administration (MDA) for schistosomiasis (SCH) and soil-transmitted helminths (STH) in Nigeria since 1999 and 2013 respectively. There is growing interest in transitioning financing and implementation of school-based MDA for SCH and STH to national governments. This study presents results of a mixed methods study in four districts, known as local government areas (LGAs), before and after planned "mainstreaming." Baseline household surveys were conducted in 30 villages per LGA. All communities were eligible for STH treatment (mebendazole); 35% of these communities were also eligible for SCH treatment (praziquantel). A total of 6,112 school-age children—the target population for STH and SCH MDA—were interviewed. MDA coverage in treatment-eligible communities ranged from 70.0% to 85.1% for STH and 69.9% to 100% for SCH, respectively. Reasons for not taking MDA were primarily attributed to lack of access (STH: 88.9%, SCH: 66.2%), including absence from or non-enrollment in school. For the qualitative component, 56 interviews and 9 focus group discussions were conducted

with key informants representing health systems, education systems, and governments at State, LGA, and community levels. Respondents were concerned about the sustainability of SCH and STH MDA following mainstreaming. A range of program strengths and weaknesses were identified that formed recommendations for effective mainstreaming, including clear budget allocation by the government, robust training of all involved parties, and advocacy to stakeholders and community members. These results suggest that access remains a key challenge to school-based MDA. Advocacy, planning and trust-building among stakeholders will be key for mainstreaming success. Recent WHO recommendations to shift to community-based MDA for SCH present further challenges to mainstreaming.

1700

AN EXCEL BASED TOOL FOR MONITORING THE SCHISTOSOMIASIS AND SOIL-TRANSMITTED HELMINTHIASIS PROGRAM

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The World Health Organization (WHO) NTD roadmap aims to eliminate Schistosomiasis (SCH) and Soil-transmitted helminthiasis (STH) as a public health problem by 2030. Evidence-based decision-making is a critical part of the M&E framework in the NTD roadmap, specifically highlighting the need for systematic data collection from baseline prevalence mapping to post-treatment impact surveillance. For this purpose, the USAID-funded Act to End Neglected Tropical Diseases (NTDs) programs | West and East developed an excel-based SCH-STH tracker to consolidate and evaluate Disease-Specific Assessment (DSA) data for SCH and STH. The data was first populated at the most granular level (site/community level) and automatically aggregated at the implementation unit level (sub-district and/or district, depending on the country). To improve the use of data for decision-making and to communicate the results of surveys in a more visually digestible way, we created an excel-based dashboard based on data in the SCH-STH tracker. This included Mass Drug Administration (MDA) related indicators, such as coverage and rounds of treatment implemented, in the dashboard to get the entire picture of SCH-STH activities in the country. We also used pivot tables to generate sub-district and district-level charts, which helped identify the number of districts/sub-districts eligible for impact assessment surveys (as per WHO guidelines, that is, implementation units that have been conducted at least five rounds of effective MDA). Importantly, pivot tables allowed for easy updating of the charts as new data was entered into the tracker. In brief, the dashboard provides a visualization of the number of endemic districts versus sub-districts, the number of districts/sub-districts by recommended treatment strategy, and the proportion of districts/sub-districts meeting WHO treatment guidelines. The objective is to use the SCH-STH integrated tracker and dashboard to complement the ESPEN Schistosomiasis Community Tool for evidence-based decision-making and advocacy both for in-country sustainability planning and donor data requests.

1701

COMMUNITY AWARENESS AND KNOWLEDGE ON SCHISTOSOMIASIS AND FEMALE GENITAL SCHISTOSOMIASIS (A NEGLECTED SEXUAL AND REPRODUCTIVE HEALTH ISSUE): FINDINGS FROM THE FAST PACKAGE BASELINE ASSESSMENT IN GHANA AND MADAGASCAR

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Female Genital Schistosomiasis (FGS) is a gynecological disease caused by untreated urogenital schistosomiasis, a form of schistosomiasis caused by *Schistosoma hematobium* found in 78 countries. FGS remains one of the most important neglected areas in women's and girls' health globally, with an estimated 56 million women and girls living with FGS predominantly in sub-Saharan Africa. Despite its prevalence, FGS awareness at the community level is lacking in places where the disease is endemic. The FGS Accelerated Scale Together (FAST) Package project surveyed 1716 community members in Ghana and Madagascar (869 in Ghana and 847 in Madagascar) using the WHO modified EPI sampling frame to understand their awareness and knowledge on schistosomiasis and FGS. Descriptive and inferential statistical analyses of the data was conducted using STATA. 88.6% (770) of all respondents have ever heard about schistosomiasis in Ghana, and 80.8% (686) in Madagascar. Fewer respondents, in Ghana and 8.32% (57) in Madagascar, were aware of FGS. 78.7% (226) of respondents indicated not knowing the major signs and symptoms of FGS in Madagascar. In both countries, females were more likely to be aware of symptoms of FGS than men ($P<0.05$). Of the majority of the respondents that were aware, 80% (46) indicated not knowing the major signs and symptoms of FGS (lower abdominal pain, pain during sex, bleeding after sex and infertility). These findings indicated that the sampled community members are unaware of FGS and its consequent risks and reproductive health sequelae. To create awareness on FGS at the community level and encourage young girls and women to visit the health facility for care and treatment, messages about FGS should be developed and delivered in communities through routine community activities and influential community stakeholders. Reproductive health and maternal health programs provide an important platform for education and diagnosis of FGS in endemic communities. More efforts should be applied to look beyond schistosomiasis programs for wider integration of FGS education and clinical services.

1702

TEMPORAL DYNAMICS OF *SCHISTOSOMA MANSONI* INFECTIONS AND ACHIEVING ELIMINATION AS A PUBLIC HEALTH PROBLEM IN LOW PREVALENCE SETTINGS WHEN ACCOUNTING FOR HUMAN MOBILITY

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Schistosomiasis, a parasitic worm infection affecting over 240 million people, is targeted by The World Health Organization for elimination as a public health problem (EPHP) by 2030. If achieved in a community however, it is unclear if the leading intervention, mass drug administration (MDA) with the anthelmintic praziquantel, should end and there are no approved indicators for when this is appropriate. Additionally, praziquantel does not prevent reinfection and interventions are often implemented over somewhat arbitrary spatial operational units (jurisdiction boundaries), ignored by diseases. This is particularly problematic for locations with low prevalence/ infection intensities on the cusp of reaching public-health targets, because they are highly susceptible to (re)introductions, which can occur as a function of habitual human mobility. Furthermore, certain people are repeatedly not treated year on year, but may greatly contribute to maintaining transmission. This can also be linked to regular travel for work or the like such that it is vital to understand how mobility impacts treatment participation and in turn projected population-level schistosomiasis dynamics. In Buikwe District, Uganda, identified as a low endemicity area after 20 rapid surveys, we recruited 1003 participants

aged 1-91-years-old from five locations. *Schistosoma mansoni* infection was identified with the Kato-Katz method and POC-CCA at several timepoints pre- and post-treatment. With 653 of these participants, detailed travel surveys were conducted, quantifying the rate of travel to high prevalence landing sites, the extent of water contact and matching this with their infection profile. Clearance and reinfection rates were quantified using a hidden Markov model framework, with the individual-based stochastic transmission model SCHISTOX used to project the impact on achieving EPHP, of ending MDA in low endemicity communities where regular travel may cause continued reintroductions.

1703

IDENTIFYING SUITABLE ENVIRONMENTAL PREDICTORS OF *SCHISTOSOMA JAPONICUM* INFECTION IN RURAL CHINA

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Across mainland China, pockets of human *Schistosoma japonicum* infection challenge elimination efforts. Schistosomiasis is a particularly difficult disease to control and eliminate due to its highly variable, environmentally mediated transmission cycle, involving zoonotic hosts species, intermediate snail hosts, and free-swimming parasitic miracidia and infectious cercariae. As such, careful study of the geographic distribution and environmental characteristics that make up host habitats has been an integral part of human schistosomiasis surveillance and control efforts to date. Nevertheless, habitat identification and density surveys for intermediate snail hosts are challenging, as the patchy and dynamic quality of snail populations makes identifying and mapping snail habitats a time-consuming and labor-intensive undertaking. In lieu of collecting snail habitat data for human risk assessments, using remotely sensed environmental data to characterize *S. japonicum*-related risks presents a promising opportunity for improving the efficiency and effectiveness of schistosomiasis surveillance activities in areas approaching elimination. In this study, we assess whether remotely sensed environmental data can serve as a suitable substitute for snail data to characterize household *S. japonicum* infection risk. In the summer of 2016, residents from ten villages in Sichuan, China were invited to participate in household *S. japonicum* infection surveys. Household GPS and snail habitat location data were also collected during this time using handheld GPS devices, transect walks and systematic sampling methods. Using a Random Forests machine learning modeling approach, we compared the predictive performance of a model that used snail habitat location data to predict household infection status to one that relied exclusively on publicly available remotely sensed environmental data from 2016. Our preliminary results suggest that the predictive capacity of the two models is similar, highlighting the potential utility of investing in remote sensing technology as schistosomiasis endemic areas move closer toward elimination.

1704

SCHISTOSOMIASIS AS A COMPONENT OF THE FOOD-ENERGY-WATER NEXUS IN DAMMED ENVIRONMENTS: A CASE STUDY OF THE SENEGAL RIVER BASIN

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Dam development improves water, food, and energy (FEW) security but often with negative impacts on human health. *Schistosoma* transmission persists in many dammed catchments despite efforts to mitigate disease with treatment campaigns. Transmission along the Senegal River has been elevated since dam construction in the late 1980›s. Through narrative analysis and qualitative content analysis of archival documents from the river basin authority in this setting, we examine health, generally, and schistosomiasis, specifically, as a component of the food-energy-water (FEW) nexus and evaluate cross-sector priorities and trade-offs across the policy-to-practice continuum. We find that health is recognized as an important component of river basin development, but that priorities articulated at the policy level are seldom translated into management practices. Managing dams in ways that mitigate their negative health impacts is possible without imposing substantial trade-offs on FEW resources but will require coordinated research and surveillance across sectors and transboundary jurisdictions to inform decision-making. Such coordinated knowledge creation is key to translating health priorities in environmental policy into practice.

1705

INTEGRATING GENOMIC AND EPIDEMIOLOGIC DATA TO ACCELERATE PROGRESS TOWARDS SCHISTOSOMIASIS ELIMINATION

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The global community has adopted ambitious goals to eliminate schistosomiasis as a public health problem, and new tools are needed to achieve them. Mass drug administration programs, for example, have reduced the burden of schistosomiasis, but the identification of hotspots of persistent and reemergent transmission threaten progress towards elimination and underscore the need to couple treatment with interventions that reduce transmission. Recent advances in DNA sequencing technologies make whole genome sequencing a valuable and increasingly feasible option for population-based studies of complex parasites such as schistosomes. Here, we focus on leveraging genomic data to tailor interventions to distinct social and ecological circumstances. We consider two priority questions that can be addressed by integrating epidemiological, ecological, and genomic information: (1) how often do non-human host species contribute to human schistosome infection? and (2) what is the importance of locally acquired versus imported infections in driving transmission at different stages of elimination? These questions address processes that can undermine control programs, especially those that rely heavily on treatment with praziquantel. Until recently, these questions were difficult to answer with sufficient precision to inform public health decision-making. We review the literature related to these questions and discuss how whole genome approaches can identify the geographic and taxonomic sources of infection, and how such information can inform context-specific efforts that advance schistosomiasis control efforts and minimize the risk of reemergence.

1706

SCHISTOSOMA MANSONI TAL-9 PROTEIN IS A CANDIDATE FOR DRUG TARGET AND VACCINE DEVELOPMENT

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The *Schistosoma mansoni* tegument represents an important source of antigens to vaccine formulations. However the tegument is also composed of molecules that are involved in the modulation of the host immune system to favour parasite survival. Using immunoproteomic tools we identified proteins from a schistosomula tegument preparation (Smteg) that were recognized by serum from Smteg-immunized mice and thus might be involved in the induction of the protective immunity observed in these animals. One of these proteins is SmTal-9, a member of the tegument-allergen-like (TAL) family. This protein has the ability to form

homodimers and to bind Mn^{2+}, Mg^{2+}, Ca^{2+}, as well as to interact with calmodulin antagonists CPZ, W7 and TFP, suggesting its involvement in a Ca^{2+}-dependent signal transduction. The aim of this study was to characterize the impact of *SmTal-9* silencing expression in the parasite development and survival and this antigen ability to induce protection. To analyze the role of SmTAL-9 in parasite survival, we used a RNAi approach. The schistosomula were exposed to *SmTAL-9*- or *GFP-dsRNA* for 4 days and parasites were inoculated into Balb-c mice. The results showed significant reduction in both parasite and egg burdens in mice inoculated with *SmTAL-9*-knocked-down schistosomula. To obtain the SmTal-9 recombinant protein (rSmTal-9) for the immunization trial, a synthetic gene containing the coding region sequence for SmTAL-9 was designed and optimized for protein expression in bacteria and mammals. A prime-boost immunization was performed using C57BL-6 mice. Mice received pcDNA 3.1V5/HIS or pcDNA 3.1V5/HIS/*SmTAL9* and fifteen days after the prime immunization with the DNA vaccine, they received two doses of the protein vaccine containing rSmTAL-9. Fifteen days after the last boost, mice were infected with *S. mansoni* cercariae and fifty days after challenge animals were perfused. Immunization using the rSmTAL-9 as an antigen conferred partial protection against challenge infection. Our results indicate that SmTAL-9 is a candidate for drug target and/or vaccine development due to its important role in parasite biology and survival.

1707

PARAGONIMUS KELLICOTTI EXCRETION/SECRETION PRODUCTS: COMPARATIVE PROTEOMICS OF IN *VITRO* AND IN *VIVO* RELEASE

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Paragonimiasis is one of the most prevalent food-borne trematode infections and an important neglected tropical disease. More than 30 Paragonimus species have been described and about one third of them is confirmed to infect humans. *Paragonimus kellicotti* is a zoonotic lung fluke infection, the agent of North American paragonimiasis, and an excellent model for Paragonimus infections. *In vitro* conditions are distinct from those within the host and that may alter *in vitro* excretory/secretory products (ESPs) compared to ESPs produced *in vivo*. In order to investigate ESPs produced *in vivo* we took advantage of the fact that adult *P. kellicotti* reproduce in the lungs of experimentally infected gerbils in tissue cysts. We performed a mass spectrometry analysis of adult *P. kellicotti* soluble somatic protein (SSPs) extracts; ESPs produced by adult worms after *in vitro* culture and lung cyst fluid proteins (CFPs) of experimentally infected gerbils. We identified 2,137 P. kellicotti proteins. Among those were 1,914 proteins found in SSP samples, 947 in ESP samples and 37 in CFP samples. *In silico* analysis predicted that only 141 of the total 2,137 proteins were secreted via a classical or non-classical pathway. The most abundant functional categories in the SSP sample were storage and oxidant metabolism. While in the ESP sample, the most abundant categories were: metabolism related proteins and signal transduction. The 37 parasite-related proteins in CFP samples could be divided in 11 functional categories. The largest group consist of proteins with unknown function, cytoskeletal proteins and proteasome machinery. From these 37 proteins, 29 were shared among the three sample types. To our knowledge, this is the first study that compares *in vitro* and *in vivo* ESP for *P. kellicotti*. Although *in vitro* ESP is a good way to simulate parasitic infections, it is difficult to emulate the real biological and chemical conditions inside the body. The results provide new insights into the molecular biology of food-borne trematodes, and might support the discovery of novel drug targets or the development novel serodiagnostics for paragonimiasis.

1708

THE PROTECTIVE EFFECT OF THE SOLUBLE EGG ANTIGEN OF *SCHISTOSOMA JAPONICUM* IN MOUSE SKIN TRANSPLANTATION MODEL

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Organ transplantation is currently an effective method for treating organ failure. Long-term use of immunosuppressive drugs has huge side effects, which severely restricts the long-term survival of patients. *Schistosoma* can affect the host's immune system by synthesizing, secreting or excreting a variety of immunomodulatory molecules, but its role in transplantation was not well defined. However, whether schistosomiasis-related products can suppress rejection or even induce long-term survival of the transplant remains not well defined. Here we explored the role of soluble egg antigen (SEA) of *S. japonicum* in mouse skin transplantation models. Each mouse was intraperitoneally injected with 100ug SEA three times a week for four consecutive weeks before allogenic skin transplant. Skin transplants were performed on day 0 and then to observe graft survival. Skin grafts received pathological examination 7days post transplantation. And the skin grafts were subjected to mRNA sequencing. Bioinformatics analysis was conducted and the expression of part hub genes was verified by qPCR.The mean survival time (MST) of mouse skin grafts in the SEA-treated group was 11.67±0.69 days, while that of the control group was 7.67±0.45 days. Pathological analysis showed that Sj SEA treatment led to reduced inflammatory infiltration within skin grafts 7 days after allogenic skin transplantation. Bioinformatics analysis identified 86 DEGs between Sj SEA treatment group and control group, including 39 genes were up-regulated and 47 genes were down-regulated. Further analysis revealed that Sj SEA mediated regulation on cellular response to interferon–γ, activation of IL–17 signaling and chemokine signaling pathways, as well as cytokine-cytokine receptor interaction. Sj SEA treatment suppressed rejection and prolonged skin grafts survival by regulating immune responses. Sj SEA treatment might be a new therapeutic strategy to facilitate anti-rejection therapy and even to induce tolerance

1709

AN EXERCISE IN RIGOR: COMPARING FECAL MICROBIOME PERTURBATIONS CAUSED BY ESTABLISHMENT OF CHRONIC *SCHISTOSOMA MANSONI* INFECTIONS IN MICE AT TWO INDEPENDENT UNIVERSITIES

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The gut microbiome, which is the compilation of microorganisms and their genomes found within the gastrointestinal tract, varies in composition depending on a multitude of host factors including age, nutrition, antibiotic usage, and disease state. Schistosoma mansoni is a parasitic worm that causes schistosomiasis, a devastating neglected tropical disease, which affects approximately 240 million people worldwide. Adult S. mansoni worm pairs mate in the mesentery and produce eggs that breach the intestinal wall to be excreted via feces. This pathobiology suggests that S. mansoni may affect the fecal microbiome composition. As experimental reproducibility is required for scientific rigor, our purpose is to determine if fecal microbiome alterations due to chronic schistosome infection will be broadly applicable or are unique to each institution. We then compared the murine fecal microbiome between two comparable, independent experiments at different institutions to elucidate the perturbations caused by chronic S. mansoni infection while accounting for institutional variation. We kept constant the PI, parasite source and strain, and animal source and strain, while modifying the academic institution, vivarium, and sequencing facility. Age-matched mice were infected with S. mansoni or left naïve. We sampled feces over a 10-week period during which time the mice developed a chronic S. mansoni infection or remained uninfected. Fecal samples were subjected to 16s rRNA sequencing and analyzed using the open source bioinformatics pipeline, QIIME. Specifically, we determined operational taxonomic unit (OTU) rarefactions, alpha and beta diversities,

and quantitative insights on murine fecal microbial communities. The longitudinal and transverse data was compared interinstitutionally to confirm reproducibility of fecal microbiome alterations induced by establishment of chronic S. mansoni infections in mice.

1710

A VACCINE FOR INTESTINAL SCHISTOSOMIASIS USING AN ADENOVIRUS VECTOR EXPRESSING *SCHISTOSOMA MANSONI* CATHEPSIN B AND ADDAVAX ADJUVANTED PROTEIN BOOSTS

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Schistosomiasis is an underestimated neglected tropical disease which affects over 236.6 million people worldwide. According to the CDC, the impact of this disease is second to only malaria as the most devastating parasitic infection. Our previous work consisted of a recombinant adenovirus expressing *Schistosoma mansoni* cathepsin B (AdSmCB) delivered intramuscularly followed by two boosts of recombinant antigen. Upon immunization with our vaccine, we observed robust cell-mediated and humoral immune responses, giving significant protection. This project tested the protective ability of AdSmCB as a novel vaccine vector when our heterologous prime and boost strategy was modified to include AddaVax as an adjuvant. AddaVax is an MF-59 mimetic which is the most effective adjuvant in human influenza vaccines. Our novel vaccine formulation resulted in robust antibody production including antigen specific IgG1 with significant expansions in IgG2c and serum IgA. Cell mediated immune responses from our recombinant adenovirus vaccine mimicked homologous vaccination with AddaVax adjuvanted protein in its expression of Th2 effectors, while uniquely eliciting Th1 mediators such as IFNɣ. We hypothesize that this increased immunogenicity will push protection upwards of 90% from the 72% delivered by unadjuvanted formulations. An effective vaccine for schistosomiasis would benefit populations in endemic regions aiding the interruption of disease transmission as well as international travelers visiting tropical regions.

1711

THE SNAIL *BIOMPHALARIA GLABRATA* AS A MODEL ORGANISM TO INVESTIGATE THE MOLECULAR BASIS OF TAU PROTEIN EXPRESSION IN AGEING

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Mollusks are extremely suitable as animal models for studying molecular mechanisms of ageing and neurodegenerative diseases, such as Alzheimer's disease (AD). Their suitability is based on the fact that they have a simplistic central nervous system (CNS) that has a major gene homolog associated with human ageing. Recently, we identified the *B. glabrata* homolog of human microtubule-associated protein tau. The snail sequence (accession number NP_001116538.2) is 44.81% identical to the human protein isoform 6. Because of the similarity of tau nucleotides in the snail and human, and its significant role in CNS, we hypothesize that *B. glabrata* can serve as a useful animal model to observe the expression of Tau in relation to ageing brains and to the pathogenic characteristics of age-related neuropathy. Previous studies indicate that several changes occur as *B. glabrata* ages. It should be noted that this snail no longer serves as an efficient host for the reproduction of the larval stages of the parasite that causes the tropical disease, schistosomiasis. Further studies in our laboratory indicate that the ability to relocate gene loci in response to parasite infection in the spatial epigenetics of snail susceptibility to infection becomes impaired. In the proposed study, we will test the hypothesis that the expression of tau relates to both ageing and susceptibility, as well as produces structural changes in the CNS between juvenile and adult snails responding to parasite infection. To examine the expression of RNA corresponding to Tau, juvenile and adult BBO2 snails with and without infection to the parasite *S. mansoni* were analyzed qualitatively and quantitatively. The results suggest that the expression of Tau transcript is elevated in an ageing *B. glabrata* snail by two-fold. Moreover, we observed Tau protein accumulation by 2.5-fold in an ageing snail post infection to *S. mansoni*, indicating probable stress response and neuronal injury in the snail host.

1712

SINGLE-CELL RNA SEQUENCING REVEALS A PERIPHERAL LANDSCAPE OF IMMUNE CELLS IN SCHISTOSOMIASIS JAPONICA

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Schistosomiasis is one of the most devastating parasitic diseases, bringing a heavy social and economic burden to the world. This kind progressive and debilitating helminth disease is often linked to poverty and chronic poor health. However, there is no effective vaccine and only praziquantel is available. In addition, praziquantel is incapable of preventing reinfection and drug resistance occurs. Immunopathology plays a critical role in the pathogenesis of schistosomiasis. However, the underlying immune mechanism in the progression of schistosomiasis is far from well-defined. Thus, further investigation is needed to deepen our understanding of the immune mechanisms in schistosomiasis to facilitate identification of new therapeutic targets. Peripheral blood mononuclear cells (PBMCs) were isolated from patients with chronic schistosomiasis japonica or advanced schistosomiasis japonica and PBMCs from healthy volunteers were served as a control. Single cell RNA sequencing (scRNA-seq) was used to profile the immune landscape of schistosomiasis japonica with PBMCs in health control group (n=2), chronic schistosomiasis group (n=2) and advanced schistosomiasis group (n=2). 22 major cell clusters out of 52214 cells were eventually included in our analysis. Neutrophils accounted for the major part in the chronic group and the healthy group, while monocytes were dominated in the advanced group. The preliminary study showed that MHC molecules of monocytes, B cells and DCs in the advanced group were obviously lower when compared with the chronic group and the HC group, while *FOLR3* and *CCR2* were highly expressed in the advanced group. Downregulated MHC molecules in antigen presenting cells is related to the immune cell dysfunction of advanced schistosomiasis. This study deepens our understanding of the immune mechanisms in schistosomiasis, and will provide a transcriptional atlas of peripheral immune cells facilitating elimination of schistosomiasis.

1713

SOLUBLE EGG ANTIGEN OF *SCHISTOSOMA JAPONICUM* INDUCES DIFFERENTIATION OF MYELOID-DERIVED SUPPRESSOR CELLS TO SUPPRESS HOST IMMUNITY

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Myeloid-derived suppressor cells (MDSCs) with immunosuppressive functions are a heterogeneous population of immune cells from the myeloid lineage. MDSCs encompass two primary subtypes that are monocytic MDSC (M-MDSC) and granulocytic MDSC (G-MDSC). Some research showed that there were increased levels of MDSCs in Schistosome-infected mice. However, the relationship between MDSCs and soluble egg antigen (SEA) of Schistosoma japonicum remained unclear. Single cell RNA sequencing and flow cytometry profile MDSCs in patients with Schistosomiasis. SEA was used to induce MDSCs in allogeneic skin transplant mice and bone marrow cells. The expression of zinc finger protein 36 (ZFP36) and levels of phosphorylated P65 were determined by qPCR and Western blot analysis. G-MDSC was significantly accumulated in patients with Schistosomiasis. Single-cell sequencing

revealed that G-MDSC was significantly different between healthy people and patients with Schistosomiasis, and ZFP36 expression was up-regulated in the latter. SEA could induce the differentiation of MDSC through increasing ZFP36 and inhibiting the NF-κB signaling pathway. SEA promotes the transformation of bone marrow primordial cells into MDSC, which could improve the survival of allogeneic mouse skin grafts. Overall, SEA could promote the expression of ZFP36 to inhibit NF-κB signaling pathway in MDSCs and suppress host immunity which provides a new promising mechanism for immunotherapy.

1714

NEONATAL IMMUNOLOGICAL ENVIRONMENTS COULD ALTER THE CELLULAR IMMUNE RESPONSES TO CHILDHOOD VACCINES

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The expanded program on immunization has ensured that children, particularly in less developed countries have access to life saving vaccines. Despite this advancement, several studies have indicated reduced effectiveness of these vaccines in less developed countries. Such responses have been attributed to logistic and biological deficiencies including maternal and childhood infections. This study evaluated if fetal/neonatal immunological environments could alter the cellular immune responses to diphtheria toxoid (DT) and *Haemophilus influenzae* (HiB) vaccines. 104 Kenyan mother/infant pairs were enrolled in the study and tested for malaria, lymphatic filariasis and *S. haematobium* infection. Participants received HiB and DT vaccines at 6, 10, and 14 weeks of age. Neonates' cord blood lymphocyte were stimulated with malaria (M42, MSP), schistosome (SWAP, SEA) and filarial antigens and IL-2, IL-5, IL-6, IL-10, IL-13, GM-CSF, IFN-y and TNF-α specific immune responses measured. Children sickness profile, infection status and hemoglobin (Hb) levels were recorded at every visit to the hospital. At 18 months, peripheral blood mononuclear cells (PBMC) were stimulated with DT and HiB antigens and IL-5, IL-13, IL-10 and IFN-y levels measured. Using a principal component analysis of cytokine responses, children fell into two clusters, those characterized by elevated levels of IFN-y, and the other with increased IL-10. There was no correlation between vaccine stimulated responses and children sickness, infection status or Hb levels. However, there was an association with cord blood cytokine responses and DT and HiB driven cytokine responses at 18 months of age. Children in IFN-y cluster compared to those in the IL-10 cluster had higher levels of malaria driven M42-IL-5 (P=0.053), MSP-TNF-α (p=0.047) and M42-TNF-α (p=0.037). By contrast, children in IL-10 cluster had higher levels of helminth driven SWAP-IL-5 (0.044) and MFE-IL-10 (0.058) and increased spontaneous production of IL-2 (0.040). This data shows that immune responses to childhood vaccines are affected by in-utero priming to parasites which may affect vaccine efficacy.

1715

GUT MICROBIOTA SIGNATURES IN *SCHISTOSOMA JAPONICUM* INFECTION PATIENTS

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As an intestinal parasite, *Schistosoma japonicum* can cause pathological damage to the host liver and intestines. Studies have reported that microbes are closely related to liver and intestinal diseases. We therefore, sought to explore how the gut microbiota of patients with Schistosoma japonicum infection progresses from chronic to advanced stage. From June 2021 to January 2022, 20 patients with chronic S. japonicum, 19 patients with advanced schistosomiasis and 13 healthy people were enrolled. Fecal samples were collected and used for 16S rRNA gene sequencing (particularly, the hypervariable V4 region) using the Illumina MiSeq system. Wilcoxon Rank-Sum and PERMANOVA tests were used for analysis. Eight hundred and seven operational taxonomic units (OTUs) were detected, of which, 491 were common between chronic schistosomiasis and advanced schistosomiasis, whereas 123 and 193 were unique to the chronic schistosomiasis and advanced schistosomiasis groups, respectively. Observed species, Chao, ACE, Shannon, Simpson, and Good's coverage indexes, used for alpha diversity analysis. Beta diversity was evaluated by weighted UniFrac distances.The relative abundance of species belonging to the Firmicutes was lower in advanced schistosomiasis patients than chronic schistosomiasis individuals. Schistosomiasis infection can lead to changes in intestinal flora. There are significant differences in the composition of intestinal flora between patients with chronic schistosomiasis infection and those with advanced. Compared with patients with chronic schistosomiasis, the abundance of Firmicutes and Fusobacterium in patients with advanced schistosomiasis is significantly reduced, which is a target for the diagnosis and evaluation of treatment effect of Schistosoma japonicum in the future.

1716

MACROPHAGES REGULATE THE FORMATION OF *SCHISTOSOMA JAPONICUM* GRANULOMA THROUGH MODULATING LYMPHANGIOSIS

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The formation of hepatic granulomas due to parasite's eggs trapped in the portal vein system plays a key role in the pathogenesis of schistosomiasis japonicum. Evidences demonstrated that macrophages are critical in the progression of granulomas. However, the mechanism was not well defined. This study aimed at to investigate the role of macrophages in the formation of Schistosoma Japonicum granuloma and the underlying mechanism. We used Schistosoma japonicum-infected mice, divided them into two groups, one of the group treated with M-CSF inhibitor(Down-regulation of LYVE-1(+) macrophages). Immunohistochemistry analysis indicated that LYVE-1(+) macrophage infiltration around the granuloma,and lymphogenesis is negatively correlated with the size of Schistosoma granulomas. However, in vitro experiments, lymphogensis is positively correlated with LYVE-1(+) macrophages. The M-CSF inhibitor-treated group showed a more severe degree of fibrosis and increased area of schistosome granulomas when compared with those without M-CSF inhibitor administration. Flow cytometry analysis demonstrated a lower numbers of LYVE-1(+) macrophages in the liver in the M-CSF inhibitor treatment group. Pathological examination indicated reduced peripheral lymphatic vessels when received M-CSF inhibitor treatment. In conclusion, LYVE-1(+) macrophages contributed to the lymphogenesis within liver, leading to a lower degree of granuloma and liver fibrosis caused by schistosomal infection. Promoting liver lymphatic vessels generation may be a new direction for the treatment of granuloma and liver fibrosis in schistosomal infection.

1717

THE PROGRESSION OF SCHISTOSOMIASIS JAPONICA EXPRESS DIFFERENT IMMUNE STATES

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Schistosomiasis is a global tropical disease that has caused heavy socio-economic burdens in the world. This kind of parasitic disease is classified as acute schistosomiasis, chronic schistosomiasis, and advanced schistosomiasis. Although acute schistosomiasis is easy to be diagnosed, it is hard to differentiate chronic from advanced schistosomiasis. Immunology plays a critical role in the progression of schistosomiasis, but its role in diagnosis of schistosomiasis remains unclear. The aim of

this study was to explore the difference between the immune status of chronic and advanced schistosomiasis japonicum and find potential biomarkers to facilitate in diagnosis. Since March 2020 to April 2021, 77 chronic schistosomiasis patients and 36 advanced schistosomiasis patients from Dongting Lake were included and 24 healthy volunteers were included as the control group. Through flow cytometry, the patients' immune cells in the peripheral blood were analyzed. SPSS was used to analyze the data. Flow cytometry data showed that the immune states in chronic schistosomiasis were different from that in advanced schistosomiasis japonica. We found CD3+CD8+T cells percentage(Pearson correlation coefficient r=-0.301), CD3+CD8+T cells percentage(r=-0.204), CD16+CD56+nature killing cells percentage(r=0.238) and CD19+B cells percentage(r=0.239) were related to disease progression and had statistically significant differences($p<0.05$) in different stages of schistosomiasis japonicum. In order to measure the weights between different indicators, principal components analysis (PCA) was used and showed that CD3+CD8+T cells percentage (index weight=0.303) and CD16+CD56+nature killing cells percentage (index weight=0.279) were most informative markers.The progression of schistosomiasis japonicum was characterized with different immune states. CD3+CD8+T cells percentage and NK cells percentage may be potential biomarkers to facilitate in the diagnosis of chronic schistosomiasiss and advanced schistosomiasis.

1718

WHOLE PROTEOME DIFFERENTIAL SCREENING IDENTIFIES HELMINTH DEFENSE MOLECULE AS NOVEL SCHISTOSOMIASIS JAPONICA VACCINE CANDIDATE

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To identify vaccine candidates for Schistosomiasis japonica, differential screening of an adult worm cDNA library was employed using sera and epidemiologic data from a praziquantel treatment reinfection cohort (N = 300) in a holoendemic region of the Philippines. This approach enables the identification of schistosome antigens recognized by antibodies expressed by resistant, but not susceptible, individuals. 1 x 106 clones were differentially screened of which 32 were recognized by antibodies in both resistant sera (RS) and susceptible sera (SS), 38 were recognized by antibodies in SS, and five were uniquely recognized by RS. Of the five uniquely recognized clones, four were identified as SjHDM-1, a helminth innate immune cell modulator. The population profile of rSjHDM-1-specific antibodies in the praziquantel treatment reinfection cohort was assessed using a bead-based assay. Cohort participants demonstrated a 2.7-fold increase in rSjHDM-1-specific IgG antibody responses compared to SWAP-specific IgG responses ($p<0.0001$) and a 3.7-fold increase compared to SEA-specific IgG responses ($p<0.0001$). Compared to North American controls, study participants displayed a significant increase of rSjHDM-1-specific IgG antibody responses ($p=0.007$). Immunofluorescence staining of SjHDM-1 in adult S.japonicum worms exhibited localization to the tegument in female and male worms. Mouse protection studies will be conducted to characterize SjHDM-1 as a vaccine candidate, with efficacy assessed in a buffalo challenge study. SjHDM-1 yields promise as a novel schistosome vaccine antigen given its host immune accessibility and its antigen-specific IgG profile in holoendemic populations.

1719

A HIGH-THROUGHPUT PHENOTYPIC SCREEN UNRAVELS *PLASMODIUM FALCIPARUM* GENES ESSENTIAL FOR GAMETOCYTE DEVELOPMENT

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Plasmodium falciparum transmission to new hosts is crucial to the parasite's life cycle and is mediated by the development of mature intraerythrocytic sexual stages, called gametocytes. A better understanding of molecular mechanisms governing sexual development is needed to accelerate antimalarial research to block human-to-vector transmission. The purpose of this study is to identify key genetic determinants and delineate the pathways and processes essential for gametocyte development. To address this goal, we are using forward genetic screens of libraries of single-insertion *piggyBac* mutants. We identified mutants of two distinct phenotypes that are 'Hyper' and 'Hypo' producers of gametocytes. Two new genes one from each of the phenotypic categories were further characterized for their role in gametocyte development, expression patterns, and evolutionary conservation in other *Plasmodium* species. Functional analysis and IFA studies revealed morphological defects in the inner membrane complex and an inability to mature to stage V gametocytes. Through multiple such screens, we anticipate closing an important gap in the *P. falciparum* life cycle whilst enabling the prioritization of novel transmission-blocking targets.

1720

DCIFER: AN IDENTITY BY DESCENT (IBD)-BASED METHOD TO CALCULATE GENETIC DISTANCE BETWEEN POLYCLONAL MALARIA INFECTIONS

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Malaria genetic data can provide valuable information for relatedness inference, which in turn can serve as a critical step toward understanding transmission dynamics and informing intervention efforts. Relatedness measures based on identity by descent (IBD) aim to address shared ancestry directly; however, for polyclonal malaria infections, which are common even in near-elimination settings, this approach presents conceptual and methodological challenges, resulting in the lack of established methods. Addressing this gap, we present Dcifer, a method to calculate genetic distance between polyclonal infections by estimating relatedness from unphased biallelic or multiallelic data. By performing simulations based on various available genotyping panels, we show that Dcifer delivers interpretable results with reliable inference. Compared to an identity by state (IBS) approach, Dcifer consistently demonstrated greater power to detect related infections, with differences increasing with increased polyclonality. For example, with a 91 microhaplotype panel, the power to detect half-siblings in a pair of infections with complexity of infection (COI) of 2 was 0.81 for Dcifer and 0.43 for the IBS metric; with 455 microhaplotypes and COI of 5 that power was 0.88 and 0.22 respectively. Inference obtained from Dcifer versus IBS is also more robust to misspecifications of estimated quantities such as COI or population allele frequencies and to genotyping errors. Applying Dcifer to real data, we observe that pairwise relatedness estimates align with underlying geographic structure of the data. Dcifer is implemented in a publicly available software package, with convenient customizable options, readily available inference, and graphical visualizations. This package provides

a fast, convenient, and flexible tool that can be easily incorporated into the analysis stream of a wide range of genotyping data to understand transmission.

1721

EMERGENCE AND EXPANSION OF *PLASMODIUM FALCIPARUM* WITH PFK13 POLYMORPHISMS ASSOCIATED WITH ARTEMISININ RESISTANCE IN UGANDA

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Artemisinin-based combination therapies are the first-line treatments for uncomplicated malaria in Uganda. However, recent studies have demonstrated the emergence in Rwanda and Uganda of *Plasmodium falciparum* with PfK13 mutations previously associated in Asia with artemisinin resistance (delayed clearance after artemisinin treatment or in vitro exposure). In both countries these polymorphisms have been associated with clinical and in vitro resistance. We continued spatio-temporal surveillance to track *P. falciparum* isolates with PfK13 mutations in Uganda. Since 2016, we have collected blood samples from up to 100 subjects diagnosed with malaria by microscopy or rapid diagnostic test at up to 16 health facilities across Uganda. Parasites were genotyped by dideoxy and molecular inversion probe deep sequencing of the *pfK13* gene and 8 microsatellites flanking this gene. Of the 1357 samples collected in 2020, 1179 were successfully analysed. We observed 11 mutations in the propeller region of the *pfk13* gene, 6 of which (F442L, C469F, C469Y, A675V, L713F, A724P) were seen at a prevalence of >5% in at least one site. Most noteworthy were three mutations previously associated with delayed clearance in southeast Asia, with prevalence of C469Y (0-45.6%) highest in northern Uganda, A675V (0-26.6%) highest in northern Uganda, and, newly in 2020, C469F (0-28.2%) highest in southwestern Uganda. Prevalences of the C469Y and A675V mutations remained stable in northern Uganda and these mutations were detected at more sites than in prior years. Analysis of 8 microsatellites flanking the *pfk13* gene suggested single emergences and then spread of C469Y and A675V mutant parasites. Analysis of parasites from around the world using genome-wide putatively neutral SNPs suggested African origins for the mutant Ugandan parasites.Our results provide evidence of multiple local emergences and spread of *P. falciparum* with *pfk13* mutations shown previously to associate with artemisinin resistance. Evaluation of the treatment efficacies of artemisinin-based antimalarial therapies in regions of Uganda with high prevalence of mutant parasites is an urgent priority.

1722

DELETION-DUPLICATION EVENT MAY EXPLAIN GEOGRAPHICAL DIFFERENCES IN *PLASMODIUM FALCIPARUM* WITH HISTIDINE-RICH PROTEIN 3 DELETION

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Significant progress has been made in the fight against *Plasmodium falciparum* malaria, due in part to widespread adoption of rapid diagnostic tests (RDTs) that detect histidine-rich protein 2 (HRP2) and its paralog HRP3 encoded by the *hrp2* and *hrp3* genes, respectively. However, parasites with *hrp2* and *hrp3* deletion evade diagnosis by HRP2-based RDTs and appear to be spreading in the Horn of Africa. Prevalence of these parasites varies markedly across continents in a manner not explained by RDT use alone; reasons for this geographical heterogeneity are unknown. The objective of this study was to investigate the mechanism responsible for *hrp2* and *hrp3* deletion and explore geographical differences in associated chromosomal rearrangements. We analyzed over 9,000 publicly available P. falciparum field samples to select for monoclonal samples with stable genomic coverage. Reads were mapped and coverage was normalized to determine regions of deletion and duplication. Our ability to evaluate *hrp2* deletion patterns was limited by selection bias in available sequences; many studies sequenced RDT-positive samples. However, two distinct *hrp3* deletion patterns were detected: 1) segmental deletion of chr 13 just centromeric to *hrp3* extending to the end of the chromosome, with simultaneous duplication of the chr 11 subtelomeric region, and 2) deletion of chr 13 starting at various locations centromeric to *hrp3* without chr 11 duplication. Pattern 1 was exclusively found in samples from Africa and South America, while pattern 2 was observed globally but predominantly in Southeast Asia. Known hrp3-deleted HB3 was long-read sequenced using the Oxford Nanopore MinION platform and assembled with Canu. One contig mapped best to almost the entirety of 3D7 chr 11, while another mapped to a 13-11 hybrid - findings that are consistent with recombination between 13 and 11. Together, a chr 13 deletion, chr 11 duplication mechanism is one potential explanation for geographical differences in global *hrp3* deletion frequency and high prevalence in the Horn of Africa.

1723

UNDERSTANDING THE GENOMIC DIVERSITY OF *PLASMODIUM VIVAX* RELAPSES IN THE SOLOMON ISLANDS

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Plasmodium vivax, an aetiological agent of malaria, is particularly challenging for elimination efforts due to several biological characteristics that are distinct from *Plasmodium falciparum.* These include low density infections, early transmission and most notably, the establishment of a quiescent liver stage, which has been shown to cause 80% of blood-stage infections. In the last decade, *P. vivax* transmission has declined in the Solomon Islands, however the nation has seen parasite resurgence since 2015. Here, we study the genomics of *P. vivax* isolates collected during the ACT-Radical clinical trial, conducted in 2017-2018. This clinical trial compared parasite clearance following treatment with primaquine combined with artemisinin-combination therapies. Leveraging the clinical trial design, we study twenty individuals who received artemether/lumefantrine treatment only or individuals who also received primaquine for quiescent liver-stage clearance. All individuals experienced multiple *P. vivax* infections throughout the trial. Using whole genome sequencing, we describe genetic diversity and clonal relatedness of *P. vivax* to investigate potential relapses due to their treatment regimen, as well as newly acquired infections. Furthermore, we explore *P. vivax* genomic diversity in the Solomon Islands, a historically understudied parasite population, particularly with regards to past or recent selective pressures on the parasite population. Comparative analyses were also undertaken

with available amplicon sequencing data. Our genomic analysis fills an important gap in our understanding of *P. vivax* genetic diversity and infection dynamics in the context of relapse and reinfection.

1724

POPULATION GENOMICS OF *PLASMODIUM OVALE* IN SUB-SAHARAN AFRICA

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Plasmodium ovale is a relapsing malaria species that is rising in prevalence across Sub-Saharan Africa. Reference genomes were published in 2017 for the two nonrecombining species, *P.o. curtisi* (GH01) and *P.o. wallikeri* (CR01), but assembling geographically diverse field isolates for a population genomics study is challenging. Using dried-blood spots (DBS) and leukodepleted blood samples from three countries across Sub-Saharan Africa (Democratic Republic of the Congo, Tanzania, and Cameroon), we selected 20 samples from a repository of >700 P. ovale field samples for whole-genome sequencing, with more samples to be added from ongoing field studies in additional regions. To reduce human DNA contamination in DBS-extracted DNA, a hybrid capture was performed on pools of 4 libraries using RNA baits that were custom-designed to enrich P.o. curtisi and wallikeri DNA. After Illumina 150bp paired-end sequencing on the Novaseq 6000 platform, bwa-mem2 was used to competitively align reads to hybrid reference genomes of the corresponding Po species and Pf3D7 to filter out Pf reads. Po genome coverage was adequate in 11 curtisi samples and 5 wallikeri samples, with ≥10x coverage across a median of 89.8% of their genomes. These data are being used to investigate geographic population structure, identify genomic regions for use as diversity markers, and develop new tools for future Po studies. Because the GH01 and CR01 references were bioinformatically assembled from West African Pf3K isolates, we are also generating an East African reference sequence from a leukodepleted monoinfected Poc isolate using Nanopore and Illumina sequencing data. Initial Canu assembly yielded a 37.7 Mb genome with 5192 contigs and an N50 of 151,639 bp. Interestingly, the assembly's 37.7% GC content differs from the 29% reported in existing reference genomes. The newly assembled genome will be used as a scaffold during ongoing population genomic analyses of P. ovale in Sub-Saharan Africa.

1725

PARASITE GENETIC RISK FACTORS FOR EMERGING *PLASMODIUM KNOWLESI* MALARIA

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Zoonotic malaria due to the monkey parasite *Plasmodium knowlesi* (*Pk*) has become a significant health burden throughout parts of Southeast Asia, including several countries that are approaching elimination of other human *Plasmodium* species. *Pk* infection can cause severe life-threatening disease at lower levels of parasitemia relative to other *Plasmodium* species, with severe malaria representing 6.4% of total *Pk* cases presenting to primary health facilities in Sabah, Malaysia. The goal of this project is to identify key processes leading to the development of severe *Pk* malaria. We hypothesise that genetic variants involved in red blood cell binding, invasion and related virulence mechanisms can also influence the risk of symptomatic *Pk* infection and disease outcomes. We developed a gold standard variant calling pipeline optimised for *Pk* infections that combines established bioinformatics tools with novel methods, including a consensus approach for variant detection. Whole genome sequencing was performed on a unique dataset with detailed clinical phenotypes of 1311 *Pk* cases (including 342 with WHO-defined severe malaria) from Malaysia collected as part of ongoing clinical and state-wide surveillance studies. A genome wide association study (GWAS) will be used to correlate genotypes with disease phenotypes, whilst accounting for population structure and other covariates. Preliminary analyses from an initial high-quality subset (94 *Pk* samples) suggests several variants are associated with disease severity. However, further work will (i) incorporate the larger dataset to determine the validity and impact of these findings, (ii) investigate known *Pk* variants, including *P. knowlesi normocyte binding protein Xa* and *Xb*, and *Pk* genetic clusters derived from macaque hosts; and (iii) to design *Pk* population genetic tools for broader regional analyses. The final pipeline and GWAS results will be presented at the ASTMH meeting. Better understanding the underlying genetics of severe *Pk* infections could ultimately lead to targeted intervention and reduced health burden in affected countries.

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URBAN RIFT VALLEY FEVER VIRUS AS A NEW ECOLOGICAL NICHE: INTRODUCTION FROM ANIMAL PRODUCTS

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Rift Valley Fever virus (RVFV) is a globally important zoonotic arbovirus that is endemic across Africa and can cause severe disease in livestock and humans. Spread is driven by livestock movement and despite the high urban demand for meat, RVFV has not been identified in urban centers. The objectives of this study were to assess risk of RVFV to urban Kisumu, Kenya, by testing slaughtered livestock for RVFV exposure and map their origins and routes to slaughter.Blood was collected from cattle, sheep, and goats directly after slaughter and tested for RVFV exposure using a commercially available IgG kit. Slaughterhouse businessmen responded to a questionnaire about the animals' origin, marketplace, and transport. Additionally, livestock flow from origin to slaughterhouse was mapped using participatory mapping techniques in focus group discussions. Qualitative data on route influences and challenges with livestock movement was then integrated into the map to provide context.A total of 304 blood samples were collected from slaughtered livestock. 99% of animals were purchased from 28 different markets across eight counties in Kenya. A 9% overall RVFV seroprevalence was identified and seroprevalence in cattle alone was 18%. Migori county near Tanzania had a 25% seroprevalence and 80% of all positive cows came from this area. Road quality influenced decisions for transporting animals and marketplace choice was driven by price and availability of stock.This study

provided proof of concept for a novel sampling framework that can be locally implemented and rapidly deployed in response to increased regional risk. This information can be used in conjunction with participatory maps to improve active livestock surveillance for RVFV in urban centers and a basis for monitoring other livestock diseases.

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ASSESSING THE EFFECTS OF MINING PROJECTS ON CHILD HEALTH IN SUB-SAHARAN AFRICA: A MULTI-COUNTRY ANALYSIS

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The African continent hosts many industrial mining projects representing an opportunity for economic development, particularly in the sub-Saharan Africa (SSA) region. However, its implementation poses threats to the population's health, particularly for children who are threatened by exposure to mining-related air, noise, and water pollution. To assess the impact of mines on child health, we use a difference-in-difference study design to analyse socio-demographic, health, and mining data before and after several mining projects were commissioned in SSA. Data of 90,951 children living around 81 mining sites in 23 countries in SSA were analysed for child mortality indicators, and 79,962 children from 59 mining areas in 18 SSA countries were analysed for diarrhoea, cough, and anthropometric indicators. We found no effects of the launch of new mining projects on overall under-five mortality (adjusted Odds Ratio (aOR): 0.88; 95% Confidence Interval (CI): 0.68 - 1.14). However, activation of mining projects reduced the mortality risk among neonates (0-30 days) by 45% (aOR: 0.55; 95% CI: 0.37 - 0.83) and risk for a child to develop diarrhoeal diseases by 32% (aOR: 0.68; 95% CI: 0,51 - 0.90). The timing analysis showed a significant decline in the risk for childhood diarrhoea (aOR: 0.69; 95% CI: 0.49 - 0.97) and the mean height-for-age z-scores by 28 percentage points during the prospection and construction phase. No effects were found for cough, weight-for-age, and weight-for-height z-scores. The results presented suggest that the impacts of mining on child health vary throughout the mine´s life stages. Mining development likely contributes positively to the income and livelihoods of the impacted communities in the initial years of operations; however, these benefits are likely to be partially offset by food insecurity and environmental pollution during early and later mining stages, respectively. Further research is warranted to understand the dynamics of health impact and identify policies that can help sustain the positive health impacts of mining projects in the long term.

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EFFECTS OF AMBIENT TEMPERATURE AND HEAVY PRECIPITATION ON DRINKING WATER QUALITY AND CHILD HAND CONTAMINATION LEVELS IN KENYAN HOUSEHOLDS

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Climate models predict a 2-4 degree Celsius increase in mean annual temperature for East Africa by 2050 and potential increases in the intensity and frequency of extreme precipitation events. High ambient temperature and heavy precipitation have been associated with increased diarrhea prevalence, but the underlying causal mechanisms are not clear. We linked measurements of Escherichia coli (E. coli) in source water (n=1673), stored drinking water (n=8924), and hand rinses from children <2 years old (n=2660) with publicly available gridded temperature and precipitation data (at ≤0.2 degree spatial resolution and daily temporal resolution) by GPS coordinates and date of sample collection. Measurements were collected over a three-year period across a 2500 km^2 area in rural Kenya. We modeled contamination levels as a function of high temperature during the 7 days prior to sample collection (mean maximum temperature exceeded 32 degrees C) and heavy total precipitation during the 7 days prior to sample collection (total precipitation exceeded the 90th percentile). In drinking water sources, high 7-day temperature was associated with a 0.16 increase in log10 E. coli levels ($p<0.001$) and heavy 7-day total precipitation was associated with a 0.25 increase in log10 E. coli levels ($p=0.001$). The magnitude of the effect of heavy 7-day total precipitation was higher (0.72 increase in log10 *E. coli* levels ($p<0.001$)) after low (tertile) 8-week precipitation. High 7-day temperature and heavy 7-day total precipitation were not significantly associated with log10 E. coli levels in stored water. On child hands, high 7-day temperature was associated with a 0.37 decrease in log10 E. coli levels ($p<0.001$) and heavy 7-total precipitation was not significantly associated with log10 E. coli levels. The magnitude of the effect of high 7-day temperature was larger (0.68 decrease in log10 *E. coli* levels ($p<0.001$)) after low 8-week precipitation. Our findings provide insight on how future climate change could impact environmental transmission of bacterial pathogens in Kenya, and suggest water treatment could be a mitigation strategy.

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HEALTH DISPARITIES AMONG PACIFIC ISLANDERS OF THE PACIFIC ISLAND COUNTRIES AND TERRITORIES OF THE WESTERN PACIFIC: PRIORITIES FOR RESEARCH AND ACTION ON *CHLAMYDIA TRACHOMATIS* AND *NEISSERIA GONORRHOEAE* SEXUALLY TRANSMITTED INFECTIONS

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The Western Pacific Region (WPR) has the highest prevalence of *Chlamydia trachomatis* (Ct) and *Neisseria gonorrhoeae* (Ng) sexually transmitted infections (STI) in the world today with over 60 M cases compared to 220 M globally. However, studies of these STIs among Pacific Islanders of low and middle-income countries (LMIC) in the Pacific Island Countries and Territories (PICT) of this region are lacking. Both can lead to the devastating sequelae of pelvic inflammatory disease, infertility, and pre-term birth. We reviewed original research and surveillance studies, including reports from the World Health Organization and South Pacific Commission, to determine the prevalence, management, and treatment of Ct and Ng from 1980 to 2021 in the PICTs. Of 439 articles, only 31 included Pacific Islanders with data on Ct and/or Ng. Most studies examined pregnant women, and few included men. The prevalence of Ct was >17% among pregnant women across 6 PICTs in the 1980s, and up to 38% in prenatal adolescents, 36% in nonpregnant women, and 24% among men who have sex with men and transgender women—numbers that have continued to the present. Ng cases ranged from 9% for pregnant women and up to 36% for sex-workers or "bar-girls" over the same period. This enormous STI burden is likely a major contributing factor to the extremely high rates of infertility among the PICTs where syndromic management is practiced. In contrast, HIV cases among the general population remained at <1% over the same timeframe; estimates of syphilis ranged from <1% to 12%; their relatively low prevalence are a result of prioritizing active surveillance and early treatment, highlighting what is possible for Ct and Ng with appropriate resources. Here, we identify a significant lack of surveillance for Ct and Ng, which remain hyperendemic among Pacific Islanders in the PICTs. These health disparities require robust epidemiologic research to identify risk factors and test appropriate interventions and control measures. Local governmental support but also regional and international aid will be required to improve sexual and reproductive health among these vulnerable and under-studied populations.

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EFFECTS OF HYDROMETEOROLOGICAL FACTORS ON COVID-19 REPRODUCTION NUMBER IN THREE CONTIGUOUS COUNTRIES OF TROPICAL ANDEAN SOUTH AMERICA: A SPATIOTEMPORALLY DISAGGREGATED TIME SERIES ANALYSIS

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South America has been hit harder by the COVID-19 pandemic than other lower income regions, with some of the highest case fatality and excess mortality rates. Since SARS-CoV-2 first emerged, the role of climate on its transmission has been explored but with inconclusive findings, mostly from high income, mid-latitude countries. This study modeled the effect of weather on the SARS-CoV-2 reproduction number (R_t) for Colombia, Ecuador, and Peru, three contiguous countries of Tropical Andean South America, adjusting for other factors. Time series data on SARS-CoV-2 cases from May to December 2020 were sourced from national health authority websites and used to calculate district-level daily R_ts. These 786,940 unit-day observations were merged by district and date with 6 earth observation (satellite)-derived hydrometeorological variables and covariates including region, healthcare access, government policy response and population density and age structure and a generalized additive time series model was fitted. Specific humidity had the largest magnitude effect size of the hydrometeorological variables, an inverse association most pronounced in the bottom half of the distribution. An approximately 0.25 lower R_t was predicted at 10g/kg humidity compared to 0g/kg. Solar radiation's effect was slight and direct below, and pronounced and inverse above, a threshold of approximately 600 KJ/m^2, predicting an R_t of approximately 0.8 at the highest extreme. R_t increased with increasing wind speed above a 2.5m/s threshold, up to a predicted value of around 1.2 at 10m/s. Temperature, precipitation and soil moisture had small, inverse associations with R_t. Travel time to a health facility and population density had similar direct, and broadly linear effects that were larger than for any other variable, while effects of policy and age structure were negligible. Increased humidity and solar radiation may have a larger suppressing effect on SARS-CoV-2 than government response or population age structure, but population density and healthcare access are more influential than any environmental factor.

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THE IMPACT OF COVID-19 ON MIGRATION AND RESIDENCE PATTERNS IN A LARGE TOWNSHIP IN JOHANNESBURG, SOUTH AFRICA

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The Covid-19 pandemic and associated lockdown regulations have had devastating effects on individuals and households leading to socioeconomic instability mainly due to loss of income particularly among low-income populations. This study explores the patterns of migration and residential mobility in Soweto, Johannesburg using panel data from an urban Health and Demographic Surveillance System, focusing on outbound movement. The goal of the study is to understand the effect of COVID-19 on mobility, out-migration and emigration and the socioeconomic factors associated with migration pre- and post- Covid 19. The Child Health and Mortality Prevention Surveillance (CHAMPS) Soweto and Thembelihle (SaT) Health and Demographic Surveillance System (HDSS) includes 120,000 individuals from 34,000 households, with twice annual data collection since 2018 to current. We explored trends in migration events over two years 2019-2020. Mobility was defined as outward movement from a previous home address to settle in another location in Soweto, out-migration, to anywhere outside Soweto but within South Africa and emigration to other countries. Multinomial logistic regression was conducted to understand the sociodemographic factors associated with the increase in the number of migration events from 2019 to 2020. Migration events increased comparing pre- to post- Covid-19 outbreak. We observed 47,450 total migration events, of which 43.7% [95% CI 0.43.2–44.1%] were in 2019 and 56.3% [95% CI 55.9–56.8%. were in 2020 Relative Risk Ratio (RRR) of out-migration [RRR=1.719; 95% CI 1.519 – 1.997] and emigration [RRR=5.910; 95% CI 2.483 – 14.065] showed the number of events increased in 2020 compared to 2019. Among the reasons for migration, returning home and job loss were shown to be associated with increased risk of migration in 2020 compared to 2019. The emergence of Covid-19 led to an increase in the migration events in the surveillance population, mostly due to job loses or the need to return home during Covid-19 control lockdown periods.

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THE ROLE OF UNIVERSAL HEALTHCARE COVERAGE IN BUILDING RESILIENCE AGAINST PUBLIC HEALTH CRISES: A CASE STUDY OF THE COVID-19 PANDEMIC AND CHILDHOOD IMMUNIZATION COVERAGE

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Several studies have indicated that universal health coverage (UHC) improves countries' service coverage, utilization, and health outcomes. These studies, however, have primarily assessed the peacetime impact of UHC, limiting our understanding of its potential protective effects during public health crises. We tested the hypothesis that greater progress towards UHC safeguards countries' ability to deliver essential health services in times of public health crises. To do so, we acquired the national immunization data on 14 childhood vaccines for 180 countries between 1997-2020 from the WHO/UNICEF Joint Estimates of National Immunization Coverage and conducted a quasi-experimental difference-in-difference (DiD) analysis. We used the COVID-19 pandemic as a natural experiment to define the pre/post variable, and used the 2019 UHC Service Coverage Index (UHC SCI) to define treatment (UHC SCI &get 80) and control (UHC SCI &lt 80) groups. We quantified the effect of UHC on childhood immunization coverage before and during the pandemic using the DiD model. All analyses were controlled for calendar year and countries' income group, geographical region, and preparedness for an epidemic/pandemic. We replicated our analysis using a lower cutoff value of 50 for the UHC SCI to define treatment and control groups for a robustness check. The coefficient for the DiD term was significantly positive (2.93, *p-value* = 0.01), suggesting that countries with an UHC index above 80% was able to prevent a 2.93% decline in childhood immunization coverage against the shock of the COVID-19 pandemic. We also found in our robustness checks that the DiD coefficient became not significant (-0.61, *p-value* = 0.42) when a lower cutoff value of 50 was used for the UHC SCI. Countries with greater progress towards achieving UHC appeared to be insulated from a pandemic-induced decline in childhood immunization coverage. Further, this impact was only observed among countries who achieved high effective service coverage of UHC. Our findings strongly suggest that policymakers should continue to advocate for policies aimed at achieving UHC even during a public health crisis.

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CHOLERA SURVEILLANCE IN BANGLADESH: RISK FACTOR ANALYSIS ALONG WITH ANTIMICROBIAL RESISTANT PATTERN FOR THE YEAR 2014-2021

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Cholera, an epidemic-prone diarrheal disease, is considered a major public health problem in the world, particularly in low and middle-income countries in Asia and Africa. The GTFCC launched a new strategy, "Ending Cholera-A Global Roadmap to 2030". The establishment of surveillance systems is an important tool to detect hotspots and monitor the impact of the interventions planned for the cholera end game. This article aims to describe an epidemiological summary including the effect of different predisposing factors of cholera and antimicrobial resistance patterns for the period 2014 to 2021 in Bangladesh by using data from nationwide cholera surveillance that has been carried out by collaborative efforts between the icddr,b, and IEDCR. For this purpose, weekly, 20 participants were targeted for enrollment at each sentinel site and participants who met the case definition were enrolled in the surveillance. Sociodemographic, clinical data and the biological sample (stool/rectal swab) were collected from the enrolled participants. The microbiological culture was done in the central laboratories. Antibiotic susceptibility testing was done for a randomly selected sub-sample. *V. cholerae* was confirmed among 5.2% of suspected cases through microbiological culture. The proportion of cholera positivity was higher in Chattogram (16.7%), Narayanganj (14%) and Barisal (11.2%). The estimated annual incidence rates were ranged from 0.1 to 0.98 cases/10,000 population. It was found that the odds of cholera were 4.2 times higher among suspected cases, in 5-17 years and 2.9 times higher in 18-45 years of age compared to those <5 years of age. A distinct antimicrobial resistant pattern was detected for commonly used antibiotics (Ampicillin, Ciprofloxacin, Cefixime, Erythromycin, and Doxycycline). More resistance was found against beta-lactams, macrolides for Ogawa, and tetracycline for Inaba. The insights obtained from this surveillance are valuable for designing and monitoring the progress of prevention strategies to achieve the target of the GTFCC ending cholera global roadmap.

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REVISITING CULTURE AS A DIAGNOSTIC IN THE ERA OF ENDING CHOLERA ROADMAP

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Stool culture is considered the gold standard for confirmation of *V. cholerae* infection. However, the sensitivity of culture can be low, especially in settings with high antibiotic use and where culture is not done immediately onsite, a common reality in many cholera-endemic settings. This variable sensitivity can lead to challenges in interpreting surveillance data. Several cholera endemic countries are in the process of improving their cholera surveillance systems as part of their national cholera control plans and pairing the appropriate diagnostic tests to the environmental context is necessary for achieving disease elimination. In January 2021, we began clinical cholera surveillance at two healthcare facilities in the Sitakunda subdistrict of Chattogram, Bangladesh. Stool samples were collected from all suspected cholera cases, those experiencing acute watery diarrhea, and immediately tested using the Cholkit RDT. All stool samples were blotted on filter paper and transported to Dhaka; all RDT positive samples and a subset of RDT negative samples were tested by PCR. All RDT positive samples were additionally stored in Cary-Blair transport media and transported to Dhaka for culture. To date, we enrolled 2,496 suspected cases, among whom 12.5% (n=313) have tested positive for cholera by RDT; 75% (n=1,870) of suspected cases reported use of any antibiotic 24 hours prior to the hospital visit, including Metronidazole, Ciprofloxacin and Azithromycin. Among those that were RDT-positive, 79% were positive by PCR and 58% were positive by culture. However, these varied by prior antibiotic use with 54% of RDT+'s reporting previous antibiotic use testing positive by PCR and 50% by culture. At the time of writing this we are testing RDT-negative samples and will estimate performance of each assay with a Bayesian latent class model with and without antibiotic use. We will provide examples of how reliance on culture without locally tailored estimates of sensitivity can lead to biased estimates of cholera incidence and illustrate how the use of RDTs and PCR may lead to more refined estimates of cholera incidence.

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MODELING THE IMPACT OF TREATING MODERATE CHOLERA DISEASE WITH ANTIBIOTICS ON COMMUNITY TRANSMISSION

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Despite the existence of effective prevention strategies, cholera outbreaks continue to occur worldwide and remain an important cause of diarrhea morbidity and mortality. Under current guidelines, all cholera patients receive rehydration therapy, but only severely dehydrated patients receive antibiotics, which decrease the volume of stool and duration of shedding, thereby reducing transmission. Once rehydrated, all cholera patients are discharged back into the community. Here, we modeled the impact on community transmission of expanding antibiotic treatment to include moderately dehydrated cholera patients. We built an SEIR model to simulate a cholera outbreak in a fully susceptible (cholera naïve) population to quantify the impact of expanded antibiotic treatment on outbreak size, morbidity, and mortality. Based on prior studies, we assumed that non-antibiotic-treated infected individuals continued to shed pathogen after symptoms resolve, but that severely dehydrated patients stop contributing to transmission after presenting to care (and receiving antibiotics). We employed Latin-hypercube sampling to explore a range of possible parameter values. We found that treatment of moderately dehydrated cholera patients with antibiotics reduced the total number of cases in a cholera outbreak. On average, treating no moderately dehydrated cholera cases resulted in 50% (sd=0.33) of the total population being infected with cholera. However, when 40% and 80% of moderately dehydrated cases were treated with antibiotics, we found only 20% (sd=0.25) and 10% (sd=0.17) of the total population was infected during the outbreak, respectively. This relationship was consistent across a range of possible parameter values, and the range of outcome variability decreased as proportion of moderate cases treated increased. Through this simulation model, we provide early evidence that expanding antibiotics to moderately dehydrated cholera patients could have a substantial impact on reducing community transmission and therefore morbidity and mortality of cholera outbreaks.

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EPIDEMIOLOGY OF ENTEROTOXIGENIC *ESCHERICHIA COLI* AND IMPACT ON CHILDREN IN THE FIRST 2 YEARS OF LIFE IN PERU

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Enterotoxigenic *Escherichia coli* (ETEC) is a leading bacterial cause of diarrhea, that is continued to be associated with significant morbidity, and mortality among children <5 years of age. However, data on the disease burden and the impact of ETEC at the community level are limited. We followed a birth cohort of children for 24m to estimate ETEC infection and diarrhea incidence in Lima, Peru. Stool samples from all diarrheal episodes and non-diarrheal samples every 3m were tested using quantitative PCR for heat labile (LT) and heat stable toxins (STh and STp). Colonization factors were detected by multiplex PCR. Length and height of the children were measured every month. Among the 345 children followed, about 70% suffered from one or more (up to 7) ETEC diarrhea episodes. The overall incidence rate of ETEC diarrhea was 72.9 per 100 child years and ETEC-attributable diarrheal burden at the population level (PAF) was 5.2% (95% CI: 2% - 8.3%; p=0.004). ETEC was detected in 22.1% of the non-diarrheal specimens. ETEC diarrhea began early after birth and increased with age with the highest incident rate of 106.4 per 100 child year and the highest PAF of 17% (95% CI: 4.6 – 27; p=0.026) at 21 to 24m age. The overall incident rate of ST-ETEC was the highest (32.1 per 100 child years). The maximum length of ETEC shedding was 37 days (mean10.6 days, SD 7.4). The commonly occurring CFs in ETEC diarrhea were CFA/I (16.4%), CS12 (13.2%), CS21 (10.5%), CS3 (7.2%) and CS6 (6.6%). Homologous protection was observed with LT-ETEC, CS21, CS1 and CS8. ETEC diarrhea episodes over the length of the follow up was associated with significant reduction in the weight for age (WAZ) and weight for length (WLZ) of the children at 24m of age. ETEC is a significant pathogen in the Peruvian children, experience serial infections with multiple pathotypes. The data from this study will strengthen modeled disease burden estimates, increase understanding of the impact of ETEC infections on child health, and would facilitate design of new and improved interventions including vaccines to prevent and treat the life-threatening and disabling episodes of ETEC infections.

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POPULATION GENOMICS OF DIARRHEAGENIC *ESCHERICHIA COLI* UNCOVERS HIGH CONNECTIVITY BETWEEN URBAN AND RURAL COMMUNITIES IN ECUADOR

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Human movement may be an important driver of transmission dynamics for enteric pathogens but has largely been underappreciated other than for international 'travelers' diarrhea or cholera. Phylodynamic methods, which combine genomic and epidemiological data, can be used to examine rates and dynamics of disease matching underlying evolutionary history and biogeographic distributions, but these methods have not often been applied to enteric bacterial pathogens. We used phylodynamics to explore the phylogeographic and evolutionary patterns of diarrheagenic *Escherichia coli* in northern Ecuador to investigate the role of human travel in the geographic distribution of strains across the country. Using whole genome sequences of diarrheagenic *E. coli* isolates, we built a core genome phylogeny, reconstructed discrete ancestral states across urban and rural sites, and estimated migration rates between *E. coli* populations. We found minimal structuring based on site locations, urban vs. rural locality, pathotype, or clinical status. Ancestral states of phylogenomic nodes and tips were inferred to have 51% urban ancestry and 49% rural ancestry. Lack of structuring by location or pathotype *E. coli* isolates imply highly connected communities and extensive sharing of genomic characteristics across isolates. Using an approximate structured coalescent model, we estimated that the rates of migration among circulating isolates were 6.7 times larger for urban towards rural populations compared to rural towards urban populations. This suggests increased inferred migration rates of diarrheagenic *E. coli* from urban populations toward rural populations. Our results indicate that investments in water and sanitation prevention in urban areas could limit the spread of enteric bacterial pathogens among rural populations.

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T HELPER CELL RESPONSES IN ADULT DIARRHOEAL PATIENTS FOLLOWING NATURAL INFECTION WITH ENTEROTOXIGENIC *ESCHERICHIA COLI* ARE PRIMARILY OF THE TH17 AND TFH TYPES

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CD4$^+$ helper T cells, particularly T follicular helper (Tfh) and T helper 17 (Th17) cells, play important roles in many enteric infections by promoting the development of B-cell memory and mucosal antibody production. However, T helper (Th) cell responses to natural enterotoxigenic Escherichia coli (ETEC) infection remain to be analyzed. The main objective of this study was to analyze the frequencies, cytokine production of Th cells in PCR confirmed ETEC infected adult diarrhoeal patients (n=30) enrolled at the Dhaka hospital, icddr,b and in healthy adults (n=21). Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples collected on day 2, 7, 30 and 90 after hospitalization. Th responses were determined by flow cytometric analyses and ELISA measurements of cytokines in culture supernatants of PBMCs stimulated with ETEC antigens. ETEC specific IgA antibodies in serum and secretions from circulating plasmablasts were measured by ELISA. Flow cytometric results showed that proportions of memory (CD45RO$^+$) cTfh cells (CXCR5$^+$) expressing the activation marker inducible co-stimulator (ICOS) increased significantly among CD4$^+$ T cells on day 7 after hospitalization in patients compared to healthy individuals. ETEC patients also mounted significant antibody secreting cell and plasma IgA responses against heat labile toxin binding subunit (LTB) and colonization factors (CFs) on day 7. Antigen stimulation of PBMCs revealed IL-17A responses to LT, more clearly observed after stimulation with double mutant heat labile toxin (dmLT), than with LTB, and to the CF CS6 in samples from patients infected with LTB+ or CS6+ ETEC. Levels of LTB-specific IgA antibodies in ALS, but not plasma samples correlated with both IL-17A (r=0.5, p=0.02) and IFN-γ (r=0.6, p=0.01) responses to dmLT. Our results show that ETEC diarrhea induces T cell responses, which are predominantly of the Th17 and Tfh types. The correlations between IL-17A and IFN-γ and intestine-derived antibody secreting cell responses support that Th responses may contribute to the development of protective IgA responses against ETEC infection.

1739

EFFECTS OF EARLY-LIFE FEEDING PRACTICES ON CHILDREN'S ACQUISITION OF EXTENDED-SPECTRUM B-LACTAMASE (ESBL)-PRODUCING *ENTEROBACTERIACEAE* IN AN URBAN INFORMAL SETTLEMENT OF LIMA, PERU

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Young children living in low-resource settings may be gut-colonized with ESBL-producing *Enterobacteriaceae* within the first few months of life, with potential consequences for subsequent infection and onward transmission. We explored whether breastfeeding protects children against incident gut colonization with ESBL-producing *Escherichia coli* (ESBL-*Ec*) and ESBL-producing *Klebsiella*, *Enterobacter*, or *Citrobacter* spp. (ESBL-KEC), and alternatively, whether formula feeding increases risks of acquisition. We leveraged monthly stool samples and 52,816 daily survey visits collected from 112 children during a 2016-19 prospective cohort study of norovirus infection in a Lima shantytown. We used CHROMagar ESBL media to screen lactase-producing colonies previously isolated from 937 stool samples collected at ages 1, 3, 4, 5, 6, 7, 9, 12 and 16 months for the presence of ESBL-*Ec* and ESBL-KEC. We used conditional Poisson regression models to examine whether daily exclusive breastfeeding (ref: no exclusive breastfeeding), daily formula feeding (ref: no formula feeding), and daily non-exclusive breastfeeding (ref: no breastfeeding) in the past 30 or 14 days were associated with incident colonization events at the time of stool sampling. From 6-16 months of age, daily breastfeeding during the past 30 and 14 days significantly reduced children›s risk of acquiring ESBL-*Ec* by 52-58% (95% CI: 0.24, 0.66), compared to children who were not breastfed at all during these times frames. From 1-6 months of age, daily exclusive breastfeeding in the past 30 days reduced children›s risk of acquiring ESBL-KEC (RR: 0.58, 95% CI: 0.31,1.07). Conversely, daily formula feeding in the past 14 days was associated with 60% higher risk of ESBL-KEC acquisition (95% CI: 0.94, 2.71). Breastfeeding conferred marginal to significant protection against young children›s incident gut colonization with ESBL-*Ec* and ESBL-KEC. Meanwhile, formula feeding was associated with increased risks of ESBL-KEC acquisition. Further work is needed to assess the generalizability of these findings and to identify the mechanism(s) by which breastfeeding confers protection.

1740

AEDES MOSQUITO SALIVA INHIBITS FLAVIVIRUS INDUCED INFLAMMASOME BY TARGETING EARLY VIRUS DETECTION

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Flaviviruses represent a major public health problem due to globalization and propagation of susceptible vectors worldwide. Mosquitoes do not passively transfer virus from one individual to another, Instead, mosquito-derived factors have an important influence on infection and disease, aiding replication and dissemination within the host. *Aedes* mosquitoes spread several flaviviruses, therefore developing vaccines against mosquito could serve as universal approach against mosquito-borne viruses. Numerous studies have demonstrated the role of mosquito saliva in virus transmission. In addition, one of the key innate immune host responses to viral infections includes the release of inflammatory cytokines such as interleukin (IL-1 beta and IL-18) through the activation of inflammasome that causes the severity of diseases. Dengue and Zika virus trigger NLRP3-specific inflammasome, however, understanding the role of mosquito saliva in modulating the host innate immune response is a key step in developing transmission-blocking vaccines. Here, we show that *Aedes aegypti* salivary gland extract (SGE) inhibits the inflammasome activation by reducing expression of NLRP3, Caspase-1 activation and secretion of 1L-1beta in cell supernatant, compared to virus alone. *Aedes* SGE specifically targets NLRP3 gene as compared to other NOD like receptors during virus infection verified using CRISPR knockout (KO) macrophages and by using agonist of potential other inflammasomes genes. Furthermore, RT-2 PCR profiler and western blots show that SGE downregulates innate immunity signaling gene expression like NF-kappa B, interferons and other inflammasome genes in mRNA and protein levels. Together, these results show the role of SGE in inhibiting virus detection in early virus infection and thereby inhibiting Inflammasome activation at the inoculation site. This study provides insights into how mosquito saliva modulates the host innate immunity during viral infection. A better understanding will aid the development of anti-viral treatments by targeting mosquito saliva factors that are common to many distinct infections.

1741

SUCCESSIVE BLOOD FEEDING ALTERS DENGUE VIRUS DISSEMINATION IN *WOLBACHIA* TRANSINFECTED *AEDES AEGYPTI*

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Aedes aegypti is a highly efficient vector of numerous medically relevant arboviruses including dengue virus, Zika virus, and chikungunya virus. Some of this efficiency is due to the tendency of *Ae. aegypti* to feed on humans, develop in and around homes, and feed frequently (around every 2-4 days). The impact of frequent feeding has been understudied in traditional vector competence assays but we have recently shown that this feeding behavior significantly shortens the extrinsic incubation period for dengue virus (DENV) and increases the number of potential infectious bites. One of the leading strategies to reduce DENV transmission is through the replacement of wild *Ae. aegypti* populations with *Ae. aegypti* stably transinfected with the bacterial endosymbiont *Wolbachia pipientis.* These transinfected *Ae. aegypti* have a significantly reduced capacity to support DENV infections, however, these studies failed to consider how additional blood meals could alter *Wolbachia*-mosquito-virus interactions. To address this shortcoming, we tested the competency of stably transinfected *Ae. aegypti* under single and double feed scenarios. We found that in the presence of the wAlb strain of *Wolbachia*, a significantly higher proportion of mosquitoes had disseminated DENV at 7 days post infection when given a second bloodmeal. When the wMel *Wolbachia* strain was used, the trend was still present but was less strong, indicating a more robust or midgut-specific DENV-blocking effect. *Ae. aegypti* mosquitoes transinfected with the wMel strain of *Wolbachia* are currently being released in several countries and additional combinations of mosquito species and strains of *Wolbachia* are also being considered for pathogen control. Although wMel *Wolbachia* has been shown to be highly effective against DENV in lab and field trials, understanding the limits and interplay of this bacterium with mosquito behavior, physiology, and viral dynamics is critical for control efforts and modelling of virus transmission. Additional combinations of mosquito species and *Wolbachia* strains should be tested under frequent feeding scenarios when assessing efficacy before release.

1742

EVIDENCE THAT UNTRANSLATED GENOMIC SEQUENCES ARE KEY DETERMINANTS OF INSECT-SPECIFIC FLAVIVIRUS HOST RESTRICTION

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Most flaviviruses cycle between arthropods and vertebrates. Others, such as Long Pine Key virus (LPKV), are insect-specific. We investigated whether untranslated regions (UTRs) in the genome of LPKV are critical determinants of its host restriction. A chimeric virus was created by inserting the entire 5′ and 3′ UTRs and capsid gene of LPKV into the genetic backbone of Zika virus (ZIKV). The virus replicated in mosquito cells but not vertebrate cells. Three additional chimeras were created by exchanging specific regions in the 5′ and 3′ UTRs of ZIKV with the corresponding regions of LPKV. One chimera, which contained stem loop A (the viral promoter) of LPKV in the genetic background of ZIKV, produced virus that replicated in mosquito and vertebrate cells. These data suggest that the ZIKV NS5 polymerase recognizes the LPKV promoter and that untranslated genomic regions, other than SLA, are key determinants of insect-specific flavivirus host restriction.

1743

ATTENUATION OF THE NEUROINVASIVE PHENOTYPE OF WEST NILE VIRUS BY MUTATIONS OF CONSERVED RESIDUES IN THE E PROTEIN HINGE REGION

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West Nile virus (WNV) is a mosquito-borne flavivirus and has caused over 25,000 cases of neurological disease and 2,300 deaths in the United States since 1999. There is no licensed human WNV vaccine WNV. The development of live-attenuated vaccines (LAVs) is a priority for public health. Candidate WN LAVs will require multiple mutations to prevent the reversion to the virulence phenotype. The objective of this study is to rationally design mutations in the envelope (E) protein that fully attenuate the virulence phenotype of WNV. The E protein is the major structural protein on the virion and acts as a class II fusion protein to mediate viral entry. The cell entry of WNV requires the fusion of viral and cell membranes induced by the conformational change of the E protein from the dimer to the trimer. The conformational change of the E protein is due to the rearrangement of its three domains, EDI, EDII, and EDIII. The hinge region between EDI and EDII uses eight conserved hydrophobic residues to control the interdomain movement. The EDI-EDII interdomain movement exposes the fusion loop to drive the fusion of viral and cell membrane. Herein, we report that mutations of the conserved hydrophobic residues in the EDI-EDII hinge region can attenuate the virulence phenotype of WNV in mice. Each hydrophobic residue in the infectious clone of WNV NY99 strain (WNV-NY99ic) was replaced with an amino acid of lower hydrophobicity by site-directed mutagenesis. The single E-A54S and E-Y201P mutations were shown to interfere with viral entry and significantly reduce multiplication kinetics in cell culture. The E-Y201P mutation can impair the conformational change of the E protein from dimer to trimer, as observed with the lower pH required for hemagglutination activity. Importantly, the E-A54S and E-Y201P mutations partially and fully attenuated the neuroinvasive phenotype of WNV in four-week-old outbred Swiss Webster mice challenged with the intraperitoneal route. Our results provide the proof-of-concept that mutations of the flavivirus conserved amino acids in the EDI-EDII hinge region can be targeted for the rational design of attenuating mutations for WNV.

1744

METABOLIC SYNDROME ENHANCES FLAVIVIRUS DISEASE SEVERITY AND REDUCES VACCINE EFFICACY IN MICE

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Metabolic syndrome (MetS) is a cluster of conditions linked by chronic inflammation that increase the risk for comorbidities. Currently, 1/3 of United States adults have MetS. Globally, obesity rates have tripled since 1975, which is notable since it is a criterium used to diagnose MetS. Further, global areas plagued by a dramatic increase in obesity rates have also seen a significant increase in emerging arboviral pathogens. Regions of South and Central America have particularly suffered from this double disease burden. Studies done using SARS-CoV-2, influenza, West Nile and dengue viruses have revealed that MetS patients show higher mortality post-viral infection and poor vaccination outcomes when compared to metabolically healthy humans. However, the mechanisms driving MetS-induced immune dysfunction are unknown. Based on our preliminary studies and previously published work, we hypothesize that MetS-associated chronic inflammation alters the programming of adaptive immune cells critical for viral control, thus enhancing viral disease severity and reducing vaccine efficacy. To challenge this, we use West Nile virus in a MetS murine model. By infecting or vaccinating chow fed wild type (WT) and high fat diet induced MetS mice, we compared immune responses over time. Our results indicate that MetS mice have higher mortality rates post infection, heightened viral titers, severe organ pathology, dysfunctional T and B cell responses and reduced neutralizing antibody efficacy when compared to WT mice. Further, MetS alters antibody and T cell responses post-vaccination, rendering vaccination insufficient for protecting against severe viral disease. Our results imply that MetS enhances viral disease severity and reduces vaccine efficacy. Ongoing studies in our lab are focused on determining the mechanism by which MetS alters adaptive immune cell function, with our data implicating chronic inflammation as an inducer of immune cell epigenetic changes that alter their differentiation landscapes and consequently effector functions.

1745

INCREASING THE RESOLUTION ON WEST NILE VIRUS TRANSMISSION UNDER CLIMATE CHANGE BY ASSESSING POPULATION SPECIFIC EFFECTS OF TEMPERATURE

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Temperature is increasing across the globe and vector-borne diseases are uniquely susceptible to such increases. Current models that predict vector-borne disease transmission under climate change do not consider the populations specific effects of temperature. Mosquitoes and the pathogens they transmit are ectotherms, which means they are subject to fluctuations in temperature. The most common arboviruses vectored by mosquitoes are those which belong to the *Flaviviridae* family, including West Nile virus (WNV), Zika virus (ZIKV) and dengue virus. There is a correlation between increases in WNV prevalence and increased temperature in New York State (NYS), but the extent to which this effect varies among populations and regions is not fully understood. Temperature has been shown to influence mosquito life history traits, yet this influence is variable among *Culex* spp. populations. This suggests that there is a heterogeneous relationship among temperature and flavivirus prevalence. Temperature sensitivity will likely be subject to evolutionary pressures with changing environments. The purpose of this study was to assess the complex interplay among population and environment in New York

State and utilize novel empirical data to inform more accurate predictive models of WNV transmission under climate change. Two unique *Culex pipiens* populations from upstate and downstate NYS were reared at mean temperatures of 22, 25 or 30°C, mimicking current and future regional means. Life history traits were monitored at each temperature. Trait-based models were then used to characterize temperature-dependent transmission of WNV by *Culex pipiens* in NYS under climate change. Overall, temperature influences several life history traits associated with pathogen transmission, yet this effect is population dependent. Upstate and downstate *Culex spp.* populations demonstrate differences is optimal WNV transmission that generally correlate to historic regional climactic differences. These differences will likely contribute to regional differences in transmissibility under future climate change.

1746

FUTURE PROJECTIONS OF THE WEST NILE VIRUS RISK IN EUROPE

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West Nile Virus (WNV) is a mosquito-borne pathogen that has recently emerged as a major public health concern in Europe. The virus is maintained in nature in an enzootic bird-mosquito cycle, even though horses and humans are dead-end hosts developing in some cases encephalitis and meningitis. Like other mosquito-borne diseases, the expansion of WNV in Europe has been mainly attributed to environmental changes, such as rising temperatures, heat wave frequency and intensity, and arable land establishment. Here, we implemented a boosted regression tree method to construct correlative models of the environmental factors associated with WNV occurrence in Europe. We gathered West Nile virus occurrence data between 2007 to 2021 in Europe obtained from the European Centre for Disease Prevention and Control (ECDC), as well as environmental data for the same time period retrieved from the Inter-Sectoral Impact Model Intercomparison Project (ISIMIP). Our present time ecological niche model was trained using a spatial cross-validation procedure aiming to mitigate the impact of spatial auto-correlation. In addition, to explore future projections associated with different climate and land use change scenarios, we exploited our trained ecological niche model trained to perform future projections based on three climate change scenarios (i.e. three representative concentration pathways: declining, stabilizing, and rising emissions) and for three different time periods (2021-2040, 2041-2060, and 2061-2080). Consistently with other studies, temperature above 20°C in summer and cropland densities above 40% were two environmental factors positively associated with the ecological suitability for WNV occurrence. Regarding future projections, our analyses based on the scenarios based on stabilizing and rising emissions confirm the risk of a WNV expansion in Europe from 2041 onwards, involving geographic areas where the virus has not been reported yet. For the declining emissions scenarios, our projections reveal a rather stable map of ecological suitability.

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BAYESIAN FRAMEWORK TO ESTIMATE SARS-COV-2 REINFECTIONS FROM SERIAL SEROLOGIC SURVEYS IN AN URBAN SLUM POPULATION

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Serological surveys are important tools to measure the incidence of symptomatic and asymptomatic SARS-CoV-2 infections. As seroprevalence increases, we will need new methods to reliably estimate the incidence of recurrent infections from such data. We conducted household-based serosurveys in an urban slum in Salvador, Brazil, in November 2020-February 2021 and July-October 2022, after the 1st and 2nd epidemic waves. Using a commercial ELISA assay, we measured SARS-CoV-2 anti-S IgG optical density in the sera of consenting participants. Of 1,571 individuals who participated in both surveys, 228 had serologic evidence of prior infection in the 1st survey and were unvaccinated at the time of the 2nd survey. Thus, in this subset, increases in IgG can be attributed to either assay/sample variation or reinfection. We computed the change in IgG between the two surveys and fitted a Bayesian mixture model assuming that the observed values are drawn from two underlying Gaussian distributions: one distribution reflecting random variation around a mean change of zero; and the other reflecting increases in IgG due to reinfection. From November 2021 to March 2022 we conducted active surveillance of respiratory illness and measured anti-S IgG in individuals with PCR-confirmed SARS-CoV-2 infection. We assessed model performance in this subset of 86 positive controls, and 238 negative controls with no documented history of infection. The model showed excellent discrimination (area under ROC curve 0.989 [95% CI 0.979-0.999]). Applying the model to our entire cohort, we estimate that during the 2nd epidemic wave, 27.1% (95% bootstrap CI 25.4-28.8%) of unvaccinated individuals were reinfected. In contrast, 47.4% [95% CI 37.3-57.8%] of unvaccinated individuals with no prior infection experienced a primary infection in the same period. We developed a model to identify undetected reinfections based on serial serology and quantify uncertainty in serostatus, revealing a high incidence of reinfection in this urban slum population. This novel approach can strengthen SARS-CoV-2 surveillance as recurrent and sub-clinical infections become more frequent.

1748

TRANSCRIPTOMICS REVEALS COMMON AND UNIQUE DIFFERENTIALLY EXPRESSED GENES IN HOSPITALIZED PATIENTS WITH SEVERE COVID-19 FROM DIVERSE ANCESTRAL GROUPS

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American Indian/Alaska Native (AI/AN) populations have the highest hospitalization rates and second-highest proportion of cases and mortality from COVID-19 in the US. AI/AN people in New Mexico suffered the highest rates of all three metrics. Since the pathogenesis of severe COVID-19 remains largely undefined, we are conducting a prospective observational study in a diverse cohort of hospitalized patients. Here, we present temporal transcriptomic results from peripheral blood collected on days 0-3, 6, 9, and 14 in a subset of patients (n=39) infected with SARS-CoV-2 strains 20A and 20C. Severe COVID-19 (n=27) was defined as admission to the ICU and/or death, while non-severe patients (n=12) did not require ICU support. There were 249 and 432 uniquely expressed genes in severe and non-severe disease, respectively, with 15,148 co-expressed genes. A comparison of differentially expressed genes (DEG) between the two groups revealed 3,472 up-regulated and 2,465 down-regulated genes. Enrichment analysis revealed common and unique DEGs for the COVID-19 Immune Dysregulation Pathway (P=2.33x10^{-4}) in diverse patients with severe disease. Common features of severe COVID-19 were NF-κB signaling down-regulation and subsequent decreases in CCL2 and CCL8, chemokines that promote mononuclear cell chemotaxis to infected cells. Severe disease was also characterized by down-regulation in MHC class II genes for antigen processing, decreased TLR7 for sensing viral ssRNA, and increased expression of GLUT1 for glycolytic processes. Genes implicated in the systemic inflammatory response including IL-1β, IL-4, MIG, MIP-1α, and TNF-α were decreased, whereas IL-10 and GRO-2 were up-regulated. Unique up-regulated DEGs among AI/AN patients with severe disease were HIF-1A for activation of inflammatory mediators and glycolytic genes (i.e., F263). The AI/AN group also had reduced expression of IL-6, CXCL-16, and CCR5, and a greater perturbation in MyD88 signaling for antiviral defense. Collectively, these results provide novel insight into common and unique DEGs that influence COVID-19 severity and identify potential therapeutic targets.

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INFLUENZA, RSV AND SARS-COV-2 SURVEILLANCE IN RURAL ZAMBIA FROM 2019-2021

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Respiratory infections are a major cause of morbidity and mortality globally but are relatively understudied in sub-Saharan Africa. To assess their burden, surveillance for influenza-like illness (ILI), influenza virus and respiratory syncytial virus (RSV) was established in December 2018 at Macha Hospital in Zambia. Here, we compared the burden of influenza A/B virus, RSV, and SARS-CoV-2 among outpatients before and during the COVID-19 pandemic. An age-stratified sample of patients with ILI were enrolled and a nasopharyngeal swab was collected and tested on-site using GeneXpert. The pathogen prevalence among outpatients with ILI was estimated through direct standardization using the age distribution of outpatients with ILI and the age-specific pathogen prevalence among participants. From January 2019 to December 2021, 61,735 outpatients were screened for ILI. The prevalence of ILI decreased from 16.9% in 2019 to 9.7% in 2020 to 6.9% in 2021. In 2019, influenza A virus was detected from April (prevalence: 8.3%) to November (14.0%), with a peak (50.4%) in August. Influenza B virus was detected from August (25.8%; peak) to November (13.0%). RSV was detected from January (24.0%) to May (5.6%), with a peak (64.0%) in March. In 2020, RSV was only detected in May (3.0%) and June (1.6%), and no cases of influenza A/B virus or SARS-CoV-2 were detected. The first COVID-19 case at Macha Hospital was detected on December 18, 2020. The pattern in 2021 was similar to 2019. Influenza A virus was detected from March (15.8%) to December (7.7%), with a peak (36.7%) in June. Influenza B virus was detected from June (6.4%) to December (11.3%), with a peak (54.3%) in September. RSV was detected from January (42.3%) to April (7.0%), with a peak (66.0%) in February. SARS-CoV-2 was detected throughout the year, with a peak (16.5%) in December. In summary, this area has a significant burden of respiratory infections. COVID-19 mitigation measures reduced the burden of these pathogens in 2020 but they returned to prior levels in 2021, and co-circulated with SARS-CoV-2, once initial measures were eased in late 2020.

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HOUSEHOLD TRANSMISSION OF THE SARS-COV-2 OMICRON VARIANT IN AN URBAN SLUM SETTLEMENT IN BRAZIL

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SARS-CoV-2 Omicron variant has spread to cause epidemic waves globally, yet our understanding is limited on the transmission of this variant in urban informal settlements. During the Omicron wave in Salvador, Brazil, we conducted an active case finding as part of a community-based intervention in a slum community and estimated the household secondary attack rate (SAR). From Nov11, 2021, to Mar21, 2022, we conducted biweekly visits in 1150 households with 3156 residents and identified individuals with COVID-19-related symptoms. We interviewed symptomatic individuals and their household contacts and collected anterior nasal swabs to identify SARS-CoV-2 infection by RT-PCR. The index case was defined as a PCR-confirmed symptomatic case with the earliest reported date of symptom onset. Secondary cases were defined as an RT-PCR-confirmed infection identified within 14 days following the index case's onset of illness. We performed 5636 household visits and identified 90 RT-PCR-positive cases in 58 households. Whole-genome sequencing identified the Omicron variant as the cause of 50 (96%) of 52 cases. Among 35 households with ≥2 household contacts, the crude household SAR was 50% (95%CI 38-62%). When comparing 31 PCR-positive and 31 PCR-negative household contacts, women (20/31[65%] vs 11/31 [36%] male; p=0.04) and older individuals (median, 37 years [IQR 20-43] vs 22 years [13-31]; p=0.04) had significantly increased risk for SARS-CoV-2 infection. The risk of secondary household infection was non-significantly associated with lower PCR Ct values (reflective of higher viral load) in index cases (median, 24.3 [IQR 21.4-26] vs 25.9 [22.6-27.7] p=0.07). Household SAR with Omicron variant in this informal settlement was like those found in diverse settings and in upper-income countries. These findings suggest that the similarity in these rates may be due to the high intrinsic transmissibility of the Omicron variant and less dependent on social determinants such as crowding and poverty. Nevertheless, the high SAR underscores the urgent need to implement booster vaccination and provide access to rapid testing in vulnerable slum populations.

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DETECTING SARS-COV-2 VIRUS AT INDOOR DINING ESTABLISHMENTS DURING DELTA AND OMICRON TRANSMISSION WAVES

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Throughout the SARS-CoV-2 pandemic, restaurants have been identified as a potential source of community-based transmission, and have been subject to limitations on operations in an effort to slow the pandemic. Improved understanding of the factors involved in indoor transmission of SARS-CoV-2, especially during time periods with increasing case counts and introduction of new strains, is crucial for future standards and practices set by businesses to protect community health. This research sought to evaluate air sampling methods for capture of SARS-CoV-2 in an indoor restaurant environment and assess viability of captured SARS-CoV-2. The study was conducted in three stages: 1) environmental sampling; 2) molecular detection of SARS-CoV-2 via qRT-PCR; and 3) viral culture of SARS-CoV-2. The restaurant used for sampling enforced all state and local COVID-19 guidelines, including mask and vaccine mandates. Two five-stage Sioutas personal cascade impactor samplers were operated with Leland Legacy pumps calibrated to a flow rate of 9 L/min and placed in high traffic locations in the dining area during times of high occupancy for 90 minutes. Samples were collected on 20 days between December 2021 and January 2022. All samples were tested for the SARS-CoV-2 N1 gene using qRT-PCR, of which SARS-CoV-2 was detected in samples from air filters from 9 (45%) of the sampling events. Positive samples were then used to inoculate VeroE6-Ace2 cells and allowed to incubate at 37℃ for 72 hours. Increases in viral titers were observed in 22/23 (95.6%) of samples following inoculation, indicating replicating virus. In summary, SARS-CoV-2 virus can be detected in indoor dining environments via our methods, and that risk assessments using such approaches should be considered in advance of - and during - future surges of transmission.

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A NEUTROPHIL-ACTIVATING MICROBE IS REDUCED IN THE NASO-OROPHARYNX OF COVID-19 PATIENTS IN AN AFRICAN POPULATION: IMPLICATIONS FOR DISEASE SEVERITY

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Microbiome dysbiosis is associated with various communicable and non-communicable diseases including COVID-19. We conducted a pilot study to evaluate the naso-oropharyngeal microbiome in an African population to detect human microbial biomarkers. We compared our results to a previous report from an European population to identify differences in signature microbes that could contribute to understanding the low disease severity in Africa. Total DNA was extracted from naso-oropharyngeal swabs from retrospectively confirmed COVID-19 positive (N= 48) and negative (N= 33) individuals and, bacterial 16S rDNA was sequenced on an Illumina platform. Further analyses revealed significantly higher within-group diversity in positive compared to negative individuals (Shannon: $p< 0.0001$), contrary to the results of the previous study. There was low but significant microbial compositional dissimilarity (ANOSIM: R=0.21, $p= 0.001$), and clustering based on UniFrac phylogenetic distances explained 7.6% variation between positive and negative individuals ($p= 0.02$). *Prevotella* and *Atopobium* were abundant in COVID-19 positives (adjusted *p-value* <0.05) similar to the European study and, were as potential biomarkers associated with SARS-CoV-2 infection ($\log_{10}$LDA> 4.0). We first report *Finegoldia*, a microbe known to induce inflammatory responses through activation of neutrophils, as a candidate biomarker that is decreased in African individuals with COVID-19 ($\log_{10}$LDA> 4.5). Our results necessitate the need for further studies to investigate the role of *Finegoldia* and the other microbes in the immune response and disease progression following SARS-CoV-2 exposure and extension of microbiome-disease association studies across Africa.

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ESTIMATING GLOBAL SPATIAL DYNAMICS AND VACCINE-INDUCED FITNESS CHANGES OF BORDETELLA PERTUSSIS

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Bordetella pertussis (Bp), which causes whooping cough, infects >24 million individuals annually despite widespread vaccination. Asymptomatic carriage and multiple circulating lineages hide the underlying dynamics of Bp from surveillance systems. Therefore, the extent of spread across spatial scales remains a mystery, as does the role of vaccines in driving changes in strain fitness. Models informed by pathogen sequences can help. Here we make use of a unique dataset of >3300 geolocalised whole-genome sequences representing 23 countries from 6 continents, including newly sequenced isolates from France (n=1012; 1994-2018) and 12 other European countries (n=320; 2014-2016). Our phylogenetic models show that >95% of infections within a community are unlinked and that increasing local population size is strongly associated with the number of circulating transmission chains. Nevertheless, there is strong spatial structure: pairs of sequences from the same district had 4.1 times the odds (95% CI: 2.8-6.1) of having a most recent common ancestor within the prior year compared to pairs coming from different ones. This fell to 1 (i.e., no difference) after a period of three years, consistent with it taking three years for Bp to be well-mixed throughout France. Likewise, it takes 5-10 years for Bp to be well-mixed throughout Europe, similar to that observed for the United States. By conditioning on spatial and temporal location of sequences, this approach adjusts for underlying sampling biases. Finally, we develop an analytical framework that quantifies the relative fitness of different circulating genotypes through time. We find that implementation of acellular vaccines is linked with large-scale changes in fitness and can explain changing dynamics of individual lineages. These novel insights into Bp dynamics and its interactions with vaccine-induced immunity are highly relevant to vaccination policies.

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INFECTIOUSNESS AND ATTRACTIVENESS OF PREGNANT WOMEN IN THE SEASONAL MALARIA TRANSMISSION ZONE OF SAPONÉ IN BURKINA FASO

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Malaria in pregnancy remains a public health concern in Sub-Saharan Africa despite scale-up of insecticide-treated nets (ITN) and intermittent preventive treatment in pregnancy (IPTp) interventions. However infection presents a risk for transmission such that understanding how pregnant women contribute to the infectious reservoir will enable development of tools to effectively address malaria transmission in communities. This study combines community-based longitudinal cohorts with mosquito infection assays and vector sampling to assess biting rates. In cohort 1, pregnant women who were parasite positive were followed monthly after their antenatal care visits (ANC). Venous blood samples were collected for direct membrane feeding assays (DMFA) prior Sulfadoxine-Pyrimethamine (SP) dosing and on day 7 or 14 post DMFA to assess infectiousness to mosquito. In cohort 2, pregnant women were age-matched to control non pregnant to minimize the heterogeneity of transmission between

households. Concomitantly, the household members of the women were enrolled in the study and had their pre-existing infection cleared using an antimalarial. Afterwards, monthly home visits were conducted to assess incident infection and to collect mosquitoes to estimate exposure to bites. In total 63 pregnant women were included in the infectiousness cohort. 153 mosquitoes feeding experiments were conducted and 7,736 mosquitoes were dissected. 3.9% of feeds were infectious to mosquitoes with 18,3 % of mosquito infection rate and 3.6% oocyst prevalence per infected midgut. A total of 240 members, including 20 pregnant women and 20 age-matched controls, will be enrolled in the incident cases cohort. Follow up will be done during the high malaria transmission season from June to October to document the incident cases of *P. falciparum* infection and collect biological and entomological samples. Key findings related to parasite and gametocyte density, duration of infection and mosquito exposure will be presented during the conference to address the hypothesis that pregnant women under IPTp may still constitute a significant source of mosquito infection

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ANTENATAL CARE BEHAVIORS, INTENTIONS, AND PSYCHOSOCIAL FACTORS AMONG YOUNG MOTHERS WITH FUTURE PREGNANCY INTENTIONS IN MALAWI AND THE DEMOCRATIC REPUBLIC OF CONGO, 2021

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Young women (15-20 years old) in sub-Saharan Africa are a vulnerable yet understudied sub-population for malaria in pregnancy. Early antenatal care seeking (ANC) is linked with receiving the recommended three doses of intermittent preventive treatment of malaria in pregnancy. Using data from nationally representative Malaria Behavior Surveys conducted in Malawi and the Democratic Republic of Congo (DRC) in 2021, we assessed the association between intention to attend ANC in the first trimester for a future pregnancy (early ANC intention) and ANC ideation (cognitive, social, and emotional factors related to behavior) among women aged 15-49 years with a live birth two years before the survey who intended to have a future pregnancy. ANC Ideation was assessed as individual measures of 8 psychosocial factors related to ANC, including knowledge, attitudes, and self-efficacy, as well as a validated composite score. Multivariable logistic regression models controlling for demographic characteristics were used to evaluate associations between early ANC intention and the individual ideation factors as well as the composite measure. Analysis included 2,148 women (Malawi:827, DRC:1321), where 20% in both countries were aged 15-20. Many young women in Malawi (77%) and DRC (59%) intended to attend ANC early in the future. ANC ideation was lower among young compared to older (21-49 years) women in Malawi, while in DRC ideation was similar across age groups. Young mothers with higher ANC ideation were more likely to intend to attend ANC early in their next pregnancy in both countries. Early ANC intention among young women was also associated with early ANC attendance in past pregnancy in Malawi but not DRC. Specific ideation factors associated with intention to attend ANC early included positive attitudes (Malawi: aOR:3.39, 95% CI 1.69-6.81), knowledge of ANC (Malawi: aOR:2.28, 95% CI 1.18-4.41), and positive self-efficacy (DRC: aOR:5.18, 95 CI% 1.92-14.00). In Malawi and DRC youth-friendly social and behavior change interventions to increase ANC-related ideation could increase future early ANC attendance among young women and improve birth outcomes.

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EFFECT OF COMMUNITY DELIVERY OF INTERMITTENT PREVENTIVE TREATMENT (IPTP) OF MALARIA IN PREGNANCY ON COVERAGE OF IPTP IN FOUR SUB-SAHARAN AFRICAN COUNTRIES

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The World Health Organization (WHO) recommends the administration of intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) for malaria prevention in pregnancy (IPTp) at each antenatal care (ANC) clinic visit and starting as early as possible in the second trimester. However, overall coverage of IPTp remains low in many countries. It has been shown that community health workers (CHWs) can successfully deliver malaria preventive interventions. The TIPTOP (Transforming Intermittent Preventive Treatment for Optimal Pregnancy) project explored a community-based approach to expand coverage of IPTp in four sub-Saharan countries: Mozambique, Nigeria, Madagascar and the Democratic Republic of Congo (DRC). The aim of the study was to assess the effect of community delivery of IPTp (C-IPTp) on coverage of three or more doses of IPTp (IPTp3+) in the 12 project districts (three per country). A quasi-experimental evaluation was designed and baseline, midline and endline surveys were carried out in 2018, 2019 and 2021, respectively. A total of 18,792 women were interviewed. IPTp3+ coverage increased sharply after the first C-IPTp implementation year in all project areas in DRC, Madagascar and Nigeria, with increases between 129.76% (Vohipeno, Madagascar) and 506.06% (Ohaukwu, Nigeria) (all p values < 0.0001). Increases in IPTp3+ coverage were statistically significant between baseline and end-line surveys in all project districts, with the exception of Murrupula (Mozambique), and ranged between 9.6% (Nhamatanda, Mozambique) and 533.57% (Ohaukwu, Nigeria). C-IPTp was associated with an increase in IPTp coverage in all countries. The increase pattern was similar in DRC, Madagascar and Nigeria. In Mozambique, the IPTp3+ increase was lower compared to the other countries; the difference might be explained by higher baseline IPTp coverage and lower ratio of CHWs per pregnant women in Mozambique. In most countries, ANC utilization either stayed the same or increased. In conclusion, C-IPTp contributed to higher IPTp uptake and it constitutes a promising strategy to optimize control of malaria in pregnancy.

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POINT OF CARE TESTING IMPLEMENTATION AND CAUSES OF FEVER IN CHILDREN AND ADULTS ATTENDING IN A SENTINEL SITE FOR MALARIA SURVEY IN LIBREVILLE-GABON

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Fever is among the most common symptoms of people in Gabon, and clinician are challenged by the similar clinical features of a wide spectrum of aetiologies. This study describes the spectrum of malaria and non-malaria febrile illnesses in children and adults population attending in sentinel site of malaria. A cross-sectional study was performed between November 2020 - July 2021 at Operational and Clinical Research Unit (ORCU). We recruited consecutive children and adults with temperature ≥ 38°C, after consent, medical history and clinical symptoms were assessed. Blood, nasopharyngeal and stool samples were collected for CRP, Procalcitonin dosage as well as Plasmodium, viruses, detection based on diagnostic rapid tests. A total of 324 febrile patients were recruited including 121 adults and 230 children. The prevalence of malaria was 9.9% (12) in adults and 36.4% (74) in children. The frequency of viral infections was 64.9% (150/231) among which arboviruses, respiratory viruses, and digestives viruses were found in 68.0% (102), 22.0% (33) and 10% (15) cases respectively. Among arboviruses the Zika virus was predominant with 58.8% (60) followed by Dengue (33.3%) and Chikungunya virus (7.8%). According to age, similar frequencies of 8.2% for the Dengue virus and 19% for the Zika virus were found in adults and in children: 7.2% for Dengue virus and 17.1% for Zika virus. Respiratory infections of viral origin were frequently due to Influenza virus type A or B or respiratory syncytial virus only in children population, when the SARS-Cov-2 virus was found in all adults. Bacterial infection were common in adults: 63.6% had a positive procalcitonin result versus 28.5% in children. This study highlights the significant frequency of viral and bacterial infections in patients attending for malaria symptoms. There is a need to improve technical platforms and in remote areas to promote the use of RDSTs for the rapid screening of febrile patients to avoid antimalarial and antibiotic overuse. In malaria endemic settings, Zika, Dengue and respiratory virus should be considered by clinicians for the differential diagnosis of fever.

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ASSESSING THE INFLUENCE OF PSYCHOSOCIAL FACTORS ON PROVIDER MALARIA CASE MANAGEMENT IN HEALTH FACILITIES IN BENIN, 2021

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Provider adherence to case management guidelines is a pillar of malaria control. Research shows that provider behavior is influenced by factors at the individual, interpersonal, facility, and system levels. However, the role of psychosocial factors beyond knowledge (e.g., attitudes and behaviors) have rarely been assessed quantitatively. We conducted a cross-sectional health facility survey in Benin with 128 health facilities and 366 health workers involved in malaria case management. A random sample of facilities within each of the 12 departments was selected using probability proportional to the facilities' 2019 malaria incidence. Providers were interviewed with structured questionnaires to assess socio-demographic and psychosocial factors affecting case management. In facilities with both testing and ACTs available on the day of the study team's visit, 55% of cases were correctly managed; this was defined as testing of febrile cases and provision of antimalarials in accordance with test results as determined through client exit interviews. The associations between provider adherence and psychosocial factors were analyzed using multivariable logistic regression. A high level of provider knowledge about case management was associated with more than a two-fold increase in the odds of correct case management (2.3 odds ratio [OR]; 1.2-4.5 95% confidence interval [CI]). Positive perceptions of colleagues' behavior were associated with increased odds of correct case management (2.6 OR; 1.2-5.5 95% CI). Positive provider perceptions about clients' expectations and treatment adherence provider attitudes towards case management were not associated with the outcome. Other factors associated with correct case management included patient age, facility type (arrondissement health center compared to hospitals and private clinics), proportion of fever cases positive for malaria, provider training, and supervision. The results suggest that efforts to improve provider case management in Benin will benefit from strengthening provider technical knowledge and addressing beliefs about their colleagues' behaviors.

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A CROSS-SECTIONAL SURVEY TO ASSESS THE FEASIBILITY AND ACCEPTABILITY OF SEASONAL MALARIA CHEMOPREVENTION AMONG NOMADIC PASTORALIST POPULATION; THE CASE OF KARAMOJA, REGION IN UGANDA

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In 2021, the Ministry of Health (MOH), Uganda, collaborated with Malaria Consortium, to conduct a 5-month phase 1 implementation research to assess seasonal malaria chemoprevention (SMC) with sulphadoxine-pyrimethamine (SP) and amodiaquine (SPAQ) as a supplementary malaria intervention in two districts of Karamoja region, where malaria transmission is highly seasonal. This study component assessed the feasibility and acceptability of SMC among key stakeholders including policymakers, implementers and beneficiaries in a predominantly nomadic pastoralist community. A mixed-methods, cross-sectional study design comprising a household (HH) survey, focus group discussions (FGDs) and key informant interviews (KIIs) was used. The HH survey used a two-stage random sampling design, which involved sampling 60 villages per district and 15 HHs per village, resulting into a total of 1800 HHs interviewed using a structured questionnaire. FGD participants were purposively sampled, considering rural and urban locations; pastoralist and mining communities. KIIs targeted stakeholders at MoH, district, health facility and community levels. Study participants included members of the extended district health management teams, health workers, village health teams, community leaders, caregivers whose children received SMC, and other community members. A total of 26 FGDs and 51 KIIs were conducted. Quantitative data were analysed using STATA 12, while qualitative data were analysed using Atlas Ti 9th version. 96.8% of eligible children in cycle 5 received Day 1 SPAQ as directly observed therapy. Among children who received Day 1 SPAQ, 99.6% then received the full three-day course of SPAQ. Full coverage - the proportion of eligible children who received the

complete 3-day course during all five SMC cycles - was 87.2% (CI: 85.2 - 89.1). Coverage of individual cycles 1, 2, 3, 4 and 5 were 92.0% (CI: 90.6 - 93.4), 95.8% (CI: 94.7 - 96.8), 95.9% (CI: 94.9 - 96.9), 93.0% (CI: 91.7 - 94.3), and 99.6% (CI: 99.2 - 99.9) respectively. SMC is feasible and highly acceptable among the various stakeholders across different levels, including the nomadic pastoralists.

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IMPROVING INSECTICIDE TREATED NET COVERAGE THROUGH ANTENATAL CARE SERVICES IN RWANDA

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Malaria in pregnancy (MIP) negatively affects pregnancy outcomes, including maternal and neonatal mortality and adverse fetal outcomes such as low birth weight. Therefore, among other malaria prevention interventions, Rwanda embarked to achieve the insecticide treated net (ITN) universal coverage through the ITN mass distribution to households and routine distribution to the most vulnerable groups including under five children and pregnant women. In the period of Jan 2020 to Dec 2021, the program improved ITN distribution and the information, education and communication on challenges related to malaria behavior during ANC visits and conducted capacity building of health care providers on malaria diagnostic and case management training, integrated malaria supportive supervision, monthly data review and validation meetings at health facilities and monitoring of use of ITN program at health facility level. A quarterly review of data from national Health Management Information System (HMIS) on ITN distributed during ANC services and changes in MIP incidence was done in the period of January 2020 to December 2021. The results show an increase from 49% (z-score (-0.8)) (Jan-Mar 2020) to 74% (z-score 0.5) (Oct-Dec 2021) coverage in the distribution of ITN among pregnant women during ANC visits. There was a decrease in malaria incidence from 65 (z-score (2)) to 17 (z-score (-1)) cases among pregnant visiting ANC services, and a decrease from 88 to 73 malaria cases in all (567,198) pregnant women for10,000 confirmed malaria case during the January-March 2020 to October-December 2021. There has been a moderate negative correlation between the proportion of pregnant women receiving ITN in ANC services and the proportion of malaria cases in pregnancy every quarter r(9) = -0.655, P (value)=0.056. Although malaria cases among pregnant women have declined and the distribution of ITN in ANC services increased over the studied period, there is a need to strategize innovation to reach the remaining pregnant women.

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MONITORING POPULATION PROGRESS TOWARD TRACHOMA ELIMINATION WITH SEROLOGY: A MULTI-COUNTRY ANALYSIS

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Trachoma, caused by repeated infections with the bacterium *Chlamydia trachomatis* (*Ct*), is the leading infectious cause of blindness worldwide and is targeted for elimination as a public health problem by 2030. Antibody responses hold promise as sensitive, objective markers to monitor progress toward trachoma elimination, but programs currently lack a framework to translate antibody data into actionable information. We evaluated approaches for serological monitoring of population-level transmission compared with other trachoma indicators. We collated IgG responses to *Ct* antigen Pgp3, ocular infections detected by PCR, and clinical signs among 31,568 children aged 1-9 years from 9 studies, including population-based prevalence surveys and randomized controlled trials, in Ethiopia, Malawi, Morocco, Niger, and Tanzania. We hypothesized that (1) age-seroprevalence curves for trachoma would consistently flatten as populations neared elimination and (2) simple serologic summaries (e.g., seroprevalence) would represent population-level transmission as effectively as more complex measures (e.g., seroconversion rate or SCR). Median cluster seroprevalence varied widely, ranging from 0 to 54% (corresponding to SCRs of 0 to 0.14 per person-year). Age-seroprevalence curves rose steeply in populations with high levels of infection and active trachoma such as Amhara, Ethiopia, reaching 54% seropositivity by age 9 years (corresponding to SCR of 0.14, 95% CI: 0.13-0.15). Across a gradient of declining transmission, age-seroprevalence curves became less steep, and populations with flat curves (SCR <0.01) were associated with low levels of infection (estimated prevalence 0%). Seroprevalence and modeled seroconversion rates aligned similarly with infections across all settings. The data support the hypotheses that age-seroprevalence curves become flat as prevalence decreases and that simple seroprevalence measures reflect transmission similarly to more complex analyses. Our results demonstrate how population-level serology measurements from young children may be used as a robust monitoring tool for trachoma programs.

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INVESTIGATING THE ROLE OF CHLAMYDIA-SPECIFIC ANTIBODIES IN OCULAR INFECTION AND DISEASE PROGRESSION

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Despite various public health measures, ocular *C. trachomatis* (*Ct*) is still endemic in 42 countries and causes severe complications that can result in visual impairment. Lack of information concerning antibody correlates of protection and trachomatous disease progression has hindered efforts to develop an effective vaccine. 92 Tanzanian children aged 6-10 were observed longitudinally between 2012-2016 with regular eye examinations / *Ct* PCR tests to determine infection prevalence and scarring progression. 91.3% had at least one infection episode during the study period, and the average participant displayed infection in 12.0% of tests performed; >90% of infections were serovar B prior to mass azithromycin administration and >75% serovar A post-treatment. Scarring progression was present in 39.2%. Serum samples were taken in 2019 to investigate antibody correlates of protection. ELISAs were

used to measure concentration and avidity of IgG specific for EB-A, EB-B, MOMP-A, MOMP-B and P2 (a serovar B peptide). Higher avidity of MOMP-A-specific IgG was significantly associated with reduced probability of scarring progression (p=0.004) but not of TF, TI or TP: states of conjunctival inflammation associated with scarring progression. Children with higher avidity MOMP-B-specific IgG (p=0.002) and lower concentration of EB-B-specific IgG (p=0.021) had increased frequency of active trachoma, but this analysis was limited by sample size. Anti-MOMP-B IgG avidity was increased compared to samples from 37/92 children who also donated samples in 2018. Younger age, but not female sex, was associated with higher probability of TF and TI. The results of this study suggest that antibody responses may be important in prediction of trachoma pathogenesis. Though higher avidity anti-MOMP-A IgG was associated with reduced scarring progression, further research is needed to determine the mechanism. Similar studies with a larger sample size would be important to investigate whether higher avidity anti-MOMP-B IgG and lower EBB-specific IgG concentration in the serum are associated with more frequent observation of active trachoma.

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THE CURIOUS CASE OF A HIGH PREVALENCE OF TRACHOMATOUS INFLAMMATION - FOLLICULAR WITH NO TRACHOMATOUS TRICHIASIS: CAN ALTERNATIVE INDICATORS OF *CHLAMYDIA TRACHOMATIS* HELP US BETTER UNDERSTAND THE EPIDEMIOLOGY OF TRACHOMA IN CÔTE D'IVOIRE?

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Trachoma, caused by *Chlamydia trachomatis,* is the leading infectious cause of blindness and is targeted for global elimination as a public health problem by 2030. Elimination targets include a prevalence of trachomatous inflammation—follicular (TF) <5% in 1-9-year-olds and of trachomatous trichiasis (TT) <0.2% in ≥ 15-year-olds. Baseline surveys in Côte d›Ivoire in 2019 indicated a TF prevalence ≥5% in 18 districts, seven having TF ≥10%, but TT prevalence below the 0.2% threshold. Given this discrepancy, in August 2021, we evaluated additional indicators of *C. trachomatis* infection (DNA from ocular swabs) and exposure (anti-Pgp3 antibodies from dried blood spots [DBS]) to better understand the epidemiology of trachoma in two evaluation units (EU) of Cote d'Ivoire. Bondoukou 1 and Bangolo 2, situated in Nassian/Sandégué/Bondoukou and Bangolo districts, had the highest baseline TF prevalences nationally (28.26% and 28.30% respectively), and low TT prevalences (0.04% and 0.0%). A multi-stage cluster sampling method was used to select communities and households for inclusion. 1-9-year-olds from each selected household were recruited. The survey was supported through the Tropical Data platform. Phenotype, DBS, and conjunctival swabs were collected from each child. Ocular swabs were tested in pools of 5 using the Cepheid GeneXpert CT/NG kit, and DBS were tested for anti-*C. trachomatis* antibodies using a multiplex bead assay. The TF prevalence in 1-9-year-olds was <1% in both districts. Infection prevalence from 2,399 total swabs was 0.3% (95% CI: 0-06-0.92) in Nassian/Sandégué/Bondoukou and 0.3% (95% CI: 0.09-0.82) in Bangolo districts, respectively. Seroprevalence was 5.0% (95% CI: 3.4-7.4) in Nassian/Sandegue/Bondoukou and 7.9% (95% CI: 6.6-9.5) in Bangolo. The seroconversion rate was 1.24 seroconversions/100 children/year (95% CI 0.77-1.75) in Nassian/Sandégué/Bondoukou and 1.91 (95% CI 1.56-2.23) in Bangolo. Despite the baseline mapping results, recent infection, antibody, and clinical data provide strong evidence that trachoma is not a public health problem in either EU.

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ENHANCING TRACHOMA ELIMINATION USING ENSEMBLE FORECASTING

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Trachoma is the world's leading cause of preventable blindness of infectious origin. Challenges to meeting the World Health Organization's criteria for elimination of trachoma as a public health problem include identification of districts that require enhanced treatment, and districts that are most likely to show re-emergence of trachoma once treatment programs are stopped. To address these challenges, we developed and prospectively evaluated forecasting models of trachomatous inflammation-follicular (TF) prevalence, leveraging ensemble-based approaches employed in weather forecasting. To incorporate the inherent stochasticity of disease transmission and challenges of population-level surveillance, we forecasted probability distributions for the TF prevalence in each geographic district, rather than predict a single value. Several candidate probabilistic models were developed to forecast district-wise TF prevalence in 2222 districts, trained using publicly available district-level data on the population prevalence of TF in children aged 1-9 years from 1985-2019. Geographical location, history of mass drug administration treatment, and previously measured prevalence data were included in these models as key predictors. The best performing models were included in an ensemble, using weights derived from their relative log-likelihood scores. The ensemble forecasts will be updated yearly as more data becomes available, and new candidate models are developed. These probabilistic forecasts are used to answer questions of interest such as the probability that a population survey will measure TF prevalence as being greater than 5% in 2030 in any single district, which we estimate as 3% (95% CI: 0% - 13%). We also used our forecasts to predict specific districts where disease re-emerges two years after treatment programs were stopped, and found our algorithms had an accuracy of 95.4%. The ensemble forecast can be used to guide efforts towards Trachoma elimination by highlighting regions to be targeted for enhanced treatment or monitored for potential resurgence of disease.

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DOXYCYCLINE RESPONDING ILLNESSES IN RETURNING TRAVELERS WITH UNDIFFERENTIATED NON-MALARIAL FEVER: A MULTICENTER PROSPECTIVE COHORT STUDY

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Diagnosis of undifferentiated non-malarial fevers (NMF) in returning travelers is a great challenge. Currently, there is no consensus about the use of empirical antibiotics in these patients. Some studies in endemic areas showed that a wide range of pathogens implicated in undifferentiated NMF are treatable with doxycycline [doxycycline responding illnesses (DRI)]. However, the potential role of doxycycline in

returning travelers with fever still has to be explored. This is prospective European multicenter cohort study of febrile international travelers (November 2017-November 2019). Immunological and molecular diagnostic techniques for DRI agents such as *Anaplasma phagocytophilum*, Spotted Fever Group *Rickettsia* spp., Typhus Group *Rickettsia* spp., *Coxiella burnetti*, *Bartonella* spp., *Orientia tsutsugamushi, Borrelia miyamotoi, Borrelia recurrentis* and *Leptospira* spp. were systematically performed in all patients with undifferentiated NMF to estimate the prevalence and predictive factors of DRI in returning travelers with undifferentiated NMF. Among 347 travelers with undifferentiated NMF, 106 (30·5%) were finally diagnosed with confirmed or probable DRI. The main causes of DRI were: 55 (51·9%) *Rickettsia* spp., 16 (15·1%) *Coxiella burnetti*; and 15 (14·2%) *Bartonella* spp.; 13 (12·3%) *Leptospira* spp.; and 10 (9·5%) *Anaplasma phagocytophilum*. At first visit, DRI were clinically suspected in only 26 (24·5%) cases. The only risk factor associated with DRI was presenting an eschar (aOR 39·52, 95%CI 4·85-322·18). Clinical features of dengue such as retro-orbital pain (aOR 0.40, 95%CI 0.21-0.76) and neutropenia (aOR 0.41, 95%CI 0.21-0.79) were inversely related with DRI. Our findings suggest that a wide range of pathogens (30%) causing undifferentiated NMF in travelers would respond to doxycycline. Empirical treatment with doxycycline should be considered in returning travelers with undifferentiated fever and a negative malaria test, particularly when presenting risk factors for rickettsiosis or no features of dengue.

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LONGITUDINAL PHASE 2 CLINICAL TRIALS OF LIVE, ATTENUATED TULAREMIA VACCINE IN OTHERWISE HEALTHY RESEARCH LABORATORY WORKERS OPERATING IN CONTAINMENT LABORATORIES

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Tularemia is a bacterial disease caused by the intracellular bacterium *Francisella tularensis* (*F. tularensis* or *Ft*). It has been weaponized historically by multiple state actors due to its low infectious aerosol dose, high morbidity and high mortality rate of the pneumonic form. The US Army developed the attenuated Live Vaccine Strain (LVS) tularemia vaccine from cultures provided by the former Soviet Union in the 1950s. Two sequential LVS trials in at-risk laboratory personnel working on tularemia in bio-containment are reported. Volunteers received a single dose of LVS by scarification under 2 FDA-regulated single-arm protocols (IND 157) from 2004 to 2017 when the last volunteer was vaccinated. Positive immunization was based on local scarification site 'take reaction', and either a >1:20 tularemia antigen microagglutination (MA) titer (protocol FY03-24; 2004-8) or greater than 4-fold rise in MA titer (protocol FY07-15; 2009-2017). Those still negative by week 4 were offered a second dose. The LVS vaccine was safe, well tolerated and highly immunogenic. Between the two studies, all recipients (100%) had positive 'take reactions', with 95.5% of those in study FY03-24 having a positive response following initial vaccination. All but 3 subjects (98%) in protocol FY03-24 had positive MA titer results defined as >1:20, most within 28-35 days. In protocol FY07-15, 95% of subjects had a 4-fold or greater rise in MA titer, the primary immunogenicity endpoint for that study. LVS vaccine administered over a 12 year period was safe and highly immunogenic. Findings were in line with more than 4 decades of prior similar results. Response rates remained robust despite the vaccine lots employed having been manufactured decades prior to the present studies (1962). In the absence of a commercial development effort, or another tularemia vaccine in clinical development, a vaccine protocol under investigational new drug (IND) application could be considered based on the large body of favorable data for this vaccine. The results as well as historical comparator data presented here serve as a benchmark for future studies.

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IN VITRO TIME-KILL ASSAYS OF AMOXICILLIN/CLAVULANATE IN COMBINATION WITH RIFAMPICIN/CLARITHROMYCIN AGAINST *MYCOBACTERIUM ULCERANS*

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Buruli ulcer (BU) is a skin neglected tropical disease caused by *Mycobacterium ulcerans (Mul).* WHO recommended treatment requires 8-weeks of daily rifampicin and clarithromycin with extensive wound care. Minimum Inhibitory Concentration and checkerboard assays showed that beta-lactams combined with rifampicin/clarithromycin were synergistic against *Mul* (PMID:30689630). *In vitro* time kill assays (TKA) provide more granular information on the degree of drug interactions. TKA quantify the antibiotic concentration-effect relationship in a time-dependent manner. However, these are performed by quantifying colony forming units (CFU), a cumbersome methodology in BU research due to the slow growth of *Mul* (2-4 months to form colonies). The aim of this study was to compare four different methodologies to perform TKA using different combinations of rifampicin (R), clarithromycin (C) and amoxicillin/clavulanate (A) against a clinical *Mul* strain (ITM M000932). Bacterial loads were quantified after 1, 3, 7, 10, 14, 21 and 28 days of treatment. TKA methodologies included: (i) the gold-standard bacteriological assessment (CFU/ml) versus (ii) optical density (OD_{600}); (iii) BacTiter-Glo cell viability assay (Relative Luminescence Units, RLU); and; (iv) 16S rRNA RT/IS*2404* qPCR assay (number of gene copies). Bacterial load significantly decreased from day 3 in cultures treated with amoxicillin/clavulanate in combination with rifampicin (A+R) and with rifampicin/clarithromycin (A+R/C). On day 28, both combinations showed a mean of OD_{600}<0.2, less than 1,000 CFU/ml, $1.78x10^4$ RLU, and $5.62x10^5$ 16S rRNA copies/cDNA, being significantly lower values than the rest of conditions. All four methodologies provided comparable results showing that amoxicillin/clavulanate is strongly synergistic with rifampicin/clarithromycin against *Mul.* Our study suggests that alternative and faster TKA methodologies can be used in BU research beyond CFU quantification to understand the degree of drug interactions. These studies are supporting an ongoing clinical trial (*NCT05169554*) to determine the bacterial clearance rate in patient lesions.

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MOLECULAR DETERMINANTS OF TISSUE SPECIFICITY OF FLAVIVIRUS NONSTRUCTURAL PROTEIN 1

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Vascular leak is a hallmark of severe dengue caused by the positive-sense RNA flavivirus, dengue virus (DENV). DENV nonstructural protein 1 (NS1) is a secreted glycoprotein with 3 domains: the β-roll, wing, and β-ladder. NS1 causes endothelial hyperpermeability directly by disrupting the endothelial glycocalyx layer (EGL) *in vitro*, as well as inducing vascular leak *in vivo*. We have shown that different flavivirus NS1 proteins bind to human endothelial cells (EC) and induce vascular leak in a tissue-specific manner, consistent with the virus' respective disease tropism. NS1 from systemic DENV affects EC from all tissues including the lungs, while NS1 from neurotropic West Nile (WNV) and Zika (ZIKV) viruses affects brain EC, with ZIKV NS1 additionally affecting umbilical vein EC. We recently identified the wing and β-ladder domains to be important for binding to EC and causing EC barrier dysfunction, respectively. However, the molecular determinants of flavivirus NS1 that dictate differential EC tissue specificity

remain unknown. We exchanged the wing and β-ladder domains of DENV, WNV, and ZIKV NS1 pairwise to create chimeric NS1 proteins. Chimeras containing DENV NS1 wing domain bound to lung EC, while chimeras with WNV or ZIKV NS1 wing domains lost this capacity. Similarly, chimeras containing ZIKV NS1 wing domain bound to umbilical vein EC, whereas chimeras with WNV NS1 wing domain lost this ability. We then generated site-specific mutants with 3-4 amino acid (aa) exchanges between DENV and WNV NS1 within a non-conserved region of the wing domain and identified a 3-aa motif from DENV NS1 that confers gain-of-function binding to lung EC. Next, we used the DENV/WNV NS1 chimeras in a mouse model of localized dermal leak and found that chimeras containing DENV NS1 wing domain induced vascular leak *in vivo*. We also showed that DENV but not WNV NS1 β-ladder induced endothelial hyperpermeability in lung EC, as measured by trans-endothelial electrical resistance. Taken together, these results identify molecular determinants of DENV NS1 that confer NS1 binding and vascular leak and highlight the importance of NS1 wing domain for flavivirus pathogenesis.

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IDENTIFICATION OF ENDOTHELIAL CELL RECEPTORS FOR DENGUE VIRUS NONSTRUCTURAL PROTEIN 1

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Dengue virus (DENV) is a medically important human pathogen posing a major public health threat worldwide. DENV infection can result in potentially fatal cases of severe dengue associated with vascular leak as a result of endothelial dysfunction. We and others have previously defined a direct role for the DENV nonstructural protein 1 (NS1) in mediating endothelial dysfunction *in vitro* and vascular leak *in vivo* via interactions with endothelial cells. While we have defined an essential role for clathrin-mediated endocytosis in NS1-triggered vascular leak, the specific cellular receptors required for internalization of NS1 into endothelial cells are unknown. Validation of a panel of cell surface glycoproteins transcriptionally upregulated in response to DENV NS1 implicated a role for the G protein-coupled receptor beta-2-adrenergic receptor (β2AR) and the receptor tyrosine kinase epidermal growth factor receptor (EGFR) in NS1-mediated endothelial dysfunction. Genetic depletion, small molecule inhibition, and antibody blockade strategies targeting β2AR and EGFR implicate their involvement at the step of internalization of NS1 into cells, leading us to hypothesize that β2AR and EGFR may serve as NS1 receptors. Consistent with this hypothesis, we detect protein-protein interactions between NS1 and β2AR/EGFR resulting in a transient depletion of β2AR/EGFR protein levels. Functionally, this interaction results in inhibition of canonical β2AR signaling. Importantly, we demonstrate sufficiency by showing that overexpression of β2AR and EGFR in cell lines that do not internalize NS1 render them permissive to NS1 uptake. Further, we found that isoproterenol, the beta-blocker carvedilol, and erlotinib, which target β2AR or EGFR, are sufficient to inhibit NS1-mediated vascular leak *in vivo*. These data indicate a critical role for β2AR and EGFR in internalization of DENV NS1 into endothelial cells, which is essential for NS1-mediated vascular leak.

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AN 8-GENE MACHINE LEARNING MODEL IMPROVES CLINICAL PREDICTION OF SEVERE DENGUE PROGRESSION

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Each year 3-6 million people develop life-threatening severe dengue (SD). Clinical warning signs for SD manifest late in the disease course and are nonspecific, leading to missed cases and excess hospital burden. Better SD prognostics are urgently needed. We integrated 11 public datasets profiling the blood transcriptome of 365 dengue patients of all ages and from seven countries, encompassing biological, clinical, and technical heterogeneity. We performed an iterative multi-cohort analysis and identified eight differentially expressed genes (DEGs) between non-severe patients and SD progressors. Using these eight DEGs, we trained an XGBoost machine learning model on public data to predict progression to SD. All model parameters were "locked" using public data, after which we validated the model in an independent, prospectively enrolled cohort of 377 dengue patients in Colombia. We measured expression of the eight DEGs in whole blood samples collected prior to SD progression. We then compared the accuracy of the locked 8-gene XGBoost model to clinical warning signs in predicting subsequent SD. The 8-gene XGBoost model accurately predicted SD progression in the independent validation cohort with 86.4% (95% CI 68.2-100) sensitivity and 79.7% (95% CI 75.5-83.9) specificity. Given the 5.8% proportion of SD cases in this cohort, the 8-gene model had a positive and negative predictive value of 20.9% (95% CI 16.7-25.6) and 99.0% (95% CI 97.7-100.0), respectively. Compared to clinical warning signs at presentation, which had 77.3% (95% CI 58.3-94.1) sensitivity and 39.7% (95% CI 34.7-44.9) specificity, the 8-gene model led to an 80% reduction in the number needed to predict (NNP) from 25.4 to 5.0. Importantly, the 8-gene model accurately predicted subsequent SD in the first three days post-fever onset and up to three days before SD progression, when SD prediction remains clinically difficult. The model has potential to be translated to a point-of-care prognostic assay to reduce dengue morbidity and mortality without overwhelming limited healthcare resources.

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TRADE-OFFS SHAPING ARBOVIRUS TRANSMISSION IN NATIVE AND NOVEL HOSTS

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Studies of the trade-offs that shape pathogen virulence evolution focus predominantly on the impact of mortality in truncating duration of transmission, with relatively little attention paid to the role of immune clearance. Our study sought to elucidate the interplay among infecting virus dose, virus replication, immune response, and transmission by mosquito-borne dengue (DENV) and Zika (ZIKV) viruses in both native (cynomologous macaques) and novel (squirrel monkey) primate hosts. To infect macaques, cartons of either 1 (n = 4 monkeys) or 10 (n = 5) *Aedes albopictus* mosquitoes that had been inoculated with a sylvatic strain of DENV or 10 control mosquitoes (n = 4) were allowed to feed upon each monkey. To infect squirrel monkeys, groups of 15 *Ae. albopictus* inoculated with either a sylvatic DENV or sylvatic ZIKV strain (n = 10 monkeys each) or control mosquitoes (n = 4) were allowed to feed. Two days post-feeding, engorged mosquitoes were force-salivated to estimate virus dose delivered. Uninfected mosquitoes were then fed at regular intervals upon each animal, incubated for 14 days and titered to detect transmission. Blood was collected at the same intervals to monitor viremia and physiological/immune responses, including cytokines, complete blood counts, natural killer cells and plaque reduction neutralization titers (PRNTs). The dynamics of DENV viremia in macaques and squirrel monkeys were similar, with relatively few monkeys sustaining low viremia that persisted until, at latest, 14 days post-infection, and resulted in few mosquito infections. The dynamics of DENV and ZIKV viremia in squirrel monkeys were dramatically different. ZIKV produced high viremia in squirrel monkeys over a short duration of time, with most monkeys transmitting to a high proportion of mosquitoes. Interestingly, PRNTs were significantly lower to ZIKV than DENV in squirrel monkeys, but PRNTs to DENV in macaques and squirrel monkeys were similar. In both species, infection was associated with significant differences in Natural Killer cell abundance, as well as other immunological shifts.

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SULFATED B-GLUCAN FROM *AGARICUS SUBRUFESCENS* INHIBITS FLAVIVIRUS VIRUS INFECTION AND DENGUE VIRUS NONSTRUCTURAL PROTEIN 1-MEDIATED PATHOGENESIS *IN VITRO* AND *IN VIVO*

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Dengue and Zika are diseases with substantial morbidity and mortality rates with no existing specific therapeutic agents available. Moreover, dengue virus (DENV) and Zika virus (ZIKV) nonstructural protein 1 (NS1) can directly trigger endothelial barrier dysfunction and vascular leak. We tested the capacity of a unique fungal cell wall glucan component ((1-6,1-3)-β-D-glucan) isolated from *Agaricus subrufescens* fruiting bodies (FR) and its sulfated derivative (FR-S) to prevent DENV2 and ZIKV replication as well as DENV2 and ZIKV NS1-induced endothelial dysfunction. FR-S, but not FR, significantly inhibited DENV2 and ZIKV replication in human monocytic cells (EC_{50}=36.5 and 188.7 µg/mL, respectively) when added simultaneously with viral infection. FR only displayed slight anti-DENV activity (25.5 % of inhibition at 500 ug/mL), indicating that sulfation contributes to the antiviral effect. In an *in vitro* model of endothelial permeability using human pulmonary microvascular endothelial cells (HPMECs), FR and FR-S (0.12 µg/mL) inhibited DENV2 NS1- and ZIKV NS1-induced hyperpermeability by 50% and 100%, respectively, as measured by Trans-Endothelial Electrical Resistance. Treatment with 0.25 µg/mL of FR and FR-S inhibited DENV2 NS1 binding to HPMECs. Agarose gel electrophoretic mobility shift assay indicated an interaction between FR-S and DENV2 NS1 that destabilized the oligomeric form of NS1. Further, we found that FR-S significantly reduced (p=0.048) intradermal hyperpermeability induced by DENV2 NS1 in wildtype C57BL/6 mice. In a systemic model of DENV2 infection in *Ifnar*$^{-/-}$ mice, oral treatment with 14 mg/kg of FR-S twice per day for 5 days, starting the day of infection, significantly reduced morbidity (p=0.0025) and mortality (p=0.0253). Thus, we demonstrate efficacy of FR-S against DENV and ZIKV infection and NS1-induced endothelial permeability *in vitro* as well as anti-leak and anti-dengue activity *in vivo*. Therefore, FR-S and other glycans may serve as potential therapeutics to treat flavivirus infections.

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GENOME EVOLUTION OF DENGUE VIRUS UNDER SELECTION BY *WOLBACHIA PIPIENTIS* IN *AEDES AEGYPTI* MOSQUITOES

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The *Wolbachia* approach is a public-health intervention that introgresses antiviral strains of *Wolbachia (w*Mel and *w*AlbB*)* into *Ae. aegypti* mosquito populations to control dengue. Plausibly, dengue virus (DENV) could evolve to bypass the antiviral effects of *Wolbachia* and undermine this approach. Here, we report on genomic outcomes after serial-passage of the dengue virus 1 (DENV-1) in *w*Mel-infected *Ae. aegypti*. An amino acid substitution, E203K, in the DENV-1 envelope protein was more frequently detected in the consensus sequence of virus populations passaged in *w*Mel-infected *Ae. aegypti* than wild-type counterparts. Positive selection at residue 203 of envelope was reproducible as it occurred in passaged virus populations from six independent DENV-1-infected patients. The findings provide proof of concept that *w*Mel-associated selection of virus populations can occur. The E203K change is located in the envelope domain II (EDII) containing the fusion loop which plays a significant role in membrane fusion and mediate irreversible conformational changes during the fusion. Field-based studies are needed to explore whether *w*Mel imparts selective pressure on DENV evolution in locations where *w*Mel is established. The genomic stability of viruses carrying the envelope (E203K) variant in wild type *Ae. aegypti* and human cultured cells will also be reported.

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A SINGLE HISTIDINE TO ARGININE SUBSTITUTION ON THE PRE-MEMBRANE (PRM) PROTEIN ATTENUATED A TYPE-2 DENGUE VIRUS THAT CAUSED THE SOUTH PACIFIC ISLAND OUTBREAKS IN THE 1970S

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Dengue is an acute mosquito-borne viral disease that is caused by four antigenically distinct dengue viruses (DENVs). Transmitted by *Aedes* mosquitoes, DENVs are hyperendemic throughout the tropics and subtropics, with frequent cyclical and explosive epidemics. Despite the worsening trends, the molecular basis of DENV fitness in its natural epidemiological settings remain poorly understood. We examined the American genotype DENV-2 which caused outbreaks in the South Pacific Islands in the 1970s, where the disease that was initially severe became attenuated when the virus, which first emerged in Tahiti, reached the Kingdom of Tonga. Phylogenetic analysis found three main amino acid changes within the pre-membrane (prM) and non-structural genes NS2A and NS4A that defined the Tongan viruses. We constructed infectious clones of these DENVs using published viral genome sequences, and identified a single Histidine to Arginine substitution at position 86 of the prM protein ($H_{86}R$) as the main driver of DENV-2 attenuation seen in Tonga. This single substitution reduced the *in vitro* and *in vivo* viral replication rate of DENV-2 in mammalian systems; however viral replication remained unimpaired in *Aedes aegypti* mosquitoes. Reversing arginine back to histidine on a Tongan DENV backbone restored virus replication to levels comparable to the New Caledonia DENVs, where a large outbreak of severe disease occurred. The prM $H_{86}R$ switch did not compromise DENV maturation. Instead, our findings suggest that prM may have functional roles in influencing DENV egress from infected cells and may have other functions besides a chaperone for the envelope protein. These functions may be critical for the epidemiological fitness of DENVs.

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A NINE-GENE BLOOD-BASED SIGNATURE MEETS THE WORLD HEALTH ORGANIZATION TARGET PRODUCT PROFILES FOR DIAGNOSIS OF ACTIVE TUBERCULOSIS AND PREDICTING PROGRESSION FROM LATENT TO ACTIVE DISEASE

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As part of its End TB strategy, the World Health Organization (WHO) has identified the need for non-sputum-based diagnostics that meet target product profiles (TPPs) of 90% sensitivity and 70% specificity for diagnosis of active tuberculosis (ATB) and 75% sensitivity and specificity for predicting progression from latent tuberculosis infection (LTBI) to active disease. The successful translation of a 3-gene blood-based signature, identified using diverse datasets, into a prototype point-of-care diagnostic, that meets the WHO TPPs, has demonstrated the power of integrating large amounts of heterogeneous data to identify robust and generalizable

disease signatures. Here, we hypothesized that integration of more diverse datasets, comprising patients with ATB or other inflammatory lung diseases (e.g., COPD, viral infections, sarcoidosis, lung cancer, etc.), would identify novel robust signatures, for diagnosing ATB and predicting progression from LTBI to ATB, that meet the WHO TPPs. By integrating data from 3615 peripheral blood samples across 49 publicly available transcriptomic datasets, we identified a 9-gene signature for diagnosing ATB patients from healthy controls, or individuals with LTBI or other diseases. The signature achieved 90% sensitivity and 82% specificity in retrospective validation cohorts (3836 peripheral blood samples, 28 datasets) and 90% sensitivity and 69% specificity in a prospective cohort from Moldova (360 blood samples). In a longitudinal cohort of adolescents, the 9-gene signature predicted progression from LTBI to ATB up to 1 year prior to sputum conversion with 76% sensitivity and 83% specificity. Finally, in the Catalysis Treatment Response Cohort, the signature could be used to monitor treatment response and predicted prolonged lung inflammation and risk of subclinical Active TB post-treatment. Overall, the 9-gene signature meets the WHO TPPs required for the End TB strategy.

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ADDRESSING VITAMIN DEFICIENCIES AMONG HOUSEHOLD CONTACTS OF TUBERCULOSIS PATIENTS IN INDIA

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Deficiencies in Vitamins A and D are each associated with increased risk of progression from latent to active tuberculosis (TB). It is unknown whether low vitamin levels are found more among undernourished (body mass index [BMI] <18.5 kg/m^2) individuals compared to well-nourished ones (BMI ≥18.5 kg/m^2). Data are also lacking on the role of multivitamin and food supplementation to improve vitamin levels and decrease risk of progression to TB. Tuberculosis:Learning the Impact of Nutrition (TB-LION) is a 5-year prospective clinical trial in Puducherry and Tamil Nadu, India enrolling QuantiFERON-plus positive household contacts of TB patients. Undernourished participants are given a 2600 kcal food package and multivitamins for six months and followed for two years. On a subset of participants, we measured serum levels of Vitamins A (deficient <30µg/dL) and D (deficient <20 ng/mL; insufficient 20-29 ng/mL) at baseline and 6 months. Of 70 participants enrolled in TB-LION, we measured vitamin levels in 33 participants at baseline (18 undernourished; 15 well-nourished) and 18 at six months (10 undernourished; 8 well-nourished). At baseline, 78.8% had Vitamin A deficiency (VAD) and 97.0% were deficient or insufficient in Vitamin D. VAD was seen in both the undernourished and well-nourished groups (72.2% and 86.7%, respectively), with average levels of 27.8 µg/dL and24.4 µg/dL, respectively. Similarly, Vitamin D levels were deficient or insufficient in 94.4% of the undernourished (average 20.7 ng/mL) and 100% of the well-nourished (average 18.4 ng/mL). At 6 months among the 10 undernourished given multivitamins and food, 50.0% had VAD (average 35.7 µg/dL) and 40.0% were Vitamin D deficient or insufficient (average 35.4 ng/mL). These data show that Vitamin A and D deficiencies are common among household contacts of TB patients regardless of BMI, and that food and micronutrient supplementation can increase serum levels of these essential micronutrients. Future analyses will show whether this increase is associated with lower risk of progression to TB and whether nutritional supplementation should be pursued as a public health measure to prevent TB.

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IMPACT OF NUTRITION ON TUBERCULOSIS TREATMENT OUTCOMES IN INDIA: A MULTICENTER PROSPECTIVE COHORT ANALYSIS

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Undernutrition is one of the leading risk factors for tuberculosis (TB) disease worldwide and is associated with increased TB incidence and mortality. However, the impact of undernutrition on treatment outcomes is poorly defined. In this retrospective cohort study, we assessed the impact of acute and chronic undernutrition on TB treatment outcomes. We analyzed prospectively collected data for patients aged ≥18 years with pulmonary TB from five Regional Prospective Observational Research for Tuberculosis (RePORT)-India sites. We used multivariable Poisson regression o calculate the independent associations between treatment failure (defined as clinical or bacteriological failure, death, relapse, remission, or loss to follow up) and baseline body mass index (BMI; kg/m2), stunting (height-for-age Z-score <-2), and percent change in BMI after the first two months of therapy. Models included age, sex, cough duration a priori and variables with p<0.2 in univariate analysis. Of 626 persons with TB, 347 (55.6%) were undernourished (BMI<18.5kg/m2) and 160 (25.6%) were stunted. In the first two months, the BMI of 102 (16.3%) participants decreased. In multivariate analyses, baseline BMI was associated with treatment success (adjusted odds ratio [aOR]: 1.11, 95%confidence interval [CI]: 1.04-1.18) as was increased BMI in the first two months (Table). Greater increases in BMI were associated with higher aORs for treatment success with BMI increase >2.00 kg/m2 having aOR of 4.37 (1.24-15.46). Stunting was associated with reduced treatment success, but the results were not statistically significant (aOR 0.64, 95% CI: 0.39-1.06). Nutritional status at baseline and weight gain during the intensive phase of therapy are associated with TB treatment success. Stunting, a surrogate marker for chronic undernutrition, may also predict treatment success. These findings underscore the importance of addressing undernutrition as a key comorbidity of TB. Expanding existing nutritional subsidies through India's National Tuberculosis Elimination Program may improve treatment outcomes.

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A SYSTEMATIC REVIEW AND META-ANALYSIS OF STRATEGIES TO QUANTIFY CATASTROPHIC COSTS DUE TO TUBERCULOSIS AND ACHIEVE THE WORLD HEALTH ORGANIZATION TARGET OF THEIR ELIMINATION

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Since records began, tuberculosis (TB) has killed more people than any other infectious disease. The World Health Organization (WHO) strategy to "End TB" by 2030 includes the milestone of no affected households facing catastrophic costs (CC) due to TB. Costs due to TB are usually defined as catastrophic if they exceed 20% of the pre-disease annual household income. The strategies to quantify and eliminate catastrophic costs are incompletely defined. To inform this policy, we aimed to assess the evidence for strategies to quantify or eliminate catastrophic costs due to TB. We followed the Prisma-P guidelines and screened 441 eligible studies (see DOI: 10.12688/wellcomeopenres.17521.1). 94 studies were included for the qualitative and quantitative analysis; 32 were not original research but described strategies such as how to implement CC instrument measurements; how to implement socio-economic support and strategies about cost estimates. From the 62 original research, 48 were CC surveys; including 17 National CC surveys and 31 regional surveys. Only 8 studies assessed interventions to prevent or eliminate CC. One randomized controlled trial (RCT) found that a socio-economic intervention decreased CC by 40% (Odds Ratio (OR) 0.60, 95% Confidence Interval (95%CI) [0.36–0.98])).Whilst an RCT of home-based care (versus hospital) showed a 93% reduction of CC (OR 0.07, 95%CI [0.03–0.15]). The other 6 intervention studies evaluated active (versus passive) case finding and we performed a meta-analysis that demonstrated an approximate halving of CC (OR 0.59, 95% CI [0.38–0.91]). This review found diverse strategies used to quantify CC, none of which have been compared. Furthermore, the few studies that evaluated an intervention did reduce CC, but none achieved the WHO target of eliminating CC.

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RESISTANCE PATTERNS AMONG MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN GABON: TRENDS-OVER-TIME ANALYSIS OF THE NATIONAL SURVEILLANCE DATA AND IMPACT OF XPERT MTB/RIF AND DECENTRALIZED CARE ON CASE-FINDING

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Gabon is a country with a high prevalence of multidrug-resistant tuberculosis (MDR-TB). Routinely generated surveillance data are important for monitoring the effectiveness of tuberculosis (TB) program strategies against MDR-TB. The incidence of rifampicin-resistant tuberculosis (RR-TB) is a key indicator for monitoring anti-tuberculosis drug resistance. Many efforts have been made in Gabon to improve the early detection of MDR-TB cases. We summarize in this retrospective longitudinal study the eight-year trends in the incidence of RR-TB in Gabon. National data on rifampicin-resistant (RR) tuberculosis from 2014 to 2021 were analyzed. Sputum samples from suspected MDR-TB patients in all regions of Gabon were referred to the national tuberculosis reference laboratory. Samples were analyzed using GeneXpert MTB/RIF and Genotype MTBDRsl version 2/Line Probe Assay. Of 2786 samples received during the study period, 334 patients were RR-TB. The median age was 33 years (interquartile range 26-43). One out of three patients diagnosed with RR-TB was TB treatment naïve and the proportion of HIV positive was 33% (110/334). Patients aged 25 to 35 years were the most affected (39%, 130/334). The cumulative incidence of RR-TB was 17 (95% CI 15-19)/100,000 population over eight years. The highest incidences were observed in 2020 and 2021. A total of 279 samples passed for second-line drug resistance analysis. The proportion of study participants with MDR-TB, pre-XDR-TB, and XDR-TB was 90% (253/279), 9% (25/279), and 0.3% (1/279), respectively. The most frequent resistance to fluoroquinolones occurred on gyrA WT3. The increased coverage of GeneXpert machines in the country in 2020 has significantly improved the case detection of RR-TB. The incidence of RR-TB was significantly elevated in the 25-35 years age category. The incidence of MDR-TB infection in naïve TB treatment patients is worrying. The RR-TB case finding and contact tracing strategy should be continued and improved.

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RAPID DETECTION OF *MYCOBACTERIUM TUBERCULOSIS* USING RECOMBINASE POLYMERASE AMPLIFICATION: A PILOT STUDY

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Diagnosing tuberculosis (TB) remains a challenge in resource-limited contexts, as most currently available diagnostics are insensitive or too slow. PCR-based assays are sensitive and rapid, but their cost makes them unfeasible in resource-poor laboratories. Recombinase polymerase amplification (RPA) is an isothermal DNA amplification assay which could represent a cheaper and easier alternative to PCR. In this study, we explored the use of RPA paired with lateral flow technology for detecting *Mycobacterium tuberculosis* (MTB) DNA. We used serial dilutions of MTB H37Rv genomic DNA (BEI Resources, NIAID, NIH) in molecular biology grade water to establish the assay's lower limit of detection. Then we conducted a pilot study using 19 de-identified sputum samples to obtain a preliminary estimate of the assay's sensitivity and specificity. Sputum was decontaminated using NALC-NaOH, then auramine stain and the microscopic observation drug susceptibility (MODS) assay were performed. DNA was extracted using Roche Life Sciences' (Basel, Switzerland) High Pure PCR Template Preparation Kit (16 samples) or chelex (14 samples). RPA reactions were carried out using the TwistAmp® nfo kit (TwistDx Ltd., Cambridge, UK) according to the manufacturer's instructions, amplifying in a water bath at 37° C for 30 minutes. Results were read using PCRD lateral flow strips (Abingdon Health, York, UK). Sensitivity and specificity were calculated using 2x2 tables, with MODS as the gold standard. The RPA assay could detect concentrations of MTB genomic DNA as low as 1 pg/µL. Among the samples extracted with the chelex method, the sensitivity of RPA was 85.7% and specificity was 100%. Among those extracted with the Roche kit, RPA sensitivity was 83.3% and specificity was 90%. RPA seems to have good specificity and acceptable sensitivity and could be a viable alternative to PCR to evaluate suspected cases of TB where PCR is not available, especially as a rapid initial test to rule out TB. We plan on conducting a larger study to determine RPA's sensitivity and specificity more accurately, and to assess its performance in select sub-populations, such as HIV-positive patients.

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HEALTH FACILITIES IMPROVE UTILIZATION OF AMOXICILLIN TO MANAGE CHILDHOOD PNEUMONIA THROUGH DRUG USE EVALUATION IN ETHIOPIA

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Pneumonia leads among causes of under-five child mortality in Ethiopia, contributing to 18% of under-five deaths annually. Ethiopia's standard

treatment guidelines (STGs) recommend oral amoxicillin as first line treatment for non-severe pneumonia. However, prescribing practice and use of this antibiotic have not been aligned with STGs. Between 2019 and 2021, the USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project supported a drug use evaluation (DUE) at four major health facilities to assess STG adherence, identify causes for adherence gaps, and implement interventions. At each facility, GHSC-PSM used a DUE analysis tool to review 100 medical charts of children with pneumonia. The baseline DUEs showed amoxicillin was prescribed at correct dose and duration in 13%, 55%, 48%, and 43% (at each respective facility) of cases. Amoxicillin dispersible tablets (DT) were not prescribed despite availability at no cost, dosing advantages, and storage convenience. Staff at these facilities cited limited availability and inconsistent use of STGs, prescriber knowledge gaps (including on dosing), misperceptions on amoxicillin efficacy, and weak drug information services as reasons for poor STG adherence and low amoxicillin use. GHSC-PSM designed and implemented interventions based on the findings: disseminate DUE findings and STGs, post amoxicillin dosing charts in treatment areas, encourage prescription of and implement order sheets for amoxicillin DT, and conduct supportive supervision visits. Post-intervention DUEs at the four facilities (conducted after one year) indicated children appropriately treated with amoxicillin at the correct dose and duration improved by 73%, 26%, 52% and 40% at the respective facilities; and the prescribing practice of amoxicillin DT increased from zero at each facility to 12%, 14%, 41% and 45%, respectively. Conducting facility-specific DUEs and implementing data-based interventions are effective strategies to improve use of amoxicillin for management of childhood pneumonia and could be scaled-up to improve practices at other facilities across Ethiopia.

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THE DURATION OF PROTECTION AGAINST CLINICAL MALARIA PROVIDED BY THE COMBINATION OF SEASONAL RTS,S/AS01E VACCINATION AND SEASONAL MALARIA CHEMOPREVENTION, VERSUS EITHER INTERVENTION GIVEN ALONE

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Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine is now deployed at scale, but there remains a high burden of malaria in several countries with successful SMC programmes. A recent trial of 5,920 children in Burkina Faso and Mali showed that the combination of seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine and SMC was markedly more effective than either intervention given alone in preventing clinical malaria, severe malaria, and deaths from malaria. Data from the trial were reanalysed to estimate the duration of protection against clinical malaria provided by RTS,S/AS01$_E$ when deployed seasonally, and by SMC. Three methods were used (Piecewise Cox regression, Flexible Parametric Survival models and Smoothed Schoenfeld Residuals from Cox models) in order to confirm consistency of the estimated profile of protection using different statistical models. The overall protective efficacy from RTS,S/AS01$_E$ over 6 months was at least 60% following the primary series and the two seasonal booster doses. The profile of protective efficacy remained at a high level over the full malaria transmission season, before appearing to wane more rapidly in the early dry season. Protection from SMC was initially very high, but was not complete, even immediately post-administration. Efficacy begins to decline from approximately day 21, and then declines more sharply after day 28, indicating the importance of preserving the delivery interval for SMC cycles at a maximum of four weeks. Both interventions have high efficacy when administered seasonally. These results will help to optimise scheduling of the combined intervention of SMC and malaria vaccination in areas of seasonal transmission with differing epidemiology. These methods could be applied to other malaria control interventions to estimate duration of protection.

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NON-RANDOMIZED CONTROLLED TRIAL TO ASSESS THE PROTECTIVE EFFECTIVENESS OF FIVE CYCLES OF SULFADOXINE/PYRIMETHAMINE AND AMODIAQUINE FOR SEASONAL MALARIA CHEMOPREVENTION AMONG CHILDREN 3 TO 59 MONTHS, IN THE CONTEXT OF HIGH ANTIFOLATE AND AMINOQUINOLINE RESISTANCE, KARAMOJA REGION, UGANDA

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To date, due to widespread prevalence of markers associated with sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) resistance in east, central and southern regions of Africa, seasonal malaria chemoprevention (SMC) has not been scaled-up in these regions. This element of the study assessed the protective effectiveness of monthly administration of SPAQ to children aged 3 - 59 months in Karamoja region, where antifolate and aminoquinoline resistance are assumed to be high and malaria transmission is seasonal. A quasi-experimental non-randomized trial was conducted between May and September 2021, where children in two intervention districts received five monthly courses of SPAQ, whereas those in a control district did not receive SMC. A cohort of 200 children 3-59 months per district were selected and followed for five months for breakthrough confirmed malaria attacks. Malaria incidences among children in the two arms were compared. Molecular markers associated with resistance to SP (PfDHFR 164L, PfDHPS 581G, PfDHFR 51I, 59R, 108N, PfDHPS 437G and 540E) and AQ (PfCRT and PfMDR1) were analyzed on 300 samples from children 3-59 months with parasitaemia in both intervention and control districts. The malaria incidence rate was 3.0 and 38.8 per 100 person months in the intervention and control groups respectively. The incidence rate ratio was 0.078 (95% CI: 0.063 - 0.096), which corresponds to a protective effectiveness of 92% (95% CI: 90 - 94) among children in the intervention area. In the intervention areas 90% (361) of children never experienced any malaria episode, compared to 15% (29) in the control area. The prevalence of important resistance mutations associated with antifolate and aminoquilone anti-malaria drug resistance in the three districts was 0% for PfDHPS A581G, 95% for pfdhps-540E and 10% for CRT 76. Despite high prevalence of markers associated with antifolate resistance, SMC using SPAQ provided high protective effectiveness against malaria in the eligible age group of children in the Karamoja sub-region of Uganda.

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INTERMITTENT PREVENTIVE TREATMENT WITH DIHYDROARTEMISININ-PIPERAQUINE FOR THE PREVENTION OF MALARIA IN PREGNANCY: IMPLEMENTATION FEASIBILITY IN A ROUTINE HEALTHCARE SYSTEM SETTING IN WESTERN KENYA

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Malaria in pregnancy has devastating consequences for the mother and foetus. WHO recommends intermittent preventive treatment in pregnancy (IPTp) with sulphadoxine-pyrimethamine (SP) to prevent adverse birth outcomes, but high-level SP resistance threatens its efficacy. Dihydroartemisinin-piperaquine (DP) is the most promising candidate to either replace or be co-administered with SP for IPTp. Unlike SP, DP is a weight-based multiday regimen. It is critical to assess the feasibility of delivering IPTp-DP in routine healthcare settings to guide future policy on IPTp-DP. This study aimed to assess the health system's effectiveness in delivering IPTp-DP compared to IPTp-SP. We conducted a three-arm open-label cluster randomised trial in 15 antenatal care (ANC) clinics in western Kenya, involving a 10-month implementation phase (Nov 2019 to Sep 2020) and a 4-month evaluation phase (Sept-Dec 2020). The IPTp-SP control arm delivered SP as a standard single-day 3-tablet dose; the IPTp-DP arm delivered a standard 3-day course of 3 to 5 tablets per day based on body weight; IPTp-DP-Plus arm delivered the IPTp-DP alongside targeted information transfer. Delivery effectiveness, defined as women receiving the correct number of tablets and repeating the dosing instructions correctly, was assessed by trained fieldworkers using ANC exit interviews. We used generalised linear mixed models to assess predictors of delivery effectiveness. In total, 1189 exit interviews were done. Relative to IPTp-SP, IPTp-DP delivery effectiveness was 17% lower (71.9% vs 90.7%, aRR 0.83, 95% CI 0.75-0.93, p=0.001). The delivery effectiveness of IPTp-DP-Plus (81.2%) was similar to IPTp-SP (aRR 0.93, 0.85-1.01, p=0.070). The delivery effectiveness of IPTp-DP-Plus was 15% higher than IPTp-DP only (aRR 1.15, 1.02-1.29, p=0.019). Predictors of lower delivery effectiveness included facilities with clinical staff in ANC (aRR 0.93, 0.86-0.997, p=0.041) and pregnant women who visited multiple ANC clinics (aRR 0.93, 0.88-0.99, p=0.016). Targeted information transfer interventions can significantly boost the health system's effectiveness in delivering IPTp-DP.

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PERFORMANCE AND LONGEVITY OF SEVEN BRANDS OF LONG-LASTING INSECTICIDAL NETS (LLINS) UNDER VARIOUS FIELD CONDITIONS IN AFRICA, EXAMPLE OF BENIN AFTER THREE YEARS OF MONITORING

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Long-lasting insecticide-treated mosquito nets (LLINs) are important tool for malaria control. Durability, physical integrity, and bio-efficacy are key effectiveness variables of LLINs. The goal of this investigation was to determine the factors that impact the survival of seven brands of LLINs with different physical characteristics. A cohort consisting of 270 nets of each brand was studied semiannually from August 2017 to September 2020 in Zagnanado, Benin. Brands included PermaNet®2.0, PermaNet®3.0, OlysetNet®, Royal Sentry®, (with a reinforced border), and three nets with alternate specifications: DCT aspirational net (66g/m2 fabric weight, polyester, 150denier), DawaPlus®2.0 (40g/m2 fabric weight, polyester, 150denier), and Yorkool® (85 g/m2 fabric weight, polyester, 75denier). Globally, 330 LLINs of the 1,890 distributed were found at 36 months post-utilization. The total LLINs attrition rate was 82.5%. The main reasons of those that were loss were movement (52.9%), accidental tears (38.7%), and repurposing (8.4%) (p<0.001) with a significant difference between the different brands of LLINs (p=0.04). The median proportionate hole index (pHI) ranged from 25 to 221 with a significantly lower pHI for PermaNet®3.0 compared to the Yorkool® (P<0.05). After 36 months of use, 78.6% were in good condition (0≤pHI≤64), 14.6% were damaged (65≤pHI≤642) and 6.8% were too torn (pHI≥643). A significant decrease in the physical survivorship of LLINs (all brands) was observed at 36 months (25.7%, range 23.3-28.2%) compared to 6 months (91.8%, range 90.5-92.9%) (p<0.001). The bio-efficacy of LLINs after 2 years was greater than 70% in mosquito mortality. The decrease in LLINs survivorship during this study underlines the necessity of developing and implementing new strategies to manage this important vector control tool.

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COST-EFFECTIVENESS OF COMMUNITY-BASED DISTRIBUTION OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY

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Malaria in pregnancy is a major health problem in sub-Saharan Africa (SSA). Since 2012, the World Health Organization (WHO) recommends the administration of intermittent preventive treatment (IPTp) at the antenatal care visits (ANC), to start in the second trimester and until delivery. Despite being a very cost-effective strategy, coverages of IPTp are suboptimal.IPTp delivery through community health workers (CHW) has been identified as an effective strategy to increase coverage and improve health outcomes at low incremental costs for the health system. Recently, the TIPTOP project aimed to explore the impact of a community-based approach for IPTp delivery (C-IPTp) in rural areas in Democratic Republic of Congo (DRC), Madagascar (MDG), Mozambique (MOZ), and Nigeria (NGA). Using the evidence generated by the TIPTOP project, we estimated costs, effects, and cost-effectiveness of C-IPTp. Delivery costs were calculated following two alternative approaches: (i) the evidence generated from TIPTOP project; (ii) an approximation to costs in programmatic mode (i.e. implementation costs by the government). We estimated disability-adjusted-life-years (DALYs) associated with clinical malaria, anaemia at delivery, low birthweight (LBW) and neonatal mortality. The net incremental cost of c-IPTp were $6,138-$47,177 (DRC), $5,552-$31,552 (MDG), $10,202-$53,221 (MOZ) and $667-$28,645 (NGA) per 1,000 pregnant women, and the intervention averted a total of 396 (DRC), 591 (MDG), 98 (MOZ) and 435 (NGA) DALYs. Resulting incremental cost-effectiveness ratios (ICER) ranged between $15-$119 (DRC), $9-$53 (MDG), $104-$543 (MOZ) and $2-$66 (NGA) per DALY averted. Results remained robust to sensitivity analysis, with ICERs below the standard cost-effectiveness thresholds based on 3 times the gross domestic product (GDP) per capita. This study showed that C-IPTp may be a cost-effective intervention when incorporated into governmental programs. These findings are essential to guide policymakers in the decision on whether to prioritize investments to scale up C-IPTp and should serve as a guide for WHO policy recommendations.

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MULTI-COUNTRY REVIEW OF ITN ROUTINE DISTRIBUTION DATA: ARE ANC AND EPI CHANNELS ACHIEVING THEIR POTENTIAL?

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In many sub-Saharan African countries, routine distribution of ITNs through ANC and EPI has been the backbone of continuous distribution (CD) since 2007, when WHO RBM guidelines recommended CD of ITNs to complement mass campaigns. According to the 2020 WHO World Malaria Report, 28 of the 38 African countries that distribute ITNs through ANC also distribute through EPI. A 2019 review by Theiss-Nyland et al found that, in countries with ANC and EPI distribution, an average of 54% of children slept under an ITN, versus 34% with only ANC and 24% with no facility-based distribution. However, in contrast to mass campaigns, CD channel performance is rarely monitored at the national or global level. The PMI VectorLink project reached out to National Malaria Programs in several countries to compile and analyze ANC and EPI ITN issuing data from the national HMIS and conduct assessments of routine distribution channels. Primary metrics examined were the percentage of pregnant women attending ANC and children attending EPI who were issued an ITN. Key informant interviews were conducted at multiple levels to examine forecasting, quantification, logistics, last mile delivery, financing, and data collection and use. ITN issuage varied greatly across countries and channels. The percent of women receiving an ITN at ANC ranged from 25-91%, while the percent of children receiving an ITN through EPI ranged from 27-88%. Large differences were observed between channels, even within the same country. In one country, 89% of pregnant women received an ITN through ANC while only 40% of children received a net through EPI. Key findings from the assessments carried out in five countries revealed that ITN stock was inconsistently available and sometimes inadequate and that CD guidelines were either not available or out of date. These findings enable countries to better understand the contextualized successes and issues within their health system to support strong routine distribution of ITNs. They also highlight key areas for increased focus and resourcing at the global level. Future analyses will include insights from available supervision data of routine ITN distribution.

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SYSTEMATIC REVIEW AND META-ANALYSIS OF SEASONAL MALARIA CHEMOPREVENTION ON MALARIA INCIDENCE

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Seasonal malaria chemoprevention (SMC) aims to prevent malaria in children aged 3-59 months in highly seasonal malaria transmission areas using up to four monthly courses of amodiaquine plus sulfadoxine-pyrimethamine (SP+AQ) beginning at the start of the transmission season. However, many countries are interested in using different antimalarials, expanding age groups, and increasing the number of courses. We conducted a systematic review of the protective efficacy of full monthly treatment courses of antimalarials administered during the transmission season in children up to 15 years, stratified by age < 5 years (younger) and ≥ 5 years (older). The primary outcome was incidence of laboratory-confirmed uncomplicated malaria, with secondary outcomes of malaria and anemia prevalence, and incidence of severe malaria, all-cause hospitalization, and all-cause mortality. Following literature search (1998 studies), title and abstract screening and full text review by two independent reviewers, 12 eligible randomized controlled trials were included in meta-analyses. We assessed risk of bias and used GRADE definitions of certainty of evidence (CoE) to grade the quality of evidence for outcomes. Risk of bias was low for nine and moderate for three included studies. Risk reductions in malaria incidence were associated with three to four cycles of SP+AQ among younger children (RR: 0.28, 95% CI 0.26-0.31) and older children (RR: 0.39 (95% CI 0.35-0.44), with larger risk reductions for five to six cycles of AQ+SP among younger children (RR: 0.22, 95% CI 0.18-0.25) and among older children (RR: 0.17, 95% CI 0.15-0.20). Among the two studies that reported outcomes separately by children <5 years and ≥ 5 years, there was no difference in RR by age group. CoE was rated moderate for these outcomes. The risk reduction in the incidence of uncomplicated malaria among children older than five years receiving SMC is comparable to that of children under five years. Children receiving five to six cycles of SP+AQ have a greater risk reduction in the incidence of malaria than those who receive three to five years of four cycles. Secondary outcomes will also be presented.

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SARS-COV-2 SPIKE TRIGGERS BARRIER DYSFUNCTION AND VASCULAR LEAK VIA INTEGRINS AND TGF-B SIGNALING

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Severe COVID-19 is associated with epithelial and endothelial barrier dysfunction within the lung as well as in distal organs. While it is appreciated that an exaggerated inflammatory response is associated with barrier dysfunction, the triggers of this pathology are unclear. Here, we report that the Spike (S) glycoprotein of SARS-CoV-2 is sufficient to trigger epithelial/endothelial barrier dysfunction. We found that S-treated barrier cells displayed a disrupted glycocalyx layer as well as an upregulation of enzymes responsible for degrading key cell surface glycans. This phenotype was apparent for both soluble and virion-associated S. Further, we found that administration of SARS-CoV-2 S into the lungs of mice is sufficient to cause systemic vascular leak. To understand the mechanism(s) by which S triggers barrier dysfunction, we conducted RNA-seq analyses of S-treated endothelial cells and identified a transcriptional response associated with extracellular matrix reorganization and TGF-β signaling, which was independent of ACE2 expression. Using genetic knockouts and specific inhibitors, we demonstrated that glycosaminoglycans, integrins, and the TGF-β signaling axis are required for S-mediated barrier dysfunction *in vitro* and *in vivo*. Further, we found that S treatment of barrier cells is associated with enhanced release of TGF-β into the extracellular space. Finally, we demonstrate that TGF-β is sufficient to trigger barrier dysfunction. Altogether, our study provides a model in which S engages glycans and integrins on the surface of barrier cells, which in turn triggers the release of TGF-β, whose engagement with the TGFβ receptor induces barrier dysfunction. As high levels of TGF-β are a clinical correlate of COVID-19 severity, our study suggests that interaction between S and barrier cells in COVID-19 patients is a contributing factor to vascular leak. Ultimately, our mechanistic study provides a starting point for development of therapies targeting S-mediated vascular leak.

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BASELINE NATURAL KILLER CELL FREQUENCIES ARE GREATER IN INDIVIDUALS WITH ASYMPTOMATIC SARS-COV-2 INFECTION COMPARED TO THOSE THAT DEVELOP SYMPTOMATIC ILLNESS

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As NK cells are critical for control of viral infections, we tested the hypothesis that individuals with asymptomatic SARS-CoV-2 infection have greater NK cell frequencies prior to infection than individuals with symptomatic infection. Participants were marine recruits that elected to participate in the COVID-19 Health Action Response for Marines (CHARM) study. Participants were prospectively followed for two months with twice weekly symptom questionnaires and PCR testing for SARS-CoV-2 infection. Peripheral blood mononuclear cells obtained prior to infection and at various time points post-infection from 47 participants diagnosed with asymptomatic infection and 49 with symptomatic infection were analyzed by multicolor flow cytometry for frequencies of total NK cells, NK cell subsets, and surface expression of activating and inhibitory receptors. Consistent with our hypothesis, frequencies of total ($CD3^-CD14^-CD19^-CD56^+$) NK cells were significantly greater at baseline in asymptomatic vs symptomatic individuals (10.38% vs 8.28%, p = 0.015). This difference was due to increased frequencies of mature ($CD56^{dim}CD16^+$) NK cells in asymptomatic individuals (76.3% vs 69.8 %, p = 0.049). No differences were observed in baseline frequencies of immature ($CD56^{bright}CD16^-$) or adaptive ($CD56^{dim}CD16^+NKG2C^+CD57^+$) NK cells, or in surface expression of activating (NKG2C, NKG2D) or inhibitory (NKG2A, KIR2DL1, KIR2DL2/L3/S2, KIR3DL1) receptors. Frequencies of total and mature NK cells decreased significantly post-infection, reaching a nadir at 3-4 weeks. In contrast, frequencies of immature NK cells increased by 4 weeks. These results suggest that NK cells may play a protective role against symptomatic SARS-CoV-2 infection.

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RECENT MALARIA DOES NOT IMPACT COVID-19 ANTIBODY RESPONSE OR RATES OF SYMPTOMATIC SEROCONVERSION IN COMMUNITIES WITH HIGH MALARIA AND COVID-19 TRANSMISSION, MALI, WEST AFRICA

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Malaria has been hypothesized as a factor that may have reduced the severity of the COVID-19 pandemic in sub-Saharan Africa. To evaluate the effect of recent malaria on COVID-19 we assessed a subgroup of individuals participating in a longitudinal cohort COVID-19 serosurvey that were also undergoing intensive malaria monitoring during the 2020 transmission season in Mali. In 1314 individuals, 711 had intercurrent malaria, 442 were symptomatic with clinical malaria and 269 had asymptomatic parasitemia. Intercurrent malaria was not associated with new COVID-19 seroconversion (29.7% (211/711) vs. 30.0% (181/603), p=0.9038) or with rates of reported symptomatic seroconversion during the malaria transmission season. In the subsequent dry season, prior malaria was not associated with new COVID-19 seroconversion (22.0% (133/605) vs. 22.1% (108/488), p>0.9999), with symptomatic seroconversion, or with reversion from seropositive to seronegative (prior malaria: 36.2% (64/177) vs. no malaria: 30.1% (37/119), p=0.3842). In communities with intense seasonal malaria and a high incidence of primarily asymptomatic or mild COVID-19, we did not demonstrate a relationship between recent malaria and subsequent response to COVID-19. Any effect of malaria on COVID-19 epidemiology may be related to cumulative lifetime exposure rather than recent infection, or modulation of more severe COVID-19.

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MATERNAL BREAST MILK SECRETOR PHENOTYPE DOES NOT AFFECT INFANT SUSCEPTIBILITY TO ROTAVIRUS DIARRHEA

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Rotavirus (RV) is the leading cause of diarrhea among infants worldwide. For multiple reasons, available oral vaccines underperform in resource-limited settings. We have previously shown that infants born to maternal non-secretors demonstrated significantly increased rates of antibody seroconversion post-vaccination. We hypothesized these infants would thereby demonstrate increased protection from RV diarrhea (RVD). To test this, we explored the effect of maternal breast milk secretor status on infant RVD risk among mother-infant dyads in PROVIDE, a Rotarix vaccine trial conducted among infants in Bangladesh. Secretor phenotyping was performed on stored breast milk samples by EIA. Episodes of RVD were detected through age 2 via active community diarrheal surveillance; diarrheal specimens were tested using RV stool antigen EIA. We performed multivariable logistic regression among vaccinated and unvaccinated infants, controlling for multiple covariates previously determined to be associated with RVD risk. Among 227 unvaccinated maternal-infants dyads with evaluable data, maternal non-secretor status was not associated with RVD risk through year 1 (OR 1.332, 95% CI 0.699-2.540) or year 2 (OR 0.858, 95% CI 0.465-1.583). Among 216 vaccinated maternal-infant dyads with evaluable data, maternal non-secretor status was not associated with RVD diarrhea risk through 1 (OR 0.943, 95% CI 0.376-2.367) or 2 year (OR 1.406, 95% CI 0.658-3.005). No differences were observed when vaccine seroconversion was excluded from the model, suggesting that any effect of maternal secretor phenotype was not mediated by seroconversion. Although infants born to maternal non-secretors had increased rates of seroconversion following oral RV vaccination, this did not translate into improved protection against RVD. These data highlight the limitations of immunogenicity assessments alone when evaluating vaccine performance and the need for improved RV vaccines to further combat pediatric diarrhea.

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SAFETY AND IMMUNOGENICITY FROM A PHASE I CLINICAL TRIAL OF THE RIFT VALLEY FEVER VACCINE, CHADOX1 RVF, IN UK ADULTS

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Rift Valley fever virus (RVFV), a mosquito-borne RNA virus, causes disease and death in both livestock and humans, primarily in Africa. For humans, there are currently no licensed RVF vaccines and with significant potential for much larger outbreaks, even pandemics, it is included on the World

Health Organization's list of priority pathogens for urgent research into countermeasures. Neutralizing antibodies targeting the surface glycoproteins, Gn and Gc, are associated with protection against RVFV in animals and inducing them safely is a critical goal of vaccination. ChAdOx1 RVF is a replication-deficient viral-vectored vaccine expressing RVFV Gn and Gc. It has been co-developed for use in both livestock and humans, with high levels of protection demonstrated against RVFV infection in multiple livestock species. We have now evaluated ChAdOx1 RVF in humans in a phase I clinical trial in Oxford, UK and will present the safety and immunogenicity data from this trial. Briefly, 15 healthy UK adults were vaccinated with $5x10^9$, $2.5x10^{10}$ or $5x10^{10}$ VP of vaccine. The vaccine was safe and well tolerated, and we have measured the humoral and cellular response in these volunteers up to three months post-vaccination. ChAdOx1 RVF induced a dose-dependent immune response, with all volunteers in the $2.5x10^{10}$ and $5x10^{10}$ dose groups seroconverting for RVFV neutralizing antibodies, a key attribute associated with protection. High titers of binding IgG targeting Gc were detected while those targeting Gn were low. A strong IFNγ T cell response was also elicited in all $2.5x10^{10}$ and $5x10^{10}$ dose group volunteers, peaking at 2 weeks post-vaccine and remaining above baseline 3 months later. This is the first viral vectored RVF vaccine to be trialed in humans and has demonstrated strong immunogenicity after a single dose. The COVID-19 pandemic has demonstrated that a ChAdOx1 vaccine can be manufactured cheaply and at scale. Together with its established efficacy in livestock, ChAdOx1 RVF vaccine could become a crucial tool to mitigate against the burden of RVF disease, as part of a One Health vaccine strategy in humans and livestock.

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CYTOMEGALOVIRUS ASSOCIATED DEATHS: CASE REPORTS FROM KENYA AND MOZAMBIQUE'S CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE NETWORK (CHAMPS) PROGRAM

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Cytomegalovirus (CMV) is a frequent cause of congenital infections worldwide and an important cause of neurodevelopmental disabilities in children. There are limited data on CMV as a cause of death in children. We describe CMV infection among stillbirths and child deaths (0-59 months) enrolled in two Child Health and Mortality Prevention Surveillance (CHAMPS) Network sites: Kenya and Mozambique. CHAMPS is a multi-country program that systematically identifies causes of stillbirths and under-five mortality from defined catchment areas. Between May 2017 and December 2021, underlying, comorbid, and immediate causes of death (COD) were determined by a panel of experts for 1051 children (551 in Kenya and 500 in Mozambique) using data from post-mortem minimally invasive tissue specimen testing, clinical records, and verbal autopsy. Nearly 4% of children had CMV infection in their underlying or comorbid conditions causing death: 25 (4.5%) in Kenya and 14 (2.8%) in Mozambique. Of these, 20 (51%) were infants, 9 (23%) children (12-60 months), 8 (21%) stillbirths and 2 (5%) neonates. Twenty-six (67%) children died in the hospital and 13 (33%) in the community. Twenty-four (61%) children had CMV as immediate or comorbid COD, 10 (26%) as underlying COD and 5 (13%) as other significant or contributory condition. Twenty-three of 24 (96%) children with CMV as their immediate COD had another pre-existing condition that likely increased its risk of acquisition or severity, including HIV infection (52%), malnutrition (29%), and low birthweight/prematurity (13%). The immediate COD of the 10 children who had CMV as underlying COD were sepsis (20%) and perinatal hypoxia/asphyxia (10%); 7 (70%) had no other COD. None of the deaths had a diagnosis of CMV infection ante-mortem. CHAMPS revealed CMV infection—associated pediatric deaths that would have otherwise been unreported. Malnutrition, low birthweight/prematurity, and HIV infection/disease are markers of a child at higher risk of dying from CMV infection. A high index of clinical suspicion and routine clinical audits of child deaths could be encouraged to identify, treat, and prevent CMV associated deaths.

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NON-HUMAN PRIMATES REPLICATE CONSERVED HUMAN RESPONSES TO RNA VIRAL INFECTIONS, WITH VIRAL FAMILY-ASSOCIATED DIFFERENCES IN RESPONSE DYNAMICS

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In the 21st century, a number of epidemic and pandemic viruses have emerged, with the most recent being the ongoing SARS-CoV-2-driven pandemic. The next pandemic virus is difficult to predict; however, RNA viruses make up to an estimated 44% of all emerging infectious diseases. While non-human primate (NHP) models play a critical role in understanding viral disease pathogenesis, their broad translatability across human RNA viral infections remains to be further explored. Previously, we discovered a conserved human panviral signature able to not only discern viral infections from healthy responses, but also predict disease severity. Here, we analyzed blood transcriptomic data from 19 challenge studies across Flaviviridae, Filoviridae, Orthomyxoviridae, Coronaviridae and Arenaviridae viral infections and 213 macaques to show that our human-derived panviral signature is also conserved in NHPs, robustly distinguishing RNA viral infections irrespective of the biological, clinical and technical heterogeneity. Longitudinal analysis of viral challenge studies identified distinct signature dynamics of NHP infection responses by viral family: Orthomyxoviridae and Coronaviridae infections induce signatures that peak 1-2 days post-infection while Arenaviridae and Filoviridae infection responses continue to rise past 6-7 days post-infection. We also confirm virus differences in human response dynamics across influenza, rhinovirus and respiratory-syncytial virus infections. Finally, we demonstrate that the strength of this panviral response correlates with known viral pathogenicity and is driven by myeloid cells. Together, our findings elucidate differences in conserved panviral response dynamics by virus in NHPs that both support NHPs as robust models for human RNA viral infections and also inform the design of future NHP viral challenge studies for studying current, emerging, and re-emerging RNA viruses.

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TEST COVERAGE AND PREVALENCE OF HIV, HEPATITIS B VIRUS AND SYPHILIS AMONG PREGNANT WOMEN IN NORTH SHEWA ZONE, ETHIOPIA

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HIV, hepatitis B virus(HBV) and syphilis among pregnant women are major public health problems in low-and middle-income countries due to their effect on maternal health and potential vertical transmission to the fetus resulting in adverse pregnancy and neonatal outcomes. Ethiopia has adopted the triple elimination of mother to child transmission(EMTCT) strategy developed by the world health organization. The EMTCT strategy

has program targets which include a coverage of HIV and syphilis testing of >95% and Hepatitis B surface antigen (HBsAg) testing >90%. Accordingly, HIV, HBSAg and syphilis tests are being offered to all pregnant women at their first antenatal care (ANC) contact. We conducted an analysis of the test coverage and positivity rate among pregnant women at their first ANC contact in the Birhan pregnancy and birth cohort study located in North Shewa zone of Ethiopia. Clinical and epidemiological data were collected during their facility visits for ANC. A total of 1230 pregnant women enrolled starting from their first ANC booking were included. Their mean age was 27.5+6.1 years, mean gestational age was 18.5+0.2 weeks and the majority (78.0%) were rural residents. The test coverage for the HIV, HBV and syphilis were 1136 (92.4%), 967(78.6%) and 1068(86.8%) respectively. The positivity rate for HIV, HBV and syphilis were 13(1.1%), 10(1.0%) and 35(3.3%) respectively. There were five cases of HBV and syphilis coinfection. Our study showed that the test coverage for all three infections were below the recommended targets. The reason behind the low test coverage must be explored and addressed urgently. The positivity rate for HIV and HBV are much lower than previous national estimates of 5.7% and 4.8% respectively. This may be due to the predominantly rural composition of our population and the progressively declining rate of these infections as demonstrated in previous trend analysis. The syphilis positivity rate is higher than the previous national estimate of 1.1% and requires special attention. More emphasis should be given to the syphilis testing and treatment program to avoid the complications related with congenital syphilis.

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PREVALENCE OF CURABLE SEXUALLY TRANSMITTED AND REPRODUCTIVE TRACT INFECTIONS AMONG PREGNANT WOMEN IN KENYA, MALAWI, AND TANZANIA, 2017-20

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Curable sexually transmitted and reproductive tract infections (STIs/RTIs) - syphilis, gonorrhoea, chlamydia, trichomoniasis, and bacterial vaginosis (BV) - are important causes of adverse pregnancy outcomes. Universal screening of pregnant women for syphilis at antenatal care (ANC) booking is recommended. Syndromic case management is used in low-resource areas to diagnose and treat gonorrhoea, chlamydia, trichomoniasis, and BV. However, because curable STIs/RTIs are often asymptomatic among women, syndromic-based algorithms fail to identify 70-80% of gonococcal and chlamydial infections, and 60-70% of trichomoniasis and BV cases. A malaria chemoprevention trial in Kenya, Malawi, and Tanzania enrolled 4,680 pregnant women who provided blood for rapid plasma reagin (RPR) testing at first ANC; RPR-positive samples were tested by *Treponema pallidum* particle agglutination to confirm diagnosis. A random subgroup provided vaginal swabs for gonorrhoea, chlamydia, and trichomoniasis testing by polymerase chain reaction, and BV diagnosis by Nugent Score 7-10. Overall, 1.7% (95%CI: 1.4, 2.2; 79/4,569) had syphilis, 2.7% (95%CI: 1.9, 3.6; 38/1,431) had gonorrhoea, 13.8% (95%CI: 12.1, 15.7; 198/1,431) had chlamydia, 14.4% (95%CI: 12.7, 16.3; 206/1,431) had trichomoniasis, and 28.5% were positive for BV (95%CI: 26.2, 30.9; 399/1,402). Prevalence varied by gravidity (paucigravidae (G1/2) vs multigravidae (G3+)) as follows: syphilis 1.3% (95%CI: 0.90, 1.8) vs 2.3% (95%CI: 1.7, 3.1); gonorrhoea 3.8% (95%CI: 2.6, 5.3) vs 1.4% (95%CI: 0.7, 2.7); chlamydia 17.5% (95%CI: 15.0, 20.3) vs 9.5% (95%CI: 7.5, 12.0); and BV 31.1% (95%CI: 28.0, 34.5) vs 25.0% (95%CI: 21.8, 28.6). Of 1,474 women tested for more than one STI/RTI, 148 (10.0%) were co-infected with two or more curable STIs/RTIs. Curable STIs/RTIs were common among pregnant women, especially chlamydia and BV among paucigravidae; co-infection was common across all gravidities. Alternative approaches to syndromic management are urgently needed given the high prevalence of STIs/RTIs, their tendency to be asymptomatic, and associations with adverse pregnancy outcomes.

1798

EFFECTS OF MATERNAL INTRAVENOUS IRON TREATMENT DURING PREGNANCY ON CHILD MORBIDITY IN THE FIRST POSTPARTUM YEAR IN MALAWI: A RANDOMIZED CONTROLLED TRIAL

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Child morbidity and mortality in low- and middle-income countries (LMICs) is mainly driven by infectious diseases. Better iron status in children has been associated with increased infectious disease risk including pneumonia, diarrhea and malaria. Improved maternal iron status during pregnancy leads to better iron status of children especially in the first year postpartum. Intravenous (IV) iron significantly improves iron status and is rapidly replacing oral iron for the treatment of anaemia during pregnancy. Studies have reported better iron status in children of mothers who received IV iron during pregnancy leading to concerns that children born to iron replete mothers enhanced by IV iron, could be at a greater risk of infectious disease morbidity and mortality. Our aim was to determine whether children born to Malawian mothers who received IV iron during pregnancy have increased risk to morbidity in the first postpartum year. In a randomized clinical trial comparing IV to oral iron for treatment of anaemia in pregnancy (ACTRN12618001268235), we hypothesized that IV iron use during pregnancy would not increase the risk to infectious diseases in infants in the first postpartum year. We followed up infants for all their medical care in a dedicated study clinic and conducted routine clinical and laboratory assessments every 3 months. The primary outcome was incidence of malaria, diarrhea or respiratory tract infections. From preliminary results, mean ferritin was higher amongst infants born to mothers randomized to IV iron compared to oral iron across the time points, but the difference was statistically insignificant. Overall, the incidence of disease was lower amongst infants born to mothers randomized to IV iron compared to oral iron, but the difference was not statistically significant (1.81 versus 1.92 per person-year, incidence rate ratio (IRR) 0.76 [95% CI: 0.4-1.45]) p = 0.79. Thus, there was no evidence of a difference infection risk during infancy in infants born to mothers who received IV iron compared to oral iron during pregnancy.

1799

BARRIERS TO ACCESS, SUPPLY AND DEMAND FOR CHILD IMMUNIZATION SERVICES AMONG CAREGIVERS OF CHILDREN UNDER FIVE YEARS IN WAJIR, MANDERA AND KIBRA COUNTIES, KENYA

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In Kenya, 30% of children are not fully protected against vaccine-preventable diseases by the age of one year. Both Mandera and Wajir counties are among the 10 poorest and least-developed counties in Kenya, having low child immunization coverage rate in the country (72.8% and 64.6% respectively). Kibra is the largest urban informal settlement in Kenya having only 45% fully immunized children at 12 months of age. We conducted a barrier analysis study in 2020 to explore socio-cultural norms and practices, and structural and financial barriers affecting access, supply and demand for immunization services in these 3 counties. We

collected both primary (quantitative and qualitative data) and secondary data for this cross-sectional study. In addition to desk review of relevant available documents, we conducted 1,417 interviews and 5 Focus Group Discussions with mothers of under 5 children and community health volunteers (CHVs) and had 6 key informant interviews with Ministry of Health (MoH) managers at national, county and sub-county level and community leaders. The identified major barriers to immunization service delivery at health facilities included lack of proper infrastructure, vaccine transport and commodities (shortage of syringes, safety boxes), lack of training, supportive supervision and mentorship for vaccinators and the highly mobile and migratory population in the catchment areas. The reasons for not having the children fully immunized included unavailability of vaccine and vaccinator at the facility, long distances, lack of time and lack of transportation. Although public health facilities offer free services, caregivers in Mandera (21%), Kibra (27%) and Wajir (25%) reportedly paid fees for consultation, laboratory testing, and drugs. These findings led us to plan to support MoH in capacity building and field supervision of CHVs, and for improving functionality of health facilities and outreach sites to deliver immunization services. We also developed a social and behavioral change communication plan to strengthen community acceptance and commitment by health workers for improved immunization services.

1800

PREVALENCE AND CORRELATES OF PEDIATRIC INPATIENT GUIDELINE NON-ADHERENCE FOR INITIAL MANAGEMENT OF COMMON CONDITIONS IN SIX LOW AND MIDDLE-INCOME COUNTRIES

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Despite evidence that adherence to guidelines for childhood illnesses can reduce mortality, adherence is often inconsistent. Adherence is influenced by multilevel factors that are often outside the control of the providers and, at times, purposeful (e.g., prescribing antibiotics according to local sensitivity pattern). This study evaluated the prevalence and correlates for guideline non-adherence for common childhood illnesses in low-resource settings. Data from 2,796 hospitalizations of children aged 2-23 months across eight facilities and six countries were used. We identified children who were treated with full, partial, or non-adherence according to site-specific standard-of-care guidelines for pneumonia, diarrhea, and severe acute malnutrition (SAM) within the first 24 hours of admission. Correlates for guideline non-adherence were identified using generalized estimating equations and reported as odds ratio (OR). Fully adherent care was delivered to 32% of the children admitted with diarrhea, 38% of children with pneumonia, and 28% of children with SAM when a strict definition of adherence was applied. Non-adherence to recommendations was common for oxygen and antibiotics for pneumonia; fluid, zinc, and antibiotics for diarrhea; and vitamin A and zinc for SAM. Non-adherence varied by site. Pneumonia guideline non-adherence was more likely among patients with severe disease (OR:1.82; 95% CI:1.38, 2.34), lower asset quintile groups (OR:1.16; 95% CI:1.35, 1.01), older children (OR:1.10; 95% CI:1.06, 1.13) and presenting as wasted (OR:6.44; 95% CI:4.33, 9.57) compared to those without severe disease, with higher assets, younger age, and not wasted. For SAM, guideline non-adherence was less likely when children had a history of losing weight or not gaining weight (OR:0.73; 95% CI: 0.57, 0.97) compared to their counterparts. Non-adherence to pediatric guidelines was common for specific recommendations and associated with older age, disease severity and comorbidities, and lower household economic status. This information should be used to improve guidelines and support clinicians in challenging treatment scenarios.

1801

MACHINE LEARNING-BASED PREDICTION OF CLINICAL OUTCOMES FOR CHILDREN USING LINKED ELECTRONIC HEALTH RECORDS IN MANHIÇA DISTRICT, MOZAMBIQUE

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The increasing availability of individual-level electronic health records (EHR) presents a major opportunity to understand the epidemiology of childhood illnesses but also the early identification of children at high-risk of severe disease and mortality. Predictive machine learning (ML) algorithms have been used with large HER datasets to identify the vital clinical and laboratory data to identify high-risk individuals and aid their management. ML methods result in algorithms that can identify the key patterns in large complex datasets, which may otherwise be hard to detect by traditional regression methods or by health care workers in clinical settings. However, many ML studies have been conducted in high-income populations and lack detailed pre-admission health and demographic data which has constrained their development in resource poor settings. We applied ML algorithms to identify high-risk groups and predict outcomes using three large population-level datasets from Manhiça District, Mozambique; a longitudinal child morbidity surveillance study, a demographic surveillance system (DSS) and a fever aetiology study (FIEBRE) for children under 15 years. Child out-and inpatient data were collected for 1,384,354 hospital visits between January 1997 and October 2020. These data included; medical history, physical examination, laboratory samples, diagnosis and health outcomes. These data were linked with a unique ID to the DSS which monitors a population of 201,845 bi-annually. These data include socio-economic position, immunisation history, pregnancies and use of malaria control interventions. We applied a standard set of ML classification algorithms to predict; a) admissions, b) length of stay (<72 or ≥72 hours) and c) mortality. For all visits, the median age was 3.3 (IQR 1.3-7.2) years and 49% were female, 1,315,628 were outpatients and 68,726 were inpatients, with a median length of stay of 3 days (IQR 2-5) and 4% inpatient mortality. We aim to present ML algorithms that identify the clinical and demographic data needed for early identification of high-risk groups which predict child outcomes in resource-limited settings.

1802

AGE- AND HEIGHT-BASED APPROACHES TO SIMPLIFY DOSING OF ORAL AZITHROMYCIN FOR CHILDREN 1-11 MONTHS OLD IN MASS DISTRIBUTION PROGRAMS FOR CHILD SURVIVAL

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Trachoma control programs determine azithromycin dose during mass drug administration (MDA) by height rather than weight for children ages 6 months to 15 years. World Health Organization guidelines on azithromycin distribution for child survival target children 1-11 months

old in high mortality settings. Studies on the impact of azithromycin MDA on child mortality used weight-based dosing in 1-5 month olds and the height-based approach in older children. A simplified age- or height-based approach for all 1-11 month olds could improve speed and efficiency of programs distributing azithromycin for child survival. Using data from two cluster-randomized trials on azithromycin distribution and child mortality in Niger and Burkina Faso, we developed an exhaustive search algorithm to determine optimal dose for different age groups. Conservative tolerance limits were chosen to define accuracy, with limits of 10-20 mg/kg for 1-2 month olds and 15-30 mg/kg for 3-11 month olds. We evaluated height by comparing doses that would be received using the existing trachoma dosing pole in 1-5 month olds as well as by another exhaustive search. The algorithm found that a two-tiered age-based approach with a dose of 2 ml for 1-2 month olds and 4 ml for children 3-11 month olds would result in 90-93% accuracy in both settings. The optimal three-tiered approach resulted in similar accuracy, with doses of 2, 3, and 4 ml for children 1-2, 3, and 4-11 months old respectively, resulting in 91-94% of doses within tolerance limits. Using the existing height pole with 1-5 month olds resulted in 70% doses within tolerance limits. With the exhaustive search for height, accuracy was 94% with a dose of 3 ml for children ≤ 60 cm and 4 ml for children > 60 cm (15/30 mg/kg tolerance limits). Implementation of height-based dosing for 1-5 month olds would require additional logistical work to revise the existing dosing pole and considerable training on measuring infants lying flat on their backs. Overall, the two-tiered age-based approach is preferable as it resulted in high accuracy while addressing concerns about overdosing in this young population and the ease of operations in field settings.

1803

MOVING AWAY FROM VERTICAL INTERVENTIONS: PROJECTION AND COST-EFFECTIVENESS OF VARIOUS SLEEPING SICKNESS CONTROL STRATEGIES IN CÔTE D'IVOIRE

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In 2020, Cote d'Ivoire was validated by the WHO as having eliminated *gambiense* human African trypanosomiasis (gHAT, sleeping sickness) as a public health problem, thanks to efforts by the national elimination programme and their implementing partners. Despite this, HAT control activities should be continued to reduce the remaining burden of the disease and verify interruption of transmission. In this study we use a dynamic transmission model for gHAT fitted to historical data for four endemic health districts of Côte d'Ivoire to quantitatively assess the reduction in transmission from 2000-2021. We then examine what could be the forthcoming trajectory for gHAT, focusing on various HAT control interventions, particularly those that can be integrated into the broader healthcare system. Projected costs are simulated using a model parameterised by cost and resource use data collected as part of ongoing strategies in Côte d'Ivoire, including costs for passive surveillance and active screening. Cost-effectiveness is calculated by combining these cost projections with outputs of disease burden from our compartmental transmission model using a modified net monetary benefit framework. We select a range of gHAT control strategies, discuss their feasibility, and analyse their cost-effectiveness with an aim to providing policy recommendations to guide future strategy in each location, accounting for a potential human and animal reservoir of *Trypanosoma brucei gambiense*. Our model shows a strong decline in the underlying transmission of gHAT in Côte d'Ivoire in line with the fall in the number of reported cases during 2000-2021, despite a reduction in screening activity. In all four endemic health districts the model suggests that transmission may have already been interrupted through a combination of passive and active screening, complemented by vector control in 2 health districts. Residual cases may be reported in the next few years due to historical transmission.

1804

ESTIMATING THE PROPORTION OF RELAPSE FOLLOWING TREATMENT OF VISCERAL LEISHMANIASIS (VL): META-ANALYSIS USING INFECTIOUS DISEASES DATA OBSERVATORY (IDDO) LIVING SYSTEMATIC REVIEW

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In Visceral Leishmaniasis (VL) clinical trials, the conventional follow-up period to capture relapse is 6-months. Relapses after 6-months have been reported in observational studies suggesting a longer follow-up may be warranted. A meta-analysis was carried out to quantify the proportion of relapses at 6- and 12-months using the Infectious Diseases Data Observatory (IDDO) living systematic review database (1983-2021;182 studies). Studies with a minimum follow-up of 6-months that clearly reported relapse (or absence) were included; studies in VL-HIV coinfections were excluded. A random effects meta-analysis of single proportion was carried out and estimates were reported together with 95% confidence interval [95% CI] and I2 statistics. A total of 120 studies (27,902 patients) were included; 95 were from the Indian Sub-continent (ISC), 12 from East Africa (EA), 4 from the Mediterranean, 4 from Latin America, 3 from Central Asia, and 2 were multi-regional. Overall, 25,911 patients were initially cured and 2,149 of them relapsed. In the ISC, relapse at 6-months was 3.9% [2.8%-5.4%; I2= 88%] and when stratified by drug regimens, the estimates were: 8.6% [4.1%-17.2%] for Pentavalent Antimony (PA), 3.4% [2.4%-4.9%] for single dose L-AmB, 1.2% [0.3%-4.6%] for L-AmB as a combination therapy, and 0.7% [0.2%-2.6%] for Miltefosine and Paromomycin. In EA, the overall estimate of relapse was 9.3% [5.7%-14.8%; I2= 71%] and the estimates by drug regimen were: 6.9% [1.7%-24.3%] for single dose L-AmB in a combination regimen, 9.0% [3.0%-23.9%] for PA, 6.3% [0.9%-33.5%] for Paromomycin, 10.7% [3.7%-28.0%] for Miltefosine, and 12.9% [4.4%-32.9%] for PA and Paromomycin regimen. From 19 studies that reported relapses at 6- and 12-months, the proportion of relapse was 0.5% [0.1%-2.3%] at 6-months and 1.5% [0.7%-3.8%] at 12-months. This meta-analysis estimated that approximately 5-10% of patients relapsed following VL treatment (with large heterogeneity) and this was lower following combination regimens. Limited data from studies with longer follow-up suggested conventionally adopted 6-months follow-up leads to underestimation of relapse.

1805

ELIMINATION OF ONCHOCERCIASIS TRANSMISSION IN THREE FOCI OF UGANDA

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In 2007, Uganda became the second African country to launch a national policy for onchocerciasis elimination based on annual and semi-annual ivermectin mass drug administration (MDA) and targeted vector control. Post-treatment surveillance (PTS) entomological and serological surveys were conducted in three foci: Wadelai (population at risk 25,232), Nyamugasani (population at risk 13,218), and West Nile (population at risk 543,356), which halted MDA after 2010, 2015 and 2017, respectively. In Wadelai, which delayed initiation of PTS until 2018 due to ongoing ivermectin MDA for lymphatic filariasis, no *Simulium* flies were caught in quarterly collections in two sites from 2018 to 2020. None (0%, 95% CI 0-0.13) of 2,961 children under 10 years old tested in 2020 were positive for Ov16 antibodies by ELISA analysis of dried blood spots. In Nyamugasani, only 339 *Simulium* flies were collected from two collection sites from 2016 to 2021. None (0%) of the vector heads were positive for *Onchocerca volvulus* DNA by O-150 PCR, and none (0%) of 1,564 children under 10 years of age were tested in a 2021 census of the study area were Ov16 positive. In West Nile, no *Simulium* flies were collected from quarterly catches in 6 sites from 2017 to 2020. Of 3,007 children, 15 (0.5%, 95% CI 0.3-0.82) were Ov16 positive (ELISA), but all 15 were negative for *O. volvulus* DNA by PCR of skin snip samples. These data indicate the continued absence of *O. volvulus* transmission in the three foci during PTS. In 2021, the Uganda Onchocerciasis Elimination Experts Advisory Committee recommended the three foci be reclassified as transmission eliminated, thus freeing an additional 581,806 people from the risk of onchocerciasis.

1806

COST-EFFECTIVENESS AND PREMIUM OF GAMBIENSE HUMAN AFRICAN TRYPANOSOMIASIS (GHAT) ELIMINATION CAMPAIGNS IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Gambiense human African trypanosomiasis (gHAT) is marked for elimination of transmission (EoT) by 2030. We examined the situation in the Democratic Republic of Congo (DRC), which has the highest burden of gHAT. We considered the comparative efficiency of four possible strategies for gHAT aimed at EoT by combining an epidemiological transmission model with a health outcome and economic model. Alongside passive screening (PS) in fixed health facilities, the strategies simulated were active screening (AS) at average and high coverage rates, both alone and in conjunction with vector control (VC). Scale-back of AS and VC activities were simulated when no cases were detected for three successive years. Outcomes were measured in disability-adjusted life-years (DALYs), the probability of EoT, and costs until 2040. Cost-effectiveness of the different strategies for each health zone of DRC affected by gHAT was assessed by the traditional cost-effectiveness criteria—costs per DALY averted—and by the cost to increase the probability of EoT. Analyses suggested that EoT by 2030 is feasible but will require increased coverage of AS or implementation of VC in most endemic or hyper-endemic zones. In hypoendemic zones, the current strategy (average coverage of AS and PS) led to EoT by 2030 with high probability. For hyperendemic zones, VC strategies will be cost-saving while ensuring EoT by 2030. In endemic zones, medical-only strategies (AS and PS) were cost-effective for low-to-moderate costs to avert DALYs ($0-500/DALY) but had low probability of achieving EoT by 2030. We also calculated the additional Premium of elimination in zones were the strategy that led to EoT is not cost-effective. Future strategies may employ tools in development, and this analysis suggested that these tools will yield the most return for investment if they decreasing the loss of patients between the screening and treatment steps or if diagnostic tools with better specificity lead to safe scale back of activities.

1807

CAN ACOZIBOROLE IN A "SCREEN AND TREAT" APPROACH CHANGE THE END-GAME TRAJECTORY OF SLEEPING SICKNESS IN THE PRESENCE OF ASYMPTOMATIC INFECTIONS?

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Sleeping sickness (*gambiense* human African trypanosomiasis) is a neglected tropical disease targeted for global elimination of transmission by 2030. As a disease it progresses relatively slowly with symptoms worsening as the infection progresses. Some infected individuals, however, remain asymptomatic with evidence indicating that there is the potential to "self-cure". The detection and treatment of asymptomatic infections is therefore a significant hurdle to elimination efforts particularly as current treatments require parasite visualisation in the blood. "Overtreatment" of asymptomatic individuals, without the requirement for parasitological confirmation, may be possible with acoziborole, a new drug undergoing clinical trials as a safe, single-dose cure for sleeping sickness. Here we explore how acoziborole, under different screening algorithms, impacts transmission in a model with and without asymptomatic infections. We use mathematical modelling to quantify the possible benefits of a "screen and treat" (S&T) approach (using rapid diagnostic tests) with a focus on infections that may not have detectable blood-parasitaemia. We used this model to assess the impact the S&T algorithm has on disease burden and underlying transmission in the Democratic Republic of the Congo, one of the highest endemicity regions globally. We find that predictions from the asymptomatic model are more pessimistic than a model without asymptomatic infections. Furthermore, combining screening methods to improve coverage of high-risk groups (*e.g.* door-to-door screening) with a S&T algorithm appears to be a more effective, medical-only approach to tackle infections, especially if asymptomatic infections are contributing to onward transmission. Using Bayesian statistical approaches we also assessed whether asymptomatic transmission is likely based on the available human case data and provide projections for different strategies, including S&T, for an ensemble model which captures our uncertainty in epidemiology and model parameterisation.

1808

FROM SEROLOGICAL SURVEYS TO DISEASE BURDEN: A MODELLING PIPELINE FOR CHAGAS DISEASE

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In 2012, the World Health Organization (WHO) set the elimination of Chagas disease intradomicilary vectorial transmission as a goal in its first neglected tropical diseases (NTDs) roadmap. After a decade, progress has been made, but the new 2021-2030 WHO roadmap on NTDs has set even more ambitious targets. The challenges raised require innovative and robust modelling methods to monitor progress towards these goals. We have developed a modelling pipeline using local prevalence data to obtain national burden estimates at the municipality level while propagating uncertainty in ways that are consistent when aggregated across different locations to give a broader scale perspective. Initially, local seroprevalence information is used to estimate the local trend in temporal exposure (quantified by the force-of-infection (FoI). Exposure estimates from such surveys are then used to predict spatiotemporal trends across larger geographical areas. Finally, large-scale predicted exposure estimates (based on the fine spatial resolution), are used to estimate disease burden based on a disease progression model. Using 76 serosurveys conducted in Colombia between 1990 and 2020, we estimated that the number of infected people would reach an estimated 506,000 (95% CrI: 395,000-648,000) in 2020 with a 1.0% (95% CrI: 0.8%-1.3%) prevalence in the general population and 2,400 (95% CrI: 1,900-3,400) deaths (~0.5% of those infected). Temporally, the interplay between a slight decrease in exposure was overcompensated by the large increase in population size and the gradual ageing of the population, leading to a substantial increase in the burden of Chagas disease over time. The modelling pipeline has been initially built with Colombian data but can be used on other Chagas disease endemic countries or even on other long-lasting infectious diseases for which serosurveys are conducted.

1809

SYMPTOMATIC *GIARDIA* INFECTION AND ITS IMPACT ON CHILD GROWTH IN A NICARAGUAN BIRTH COHORT

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Giardia lamblia is an intestinal protozoan associated with ~300 million symptomatic infections annually, mainly in children in low- and middle-income countries. It has also been associated with increased intestinal permeability and stunted growth. We determined the incidence, co-infections, risk factors, and clinical characteristics of symptomatic *Giardia* infection in a birth-cohort of 444 infants up to 3 years of age by qPCR. Also, association between *Giardia* and linear growth, stunting and wasting was explored. During June 2017 to July 2021, 1347 stools from 1497 diarrheal episodes were collected. Preliminary incidence of *Giardia,* based on the follow-up of 210 children was 2.8, 11.4 and 13.3 episodes per 100 children-year in the 1st, 2nd and 3rd year of life, respectively; and was frequently associated with other intestinal pathogens (25/58). Children with *Giardia* (n=58) had less stools per day (5, IQR: 4-6; p=0.003) and were less likely to seek medical care (OR=0.3; IC: 0.16-0.83; p=0.01) compared with other pathogens. Use of latrine (vs. indoor toilet) (OR: 2.1; IC: 1.13-4.02; p=0.02) and a dirt floor in the houses (vs. tiled floor) (OR=1.7; IC: 0.94-3.27; p=0.07) were risk factors associated with *Giardia*. In addition, decrements in Length-for-age (ΔLAZ) in children with *Giardia* was observed at 3 months post-infection (ΔLAZ: -0.48, IQR: -1.05,-0.02), at 2 years (ΔLAZ: -0.26, IQR: -1.08,-0.02), and 3 years of age (ΔLAZ: -0.61; IQR: -1.28, 0.37), but not for Weight-for-age. A negative impact on ΔLAZ (-0.48) at 3 months' post-infection was significantly higher (p=0.01) for *Giardia* comparing with ΔLAZ (0.47, IQR: 0.87, 0.03) by other etiologies. Moreover, cohort stunting rates were 3.8%, 6.9%, and 6.2%, in the 1st, 2nd and 3rd year of life, whereas proportions with *Giardia* were 0%, 8.3%, and 26.7%, respectively. *Giardia* detection in the 2nd (OR:3.06; IC: 0.95-9.81; p=0.029) and 3rd (OR:3.49; IC: 1.02-11.86; p=0.019) year of life was significantly associated with stunting. In brief, while symptomatic *Giardia* infection associated with less severe diarrhea than other pathogens the impact on poor growth of children in Nicaragua was substantial.

1810

UPDATING REPRODUCTION NUMBER ESTIMATES FOR MONKEYPOX IN THE DEMOCRATIC REPUBLIC OF CONGO USING SURVEILLANCE DATA

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Incidence of human monkeypox (MPX) has been increasing in West and Central Africa, especially in the Democratic Republic of Congo (DRC), where monkeypox virus (MPXV) is endemic. Most estimates of the pathogen's transmissibility are based on contact tracing data from the 1980s. New estimates are needed to characterize the virus' epidemic potential and inform outbreak control strategies. We used the package *vimes* for the R software to identify clusters of laboratory-confirmed MPX cases in Tshuapa Province, DRC between 2010 and 2017. Cases with both temporal (date of fever or rash onset) and spatial (residence during the last 12 months or village of rash onset) data were assigned to clusters based on the disease's serial interval and spatial kernel. We used the size of the clusters to infer the reproduction number, *R*, and the rate of zoonotic spillover of MPXV into the human population. Out of 1,585 confirmed MPX cases reported in Tshuapa Province, 960 had both date of symptom onset and a location with geographic coordinates. Preliminary results include an estimated *R* of 0.80 (95% CI: 0.76-0.83) and a rate of 110 (95% CI: 102-118) spillovers per year assuming a reporting rate of 0.25. This estimate of *R* is larger compared to most estimates in the literature. One potential explanation for this result is that *R* could have increased in DRC over time due to declining population-level immunity conferred by smallpox vaccination, which was discontinued around 1982. *R* could be overestimated if our assumption of one spillover event per cluster does not hold. Our results are consistent with increased transmissibility of MPXV in Tshuapa Province. This research elucidates the extent to which human-to-human spread versus spillover drives MPXV transmission patterns which could be used to prioritize interventions, such as vaccination. It also underscores the importance of continued surveillance efforts for MPX in high-risk areas.

1811

COMMCARE MOBILE APPLICATION HELPS PREVENT OUTBREAK OF RIFT VALLEY FEVER IN MADAGASCAR

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The USAID-funded Accessible Continuum of Care and Essential Services Sustained (ACCESS) Program, led by Management Sciences for Health and in partnership with Dimagi, is supporting the Madagascar Ministry of Public Health (MOPH) to scale up the use of the CommCare mobile health application to community health volunteers (CHVs). One module is for community surveillance, which tracks and reports on 16 disease-related symptoms and 3 animal health-related suspicious events that pose particular health risks to the population and have epidemic potential. Alerts are sent to higher levels of the health system via the internet or SMS. Thus, the app helps to quickly detect and report suspicious cases, which can trigger swift public health response measures and help prevent localized cases from turning into a national epidemic. The app is used by 1,891 CHVs in four regions. Through the data shared by CHVs using this app, the MOPH was able to detect 150 suspected cases of Rift Valley Fever (RVF) in the Atsimo Andrefana region in March 2021. RVF is a zoonotic disease that can easily be transmitted between animals and humans and constitutes an essential area of intervention for the One Health approach. In November 2020, CHVs in Atsimo Andrefana received 4 reports of 27 cases of bovine/sheep/goat spontaneous abortions. They entered this information into CommCare, which then alerted the MOPH of a potential outbreak of a zoonotic disease and led them to closely monitor the data over time. By March 2021, 16 new reports totaling 150 cases were recorded and the MOPH determined it was necessary to initiate an investigation. Samples from these animals were tested by the *Institut Pasteur* in Madagascar, which confirmed cases of RVF in early April 2021. Active case finding for hemorrhagic fever in humans was increased to monitor potential spread to humans, and awareness-raising campaigns were conducted. These response measures were complemented by an animal vaccination campaign and technical coordination between partners and intersectoral exchanges within the Epidemiological Surveillance and Management of One Health Alerts network. Only 2 human cases were detected.

1812

IDENTIFYING RECENT CHOLERA INFECTIONS USING A MULTIPLEX BEAD SEROLOGICAL ASSAY

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Population-level incidence of cholera infections can be estimated from cross-sectional serological data. Current laboratory methods are resource intensive and challenging to standardize across laboratories. A multiplex bead assay (MBA) could efficiently expand the breadth of measured antibody responses and improve accuracy. We tested 305 serum samples from confirmed cholera cases (collected 2-1083 days post-infection) and uninfected household contacts in Bangladesh for serological biomarkers using an MBA (IgG, IgA, and IgM for 7 Vibrio cholerae O1-specific prominent antigens related to infection) as well as the vibriocidal assay (Ogawa and Inaba serotypes) and enzyme-linked immunosorbent assay (IgG and IgA for 2 antigens). While post-infection vibriocidal responses often had much higher initial fold-changes (52 and 50 times on-average) than other markers, several MBA-measured antibodies demonstrated robust responses with similar or longer half-lives. Random forest models combining all MBA antibody and isotype measures allowed for accurate identification of recent cholera infections (e.g. in the past 200 days) including a cross-validated AUC (cvAUC200) of 92%. Simplified models based on only 3 IgG antibody responses had similar accuracy (cvAUC200 = 89%). Across different infection windows (between 45- and 300-days), predictive accuracy of models trained on MBA measurements were non-inferior to models based on traditional serological assays. An MBA-based seroincidence assay can allow for expanded serosurveillance efforts globally including the use of these antigens in multi-pathogen serosurveillance platforms.

1813

HOSPITAL ANTIBIOTIC POINT PREVALENCE SURVEY REVEALS HIGH RATES OF EMPIRIC ANTIBIOTIC PRESCRIBING AT TWO HOSPITALS IN ADDIS ABABA, ETHIOPIA

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Antimicrobial resistance (AMR) is an increasing threat to global health, leading to substantial morbidity and mortality worldwide. The WHO Methodology for Point Prevalence Survey (PPS) on Antibiotic Use facilitates standardized comparison of antimicrobial prescribing practices worldwide. To provide key data on antibiotic prescribing in Ethiopia, we conducted a PPS at two hospitals in Addis Ababa, Ethiopia. We performed two rounds of the PPS at each hospital through real-time chart review in November 2021 and January 2022. All inpatients, including neonates, infants, children, and adults, were included. The primary outcome was prevalence of antibiotic use. Sociodemographic information, antibiotic details and indication, clinical variables, and microbiological data were also collected. This study was approved by US and Ethiopian institutional IRBs. Among 1024 patients from the two hospitals 64.7% (n=646) were receiving at least one antibiotic on the day of the survey. Rate of antibiotic use was 76% (n=108) in neonates, 83% (n=76) in infants, 61% (n=58) in children, and 61% (n=399) in adults. The most common indications for antibiotic use were community-acquired infections (n=285, 42.9%) and surgical prophylaxis (n=180, 27.1%). Ceftriaxone (n=237, 29%), metronidazole (n=112, 14%), ampicillin (n=102, 12%), and vancomycin (n=90, 11%) were the most frequently prescribed antibiotics. Most antibiotics were prescribed empirically (n=455, 95.4%) without associated microbiological results. Only 75 patients (10.6%) on antibiotics had samples collected for microbiology testing with the most common sites being blood (40%), other sterile sites (29%), and wounds (13%). *Staphylococcus aureus* (n=7), *Klebsiella* spp. (n=5), and *E. coli* (n=3) were the most common microorganisms identified among positive cultures. Our study found high rates of empiric antibiotic use across a diverse spectrum of patients and revealed infrequent microbiological sampling in two Ethiopian hospitals. Future studies evaluating appropriateness of antibiotic prescribing are needed to inform future implementation of antibiotic stewardship programs.

1814

ACCEPTABILITY AND WILLINGNESS-TO-PAY FOR C-REACTIVE PROTEIN POINT-OF-CARE TESTING AT COMMUNITY PHARMACIES TO GUIDE ANTIBIOTIC TREATMENT IN PATIENTS WITH ACUTE RESPIRATORY INFECTIONS

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Use of C-reactive protein point-of-care testing (CRP-POT) to guide antibiotic treatment has been proven to reduce antibiotic prescribing for patients with acute respiratory infections (ARIs) in primary healthcare settings in low-middle income countries (LMICs). However, community pharmacies are the preferred source of care for mild illnesses, and 80% of antibiotics are dispensed there without prescription. We conducted a mixed methods study to explore the potential for introducing CRP-POT and assess the acceptability and willingness-to-pay (WTP) for CRP-POT among ARI patients at community pharmacies. We conducted a quantitative survey with 520 customers with ARIs exiting 25 pharmacies in Nam Dinh city, Vietnam (260 of whom were offered CRP-POT, and 260 were given a CRP-POT scenario). We conducted qualitative interviews with 3 customer groups (20 participants in total) and 13 other participants (including pharmacists, general practitioners, paediatricians and health officials). The data collection was conducted from March to June 2021. Our study found that 408 of 520 customers (78.5%) agreed that CPR-POT service should be provided at pharmacies. However, only 244 (44.9%) were convinced that current pharmacists could perform the test without supplementary training. Among 260 customers who were offered CRP-POT service, 258 (99.2%) had a CRP level lower than 10 mg/dL, 2 (0.8%) had between 10-40 mg/dL, and none had a higher CRP level, showing that antibiotic treatment was likely not needed in most of the cases. However, antibiotics were dispensed for 214 of 260 customers (82.3%), and 198 (92.5%) were dispensed without prescription. Patients' mean WTP threshold for CRP-POT was US$2.32 ± 1.79 for the 408 customers who accepted the service and US$2.42 ± 1.86 for 260 customers tested. Our linear multivariate regression and qualitative analyses revealed that customer's perceived effectiveness of CRP-POT and cost of antibiotic treatment increased the WTP threshold, while severity of ARI symptoms and a prior visit to doctors decreased the WTP threshold.

1815

SIMPLE AND ECONOMICAL EXTRACTION OF VIRAL RNA AND STORAGE AT AMBIENT TEMPERATURE

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RNA extraction is essential for molecular detection of common viruses, but available extraction methods and ultra-cold storage requirements create barriers to molecular testing in resource-constrained settings. Therefore, we sought to develop an economical RNA Extraction and Storage (RNAES) protocol that eliminates instrumentation, proprietary materials, and cold chain storage. We combined a low-cost, capillary-driven approach, previously reported for DNA isolation, with methods inspired by nucleic acid isolation in botany. Non-toxic buffers, additives, and membranes were systematically tested to create a low-cost, flexible, and accessible protocol. The RNAES protocol combines safe viral lysis and binding buffers with capillary flow across an RNA binding membrane in simple packets to yield RT-PCR-compatible RNA and enable RNA storage at ambient temperatures. Efficient viral lysis was achieved with a buffer containing sucrose, KCl, proteinase K and carrier RNA. Viral RNA exhibited concentration-dependent binding to glass fiber membranes, which increased with use of an acidic arginine binding buffer. Clinical evaluation of the RNAES protocol was performed using dengue virus (DENV)-positive sera from Paraguay. Samples were extracted in duplicate with the optimized protocol and once with an automated commercial instrument. DENV RNA was successfully extracted from 71/72 replicates (98.6%) in the RNAES protocol, and rRT-PCR Ct values were highly correlated between extraction methods. DENV RNA extracted from clinical samples remained stable when air dried and stored on RNAES membranes at ambient temperature for 35 days. Median eluate DENV RNA concentration demonstrated a nonsignificant decrease of 0.18 and 0.29 $\log_{10}$ copies/µL between day 0 and days 7 and 35, respectively ($p>0.2$ for both comparisons). The economical RNAES protocol provides efficient viral RNA extraction and stability for 1 month at ambient temperature. We expect this approach will provide a reliable alternative for resource-constrained settings, increase molecular testing capacity during reagent shortages, and aid the response to RNA virus outbreaks.

1816

EPSTEIN-BARR VIREMIA IN A CASE-CONTROL STUDY OF ACUTE FEBRILE ILLNESS IN THE PERUVIAN AMAZON: VIRAL DETECTION IN WHOLE BLOOD IS NOT SUFFICIENT TO ATTRIBUTE ACUTE FEBRILE ILLNESS

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The accurate diagnosis of acute febrile illness (AFI) poses a unique challenge in tropical regions where multiple endemic diseases coexist, and non-specific or overlapping symptoms make differentiation impossible when based on clinical features alone. Furthermore, a lack of adequate standardized diagnostic methods makes interpretation of testing difficult and hinders population-level surveillance. This is even true for more prevalent causes of AFI, like infectious mononucleosis due to Epstein-Barr virus (EBV), for which a combination of serology, molecular testing, and clinical context may all be required for accurate diagnosis. In the Amazonian region of northeastern Perú, year-round surveillance of AFI is ongoing using testing for a panel of endemic pathogens. In this case-control study, whole blood samples from 578 patients with AFI and their age matched controls were assessed using a modular array of qRT-PCR primers for 26 pathogens of interest. Of note, EBV-DNA was the most prevalent detection in both cases (34.5%, n=502) and controls (34.8%, n=497), and was not associated with febrile illness (OR 0.98, 95% CI 0.75 - 1.29, p=0.908). Low levels of detectable EBV DNA are known to persist for life in immunocompetent individuals, with anywhere from 5.1% to 84.6% of blood donors found to be positive in various epidemiologic studies, although this is commonly believed to be restricted to B-lymphocytes and only present in plasma during acute illness or reactivation. However, 18.1% of our cases were positive only for EBV-DNA, raising the possibility that a proportion of the cases of AFI may have been due to primary EBV infection alone. Future work will investigate ancillary means of distinguishing AFI due to EBV from background PCR positivity by contrasting quantitative results of viral load in whole blood with levels of viremia in plasma, and by using serologic testing for EBNA-1 IgG, to allow for the clinically meaningful inclusion of EBV within the AFI surveillance platform.

1817

PROACTIVE COMMUNITY MALARIA CASE MANAGEMENT: ONGOING RANDOMIZED CONTROL TRIAL IN CHADIZA DISTRICT, EASTERN PROVINCE, ZAMBIA

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The Zambian Ministry of Health through the National Malaria Elimination Centre (NMEC) continues to invest in Community Health Worker (CHW) expansion to improve access to prompt case management. The NMEC has deployed over 16,500 CHWs nationwide (161 in Chadiza) since 2011 to provide malaria community case management (CCM) for all ages using rapid diagnostic tests (RDTs) and treating positive individuals with artemisinin-based combination therapy (ACT). In 2021, we started a two-year cluster randomized controlled trial to assess whether adding proactive CCM (routine weekly household visits by CHWs to proactively identify and test febrile members with RDTs and treat those positive) to conventional passive CCM will lead to a greater reduction in malaria prevalence and incidence compared to conventional (passive) CCM alone in a moderate transmission setting. Through a restricted randomization process which balanced arms with regard to cluster population size, household dispersion, malaria prevalence, and vector control intervention coverage at baseline, 66 clusters (CHW catchment areas) were randomly assigned 1:1 to either the control arm (passive CCM) or intervention arm (proactive CCM + passive CCM). At baseline (May 2021), malaria parasite prevalence was 19.7% in the control arm and 18.8% in the intervention arm. Baseline passive testing and incidence rates reported by CHWs were also similar between arms. By the end of February 2022, 19 weeks after the start of the intervention, CHWs in the intervention arm had proactively tested 4,254 febrile individuals in 5,047 households, 857 (20.1%) of which were positive (99.2% of which received the age-appropriate ACT), and passively tested 7,913, of which 1,795 (22.7%) were positive. In the control arm, 2,795 of 8,444 tested (33.1%) were positive. In February 2022, CHWs in the intervention arm reported lower monthly incidence than control (26.9 vs. 50.9 per 1,000; p-value=0.043) despite continued similarity in passive testing rates between the two arms over time. Further analysis will continue to assess trends in malaria incidence and testing rates by arm to determine the impact of proactive CCM.

1818

ENTOMOLOGICAL IMPACT OF IVERMECTIN MASS DRUG ADMINISTRATION TO HUMANS AND LIVESTOCK: A CLUSTER RANDOMIZED CONTROLLED TRIAL IN MOPEIA, MOZAMBIQUE

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Current vector control tools (long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS)) have had a significant impact in reducing malaria transmission across Sub-Saharan Africa. However, these were designed to be used indoors and, therefore, have limited utility against outdoor mosquitoes which contribute to residual malaria transmission. The endectocidal drug ivermectin (IVM), when given to a community, has the potential to address residual transmission as its mode of action is independent of mosquito's host-seeking behaviour. When mosquitoes bite an ivermectin-treated host, their survival and reproduction fitness is significantly reduced. The BOHEMIA (Broad One Health Endectocide-based Malaria Intervention in Africa) study is a three-arm cluster randomised controlled trial conducted in Mopeia district, Mozambique. The trial aims to evaluate the impact of IVM mass drug administration (MDA) on malaria vector populations and consequently, on malaria transmission. The trial consisted of 102 clusters randomized to one of three treatment arms: 1) ivermectin MDA to humans, 2) ivermectin MDA to humans and livestock or 3) albendazole MDA to humans (control), given monthly for three rounds during the peak malaria transmission season. Bi-weekly indoor and outdoor CDC light trap mosquito collections were done in five randomly selected clusters per arm. Additionally, paired human double-net collections (HDN) were conducted in two houses per treatment arm once a month. Mosquito densities, survival rates, parity rates, and biting patterns were measured and compared across treatment arms. Furthermore, the susceptibility of local vector populations was evaluated by exposing field-caught vectors to ivermectin using a bio-efficacy assay (See poster Ominde *et al.*). Data was analysed using generalized linear mixed-effects models. These results are expected to contribute to the body of evidence for a WHO policy recommendation on IVM use as a first-in-class endectocide for reduction of malaria transmission.

1819

NO EVIDENCE OF INTER-CLUSTER CONTAMINATION IN A CLUSTER RANDOMIZED TRIAL EVALUATION OF PBO LONG LASTING INSECTICIDAL NETS IN UGANDA (LLINEUP)

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The LLINEUP trial was a large-scale cluster randomised control trial (CRT) carried out in Uganda between 2017-2019. The trial showed an increased impact of long-lasting insecticidal nets with piperonyl butoxide (PBO LLINs) compared to conventional LLINs in reducing the malaria burden (prevalence ratio 0.74; 6 months). A major concern with ecological intervention trials is the role of unaddressed spatial correlation on the trial outcome. Additionally, the presence of spillover effects, where intervention reduces disease/infection burden in adjacent control clusters, can reduce the likelihood of effect detection. We conducted a reanalysis of the initial LLINEUP trial to identify sources of spatial error that may have impacted the findings. We tested for spatial autocorrelation in the trial allocation and cluster level prevalence outcome across each of the time points using Moran's I. The trial model (GEE) was contrasted with models including a spatial GAMM with a Gaussian Markov Random Field to account for spatial correlation at a cluster level. We used open-source data to identify buildings across the region which we used to estimate the distance to discordant households and the density of structures surrounding the sampling locations. These were incorporated into the trial analysis to identify any within- or between-arm spillover effects. Significant spatial autocorrelation was present in the residuals of the primary trial model which could lead to overconfidence in the trial effect estimate. The spatial GAMM restored a significant impact in the trial effect at 18 months but did not substantively alter the efficacy estimates across the study. No significant evidence of a within- or between-arm spillover effect was observed with either the distance or density approaches. The presence of spatial autocorrelation in the primary trial analysis did not alter the

original trial findings of a significant impact of PBO LLINs. While logistically difficult, an advantage of large-scale pragmatic trials such as the LLINEUP study is that they are robust to contamination effects, a major challenge for smaller ecological intervention CRTs.

1820

LLIN EVALUATION IN UGANDA PROJECT (LLINEUP2): IMPACT OF LONG-LASTING INSECTICIDAL NETS (LLINS) TREATED WITH PYRETHROID PLUS PYRIPROXYFEN VS LLINS TREATED WITH PYRETHROID PLUS PIPERONYL BUTOXIDE ON MALARIA INCIDENCE IN UGANDA: A CLUSTER-RANDOMIZED TRIAL

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Long-lasting insecticidal nets (LLINs) provide the foundation for vector control in Africa, but their effectiveness is threatened by pyrethroid resistance. With the Ugandan Ministry of Health, we embedded a rigorous cluster-randomized trial in Uganda's mass campaign to distribute LLINs in 2020-21 to compare the impact of Royal Guard LLINs with pyrethroid plus pyriproxyfen (PPF), an insect growth regulator and PermaNet 3.0 LLINs with pyrethroid plus piperonyl butoxide (PBO), a synergist. A total of 64 clusters (public health facilities established as Malaria Reference Centres [MRCs] and surrounding target communities) were included, covering 32 high malaria burden districts in Uganda where IRS is not being implemented. Clusters were randomised 1:1 in blocks of two by district to receive: (1) PPF LLINs (n=32) and (2) PBO LLINs (n=32). LLINs were delivered to study areas from November 2020 to March 2021. The evaluation includes health facility surveillance at the MRCs to generate continuous estimates of malaria incidence for each cluster, and cross-sectional community surveys in at least 50 randomly selected households per cluster (3200 households per survey) at 12- and 24-months after LLIN distribution. The primary outcome is malaria incidence estimated using health facility surveillance; parasite prevalence in children 2-10 years of age is a secondary outcome. Preliminary results of the analysis of temporal changes in malaria incidence by LLIN arm, up to 10 months following LLIN distribution, suggest that the mean post-intervention malaria incidence per 1000 person-year is no different between the two arms (377 (240 SD) PBO arm vs 447 (SD 322) PPF arm (incidence rate ratio 0.95, 95% CI: 0.78-1.16, p=0.63). Updated incidence results and outcomes from the 12-month cross-sectional survey will be presented. The results of this innovative trial embedded within a national LLIN distribution campaign measuring malaria incidence on a large-scale will make an important contribution to malaria control policy in Uganda, and throughout Africa.

1821

EFFICACY OF PARTIAL VERSUS FULL SURFACE INDOOR RESIDUAL SPRAYING AGAINST WILD POPULATIONS OF *ANOPHELES GAMBIAE* SENSU LATO IN EXPERIMENTAL HUTS IN TIASSALÉ, CÔTE D'IVOIRE

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The current IRS practice recommended by WHO is for all interior wall and ceiling surfaces to be sprayed in all eligible structures. An alternative approach is to reduce the surface area sprayed by targeting preferred mosquito resting locations. This could reduce the quantity of insecticide and operational costs by reducing the time needed to spray a structure, enabling an increase in the geographic coverage of IRS. PMI VectorLink conducted a nine-month evaluation of the efficacy of Actellic 300CS, Fludora Fusion 56.25WP-SB, and SumiShield 50WG when partially sprayed in experimental huts against free-flying *Anopheles gambiae* sensu lato in Tiassalé, Côte d'Ivoire. The vectors were susceptible to clothianidin and pirimiphos-methyl. Two treatments of partial wall spraying were compared with full spraying - either the upper or lower half of the walls was sprayed, along with the ceilings. Mosquitoes were collected from different locations in each hut - the lower and upper halves of the wall, the ceiling, or the veranda trap. Mortality was assessed at the time of collection and after 24 hours (Actellic) or 120 hours (SumiShield and Fludora Fusion). Of 25,834 mosquitoes collected post-spraying, 69% (17,835) were *An. gambiae* s.l., mainly *An. coluzzii*. Seventy-two percent (72%) of *An. gambiae* s.l. inside the huts were found resting on the bottom half of the walls, only 11% on the top half, and 14% on ceilings. For Actellic and Fludora Fusion, no significant difference in mortality was observed between the treatments. Mean mortality over the nine months was 88.5% for Actellic fully sprayed huts, 88.2% for Actellic lower wall + ceiling, and 80.8% for upper wall + ceiling. For Fludora Fusion, the equivalent values were 86.3%, 83.9%, and 80.9%. For SumiShield, mortality in the upper wall + ceiling treatment (77.1%) was significantly lower than the other treatments (87.2% for full spraying, 85.8% for lower wall + ceiling). Partial spraying may reduce IRS costs without significant decreases in efficacy. However, its implementation may require prior knowledge of mosquito indoor resting behavior to target the spraying to surfaces where mosquitoes primarily rest.

1822

DIGITIZATION OF VECTOR CONTROL CAMPAIGNS-LEVERAGING THE DHIS2 PLATFORM TO STRENGTHEN THE DELIVERY OF INDOOR RESIDUAL SPRAYING (IRS) CAMPAIGNS DURING COVID-19

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The deployment of Indoor Residual Spraying (IRS) is a critical undertaking that requires precise planning, effective execution, and robust monitoring and evaluation to track performance against targets. As part of strengthening IRS deployment, Zimbabwe's National Malaria Control Program (NMCP) utilized DHIS2 for daily reporting and tracking the IRS campaign in 30 target districts during the 2021-2022 campaign season. The DHIS2 was critical to provide management with prompt insights on IRS deployment progress and minimizing paper reporting. Given the COVID-19 related disruptions and complexities such as delayed shipment of commodities (personal protective equipment and an insecticide deficit of 34%), increased logistical requirements to comply with C-19 and the risk of low community acceptance fearing COVID-19 transmission, real time data was found to be critical for timely responses. The DHIS2 android capture rollout process involved training field IRS data managers and their line supervisors, to capture data on daily spray performance. A weekly performance bulletin was circulated to provide management insights on areas of immediate attention and provide greater visibility of the teams' performance against targets on the spray status of rooms seen, population protected, insecticide and fuel usage. The 2021/22 campaign results show that of the 2.5m targeted rooms a spray coverage of 81% was achieved. The coverage for population protected stood at 89% of 3.7m

targeted people. The timeous digital IRS data submissions from campsites, accessible from anywhere by managers and the use of dashboards provided a chance to course-correct quickly and adjusts strategies as needed including quick identification of low coverages and, prioritize callbacks, resulting in an additional 4.8% of targeted rooms being sprayed. The NMCP was able to prioritize districts for technical support and redeployed excess insecticides from districts that had completed spraying to those that had gaps to overcome shortages attributed to delayed shipments. Overall, DHIS2 reduced the lag time between data generation, analysis, and data driven decision making.

1823

THE IMPACT OF INDOOR RESIDUAL SPRAYING (IRS) WITHDRAWAL IN THE LAKE ZONE REGIONS IN MAINLAND TANZANIA. SHOULD TANZANIA WITHDRAWAL ITS IRS PROGRAM?

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Indoor Residual Spray (IRS) has proven to be one of the most effective indoor intervention in reducing malaria transmission especially in area with high transmission. Tanzania has gone through expansion of IRS implementation with different insecticides from one district in 2007 to a maximum of 18 districts in 2012. However, this was followed by IRS withdrawal to 6 districts by 2021 - with expectation of even more withdrawal in 2022 - 2023. Here, we performed retrospective analysis to understand the impact of IRS withdrawal based on DHIS2 malaria incidence per 1000 population data. We performed interrupted time series (ITS) based on monthly data - using segmented regression analysis to investigate whether the effect due to IRS withdrawal is statistically significant or not. The analysis helps to examine the changes in level and/or trend before, during, and after the IRS withdrawal. Visual inspections on yearly time series plots indicates that withdrawing IRS after one, two, three, or even four rounds of IRS implementation results into resurgence of malaria incidence. The interrupted time series statistical model results based on monthly data indicate that the difference between the trend during IRS and after withdrawal is negative and statistically significant ($p < 0.001$) - indicating that monthly malaria incidence decreases over time during IRS. The immediate effect after the IRS is withdrawn is positive and statistically significant ($p < 0.001$) - indicating that withdrawing IRS increased the malaria incidence. The sustained effect after IRS is withdrawn is positive and statistically significant ($p < 0.001$) - indicating that each day that passes after IRS is withdrawn, the malaria incidence increases. Overall, malaria resurgence is observed in almost all the districts in which IRS was prematurely withdrawing. IRS using non-pyrethroids insecticides is recommended not only for managing insecticide resistance, but also for abrupt interruption of high malaria transmission. Therefore, Tanzania should not withdrawal its IRS program and any decision to withdrawal should ensure its replacement with an equally effective or superior intervention.

1824

LABORATORY PARAMETERS ASSOCIATED WITH MORTALITY IN EBOLA VIRUS DISEASE

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Ebola virus cycle threshold (Ct) is strongly associated with Ebola virus disease (EVD) mortality. However, the role of other laboratory parameters in EVD is not well understood. This study evaluated laboratory values and assessed their association with EVD mortality. Data from 425 patients with EVD admitted to the Mangina Ebola Treatment Center (ETC) run by International Medical Corps in the Democratic Republic of Congo from December 2018 to January 2020 were analyzed. The point-of-care (POC) Piccolo® AmLyte panel was used to measure alanine aminotransferase, albumin, amylase, aspartate aminotransferase (AST), calcium, c-reactive protein (CRP), creatinine kinase, creatinine, glucose, potassium, sodium, total bilirubin, and blood urea nitrogen. Following earlier studies, high viral load was defined as a Ct ≤ 22. Potassium, sodium, glucose, and calcium were analyzed as categorical variables (high, normal, low) as defined by laboratory reference ranges. All other variables were analyzed as continuous variables. Descriptive statistics were performed on demographics. Laboratory values were compared based on mortality outcome. Multivariable backward logistic regression yielding adjusted odds ratios (aOR) with associated 95% confidence intervals (CI) was used to quantify magnitudes of effect for the association between laboratory parameters and mortality. Of 425 patients, 57.7% were female. Median age was 26 years (range 0-80). Median number of symptomatic days prior to presentation was 4.0 (IQR 2.0-6.0). Mortality during ETC care was 48.4%. At least one AmLyte panel was available for 225 patients (52.9%). In adjusted analysis, four laboratory parameters were significantly associated with mortality: Ct value ≤ 22 (aOR=32.91, 95% CI 6.24-173.73; p<0.001), albumin (aOR=0.17, 95% CI 0.16-0.48; p<0.001), AST (aOR=1.002, 95% CI 1.001-1.002; p=0.002), and CRP (aOR=1.016, 95% CI 1.007-1.025; p<0.001). These data demonstrate significant associations between specific biochemical and molecular markers and EVD mortality, suggesting that POC laboratory assays could provide useful clinical data to guide EVD outbreak response.

1825

PRIMARY OUTCOME AND SELECT SECONDARY OUTCOMES FROM REPEAT IVERMECTIN MASS DRUG ADMINISTRATIONS FOR MALARIA CONTROL II (RIMDAMAL II): A DOUBLE-BLIND, CLUSTER-RANDOMIZED CONTROL TRIAL FOR INTEGRATED CONTROL OF MALARIA

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Ivermectin is an anthelmintic drug that has been demonstrated in lab studies to effectively kill anopheles mosquitoes that blood feed on treated people and in field trials after communities receive ivermectin mass drug administrations (MDA). Modeling studies have suggested it could be an effective new tool to limit malaria transmission and one small clinical trial (RIMDAMAL) demonstrated its potential to reduce malaria incidence in children. RIMDAMAL II is a follow-on cluster-randomized, placebo-controlled, parallel-assignment clinical trial in southwest Burkina Faso to test whether repeated high-dose MDA, integrated into a monthly delivery platform with standard malaria control measures of seasonal malaria chemoprevention (SMC) and insecticide-treated bed net distribution in the Sahel, will reduce childhood malaria incidence. The intervention phase of the study was performed over 4 months across two rainy seasons in 14 village clusters surrounding the town of Diebougou, from approximately July through November in 2019 and 2020. The clusters were randomized to the intervention and placebo arms and all eligible study participants were treated by the study team with ivermectin or placebo (~300 µg/

kg x 3 day-course, estimated by height bands) monthly each season. The primary outcome is cumulative incidence of uncomplicated malaria episodes in enrolled children ≤ 10 years of age assessed by active case surveillance; cohort children 3-59 months of age received SMC distributed by ministry of health workers, while those >90 cm (typically 5-10 years of age) received ivermectin or placebo. Secondary outcomes included safety of the intervention, and entomological, parasitological and pharmacokinetic/dynamic analyses. Approximately 3800 participants were enrolled each season and cluster sizes ranged from 123-465 participants. Preliminary analyses suggest the intervention was well-tolerated and associated with relatively few adverse events that were predominately Grade 1 (mild in severity), The primary outcome and select secondary outcome data will be presented.

1826

UTILITY OF POINT-OF-CARE ECHOCARDIOGRAPHY TO GUIDE FLUID RESUSCITATION IN DENGUE SHOCK PATIENTS

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Dengue shock syndrome is a severe life-threatening manifestation of dengue caused by increased capillary permeability and plasma leakage. Transient cardiac dysfunction occurs in severe dengue and is associated with worse outcomes. Using point-of-care echocardiography (POC echo) could define degree of cardiac impairment, volume status and potentially facilitate a more targeted and personalised strategy for fluid management. We performed a prospective cohort study at the Hospital for Tropical Diseases, Ho Chi Minh City. 90 dengue patients aged 6 to 15 years were enrolled at the time of shock. Patients had POC echo performed at seven time-points: shock onset, 1, 3, 6 (T6), 11-14 (T12), 23-25 hours and at around 5 - 7 days after hospital discharge. The outcome of interest was the occurrence of a second episode of shock (re-shock). Of 90 patients, 16 developed re-shock with a median time 14 [11 - 17] hours from enrolment. At T6, patients who developed re-shock had significantly lower values of preload-dependent parameters compared with those with no further episodes of shock. These included a reduced stroke volume index (SVI) (23 [18 - 26] ml/m^2 vs. 26 [23 - 33] ml/m^2, p = .038) and reduced left ventricular (LV) diastolic parameters such as the ratio of mitral inflow early to late filling velocities (1.43 [1.37 - 1.52] vs 1.75 [1.57 - 2.01], p = .003), mitral annular early diastolic velocity (12.0 [11.5 - 12.7] cm/s vs 15.4 [13.1 - 18.5] cm/s, p < .001). Patients who developed re-shock also had impaired global right ventricular (RV) function as evidenced by a raised myocardial performance index [0.17 [0.12 - 0.21] vs 0.10 [0.06 - 0.15], p = .014). At T12, the RV function was further impaired with reduced tricuspid annular plan systolic excursion in the re-shock group (1.38 [1.23 - 1.63] cm vs 1.85 [1.67 - 2.09] cm, p < .001). No differences were seen in the ejection fraction or other left ventricular functional parameters. In conclusion, POC echo including SVI and LV diastolic functional parameters performed at 6 hours after initial resuscitation for dengue shock is useful for identifying patients at risk of re-shock and could be used to tailor fluid management.

1827

NEGLECTED TROPICAL DISEASES | PQM+ MEDICINES INFORMATION DASHBOARD

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Limited data are available in the public domain for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) regarding country of origin, manufacturer, dosage forms/strengths, legal status, quality, availability, and price of preventive chemotherapy NTD medicinal products. Such information is useful to governments, procurement agencies, regulators, manufacturers, suppliers, and other stakeholders working to ensure adequate availability, safety, and quality of these priority NTD products. Funded by the U.S. Agency for International Development (USAID), the Promoting the Quality of Medicines Plus program (PQM+) developed a publicly available NTD Medicines Information Dashboard to assist medicines regulatory authorities, procurement agencies, NTD programs, and other stakeholders involved in the planning, forecasting of needs, procurement, and supply of NTD pharmaceutical products. This free tool, updated regularly, houses critical information compiled from the WHO prequalification program, the expert review panel, and other relevant sources, including UNICEF Supply Catalogue Indicative Pricing and WHO-Listed Authorities. With filtering and searching capabilities, the dashboard allows users to select parameters to display data of interest. The NTD products in the dashboard are albendazole, praziquantel, mebendazole, ivermectin, diethylcarbamazine, tetracycline eye ointment, and azithromycin. The dashboard assists stakeholders in identifying quality-assured APIs and FPPs of the NTD medicines, assessing areas of supply vulnerability, global outlook, and divergence across global data sources, and providing a roadmap to guide actions toward improved availability, efficiency, and alignment with regional and global needs. The dashboard also allows users to readily identify which NTD products are approved by WHO prequalification or WHO-listed authorities along with UNICEF indicative pricing. These data are particularly useful to procurement agencies and decisionmakers. Lessons learned and information gleaned from the dashboard and its implementation will be discussed.

1828

BASELINE CYTOMEGALOVIRUS VIRAEMIA AT CRYPTOCOCCAL MENINGITIS DIAGNOSIS IS ASSOCIATED WITH LONG-TERM INCREASED INCIDENT TB DISEASE AND MORTALITY - A PROSPECTIVE COHORT OF 497 UGANDAN ADULTS

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Adults with HIV-associated cryptococcal meningitis have high and over-lapping burdens of cytomegalovirus (CMV) and tuberculosis (TB) co-infections. CMV infection/reactivation is strongly associated with CMV-specific T cell activation and upregulation of type 1 interferons. This CMV-induced immune modulation may lead to increased risk of TB disease and contribute to poor outcomes. We conducted a cohort study of Ugandan adults enrolled in two prior cryptococcal meningitis trials during 2010-2021 to determine TB incidence and all-cause mortality over time stratified by baseline CMV viremia and CMV serology status. We included trial participants who survived at least 2-weeks after commencement of antifungal therapy in Kampala, Uganda. We followed 497 adults with HIV-associated cryptococcal meningitis for a mean of 2.4 years, for a total follow up time of 1,159 person-years. Overall, 40% (200/497) were women; the mean age was 35 years and median CD4+ cell count was 18 cells/μL. Overall, 20% (98/497) developed incident TB disease and 29% (142/497) of participants died. We measured baseline CMV viral load (VL) in 259 of whom 37% (96/259) had concurrent CMV viremia. CMV viremia was positively associated with higher HIV VL and higher CSF fungal burden (both p=0.002). On multivariable Cox analysis, participants with a CMV VL of >1000 IU/mL had twice the risk of incident TB disease compared to participants with no or low-level CMV viremia (aHR 2.01 (95% CI 1.00-4.01). The cumulative TB or death rate per 100 person years was 83 (95% CI 56-123) in participants with a CMV VL >1000 IU/ml, with a cumulative incidence rate ratio of 4.18 (95% CI, 2.51-6.73) compared to participants without CMV viremia at baseline (p<0.001). Amongst 59 participants with CMV serology data, there was no association between CMV IgG serology titer and incidence of TB or death (p=0.75). CMV viremia at time of cryptococcal meningitis diagnosis was strongly associated with increased

incident TB disease and mortality during long-term follow-up. Targeted anti-CMV therapy presents a potential intervention to improve TB and survival outcomes in HIV-associated cryptococcal meningitis.

1829

A THREE-YEAR ADVERSE DRUG REACTIONS ANALYSIS OF HIV PATIENTS ON DOLUTEGRAVIR-CONTAINING REGIMENS IN ETHIOPIA

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To gain greater visibility on the potential of adverse drug reactions (ADRs) for antiretroviral (ARV) therapy (ART) patients, the USAID Global Health Supply Chain-Procurement and Supply Management (GHSC-PSM) project supported the Ethiopian Food and Drug Authority (EFDA) and ART sites to improve monitoring and reporting for ADRs associated with dolutegravir (DTG). This included development of a national pharmacovigilance (PV) training course, meetings and trainings, distribution of user-friendly ADR reporting and screening tools, and supportive supervisions. With project support, ART sites collected ADR data between 2019 and 2021. GHSC-PSM then analyzed 417 ADR reports collected from 357 patients at 47 ART sites to identify the most common ADRs. The top five ADRs reported were insomnia (32.9%), hyperglycemia (20.9%), peripheral neuropathy (9.6%), weight gain (8.6%) and hypersensitivity skin reactions (5.3%). Most patients (57.1%) were between 31 and 45 of age, and in 68.8% of their cases, ADEs were noted within 15 days (about 2 weeks) of starting DTG. Most ADR findings were comparable between sexes; However, women were more likely to have hypersensitivity skin reactions (15%), musculoskeletal pain (12%), and gastrointestinal problems (10.5%); whereas more men reported hyperglycemia (18%), central nervous system side effects (13.5%) and weight loss (9%). Through site-level support, timely communications, and consultation with clinicians, health workers changed the time of ARV administration, and adjusted concomitant medicines and regimens that cause insomnia, weight loss, and hyperglycemia. National ADR reports increased from 700 to 1400 reports during this period. Next steps: the project used results to recommend a national DTG toxicity study to further assess ADRs and inform ART practices. Continuing this health system strengthening approach is expected to increase ADR awareness and improve vigilance in ADR reporting, further decentralize regional PV centers, increase regular analysis of ADR reports, and lead to timely results dissemination for faster, safer patient care.

1830

FACTORS IMPEDING THE HIV TREATMENT AMONGST UNDERPRIVILEGED PATIENTS VISITED OUTPATIENT DEPARTMENT IN A UNIVERSITY HOSPITAL IN THAILAND

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There were 470,000 people living with HIV amongst 70 million of the total population in Thailand. Limited data is available regarding the detailed barriers in Thailand's underprivileged people living with HIV data. Objectives were to determine the obstacles that impede underprivileged patients from regular outpatient visitation for HIV care and to compare the outcome of treatment between underprivileged patients with general PLWH. A bidirectional cross-sectional qualitative study was conducted on the patients visiting outpatient HIV clinic in Ramathibodi hospital, Mahidol University in Thailand, from December 2020 to March 2021. Questionnaires, in-depth interviews and data from medical records were collected.There were 100 patients in the study including 40 underprivileged patients and 60 general HIV infected patients. There is no statistically significant difference in baseline characteristics. Income was statistical difference between the two groups. The underprivileged group had more work duty as an obstacle for regular follow-up (56% versus 8%; P <0.01). Factors affecting previous loss to follow-up and non-adherence were travel expense (23%), travel distance (18%), difficulty to change an appointment (18%), and mental problems (9%).At 6-month follow-up and adherence assessment, there was no difference between the two groups. The underprivileged group used telemedicine 21% (vs 29%). Conclusions: The work duty, travel expense and travel distance are the main factors impeding HIV treatment amongst underprivileged patients. Even though many policies support free HIV essential lab tests and medications available in Thailand, the underprivileged population has been overlooked. We could make more efforts to ensure sufficient antiretroviral supply and viral load suppression to reach 95-95-95 goal in 2030.

1831

IMMUNOPEPTIDOMICS AS A TOOL TO IDENTIFY VACCINE TARGETS AGAINST CHAGAS DISEASE

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Trypanosoma cruzi (*T. cruzi*) is a complex protozoan parasite that infects around 6-7 million people worldwide, causing cardiomyopathy in a subset of patients that develop chronic Chagas disease. Efforts to develop prophylactic and therapeutic vaccines against *T. cruzi* infection are ongoing, but no vaccine is currently available in the clinic. While many evaluated vaccine antigen targets are designed to induce cytotoxic T cells (CTLs) that can kill infected cells, no systematic screening has been done to evaluate which antigen targets are actually presented by infected cells during natural infection and can be detected by CTLs. In our study, we have used an immunopeptidomics approach to detect the parasitic peptides that are presented on the major histocompatibility complex (MHC) of cells infected with *T. cruzi*. Tracing back to the origin of these peptides, we can categorize the parasite-derived proteins that are presented during natural infection and identify potential new vaccine antigen candidates. In order to identify *T. cruzi* - derived peptides presented by infected host cells, murine fibroblasts expressing $H2^{Kb}$ and $H2^{Db}$ were incubated with *T. cruzi* trypomastigotes *in vitro*. After 48 hours, extracellular parasites were washed off, and infected fibroblasts were removed from the flasks and lysed. MHC-I - peptide complexes in the cell lysate were purified using an anti-H2 monoclonal antibody coupled to an AminoLink column. Eluted peptides were separated from the MHC-I molecules using a 10kDa cutoff spin filter column and concentrated using a SpeedVac. The selected peptides were further identified by liquid chromatography coupled to mass spectrometry (LC-MS/MS). The LC-MS/MS data was searched against the mouse C57BL/6J and *T. cruzi* CL Brener reference proteomes. We identified dozens of unique T. *cruzi* peptides that traced back to 20 different *T. cruzi* proteins, including Heat shock protein DnaJ and Kinetoplastid Membrane Protein 11 (KMP-11). The immunopeptidomics approach was successfully used to identify potential vaccine antigen candidates, and DnaJ and KMP-11 are currently under evaluation as vaccine antigen targets.

1832

EXHAUSTED PD-1+ TOX+ CD8+ T CELLS ARISE ONLY IN LONG-TERM EXPERIMENTAL *TRYPANOSOMA CRUZI* INFECTION

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Infection with *Trypanosoma cruzi* (*T. cruzi*) is the most important neglected zoonosis in Latin America. This infection doesn't lead to specific symptoms

in the acute phase but chronic infection can result in Chagas disease (CD) with cardiac and/or gastrointestinal manifestations that can lead to death. $CD8^+$ T cells are highly effective and essential in controlling this infection but fail to eliminate all parasites. In this study, we show that the $CD8^+$ T cells are modulated by the transient induction of co-inhibitory receptors during acute infection of C57BL/6 mice. Therapeutic intervention strategies with blocking antibodies only had a marginal effect on the elimination of parasite reservoirs. Only long-term chronic infection gave rise to dysfunctional $CD8^+$ T cells, which were characterized by high expression of the inhibitory receptor PD-1 and the co-expression of the transcription factor TOX, which plays a crucial role in the maintenance of the exhausted phenotype. $PD\text{-}1^+ TOX^+ CD8^+$ T cells isolated from the site of infection produced significantly less IFN-γ, TNF-α and Granzyme B than their $PD\text{-}1^- TOX^-$ counterparts after *T. cruzi* specific stimulation *ex vivo*. Taken together, we provide evidence that in the context of experimental infection of mice, the magnitude of the $CD8^+$ T cell response in the acute phase is sufficient for parasite control and cannot be further increased by targeting co-inhibitory receptors. In contrast, persistent long-term chronic infection leads to an increase of exhausted T cells located in tissues of persistence. To our knowledge, this is the first description of infection-induced $CD8^+$ T cells with an exhausted phenotype and reduced cytokine production in muscles of *T. cruzi* infected mice. The persistence does not seem to be the result of the dysfunctionality of the $CD8^+$ T cells. Rather, they can control parasitemia over a long period very efficiently. However, a few parasites in the muscle evade this control for yet unexplained reasons. Deciphering these mechanisms holds the potential for new immunotherapies to further reduce the number of persistent parasites in the muscle or even eliminate them completely.

1833

ACTIVATION OF ERK PATHWAY FOLLOWING *LEISHMANIA AMAZONENSIS* INFECTION IS NECESSARY FOR INTERNALIZATION AND PATHOGENESIS

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Leishmania, an obligate intracellular protozoan parasite, binds several host cell receptors to trigger uptake by macrophages, leading to visceral or cutaneous leishmaniasis. *Leishmania* activate a series of signaling pathways upon engaging receptors during the internalization process. Establishment and persistence of infection requires repeated uptake by macrophages and other phagocytes. Therefore, preventing uptake could be a novel therapeutic strategy for leishmaniasis. However, the host machinery that mediates parasite uptake is poorly understood. In the present study, we addressed the underlying mechanisms of regulation of *Leishmania* amastigote internalization and pathogenesis. Using small-molecule inhibitors and primary macrophages lacking specific Mitogen-activated protein kinases/Extracellular signal regulated kinases (MAPK/ERK), we demonstrate that ERK1/2 mediates both phagocytosis and the efficient uptake of *Leishmania amazonensis* by macrophages. Syk and Abl/Arg family kinases mediate the ERK activation that is required for efficient uptake. Consistent with these results, MEK1 or ERK1/2-deficient macrophages are inefficient at amastigote uptake and produce large F-actin-rich phagocytic cups, showcasing a defective phagocytic process. Interestingly, ERK's role in uptake is relatively specific, as beads only mildly activate ERK and MAPK inhibitors only by mild decreased internalization. Finally, trametinib, a MEK inhibitor, significantly reduces disease severity and parasite burden in *Leishmania*-infected mice than controls. Our studies are the first to demonstrate that efficient phagocytosis and maximal *Leishmania* infection require MAPK/ERK family kinases. Our results highlight MAPK/ERK family kinase-mediated signaling pathways as potential therapeutic targets for leishmaniasis.

1834

CELLULAR DYNAMICS OF IMMUNE EVASION DURING *LEISHMANIA MAJOR* INFECTION

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There is a balance between the immune response and parasite escape mechanisms. *Leishmania majo*r parasites elicit a strong T cell response, yet evade complete clearance and persistently infect a small pool of cells. *Leishmania major* driven induction of the immunosuppressive microenvironment through recruitment of regulatory T cells at the site of infection has been proposed to prevent parasite clearance. In the presented study, we used a novel TCR transgenic mouse model, where $CD4^+$ T cells recognize an immunodominant peptide derived from *Leishmania*- glycosomal phosphoenolpyruvate carboxykinase (PEPCK), to visualize the dynamics of anti-*L. major* $CD4^+$ T cell responses and to characterize mechanisms which restrain their effector function. We show that macrophage:T cell interaction dynamics were prolonged upon antigen recognition, which leads to activation and production of high levels of IFNγ. Th1 activation can be significantly suppressed by PEPCK-specific Tregs *in vitro*, as compared to polyclonal Treg controls. Co-culture of PEPCK-specific $CD4^+$ T cells, *L. major*-infected macrophages, and Tregs shows that antigen activation leads to a substantial increase in IL-10 levels, while decreasing IL-12, TNF, and IL-2 production in the culture. Intravital microscopy studies characterizing PEPCK-specific $CD4^+$ T cell migration dynamics and tissue localization within skin lesions directly in live mice show a significant recruitment of adoptively transferred effector T cells to the lesion site *in vivo*, displaying cellular behaviours consistent with antigen recognition at early and late stages, yet both cellular dynamics are augmented at the chronic stage of infection. Upon secondary challenge with killed *L. major*, Tregs rapidly expand at the site of infection in healed mice. Currently we are evaluating how these Tregs are augmenting the cellular dynamics of Th1 cells. Collectively, our findings show for the first time that *Leishmania*-specific Tregs influence effector $CD4^+$ T cell responses and this could be a mechanism that derives antigen persistence in *L. major* infection.

1835

THE CHAGAS ANTIGEN AND EPITOPE ATLAS: DEEP SEROLOGICAL SURVEYS OF HUMAN CHAGAS DISEASE POPULATIONS

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During an infection, the immune system produces antibodies against pathogens. With time, the immune repertoires of infected individuals become specific to the history of infections and thus represent a rich source of diagnostic markers. Until now, a complete description of antibody specificities in different individuals has been hindered by the lack of powerful tools. Here, using high-density peptide arrays we examined the global human antibody repertoire developed by Chagas Disease patients. We synthesized and assayed twenty-four high-density peptide arrays each displaying 2.8 million unique peptides from 30,500 proteins encoded in the *T. cruzi* CL-Brener (TcVI) and Sylvio X10 (TcI) genomes. These were assayed with serum samples from infected subjects from Argentina, Bolivia, Brazil, Colombia, Mexico and the US, and matched negative samples. Two additional arrays were assayed with samples from

Leishmaniasis patients (to screen for cross-reactive peptides). As a result of this discovery phase screening, we obtained 21,062 reactive peptides from 7,707 proteins, corresponding to 3,868 non-redundant antigenic regions. These reactive regions were used to design new high-density peptide arrays for validation, epitope mapping and estimation of seroprevalence of each antigen/epitope. These arrays, displaying 393,000 peptides, were assayed in duplicate with a collection of 71 individual serum samples from the same geographic regions. At this stage we also performed single-residue mutational scanning of selected epitopes to define the core residues of each epitope. In this presentation we will showcase the first proteome-wide search for Chagas Disease antigens and the fine mapping of the identified linear epitopes at the individual level and across different human populations. These datasets enable the study of the Chagas antibody repertoire at an unprecedented depth and granularity, while also providing a rich dataset of serological biomarkers.

1836

POC CUTANEOUS LEISHMANIASES DIAGNOSIS: HANDHELD ULTRA- FAST PCR AND LATERAL FLOW ASSAYS FOR *LEISHMANIA* PARASITES DETECTION AND IDENTIFICATION

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Cutaneous Leishmaniasis (CL), a group of vector-borne parasitic diseases, is a major but worldwide neglected public health problem. In Tunisia and most of Old-World regions the disease is caused by 3 major endemic *Leishmania* (*L.*) species or complexes (*L. major: L.m*, *L. tropica: L.t, L. infantum/L. donovani: L.i*). Early and accurate detection of infectious diseases is a key step for surveillance, epidemiology, and control, notably timely disease diagnosis, patient management and follow-up. In this study, we aimed to develop hand-held ultra-fast duplex PCR assays coupled to amplicon detection by lateral flow (LF) immunoassay to deliver a rapid and simple molecular diagnostic test for concomitant detection and identification of the main *Leishmania* parasites encountered in Tunisia and the Old World. Two DNA targets were selected through a bibliography search and a computational analysis to amplify *L.m/L.tr* and *L i/L.t* group of species, respectively. We optimized the experimental conditions of a duplex ultra-fast PCR, where the amplification is performed by a portable Palm convection PCR machine within 18mn, and the products are detected by a PCRD cassette within 5mn. The test allows the identification of the infecting species according to the number of test lines revealed: *L.i* (line 1), *L.m* (line 2), *L.t* (line 1 & 2). Tested on a selection of DNAs of representative *Leishmania* strains of the three studied species (N=35), the ultra-fast duplex PCR-LF showed consistent, stable and reproducible results. The analytical limit of detection of the test was 20 pg for *L.m* and *L.t* and 2 pg for *L.i*. To mimic a real situation of the detection of parasites' DNA from CL samples, human blood was spiked with a known amount of *L. major* cultured promastigotes. The extracted DNA was serially diluted to investigate the analytical sensitivity of this assay. Our ultra-fast duplex PCR was able to detect 0.4 parasites. This study delivered a simple, reliable and rapid DNA test that identifies the species while minimizing time to result and sparing biological samples. Work is ongoing to prove the principle of using this assay for CL diagnosis by validating it on human cutaneous samples.

1837

A HIGH-CONTENT DRUG SCREENING APPROACH TO IDENTIFY NATURAL ANTI-LEISHMANIAL COMPOUNDS: A PROOF-OF-PRINCIPLE THROUGH NOVEL GLYCOLYSIS AND EPIGENETIC MODULATION INHIBITORS NP234 & NP008

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Leishmaniasis a vector borne parasitic disease remains a serious public health problem globally. Among NTDs, the mortality rate of leishmaniasis is the highest. All currently approved therapeutics have toxic side effects and face rapidly increasing resistance. Our group is involved in developing new therapeutics against different targets such as ion channels, carbohydrate transporters, carbohydrate metabolism and epigenetic machinery. To achieve this, we have standardized a robust pipeline integrating *in-silico* and *in-vitro* methods. We have virtually screened compounds against all these targets from the natural compound library containing over 9000 secondary metabolites from sources with known ethnobotanical value. We identified 34 hits from these libraries and we developed a screening strategy, based on a transgenic line of *L.donovani* constitutively expressing Ds-Red2 fluorescent reporter, normalized with Hoechst-33342 stained nuclei. We performed High content (HC) fluorescent live imaging screening to test these *in-silico* hits against intracellular stages and identified potent compounds having impact on parasite morphological changes and used it in a pharmacological screening approach. To provide a proof-of-principle, we have consistent data with the STD drugs i.e. Amphotericin B, Miltefosine and Pentamidine. Using this HC imaging analysis, we have previously screened a library of 96 FDA approved drugs and identified Lansoprazole and Posaconazole that inhibit Ca^{2+} pump and sterol metabolism respectively. Additionally, we have confirmed cytotoxicity in 4 different cell-lines (HEK-293, HUH-7, A549 and PBMCs). Following our integrated method, here we report two promising compounds NP234 & NP008 with antiparasitic IC_{50}s 356nM and 573nM. The specificity of these compounds was further confirmed with induced-fit docking followed by long (100ns) MD simulations to confirm the stability of the docked complexes. We propose our HC screening is a cost-effective approach to identify potential drugs from large library for treating Leishmaniasis and pave the way towards effective and more tolerable therapeutic options.

1838

DEVELOPMENT OF A LATERAL FLOW IMMUNOASSAY FOR NEUROLOGICAL TOXOPLASMOSIS THROUGH A NOVEL PROTEIN MAPPING TECHNIQUE

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Opportunistic neurological infections in persons living with HIV (PLHIV) are challenging to diagnose. CT and MRIs with a clinical suspicion can guide treatment, but definitive diagnosis remains elusive for many patients. *Toxoplasma gondii (T. gondii)* is known to cause Toxoplasmic Encephalitis in PLHIV. Though difficult to diagnose, it has up to 90% clinical response rate to treatment. Innovations in *T. gondii* diagnostics, such as our team's urine-based diagnostic western blot utilizing hydrogel nanoparticle antigen concentration, require laboratory equipment and skilled personnel, limiting its utility. To expand access to the diagnostic assay, we initiated

development of a sandwich lateral flow assay for our antigen of interest, GRA1. To identify the binding regions of antibodies we used the protein painting technique. Protein painting uses covalent dyes to coat antigen-antibody complexes. The region of the protein bound by the antibody will be protected from the covalent dye. The dyed verse undyed regions of the protein are identified with mass spectrometry. This technique was used to identify a potentially immunodominant region of GRA1. Validation of the immunodominant region was completed with peptide array. The protein painting technique offers an alternative to labor intensive hydrogen-deuterium exchange experiments and facilitates rapid identification of antibody binding regions for sandwich assay development. Future work will apply our new understanding of antibody binding sites to continue development of the lateral flow assay.

1840

VALIDATION OF THE MOBILE SUITCASE LABORATORY AS A TEST FOR CURE OF KALA-AZAR AND POST KALA-AZAR DERMAL LEISHMANIASIS

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The potential reservoirs of leishmaniasis in South Asia include relapsed cases of visceral leishmaniasis (VL), and patients with post kala-azar dermal leishmaniasis (PKDL). Therefore, accurate estimation of parasite burden and assessment of cure in terms of parasite clearance are pivotal for ensuring disease elimination. Serological tests are unable to detect relapses and/or monitor treatment effectiveness. Accordingly, parasite antigen/nucleic acid detection are the only viable options. Recombinase Polymerase Amplification (RPA) has emerged as an ideal diagnostic tool for leishmaniasis out of a mobile suitcase laboratory. In this study, the RPA test was evaluated for its diagnostic and prognostic performance as a test of cure. Total genomic DNA was isolated from peripheral blood (VL, n = 44) and lesional biopsies (PKDL, n = 64; macular and polymorphic, 1.3:1.0), before and at the end of their respective treatment. Kinetoplast-DNA based qPCR and RPA assays were performed and parasite load was expressed in term of Cycle threshold (Ct) and Time threshold (Tt) respectively. The clinical performance of the assay along with cross-reactivity and specificity was determined. The suitcase laboratory was successfully operated with a clinical sensitivity of 96% and 91.30% in patients with VL and PKDL, respectively. A significant correlation was observed between Ct vis-à-vis Tt and 100% specificity was attained by both techniques. Prognostic potential was estimated by LD-RPA and was in concordance with LD-qPCR. Overall, the findings of this study endorse the potential of LD-RPA to evolve as a point-of-care diagnostic and prognostic tool for Leishmania infections.

1841

OUTCOME OF A FOUR YEAR FOLLOW UP IN CHILDREN WITH CHAGAS DISEASE TREATED WITH A NEW FORMULATION OF NIFURTIMOX - THE CHICO SECURE CLINICAL STUDY RESULTS

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Nifurtimox, an antiprotozoal, has been used for treating Chagas disease for more than 50 years. Efficacy and safety of a new formulation was investigated in a multicenter, randomized, double blind Phase 3 trial using a historical placebo control in pediatric patients (birth to 17 years) with acute or indeterminate chronic Chagas disease. Patients were followed for 4 years post-treatment. Response to treatment was assessed as negative conversion of *Trypanosoma cruzi* (*T. cruzi*) antibodies by enzyme linked immunosorbent assay (ELISA) and indirect hemagglutination assay (IHA). Parasite clearance was evaluated by quantitative polymerase chain reaction (qPCR). A total of 330 children were assigned to a 60-day (n=219) or 30-day (n=111) treatment regimen. Of those, 318 and 282 children completed the 1 year and 4 year post-treatment follow-ups, respectively. Results of 1-year follow-up have been published elsewhere (Altcheh et al. PLoS Negl Trop Dis 2021). The 60-day nifurtimox treatment regimen showed superiority over historical placebo, with an incidence rate of seronegative conversion of 2.12% (95% confidence interval; 1.21% to 3.45%) considering the number of new cases of seronegative conversion over the study period compared with 0% for historical placebo. Decrease in antibodies was observed and seronegative conversion increased from 7 patients at 1-year to 16 patients. High parasite clearance was observed by qPCR (>95%), and only 1.37% and 0.51% of the patients in the 60-day treatment regimen had positive qPCR test at 1year and 4 year follow-ups, respectively. In the 30 day treatment regimen, seronegative conversion was reached in 4 and 8 patients at 1 year and 4 year follow up, respectively, and high parasite clearance (92%) was observed. No adverse events assessed as related to nifurtimox were observed between the 1 year and 4 year follow up timepoints. The results confirm the safety and efficacy of the 60 day nifurtimox treatment in children by showing superiority over historical placebo in the incidence of seronegative conversion.

1842

EXPLORING THE ROLE OF THE GUT MICROBIOTA IN TISSUE REPAIR DURING INTESTINAL HELMINTH INFECTION

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Intestinal helminth infection is a neglected tropical disease affecting over 2 billion people worldwide. While this chronic disease is rarely fatal, it can cause morbidities such as anemia, and intestinal obstruction. As the gut microbiome can regulate tissue homeostasis and maintenance, the interactions between intestinal parasites and the microbiome need to be elucidated. Our lab has developed a model of axenic helminth infection that can fully isolate effects of the microbiome and helminth infection. Our previous study showed that the presence of the gut microbiota was able to reduce excess type 2 immune response that would otherwise be detrimental to resolution of intestinal inflammation. We and others have previously shown that an early type 1 immune responsecontributes to tissue repair and reduction of intestinal bleeding. Thus, we hypothesize that the gut microbiota regulates type 2 protective immunity to helminth infection through promotion of the type 1 immune response. Our preliminary results showed an enhanced expression of type-2-associated genes, *Arg1,Chil3* and *Reltnb*, during chronic axenic helminth infection. In contrast, early germ-free helminth infection induced a decreased expression oftype-1-associated genes, *Cxcl9* and *Ly6a*, and a reduced production of lipocalin 2, an inflammatory molecule produced by neutrophils. To examine isolated effects of the type 1 immune response during helminth-induced tissue inflammation, we employed interferon gamma (IFNy)-receptor-knockout mice, where we observed that IFNy signalling may promote granuloma resolution. Inconclusion, our preliminary results show that the microbial-induced type 1immune response may inhibit over-exuberant type 2 immunity and subsequent pathological fibrosis. The overall goal of this project is to uncover the exact role of the microbiome during intestinal helminth diseases.

1843

WHAT CAN WE LEARN ABOUT THE SUBCELLULAR ORGANISATION OF *P. FALCIPARUM* USING U-EXM?

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Plasmodium falciparum, the deadliest cause of malaria, is responsible for ~400,000 deaths each year. Despite its clinical significance, our ability to study the fascinating physiology of this important pathogen has been significantly limited by its small size. Ultrastructure expansion microscopy (U-ExM) is a sample preparation method recently adapted for *P. falciparum* that physically increases the parasite size and therefore image resolution ~4x. We have begun a collaborative project to catalogue validated *P. falciparum* organelle markers across its intraerythrocytic development, with our focus on *P. falciparum* nucleus organization during mitosis. We have identified that the biogenesis of the *P.falciparum* microtubule organizing centre (MTOC), which nucleates the cell's microtubules, occurs near a cluster of nuclear pore complexes. Previous studies have shown that the MTOC spans the nuclear envelope, with intranuclear and cytoplasmic extensions. We have shown that these cytoplasmic MTOC extensions are only visible once the nucleus begins mitosis and that they seem to form a connection between the nuclear envelope and parasite plasma membrane (PPM). Once the parasite begins biogenesis of its apical organelles, the cytoplasmic extension of the MTOC then resides within the parasite's developing apical polar rings with the nascent rhoptries on either side of it. As the parasite begins cytokinesis, the MTOC appears to disassociate from the PPM and degrade, with no MTOC visible in mature or invading merozoites. Through this collaborative work, we aim to determine the organellar organisation of *P.falciparum* during its blood-stage replication and decipher new insights into parasite physiology.

1844

A POSITIVE FEEDBACK LOOP CONTROLS CHRONIC-STAGE DIFFERENTIATION IN *TOXOPLASMA*

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Successful infection strategies must balance parasite amplification and persistence. In *Toxoplasma gondii*, this is accomplished through differentiation into semi-quiescent chronic stages known as bradyzoites that avoid clearance by the host immune system. We recently identified a single transcription factor—Bradyzoite Formation Deficient 1, or BFD1—that is both necessary and sufficient for stage conversion, making it the master regulator of this process. Despite being transcribed throughout the *Toxoplasma* asexual cycle, BFD1 protein is not detected in acute stages, implying that its expression is translationally controlled; however, the factors involved were unknown. In the present study, we expand our model with the discovery of BFD2, a second factor indispensable for the chronic stage. BFD2 is a cytosolic RNA-binding protein expressed in acute stages and upregulated during differentiation. We show that basal levels of BFD2 are required for induction of BFD1, placing it upstream in the regulatory hierarchy. Conversely, BFD1 promotes transcription of BFD2, constituting a positive feedback loop. We show that BFD1 protein levels—but not mRNA abundance—are affected by BFD2 knockout, consistent with translational regulation. In agreement with this, BFD2 interacts with the BFD1 transcript under conditions leading to differentiation. Together, our data support a model wherein BFD2 licenses stress-dependent translation of BFD1 and acts in a feedback loop with the master regulator to enforce commitment to the chronic differentiation program. This circuit provides a mechanism for how bistable switching between proliferation and persistence is achieved during *Toxoplasma* infection.

1845

UNDERSTANDING THE EFFECTS OF GLUTAMATE ON MGLUR+ CD8 T CELLS RECRUITED TO THE T. GONDII INFECTED BRAIN

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Toxoplasma gondii (T. gondii) is one of the most effective transmissible pathogens in the world, infecting approximately two billion people. Encystment of the parasite in neurons in the brain results in a lifelong chronic infection. Within the brain, a pro-inflammatory response is essential to prevent disease from parasite reactivation. Infection in the immunocompromised leads to lethal Toxoplasmic encephalitis while in the immunocompetent, there is persistent low-grade inflammation which is devoid of clinical symptoms. This suggests that there is a tightly regulated inflammatory response to T. gondii in the brain. T cells are required to control parasite replication through the production of effector molecules such as perforin and IFNγ. However, the regulation of these cells in this critically important tissue is poorly understood. During chronic infection there is an increase in extracellular (EC) glutamate that is normally tightly controlled in the brain. High EC glutamate is not specific to T. gondii infection and can occur during multiple pathologies in the CNS, but may be an important environmental signal to tissue-specific immune cells. We hypothesize that this glutamate-rich environment plays a role in T cell function and regulation. Here we demonstrate that CD8 T cells from the T. gondii-infected brain are enriched for metabotropic glutamate receptors (mGluR's), mGluR1 and mGlur5. In addition, single cell RNA sequencing and flow cytometry analysis suggests that mGluR expression on CD8 T cells confers a memory phenotype. Furthermore, we demonstrate that brain mononuclear cell cultures treated with αCD3/αCD28 and glutamate enhance the production of IFNγ relative to controls, and IFNγ-producing cells are primary composed of mGluR-expressing CD8 T cells. Many therapies for neurodegenerative disease aim to decrease EC glutamate conditions to restore neuronal health. It is therefore important to understand the role of glutamate signaling on immune cells in the CNS in order to understand the balanced and protective inflammatory response to T. gondii in the brain.

1846

SUGAR MODIFICATIONS TO THE GPI REGULATE *TOXOPLASMA GONDII* VIRULENCE

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The development of an effective vaccine against parasitic infections like *Toxoplasma gondii* requires more understanding about the battle between host and pathogen. We are exploring the role the GPI anchor plays in T. gondii virulence and immune evasion. The glycosylphosphatidylinositol (GPI) anchor is a highly conserved glycolipid that anchors proteins to the external membrane of *T.gondii* and is found in all eukaryotes. While the core structure of the GPI is conserved, species differ in sugar modifications

made to the core structure, called "side chains". GPI-lipids (GPILs) of *T. gondii* are known to be recognized by innate pattern recognition receptors TLR-2 and -4 and are robustly targeted by IgM antibodies after infection with *T. gondii*. However, the role of the glycosyl side chain of the GPI is unknown. We have successfully characterized and knocked out the glycosyltransferase responsible for GalNAc addition to the mannose backbone of the GPI in *T. gondii*. Parasites lacking this enzyme have complete loss of both GalNAc and GalNAc+Glc GPI glycoforms, which allowed us to explore how modifications to the GPI anchor impact parasite virulence, a first for any pathogen. These mutant parasites, including type III "nonvirulent" strains, have increased virulence and decreased IgM recognition of GIPL, demonstrating that the GPI anchor sidechain modulates parasite virulence. We are currently exploring mechanisms by which the glycosylated side chain of the GPI is required for proper immune detection and resistance mechanisms to *T. gondii*, but suspect evasion of innate immune detection underpins several of these phenotypes associated with the mutants.

1847

GENETIC SCREENS IN *PLASMODIUM BERGHEI* IDENTIFY HUNDREDS OF FERTILITY GENES AND A SUN PROTEIN THAT LINKS DNA TO MICROGAMETES

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Sexual reproduction of malaria parasites is essential for their transmission by mosquitoes. Biological processes required for *Plasmodium* fertility include the formation of gametocytes, their transformation into gametes, fertilisation in the bloodmeal, meiosis, and the formation of an invasive ookinete. Stage-specific gene expression data suggest that hundreds of parasite genes are uniquely required for sexual reproduction, but previous gene knockout studies have merely scratched the surface of this important aspect of parasitebiology. We mutagenised *P. berghei* lines that make only fertile male or only fertile female gametocytes with barcoded *Plasmo*GEM vectors to screen over 1200 targetable genes for sex-specific phenotypes. Our screens identified 348 genes that affect fertility, which recapitulates existing knowledge and assigns function to unannotated genes. We pooled 125 mutants with the strongest male fertility phenotypes and sampled barcodes from purified microgametes in a motility screen. Microgamete motility was not reduced in 22 mutants, including a putative SUN domain-containing protein that has a male-specific role. SUN-KO parasites lack mitosis I spindles and microgamete DNA, and ultrastructure-expansion microscopy of SUN-KO and SUN-HA parasites revealed that SUN localises to nuclear pores to anchor microtubule organising centres to the nuclear envelope during microgametogenesis. Interestingly, immunoprecipitation of SUN-HA revealed a putative allantoi case as one of the main binding partners of SUN, which also has a male-specific fertility phenotype. Altogether, this provides an unbiased picture of the molecular mechanisms of *Plasmodium* fertility at genome-scale and identifies an essential male SUN protein that links mitosis to axoneme formation.

1848

THE IMPORTANCE OF THE UNFOLDED PROTEIN RESPONSE AND UBIQUITIN PROTEASOME SYSTEM IN *P. FALCIPARUM* ARTEMISININ RESPONSE

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Malaria remains a global health problem and drug resistance is a major barrier to treatment. Resistance to artemisinin, the cornerstone of first-line antimalarials, has been detected in Asia, Africa, and South America. Mutations in the propeller domain of Kelch13 (K13) mediate artemisinin resistance by decreasing parasite hemoglob indigestion and, consequently, artemisinin activation. Artemisinin alkylates parasite proteins and causes wide spread protein damage. We hypothesize that parasite survival following artemisinin treatment is dependent on the unfolded protein response (UPR) and the ubiquitin proteasome system (UPS). In response to artemisinin, ring stage $K13^{WT}$ (artemisinin-sensitive) parasites displayed pronounced and sustained UPR activation following artemisinin removal. In contrast, $K13^{Mut}$ (artemisinin-resistant) parasites displayed slight UPR activation and resolution following drug washout. At the trophozoite stage, $K13^{Mut}$ activated the UPR earlier than $K13^{WT}$ parasites. Previously we showed that parasites with a mutation in the β2 proteasome catalytic subunitare sensitized to artemisinin. Relative to their parent, artemisinin-treated β2mutants display elevated levels of K48-linked ubiquitination, a hallmark of proteasome malfunction. Furthermore, these β2 mutants display increased sensitivity to the UPS inhibitors epoxomicin and bAP-15, but not the unrelated drugs chloroquine or methylene blue. These data underline the importance of the UPR and UPS in artemisinin resistance.

1849

EXPLORING THE DEEPEST SECRETS OF THE TRYPANOSOMA BRUCEI NUCLEAR ARCHITECTURE

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In eukaryotic parasites, gene expression is crucially linked to genome folding. As an example, in human malaria parasites, the three-dimensional clustering of genes involved in immune evasion correlates with their regulated silencing. In the bloodstream form of our model organism Trypanosoma brucei, expression of the major antigen involves an inter-chromosomal contact bringing in spatial vicinity the active antigen gene and a major RNA maturation locus. Such functional genomic structure has been described with the use of a genome-wide chromosome conformation capture (Hi-C 2.0) method. The technique is based on quantifying frequencies of contacts between DNA loci. These contacts are generated by digestion with a restriction enzyme and ligation of fragments to their closest neighbors. The size of the fragments being ligated poses a limit to the maximum resolution of the method. In turn, a limited resolution curbs the identification of other functional roles of genome folding. Here, we dramatically improved the resolution of our architectural data by establishing a method that makes use of a micrococcal nuclease (Micro-C). Moreover, to further explore the complexity of the T. brucei nuclear architecture, we added an important piece of information to our analysis by establishing a method to map genome-wide RNA-chromatin interactions (RADICL-seq). Finally, in order to analyze such complex datasets, we developed a software to interactively visualize, process and integrate them with other types of data. Together, these tools allowed us to identify new three-dimensional features of the T. brucei genome, such as loops bringing together transcription start sites. Our data suggest that in trypanosomes transcription might occur at discrete clusters and that nuclear organization may contribute to global gene expression regulation, as shown for more complex eukaryotes.

1850

EXTRAVASCULAR SPACES ARE RESERVOIRS OF ANTIGENIC DIVERSITY IN *TRYPANOSOMA BRUCEI*

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Trypanosoma brucei lives an entirely extracellular life cycle in its mammalian host, facing a constant onslaught of host antibodies. The

parasite evades clearance by the host immune system through antigenic variation of its dense variant surface glycoprotein (VSG) coat, periodically "switching" expression of the VSG using a large genomic repertoire of VSG-encoding genes. Studies of antigenic variation *in vivo* have focused exclusively on parasites in the bloodstream, but recent work has shown that many, if not most, parasites are extravascular and reside in the interstitial space of tissues. This parasite population has gone completely uncharacterized with respect to antigenic variation. We sought to explore the dynamics of antigenic variation in extravascular parasite populations using VSG-seq, a high-throughput sequencing approach for profiling VSGs expressed in populations of *T. brucei*. Our experiments show that the expressed VSG repertoire is not uniform across populations of parasites with in the same infection and that a greater number of VSGs are expressed in tissue spaces than in the blood. More than 75% of the VSGs detected in an animal were exclusively within extravascular spaces. Interestingly, we also noticed a delay in the VSG-specific clearance of parasites in tissue spaces compared to blood. This finding aligns with a model in which parasites "hide" from the immune system in tissue spaces, where a slower immune response provides them with more time to generate new antigenic variants. Overall, our results show that extravascular spaces are significant reservoirs of VSG diversity, potentially resulting from the delayed clearance of parasites in these spaces.

1851

ELO PATHWAY IS CRITICAL FOR MAINTENANCE OF BROAD METABOLIC PROCESSES AND EFFICIENT GROWTH IN *TRYPANOSOMA CRUZI*

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The mechanisms by which *Trypanosoma cruzi* maintains the optimal membrane lipid composition are not well understood. The fatty acyl (FA) chains used for lipid synthesis/remodeling can be derived *de novo*, via a microsomal FA elongase (ELO) system, or scavenged from the extracellular environment. *T.cruzi* encodes five ELOs (ELO1-5) that act sequentially or in a modular fashion to elongate:C4:0 to C10:0 (ELO1), C10:0 to C14:0 (ELO2), and C14:0 to C18:0 (ELO3). ELO4 and ELO5 elongate very long chain FA and polyunsaturated FA. To determine the contribution of endogenous FA synthesis toward lipid homeostasis and growth of *T.cruzi*, null mutants were generated in which the genes encoding ELO1-3 were individually disrupted. Lipidome analysis of Δ*elo2* and Δ*elo3* epimastigotes revealed shortening of the FA chain length in diverse lipids sub-classes, consistent with the role of ELOs in lipid homeostasis. These changes were well-tolerated in epimastigotes as the growth of these mutants was minimally impaired. In contrast, disruption of ELO1 was associated with significant growth impairment but minimal lipidome perturbation. Unlike the other mutants, Δ*elo1* epimastigotes exhibited mitochondrial disturbances (decreased membrane potential and fatty acid oxidation; increased mROS production). Metabolicdys regulation in Δ*elo1* epimastigotes was further illustrated by marked changes in metabolites associated with glycolysis, pentose phosphate pathway, TCA cycle, and nicotinamide metabolism. Metabolic and growth phenotypes observed in the Δ*elo1* mutant were restored by genetic complementation. Thus, ELO1 is unessential for maintaining the lipid composition membranes but critical for homeostatic control of broad metabolic processes and growth of *T.cruzi* epimastigotes.

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