



RESEARCH BRIEF #3 FOR MEDIA

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Researchers Complete World's First 'Controlled Human Infection' Zika Study

An infectious disease expert from Johns Hopkins Bloomberg School of Public Health will present new results from the world's first "controlled human infection" study with Zika virus. It showed two strains of the virus can be safely and effectively used to deliberately infect human volunteers, a major advance for Zika vaccine development — and for understanding more about the disease. Infections with the mosquito-borne virus — which experts fear may be ripe for sparking new epidemics — are typically mild or asymptomatic. But vaccines are needed to prevent infections during pregnancy that, during the 2016 outbreak in the Americas, were linked to severe birth defects and disabilities among fetuses and newborns.

Zika transmission in the hotspots of the 2016 outbreak is very low at the moment. But there are concerns the disease can re-emerge more intensely on roughly 10-year cycles, meaning a new outbreak could occur in just a few years, said Anna Durbin, MD, an expert in vaccines for mosquito-borne diseases at the Bloomberg School who led the Zika controlled infection study. She said the lack of current cases means the only way to test the effectiveness of vaccines in advance of an outbreak is by developing a way to safely infect or "challenge" human volunteers with the disease. That's been controversial given the lack of a specific anti-viral drug for treating Zika. Durbin said her study was preceded by an extensive review by the U.S. National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), and the World Health Organization (WHO), which found for Zika, what's technically known as a "controlled human infection model," or CHIM, offered a safe and useful pathway for vaccine development.

She said the study evaluated two strains of the virus in female volunteers who were neither pregnant nor lactating. They agreed to be admitted as patients at a Johns Hopkins Center for Immunization Research inpatient unit in Baltimore until they were completely free of the virus and to continue using highly effective birth control methods for two months. She said the 20 women who received the test strains — eight others got a placebo — all developed laboratory-confirmed infections, but with only mild illness. She said several vaccine manufacturers have inquired about using the strains to test Zika vaccine candidates. Durbin said there are now plans

to evaluate controlled Zika infections in male volunteers, who also will remain on the inpatient unit until free of infectious virus, in part to assess how long Zika remains infectious in semen.

CONFERENCE SCIENTIFIC ABSTRACT FOLLOWS BELOW

Development of a controlled Zika human infection model (CHIM)

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Background: Zika virus (ZIKV) is a mosquito-borne flavivirus that was first isolated from the blood of a sentinel rhesus macaque in the Zika forest of Uganda in 1947. Sporadic reports of ZIKV infection and/or serologic evidence of ZIKV infection were reported from 1951 - 1981 from Africa and Asia. Brazil first identified an outbreak of ZIKV in its northeast region in early 2015. By September, increasing numbers of cases of microcephaly were being reported, particularly from regions involved in the ZIKV outbreak. Because of the devastating birth defects caused by congenital ZIKV infection, the World Health Organization (WHO) declared ZIKV a Public Health Emergency of International Concern (PHEIC) on February 1, 2016. Despite the development of numerous candidate vaccines for Zika, Phase 3 clinical trials have not been successfully performed due to the rapid resolution of the outbreak. A ZIKV CHIM could play a critical role in the licensure pathway of potential Zika vaccines as a tool to down-select candidates and provide proof-of-concept of effectiveness. **Methods:** Two different Zika human isolates were obtained and expanded under cGMP (ZIKV-SJRP/2016-184 and ZIKV-Nicaragua/2016). Normal, healthy non-pregnant and non-lactating women ages 18 - 40 who were dengue and ZIKV-naïve were recruited from the Baltimore area. Volunteers were block randomized and assigned to receive either ZIKV or placebo (5:2) in each cohort of 14 volunteers. Volunteers were admitted and housed in an inpatient unit and administered 100 PFU of ZIKV (or placebo) subcutaneously. Blood, cervico-vaginal secretions (CVS), urine and saliva were collected and assayed for ZIKV. Based on infectivity and safety, dose escalation up to 10,000 PFU could occur if needed. **Results:** Twenty-eight women have been enrolled (14 in the SJRP cohort and 14 in the Nicaragua strain cohort). The treatment assignment for 14 subjects in cohort 1 (SJRP/2016-184) and for the first 7 in cohort 2 (Nicaragua/2016) has been unblinded. Infectious ZIKV was recovered from serum in all volunteers who received a ZIKV. ZIKV was recovered by culture and quantitative PCR from multiple specimen types. The clinical presentation and viral kinetics for both ZIKV-SJRP/2016-184 and ZIKV-Nicaragua/2016 will be presented. **Conclusions:** ZIKV-SJRP/2016-184 and ZIKV Nicaragua/2016 are highly infectious and have an acceptable safety and virologic profile for use in a ZIKV CHIM for vaccine development.