
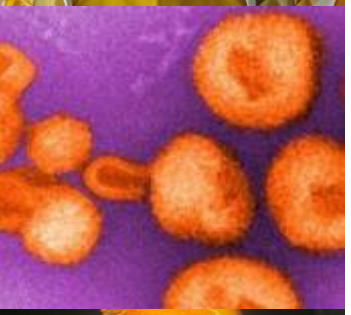

Update Course in Clinical Tropical Medicine & Travelers' Health September 27, 2025

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AMERICAN SOCIETY OF TROPICAL MEDICINE & HYGIENE
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VHF: CCHF, Marburg & Lassa

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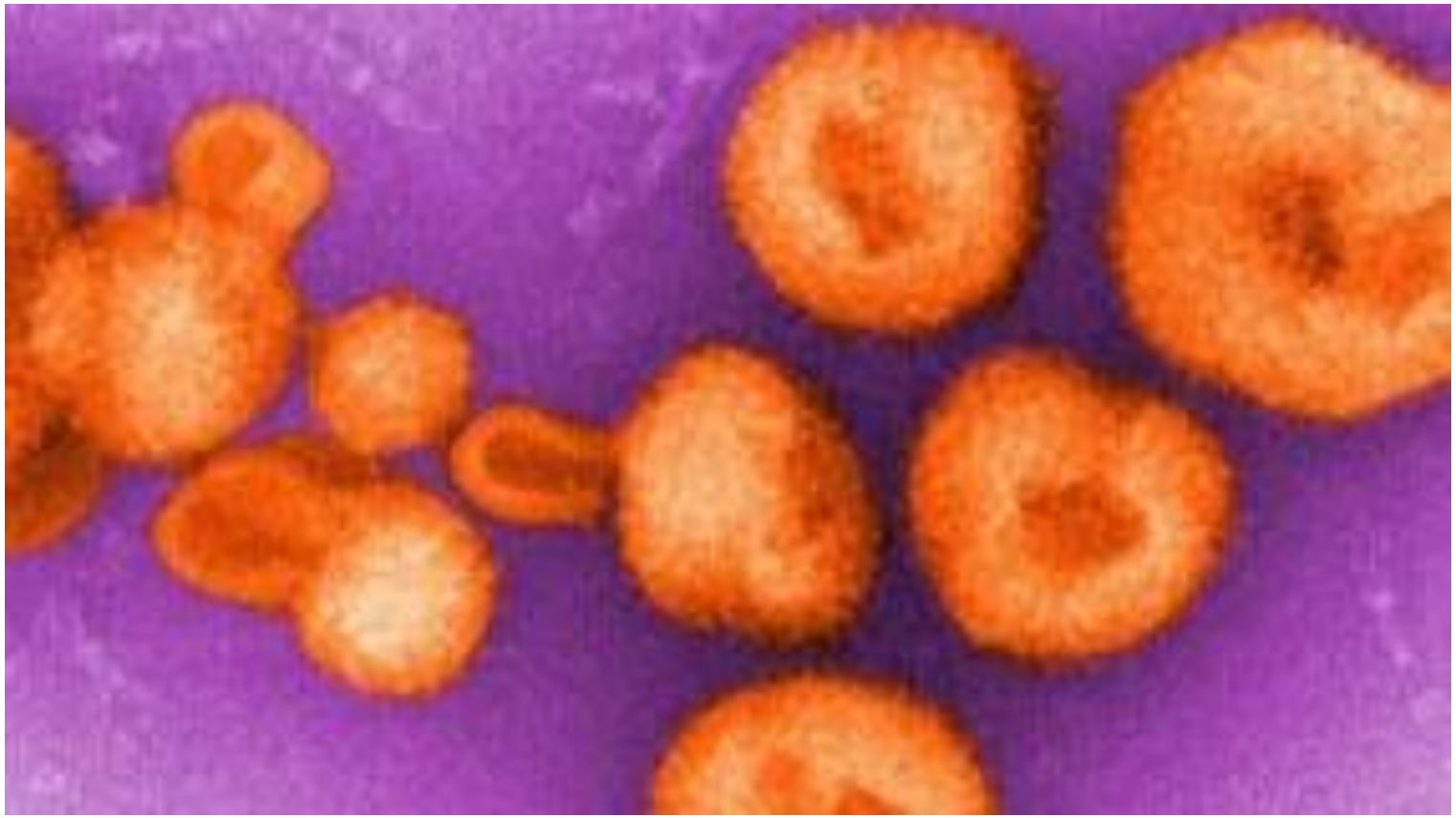
Agenda

01	Introduction: Viral hemorrhagic fevers
02	Marburg virus (MARV)
03	Lassa virus (LASV)
04	Crimean-Congo Hemorrhagic Fever virus (CCHFV)
05	Perspective-Conclusions

Viral Hemorrhagic Fevers



VHFs

- Severe multi-system syndrome with vascular involvement and bleeding
- Spectrum:

  mild symptoms →severe and lethal disease

- Most fall into one of four families:
  - *Arenaviridae*
  - *Bunyaviridae* (order)
  - *Filoviridae*
  - *Flaviviridae*

- Characteristics and common features:
  - RNA enveloped viruses
  - Survival dependant on host (animal or arthropod, natural host)
  - Distribution in areas with host presence
  - Humans not a natural reservoir: infection following contact with hosts (human-to-human transmission possible)
  - Potential risk to close contacts
  - Outbreaks may be difficult to predict

https://www.cdc.gov/viral-hemorrhagic-fevers/about/index.html (access July 2025); https://www.ecdc.europa.eu/en/viral-haemorrhagic-fevers (access July 2025); Hewson et al, Pathogens 2024

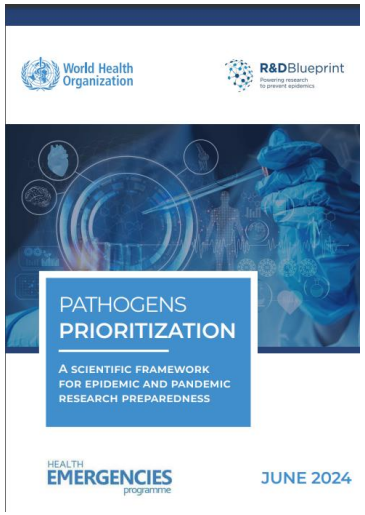
Table 1. Families and Pathogens that were prioritized in the 2024 update, as compared with the 2017 and 2018 prioritization processes[4].

	2017	2018	2024		
Family	**Priority Pathogens**	**Priority Pathogens**	**PHEIC risk**	**Priority Pathogens**	**Prototype Pathogens**
Adenoviridae			Low-Medium		Recombinant Mastadenovirus
Adenoviridae			Low-Medium		Mastadenovirus blackbeardi serotype 14
Anelloviridae			Low		
Arenaviridae	Arenaviral hemorrhagic fevers including Lassa Fever	Lassa Fever virus	High	Mammarenavirus lassaense	Mammarenavirus lassaense
Arenaviridae			High		Mammarenavirus juninense
Arenaviridae			High		Mammarenavirus lujoense
Astroviridae			Low		Mamastrovirus virginiaense
Bacteria			High	*Vibrio cholerae serogroup 0139*	
Bacteria			High	*Yersinia Pestis*	
Bacteria			High	*Shigella dysenteriae serotype 1*	
Bacteria			High	*Salmonella enterica non typhoidal serovars*	
Bacteria			High	*Klebsiella pneumoniae*	
Bornaviridae			Low		Orthobornavirus bornaense
Coronaviridae	Middle East Respiratory Syndrome Coronavirus	Middle East Respiratory Syndrome Coronavirus	High	*Subgenus* Merbecovirus	*Subgenus* Merbecovirus
Coronaviridae	Other highly pathogenic coronaviral diseases such as Severe Acute Respiratory Syndrome	Severe Acute Respiratory Syndrome	High	*Subgenus* Sarbecovirus	*Subgenus* Sarbecovirus
Filoviridae	Filoviral diseases Ebola	Ebola virus disease	High	Orthoebolavirus zairense	Orthoebolavirus zairense
Filoviridae	Filoviral diseases Marburg	Marburg virus disease	High	Orthomarburgvirus marburgense	

	2017	2018	2024		
Family	**Priority Pathogens**	**Priority Pathogens**	**PHEIC risk**	**Priority Pathogens**	**Prototype Pathogens**
Hepeviridae			Low		Paslahepevirus balayani genotype 3
Herpesviridae			Low		
Nairoviridae	Crimean Congo Haemorrhagic Fever	Crimean Congo Haemorrhagic Fever	High	Orthonairovirus haemorrhagiae	Orthonairovirus haemorrhagiae

Included in WHO pathogen priority list:

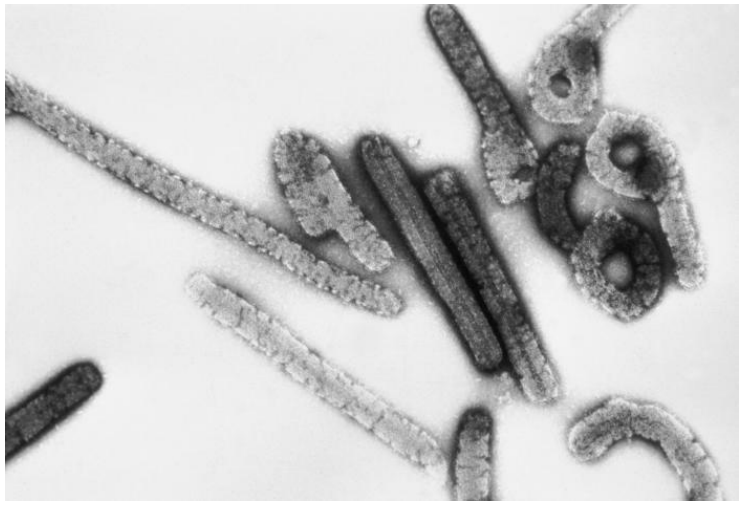
- *Mammarenavirus lassaense*
- *Orthomarburgvirus marburgense*
- *Orthonairovirus haemorrhagiae*



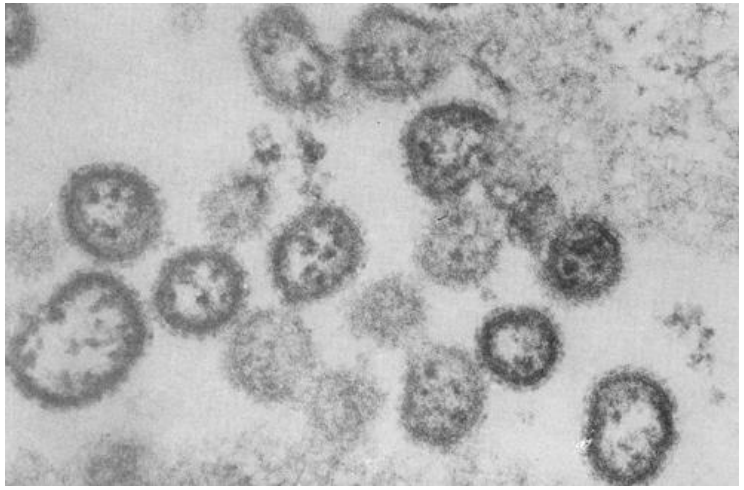
https://www.who.int/publications/m/item/pathogens-prioritization-a-scientific-framework-for-epidemic-and-pandemic-research-preparedness (access July 2025)

International Committee on Taxonomy of Viruses https://ictv.global/

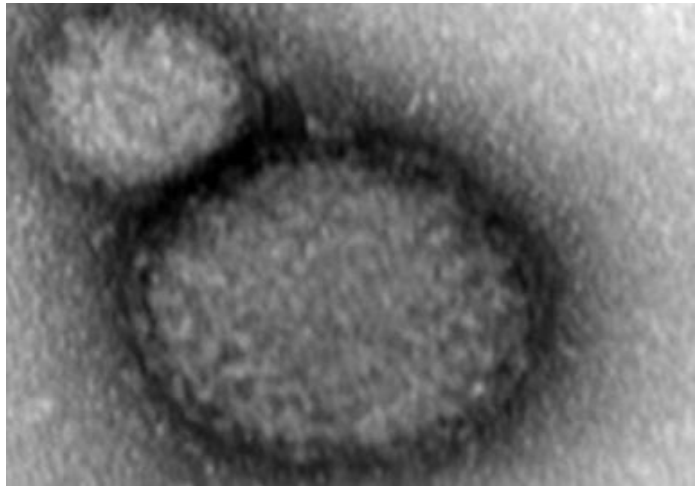
- Family*: Filoviridae*
- Genus*: Orthomarburgvirus*
- Species*: Orthomarburgvirus marburgense*
- Virus*: Marburg virus (MARV)* and *Ravn virus (RAVV)*



- Family: *Arenaviridae*
- Genus: *Mammarenavirus*
- Species: *Mammarenavirus lassaense*
- Virus: Lassa virus (LASV)



- Family: *Nairoviridae*
- Genus: *Orthonairovirus*
- Species: *Orthonairovirus haemorrhagiae*
- Virus: Crimean-Congo hemorrhagic fever virus (CCHFV)



Marburg virus

MARV: history and discovery

- First identified filovirus
- 1967: Germany (Marburg and Frankfurt) and Belgrade (former Yugoslavia, currently Serbia)

- Exposed laboratory workers→ hemorrhagic fever after contacting tissue from monkeys imported from Uganda (African Green monkey, *Cercopithecus aethiops*)
  - 32 cases, 7 deaths
- No additional cases until 1975→ case in S. Africa in traveler returning from Zimbabwe

MARV (1967-2025)

- 1967: Germany and Yugoslavia ex Uganda
- 1975: South Africa ex Uganda
- 1980: Kenya
- 1987: Kenya
- 1980: Russia (laboratory)
- 1998-2000: Durba, DR Congo
- 2004-2005: Uige province, Angola
- 2007: Kamwenge district, Uganda
- 2008: USA ex Maramagambo forest, Uganda
- 2008: Netherlands ex Maramagambo forest, Uganda
- 2012: Kabale, Uganda
- 2014: Kampala, Uganda
- 2017: Kween, Uganda
- 2021: Gueckedou, Guinea
- 2022: Ashanti region, Ghana
- 2023: Kie-Ntem, Littoral centro sur provinces, Equatorial Guinea
- 2023: Kagera, Tanzania
- 2024: Kigali, Rwanda
- 2025: Kagera, Tanzania

https://www.cdc.gov/marburg/outbreaks/index.html (access September 2025)

World Health Organization

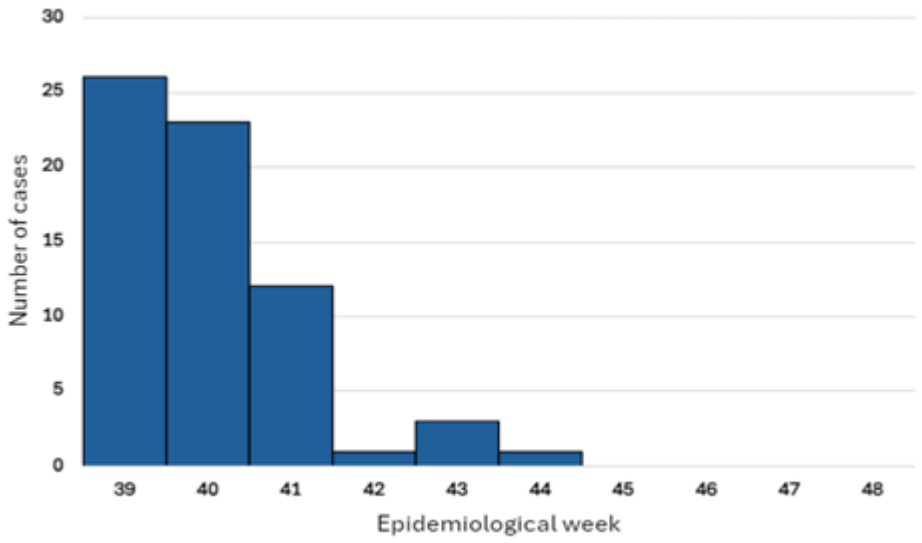
Health Topics | Countries | Newsroom | Emergencies

Home / Disease Outbreak News / Item / Marburg virus disease - Rwanda

Disease Outbreak News

Marburg virus disease - Rwanda

20 December 2024



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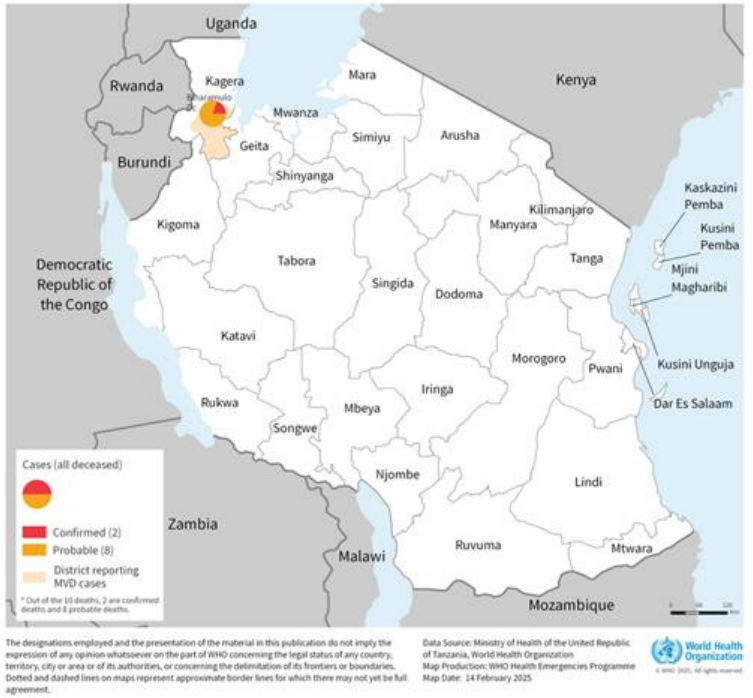
Disease Outbreak News

Marburg virus disease– United Republic of Tanzania

13 March 2025



https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON548; https://www.who.int/emergencies/disease-outbreak-news/item/2025-DON559

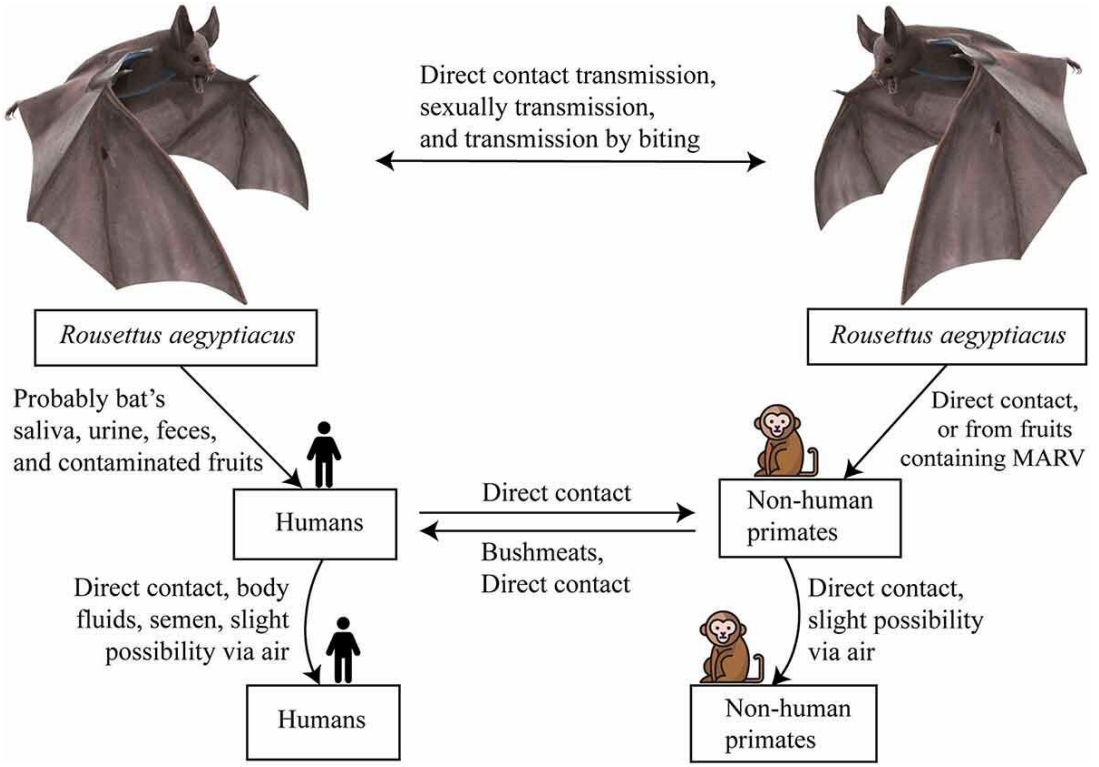
MARV: Natural ecology

- **Bats identified as viral reservoirs**
- **MARV recovered** from Egyptian fruit bats (*Rousettus aegyptiacus*) captured in a mine in Uganda where numerous cases had occurred over a 10-year period.
- Further role of bat exposure: exposed miners x5 more likely to have MARV Abs than control (non-exposed) group.

Bausch et al, NEJM, 2006, Nyakarahuka, BMC Inf Dis, 2020; Pigott et al, Trans Roy Soc Trop Med Hyg, 2015

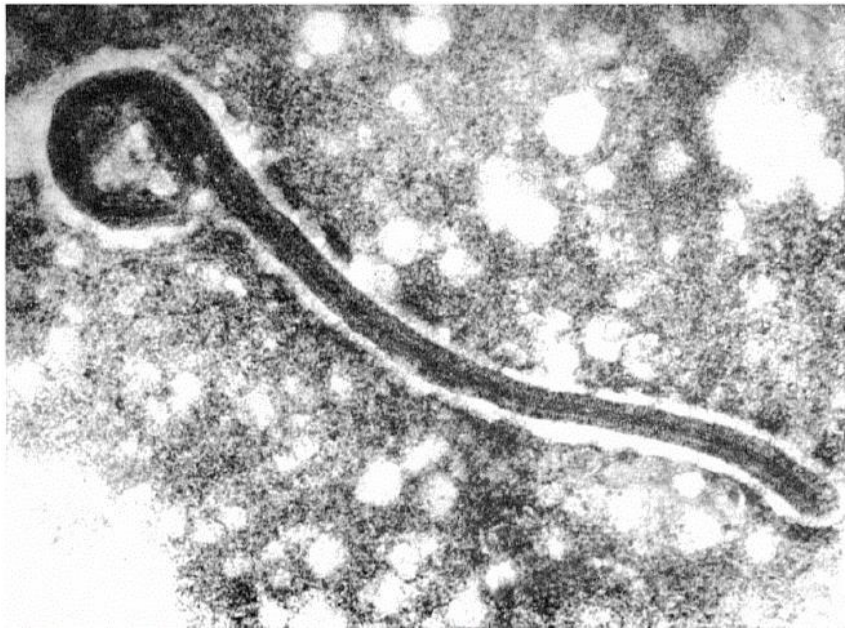
MARV: transmission

- **Human transmission** from contact with bats-other unidentified exposures
- Person to person through direct contact with blood or other body fluids
- MARV also transmitted in semen (also demonstrated for Ebola virus)
- No data to suggest transmission humans by mosquitoes-other arthropods
- Laboratory animals infected by exposure to aerosolized virus; no evidence for this mode of transmission in humans



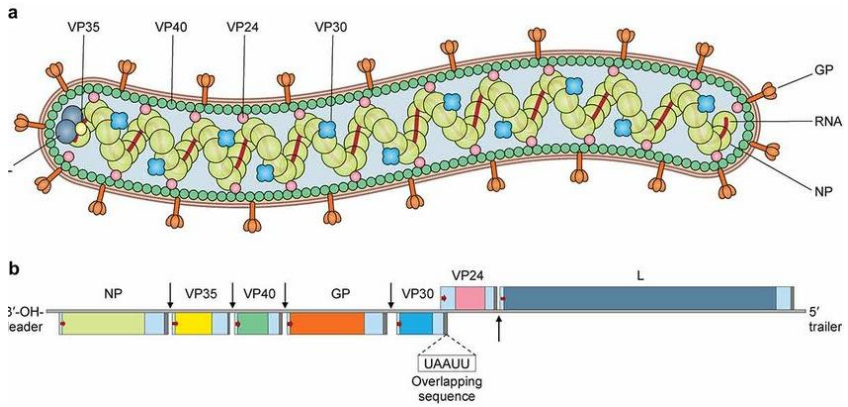
Abir MH, et al, Virulence. 2022; Coffin et al, Cell Host Microb 2018; Alves et al, Vet Pathol, 2010

MARV: structure and pathogenesis



- Family name derived from Latin "filum," "thread-like," based on filamentous structure of the virion
- MARV genome: seven structural proteins
- Cell tissue tropism and virus-cell membrane fusion determined by GP

- GP may play role in immune evasion, VP40 and VP35 are virulence factors facilitating immune evasion, minor matrix protein VP24 blocks cellular response to IFN, L protein mediates genome replication and transcription.



Abir MH, et al, Virulence. 2022; Gordon et al, Viruses, 2019; Bausch et al, NEJM 2006

MARV: clinical manifestations (I)

Incubation period: 5-10 days (range 3–21 days)

Related to infectious dose and route of infection

Transmission does not occur during incubation period.

Three phases:

First generalised phase (days 1–4)

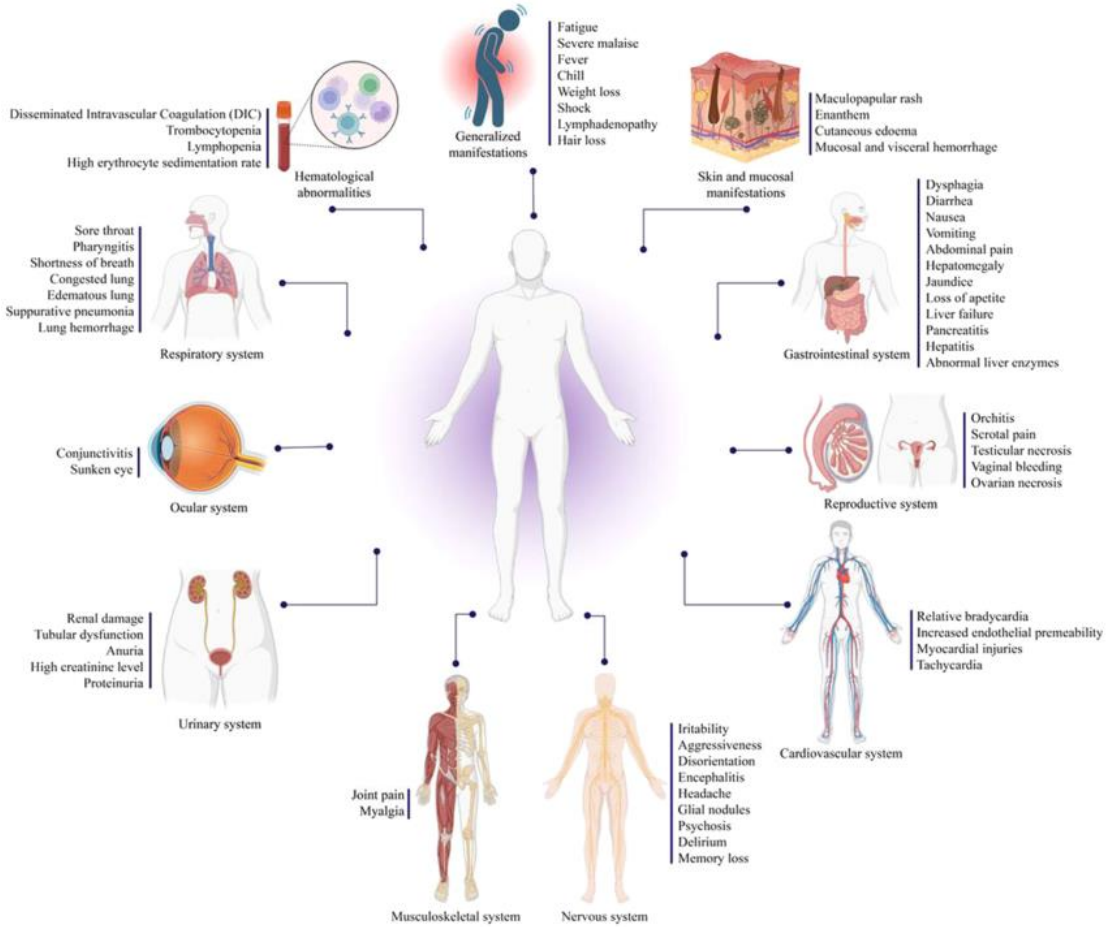
Early organ phase (days 5–13)

Late organ or a convalescence phase (days 13+)

https://www.ecdc.europa.eu/en/infectious-disease-topics/marburg-virus-disease/factsheet-health-professionals-about-marburg-virus; Mehedi M, et al. Future Virol. 2011; Shifflett K, et al. Virol J. 2019

MARV: clinical manifestations (II)

- **Abrupt onset**, non-specific, flu-like symptoms, high fever (39–40°C),
- In 50–75%: rapid deterioration, **marked gastrointestinal symptoms** (within 2–5 days).
- Days 5-7: maculopapular **rash;** symptoms **haemorrhagic fever**
- Neurological symptoms in later stages
- Complications (convalescence): joint pain, uveitis, orchitis, recurrent hepatitis, pericarditis and mental dysfunction
- Recovery or lethal outcome 8–16 days after onset.



https://www.ecdc.europa.eu/en/infectious-disease-topics/marburg-virus-disease/factsheet-health-professionals-about-marburg-virus; Mehedi M, et al. Future Virol. 2011; Shifflett K, et al. Virol J. 2019; Letafati et al, Health Science Reports, 2025

MARV: diagnosis (I)

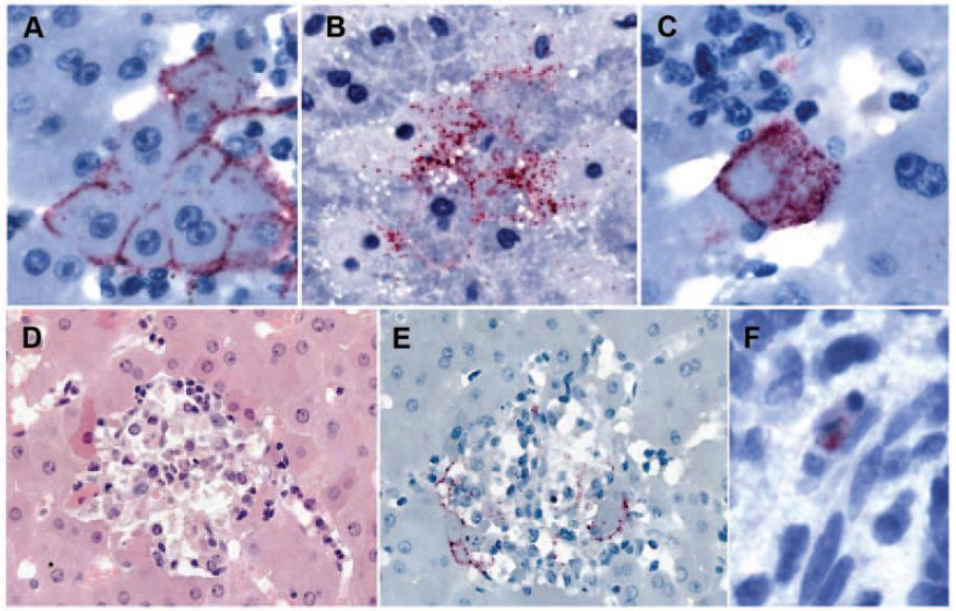
- **High index of suspicion**→ consider isolation
- Symptoms overlap with other infections: malaria, typhoid fever, dengue, other viral haemorrhagic fevers (Lassa fever or Ebola virus disease)
- Ideal sample: depends on time course of infection
- Virus isolation: limited availability
- **Molecular methods**: RT-PCR, may have limited strain coverage (depends on lab, false negatives possible)
- **Antigen detection**: antigen-capture ELISA targets proteins NP, VP40, and GP

Biosafety level 3: RT-PCR and ELISA on non-inactivated samples (BSL-2 if inactivated samples)
Biosafety level 4: virus isolation under strict biological containment circumstances.

https://www.ecdc.europa.eu/en/infectious-disease-topics/marburg-virus-disease/factsheet-health-professionals-about-marburg-virus; Emperador DM, et al . BMJ Glob Health. 2019;4(Suppl 2):e001112; Sherwood et al, J Infect Dis, 2007.

MARV: diagnosis (II)

- **Serology**: ELISA, IFA:
  - MARV IgM (appear 2–4 days after onset)
  - MARV IgG (8–10 days after onset- up to 2 years)
- Negative serology not exclusive: filovirus-infected individuals frequently die without developing humoral immune response
- Negative MARV serology in patients who recover from haemorrhagic fever could exclude MVD.
- **Histology**: antigen detection by immunohistochemistry (useful for post-mortem diagnosis)



Immunohistochemical localization of Marburg virus antigens in *Roussetus aegypticus* tissues

https://www.ecdc.europa.eu/en/infectious-disease-topics/marburg-virus-disease/factsheet-health-professionals-about-marburg-virus;
Emperador DM, et al . BMJ Glob Health. 2019;4(Suppl 2):e001112; Sherwood et al, J Infect Dis, 2007; Towner et al, PLOS Pathogens, 2009.

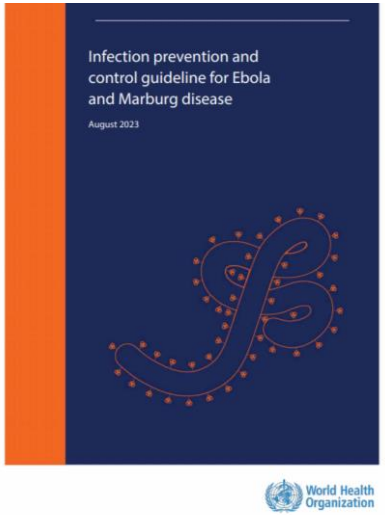
MARV: case management and treatment

- No specific antiviral treatment
- Supportive therapy improves clinical outcome
- In development: immunotherapeutics, phosphorodiamidate morpholino oligomers, lipid-encapsulated short interfering RNAs, small molecule inhibitors, interferons, antiviral nucleoside analogues
- Favipiravir and remdesivir appear beneficial in non-human primates, no demonstrated benefit in humans.
- Galidesivir effective vs MARV for up to 24 hours; clinical trials, results awaited
- Ribavirin and IFN: scarce benefit in treatment of MARV infection

Rougeron et al, J Clin Virol 2015; https://www.ecdc.europa.eu/en/infectious-disease-topics/marburg-virus-disease/factsheet-health-professionals-about-marburg-virus; Kortepeter et al, Int J Infect Dis, 2020; mehedi et al, Future Virol, 2011; Mathis et al, Clin Pharmacol Drug Dev, 2022

MARV: Public health control measures

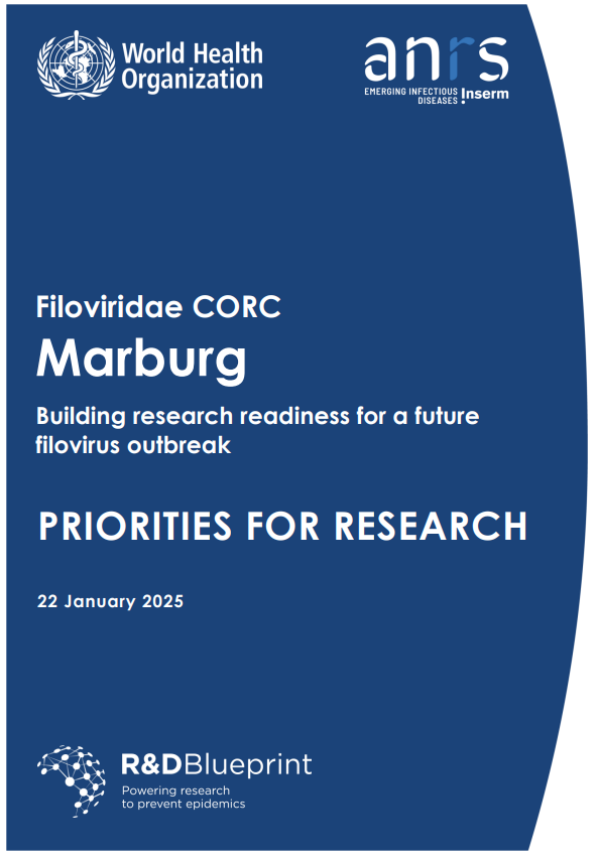
- Main goal: interruption direct human-to-human transmission.
  - Early detection
  - Systematic rapid isolation of cases
  - Timely contact tracing and close monitoring
  - Adequate personal protection
  - Safe burials
  - Community awareness



MARV: vaccine development

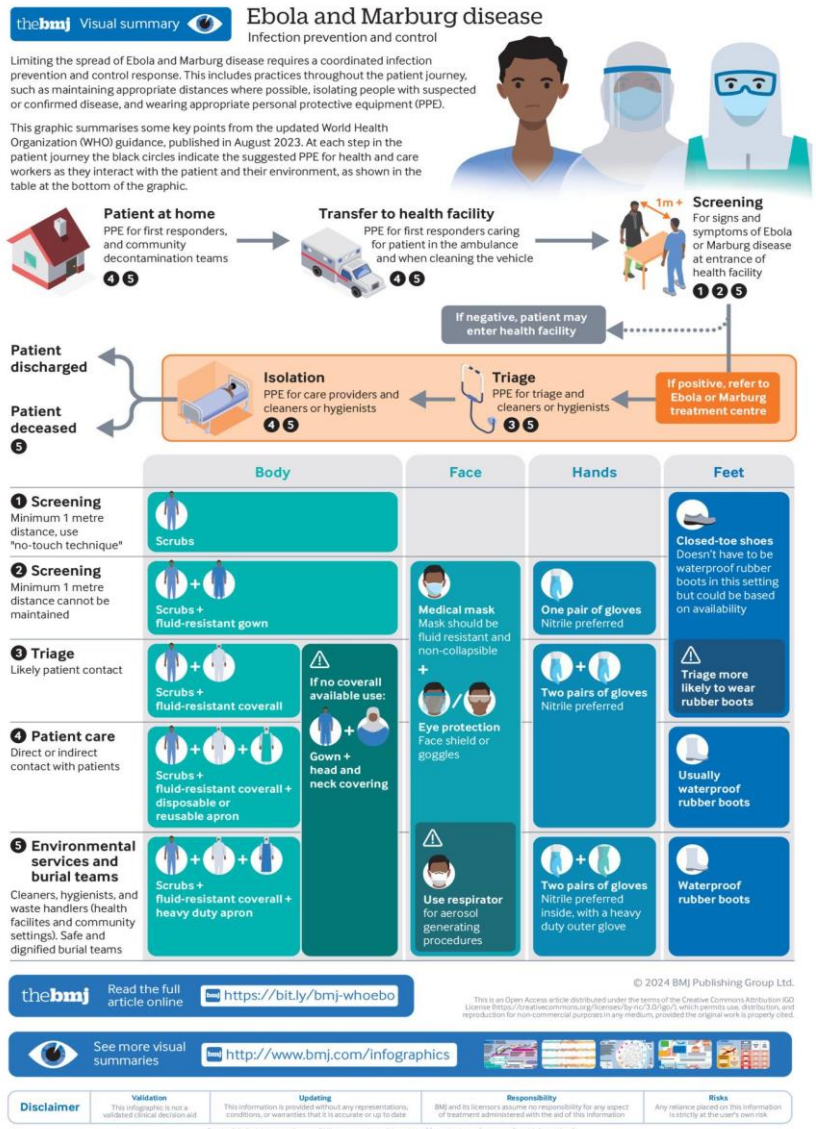
- No approved vaccine
- Ebola virus disease vaccines provide no benefit against Marburg virus.
- Efforts to develop Marburg vaccines under guidance of WHO-sponsored consortium (MARVAC), examples:

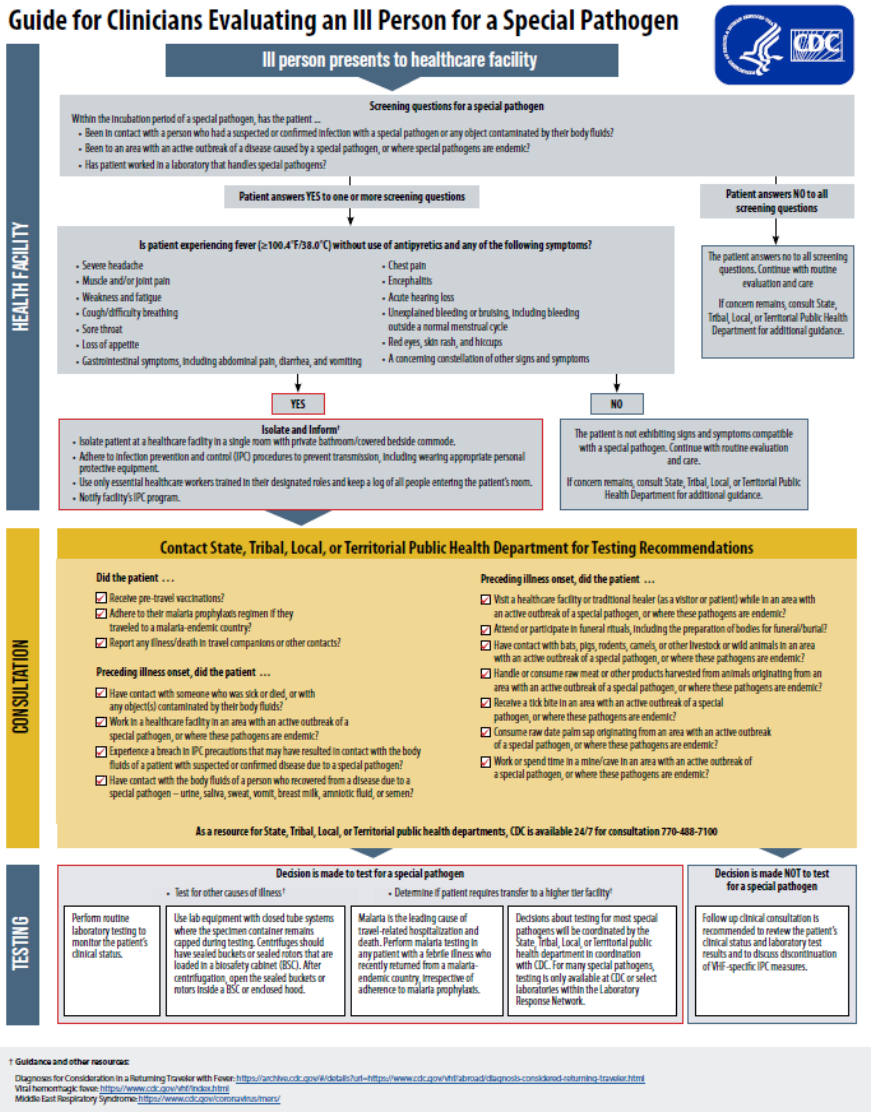
    - **Recombinant chimpanzee adenovirus vaccine** , chAd3 vaccine – (used in the response to the 2024 Marburg virus disease outbreak in Rwanda)
    - **VSV vaccines** – including trials of quadrivalent vaccine containing recombinant VSV encoding the surface glycoproteins of Marburg Angola, *Zaire* and *Sudan* species of Ebola virus, and Lassa virus (protected cynomolgus macaques against challenge by each pathogen)
    - **Adenovirus/modified vaccinia virus Ankara (MVA) vaccines**



Anywaine Z, et al, PLoS Med. 2022; Swenson DL, et al, Clin Vaccine Immunol. 2008; Milligan ID, et al. JAMA. 2016 ; Falzarano D,et al, Expert review of vaccines. 2011; Geisbert TW, et al, J Virol. 2010; Warfield KL, et al, J Infect Dis. 2011; Hamer MJ, et al, Lancet. 2023; Sabin Vaccine Institute. Sabin Vaccine Institute Delivers Marburg Vaccines to Combat Outbreak in Rwanda. Available at: https://www.sabin.org/resources/sabin-vaccine-institute-delivers-marburg-vaccines-to-combat-outbreak-in-rwanda/; Cross et al, J Clin Invest 2020; Cross et al, PLoS Pathog. 2022

Recommended reading





BMJ 2024; 384 doi: https://doi.org/10.1136/bmj.p2811 (Published 26 February 2024); https://www.cdc.gov/viral-hemorrhagic-fevers/media/pdfs/2024/07/336717-F_IG_SpecialPathogensTestingDecisionTree_022324_v2.pdf

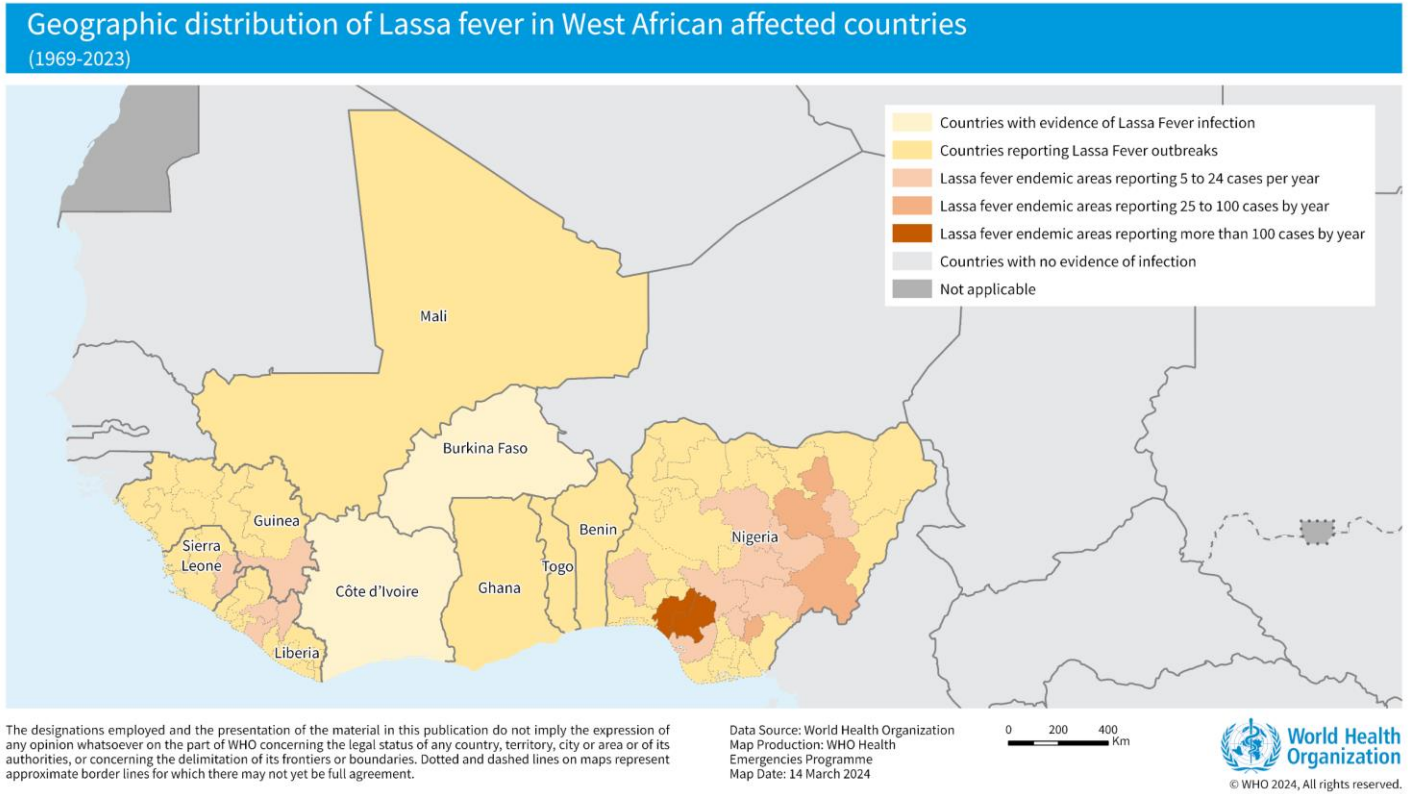
Lassa virus

LASV: history and discovery

- Lassa fever first described in Sierra Leone in 1950s
- Virus causing disease identified 1969 in Lassa, Borno State, Nigeria
- First patient: missionary nurse infected in a rural clinic near Lassa, Nigeria, died after being transported to hospital in city of Jos > 600 km away
- Samples analysed at Yale University, LASV first isolated

Garry, Nat Rev Microb, 2023

LASV: epidemiology

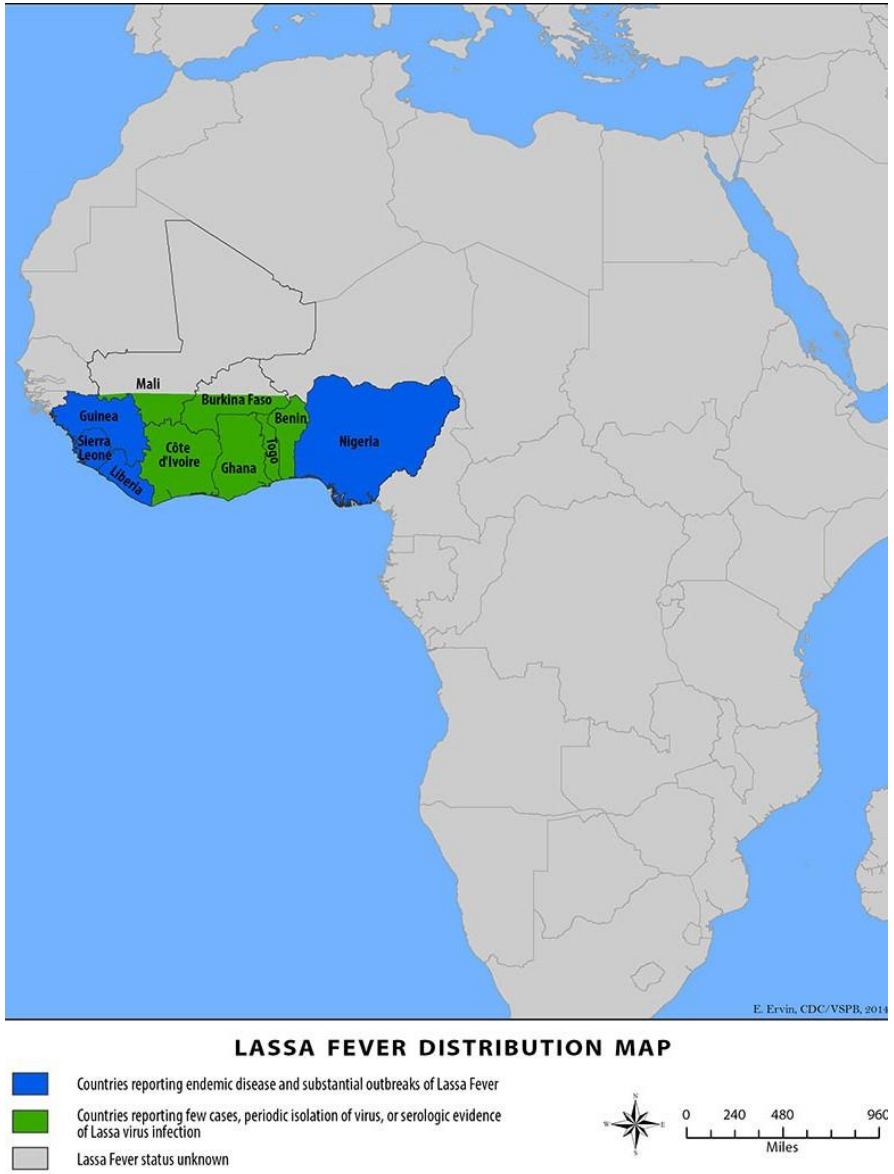


- Endemic in parts of West Africa: Guinea, Liberia, Sierra Leone, Nigeria, Benin, Ghana, and Mali
- Neighboring countries also at risk as animal vector distributed throughout the region.

https://www.who.int/multi-media/details/geographic-distribution-of-lassa-fever-in-west-african-affected-countries (access July 2025)

LASV: epidemiology

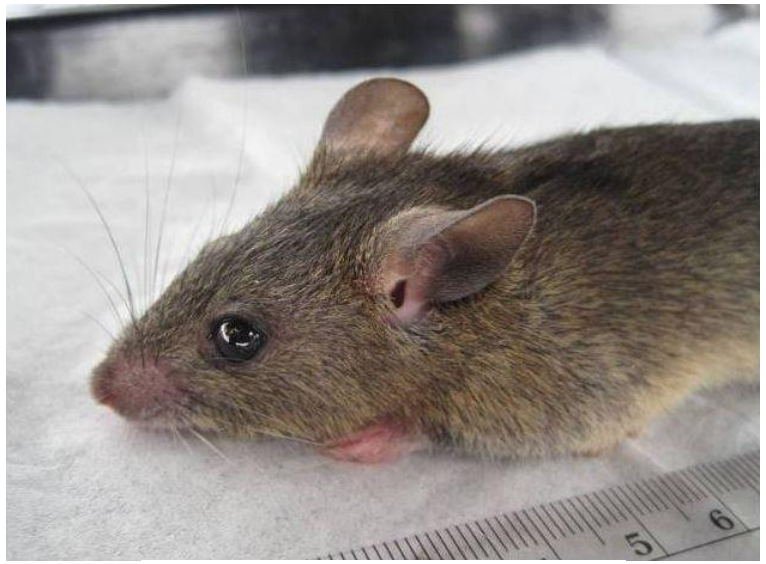
- 300,000 cases and 5000 deaths annually
- Prevalence of LASV infections varies within endemic areas
- Highest in forested regions of West Africa where Guinea, Liberia, and Sierra Leone share a border
  - Guinea: seroprevalence 4-55%
  - Sierra Leone: 8% (coastal regions)- 52% (Eastern Province).



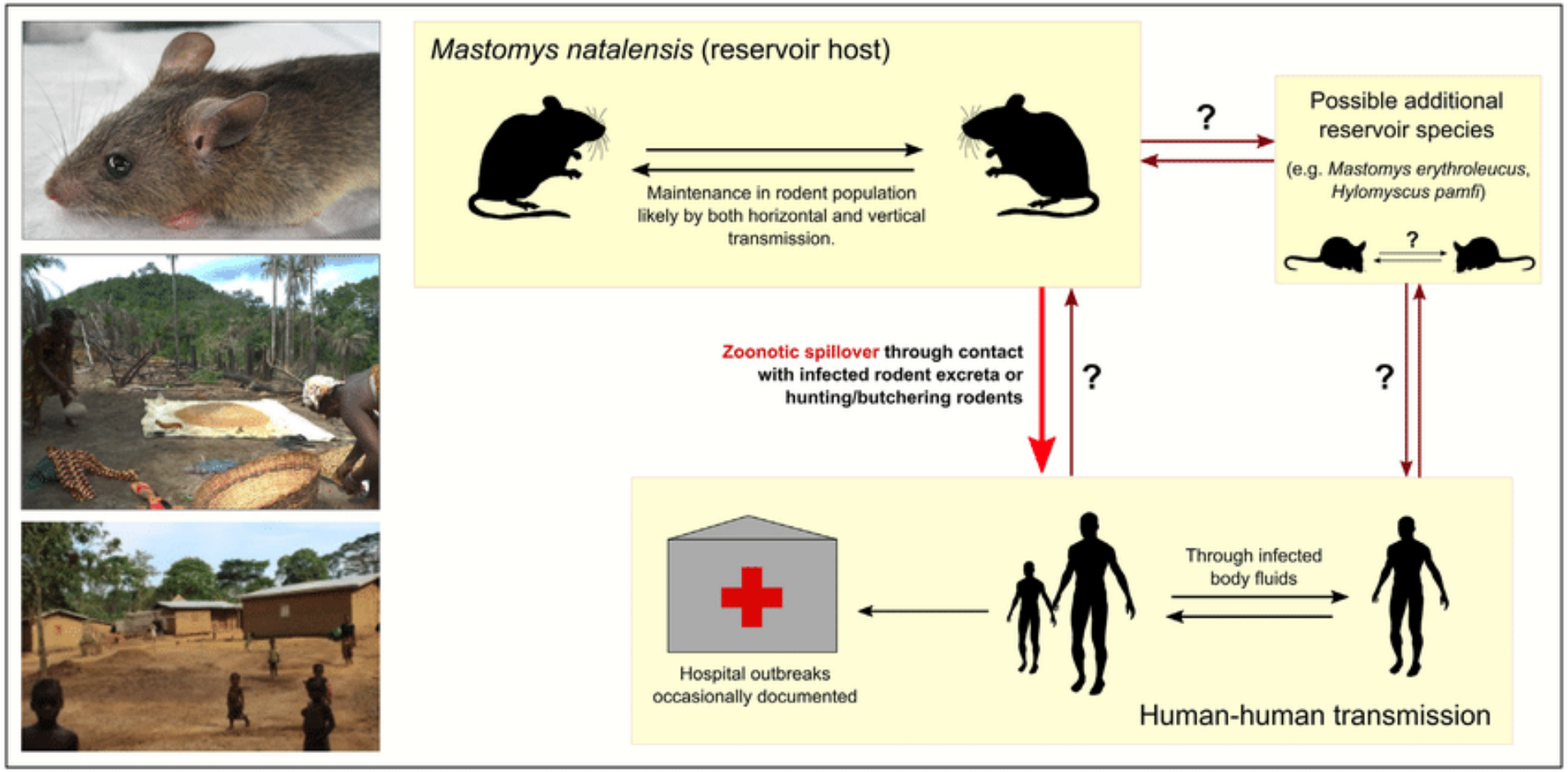
https://www.cdc.gov/lassa-fever/about/index.html (access September 2025); https://www.who.int/multi-media/details/geographic-distribution-of-lassa-fever-in-west-african-affected-countries

LASV: natural ecology

- Animal reservoir: rodent "multimammate rat" (*Mastomys natalensis*)
- Among most widespread rodent species in SS-Africa
- In W Africa, abundant in rural human homes, surrounding agricultural fields and gardens
- Transmission to humans via contact with infected rodent urine and feces and via person-to-person contact



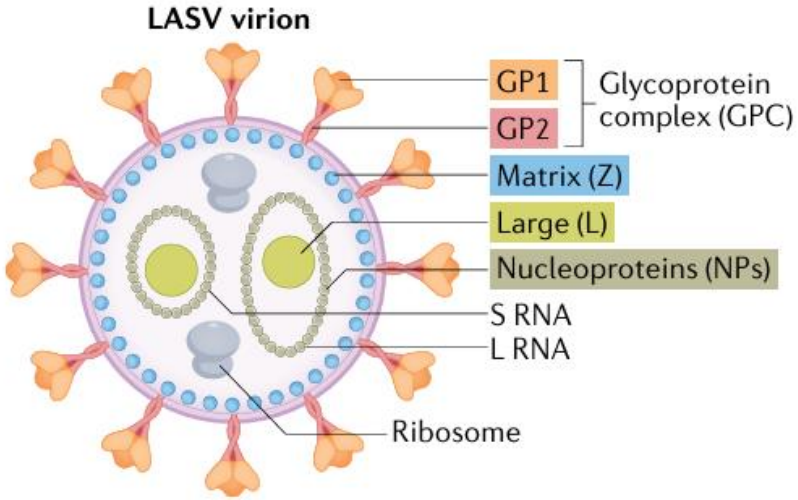
LASV: transmission

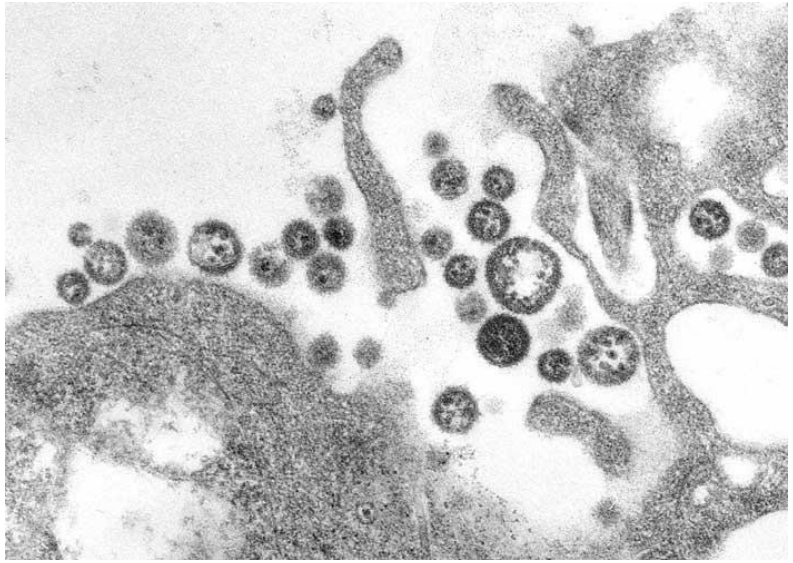


Gibb et al, Pathogens and Global Health, 2017

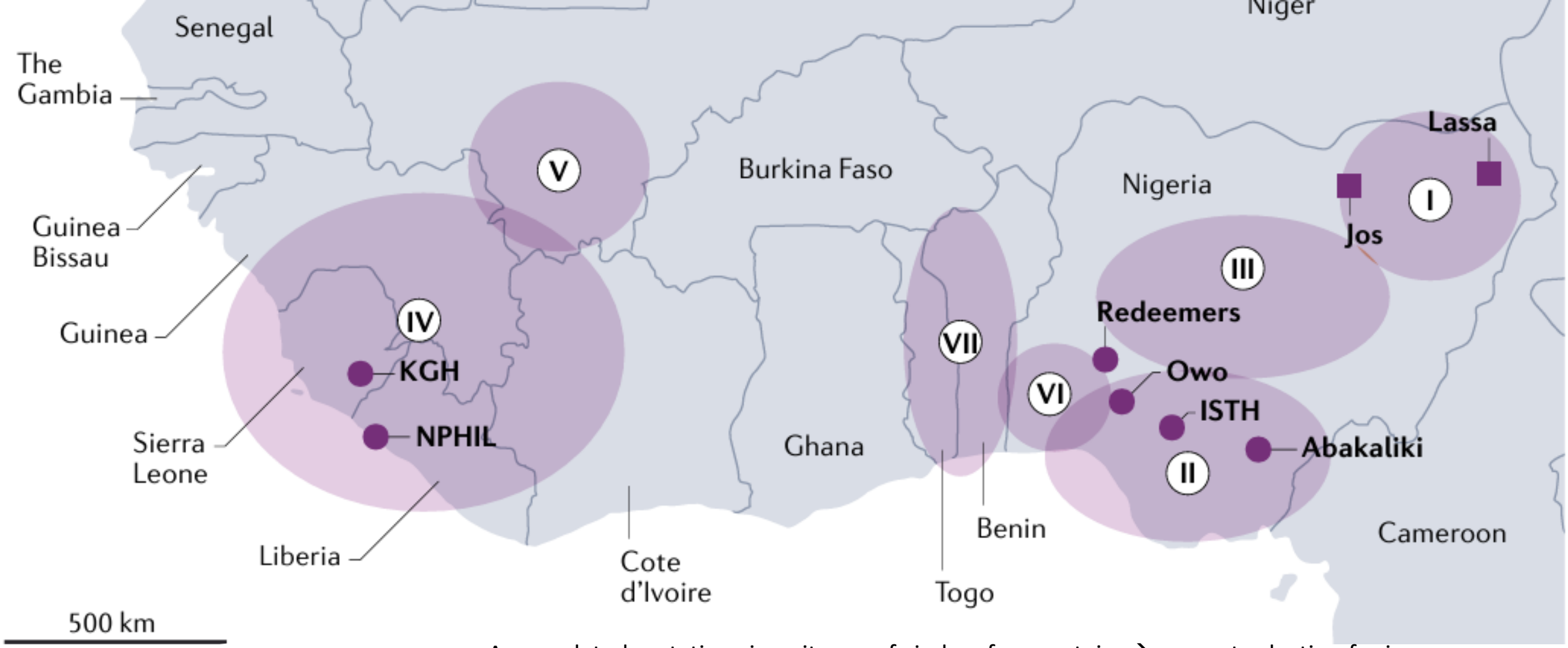
LASV: structure and pathogenesis

- Small enveloped virion appears filled with grains of sand (ribosomes)
- Virus family: *Arenaviridae* from arena/arenosus (Latin for sand/sandy)
- Infection usually via nasopharyngeal mucosa→ regional lymph nodes and disseminates to tissues.
- Severe disease from vascular instability, endothelial dysfunction and impaired hemostasis (release of soluble mediators).
- Among survivors, LASV levels peak between days 4 and 9 of illness
- Serum viral RNA detected up to three weeks after recovery
- Mainly cell-mediated immunity for survival; neutralizing antibodies after recovery.
- In fatal cases, cellular response weak.





Garry, Nat Rev Microbiol, 2023; CDC; Shieh et al, CID, 2022



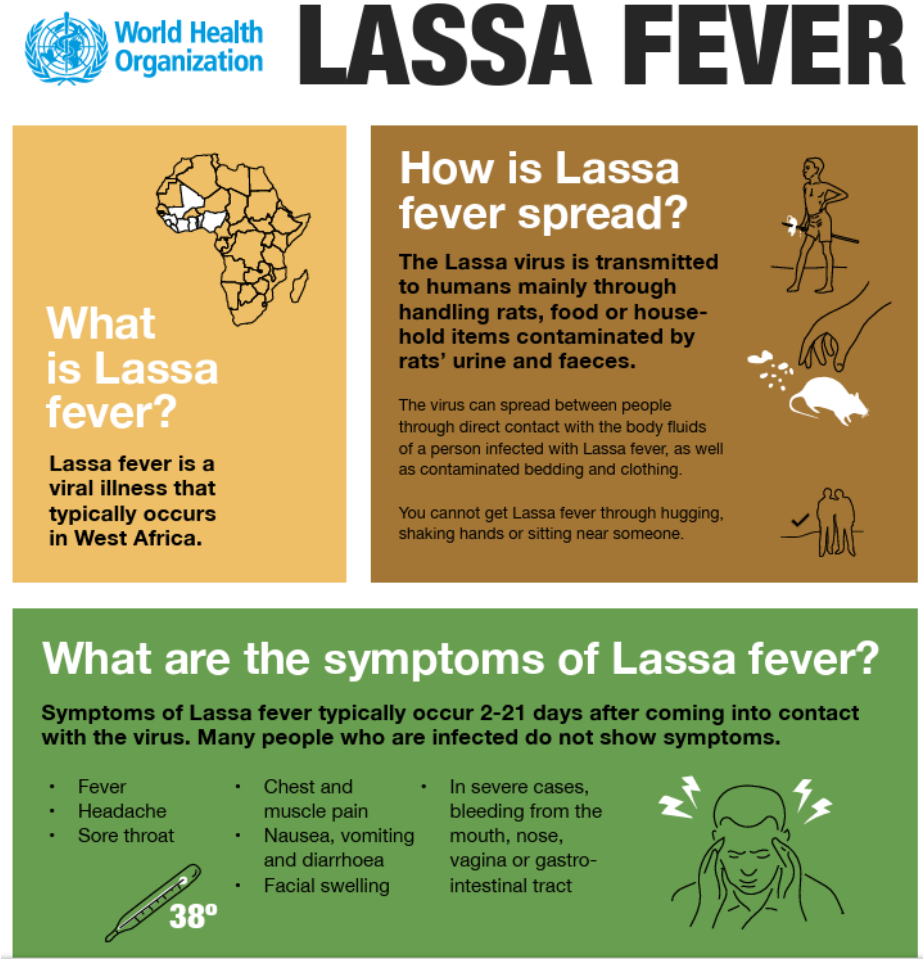
LASV: lineages

- Accumulated mutations in epitopes of viral surface proteins→ suggest selection for immune escape, most likely in rodent reservoirs. Spread and diversification of LASV ongoing
- Nigeria: north- east lineage I, lineages II and III in the south and central regions
- Lineage IV in Sierra Leone, Guinea and Liberia
- New LASV lineages, V, VI and VII, emerged in Mali, Côte d'Ivoire, Nigeria, Benin and Togo
- Relevance in human infections?

Garry, Nat Rev Microbiol, 2023; CDC

LASV: clinical manifestations

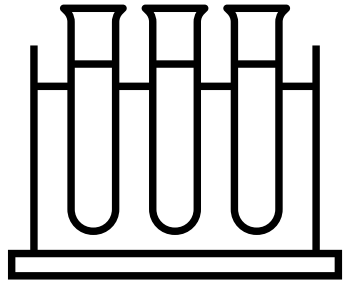
- Incubation period: 1-3 weeks
- No transmission prior to symptom onset
  - Approx 80%: **mild symptoms** (low-grade fever, malaise, headache)
  - In 20%: disease progression: **pharyngitis**, cough, N/V, diarrhea, chest pain, abdominal pain
- In severe cases: facial swelling, pulmonary edema, bleeding, hypotension.
- Shock, seizures, coma (later stages).
- Most common complication: **deafness** (30%)
- Recovery 8 -10 days after symptom onset
- Overall mortality 1 % (hospitalized patients 15-30%)



Saka et al, BMC Infect Dis, 2025

LASV: diagnosis

- **High index of suspicion**→ consider isolation



- PCR testing.
- Detection of IgM and IgG antibodies
  - IgM 10-21 days after symptom onset
  - IgG approx 21 days after symptom onset
- Variation among lineages (some assays may not have equal sensitivity)
- Some cross-reactivity between LASV, lymphocytic choriomeningitis virus, and New World arenaviruses such as Tacaribe virus
- Lassa antigen in serum
- Differential diagnosis: malaria, typhoid, secondary bacterial infections

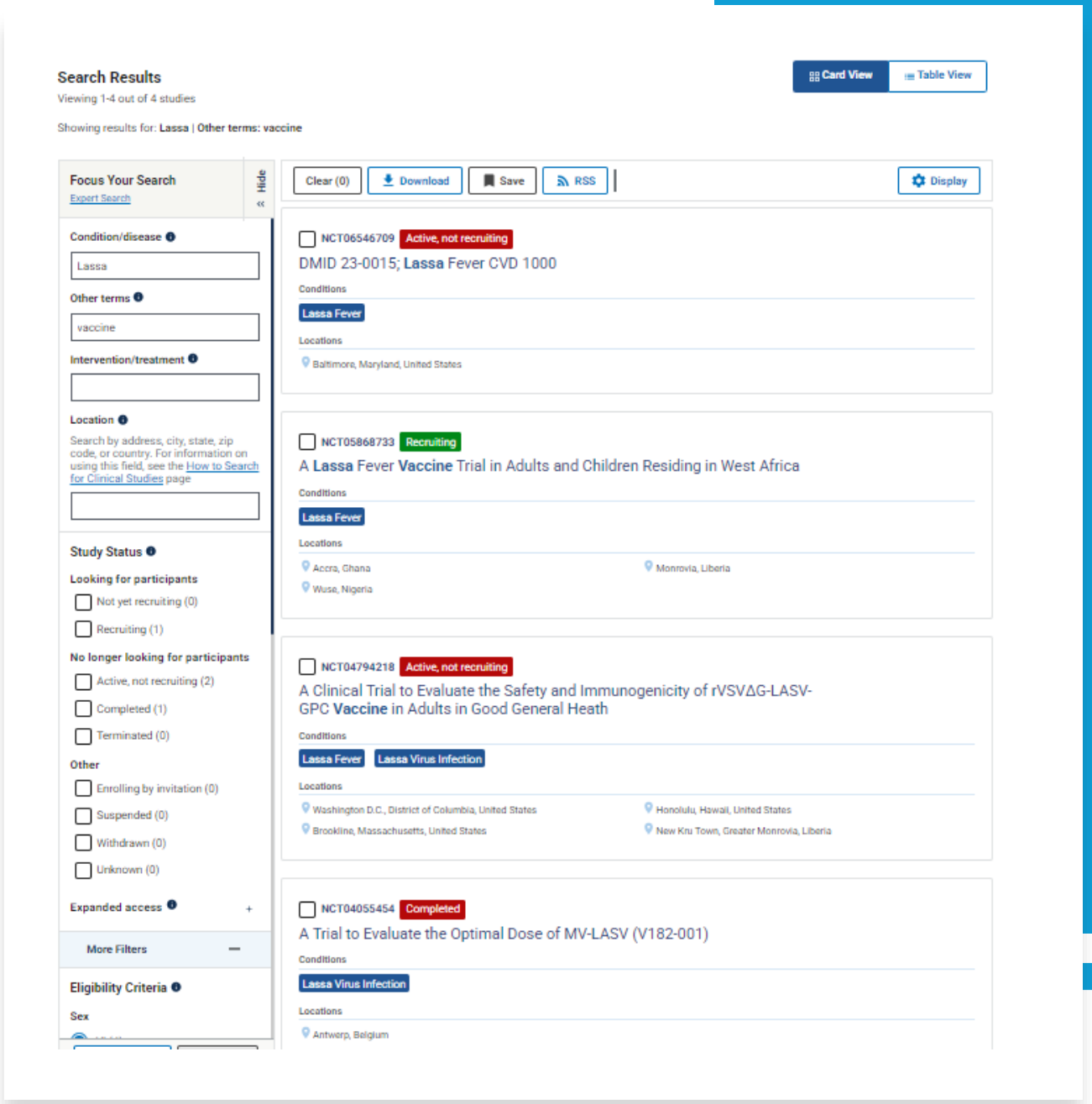
Emmerich et al, J clin Virol, 2006

LASV: case management and treatment

- Supportive care-avoid fluid overload, aspirin, NSAIDs
- Ribavirin: most effective in first 6 days after symptom onset (oral acceptable if no IV)
- Some experts withhold ribavirin if mild disease and AST <150 IU/L (increased mortality if AST <150 IU/L?).
- Specific mechanism of action of ribavirin unclear: anti-inflammatory effect vs anti-viral efficacy (questioned).
- Post-exposure prophylaxis (PEP) with oral ribavirin: consider for close contacts if risk factors for transmission

WHO, https://apps.who.int/iris/bitstream/handle/10665/205570/9789241549608_eng.pdf; McCormick et al, N Engl J Med 1986; Salam AP, PloS Negl Trop Dis 2021; Salam AP, et al PLoS Negl Trop Dis 2022; Eberhardt KA, et al, Int J Infect Dis 2019; Cheng HY,et al, Emerg Infect Dis 2022; 28:1559; Groger at el, CID 2023.

LASV: vaccine…in progress

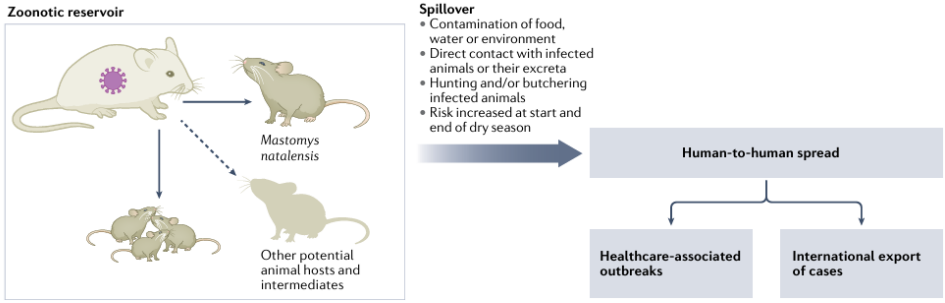


Recommended Reading

Lassa fever — the road ahead

Robert F. Garry [1,2,3]

Abstract | Lassa virus (LASV) is endemic in the rodent populations of Sierra Leone, Nigeria and other countries in West Africa. Spillover to humans occurs frequently and results in Lassa fever, a viral haemorrhagic fever (VHF) associated with a high case fatality rate. Despite advances, fundamental gaps in knowledge of the immunology, epidemiology, ecology and pathogenesis of Lassa fever persist. More frequent outbreaks, the potential for further geographic expansion of *Mastomys natalensis* and other rodent reservoirs, the ease of procurement and possible use and weaponization of LASV, the frequent importation of LASV to North America and Europe, and the emergence of novel LASV strains in densely populated West Africa have driven new initiatives to develop countermeasures for LASV. Although promising candidates are being evaluated, as yet there are no approved vaccines or therapeutics for human use. This Review discusses the virology of LASV, the clinical course of Lassa fever and the progress towards developing medical countermeasures.



Crimean-Congo Hemorrhagic Fever virus

CCHFV: history and discovery

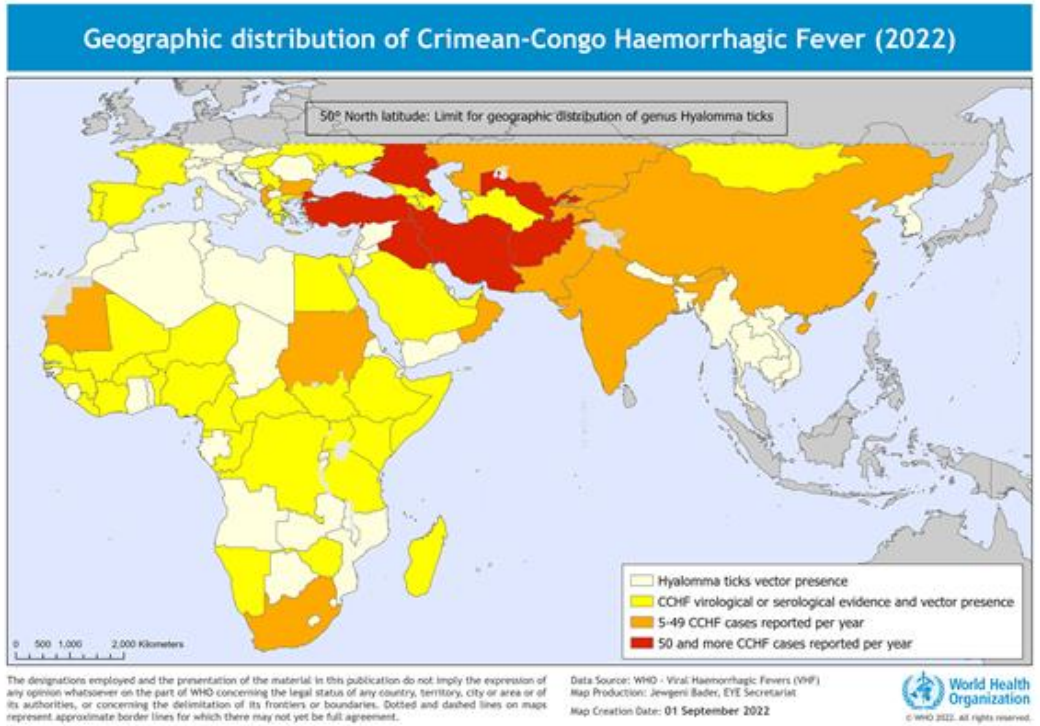
First described in Crimea in 1944 (among soldiers and agricultural workers)

In 1969 recognition that virus causing the disease identical to virus isolated from child in Congo in 1956.

Humans (and possibly non-human primates) are only animal species known to manifest severe clinical CCHF disease.

CCHFV: epidemiology

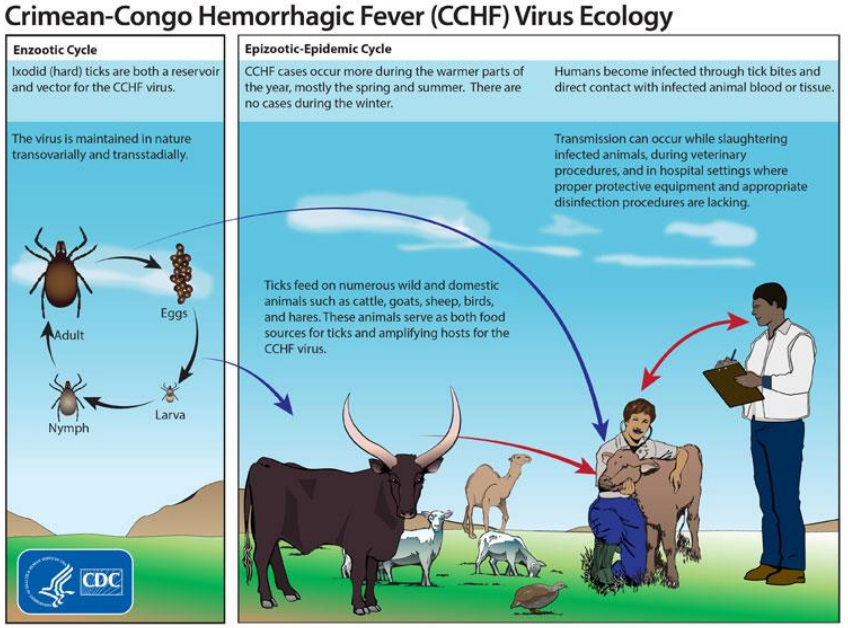
- Endemic in parts of Africa, the Middle East, Asia, and southeastern Europe, and observed in over 30 countries
- 10,000–15,000 cases/year, mortality 30-40% (up to 80%)

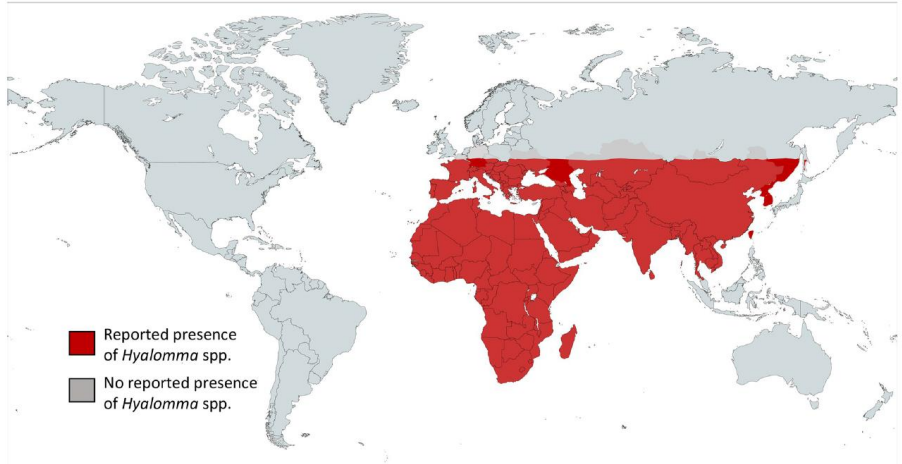


https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever

CCHFV: natural ecology

- Primary transmission: *Hyalomma* ticks (*H.marginatum)*. Also: *Rhipicephalus*, *Dermacentor* spp, others
- Distribution mirrors regions of tick presence: limit 48° N
- Viral reservoirs:
  - domestic livestock, infected by adult ticks.
  - larvae and nymphs feed on rodents, hares, hedgehogs, and ground-dwelling birds→ amplifying hosts for virus
- Tick density increases after mild winters with diminished rainfall→ increase in human cases
- Role of migratory birds in spread of disease





Bonnet SI, et al. PLoS Negl Trop Dis. 2022; Fillâtre P, et al. Med Mal Infect. 2019; CDC

CCHFV: epidemiology

- Europe (WHO region) :
  - 13 countries reported infected ticks
  - 17 countries positive seroprevalence (animals/humans)
  - 16 countries notified human cases

Contents lists available at ScienceDirect

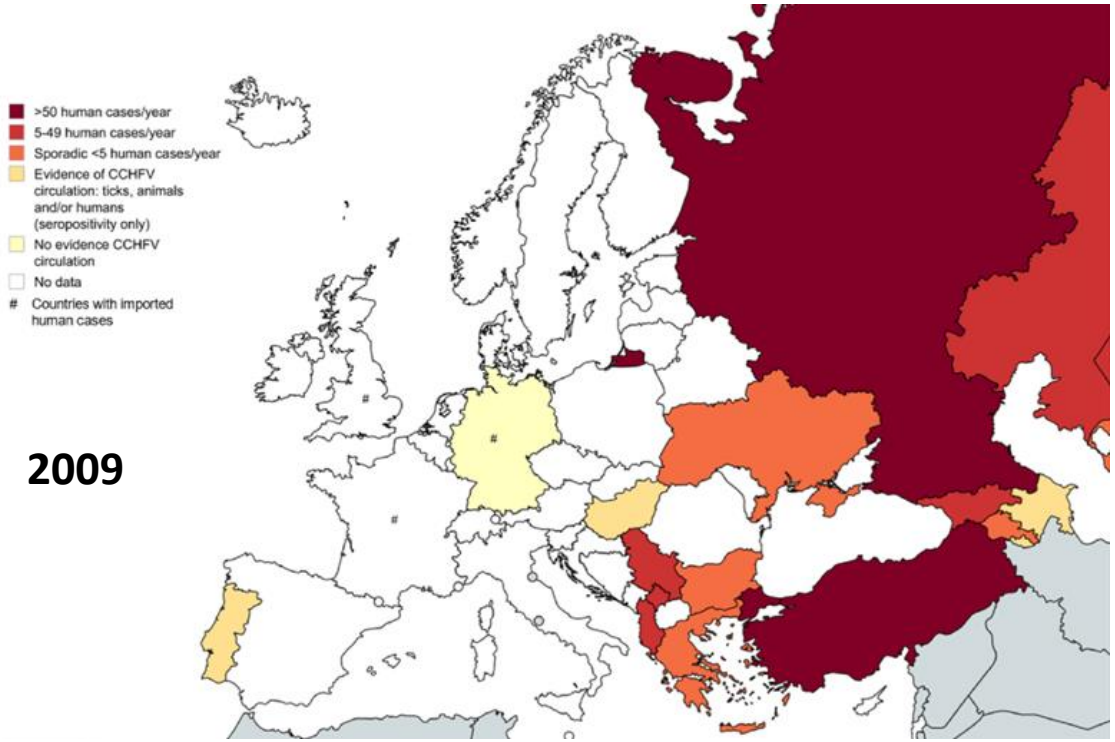
Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

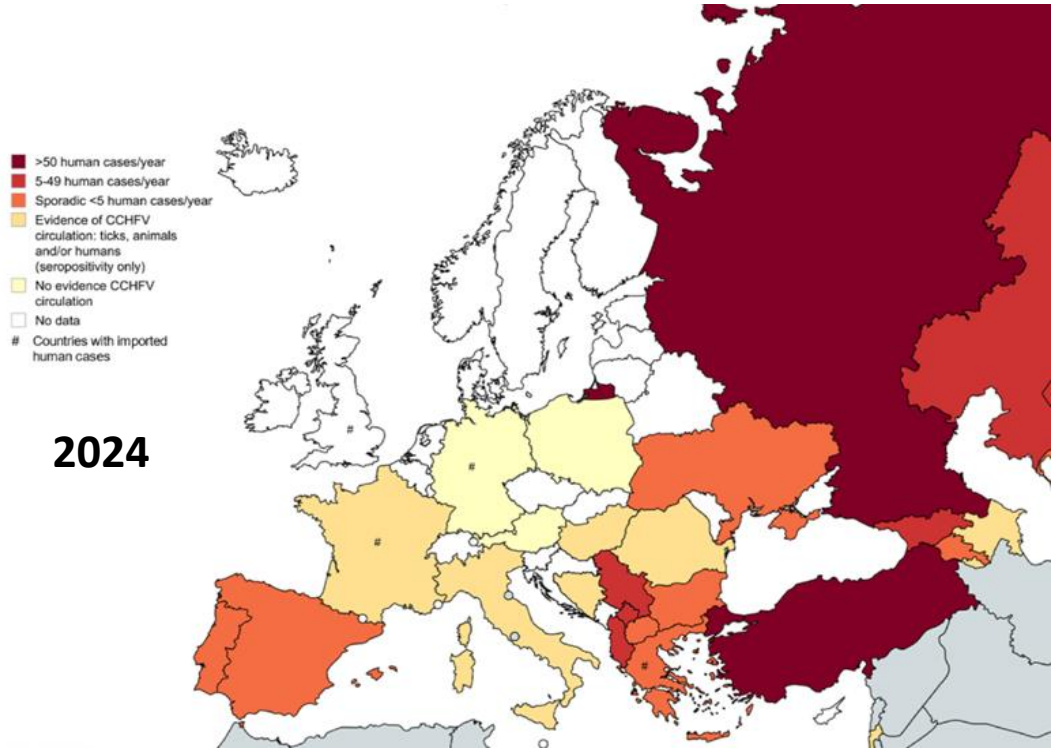
Changes in the epidemiology of Crimean-Congo hemorrhagic fever: Impact of travel and a One Health approach in the European region

Francesca F. Norman [a,b,*], Octavio A. Arce [c], Marta Díaz-Menéndez [d], Moncef Belhassen-García [e], Marta González-Sanz [a,b]

[a] National Referral Unit for Tropical Diseases, Infectious Diseases Department, Ramón y Cajal University Hospital, IRYCIS, CIBERINFEC, Madrid, Spain
[b] Universidad de Alcalá, Madrid, Spain
[c] High Level Isolation Unit. Infectious Diseases Department, Hospital Central de la Defensa "Gómez Ulla", Madrid, Spain
[d] National Referral Unit for Tropical Diseases, Department of Internal Medicine, La Paz-Carlos III University Hospital, IdIPAz, CIBERINFEC, Madrid, Spain
[e] Infectious Diseases Section, Internal Medicine Department, CAUSA, IBSAL, CIETUS, University of Salamanca, Salamanca, Spain



2009

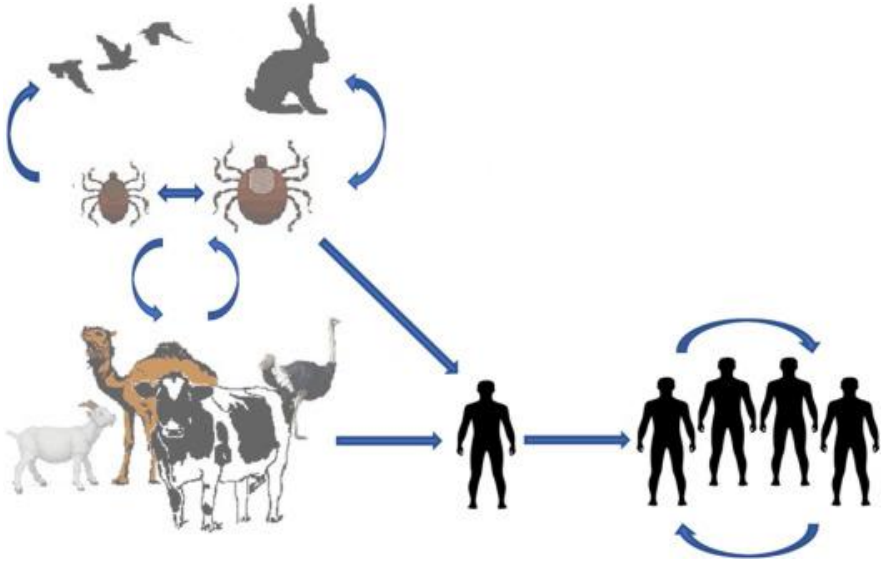


2024

CCHFV: transmission

- Tick-bites
- Direct contact blood-fluids of infected animals
- Nosocomial transmission
- Vertical transmission

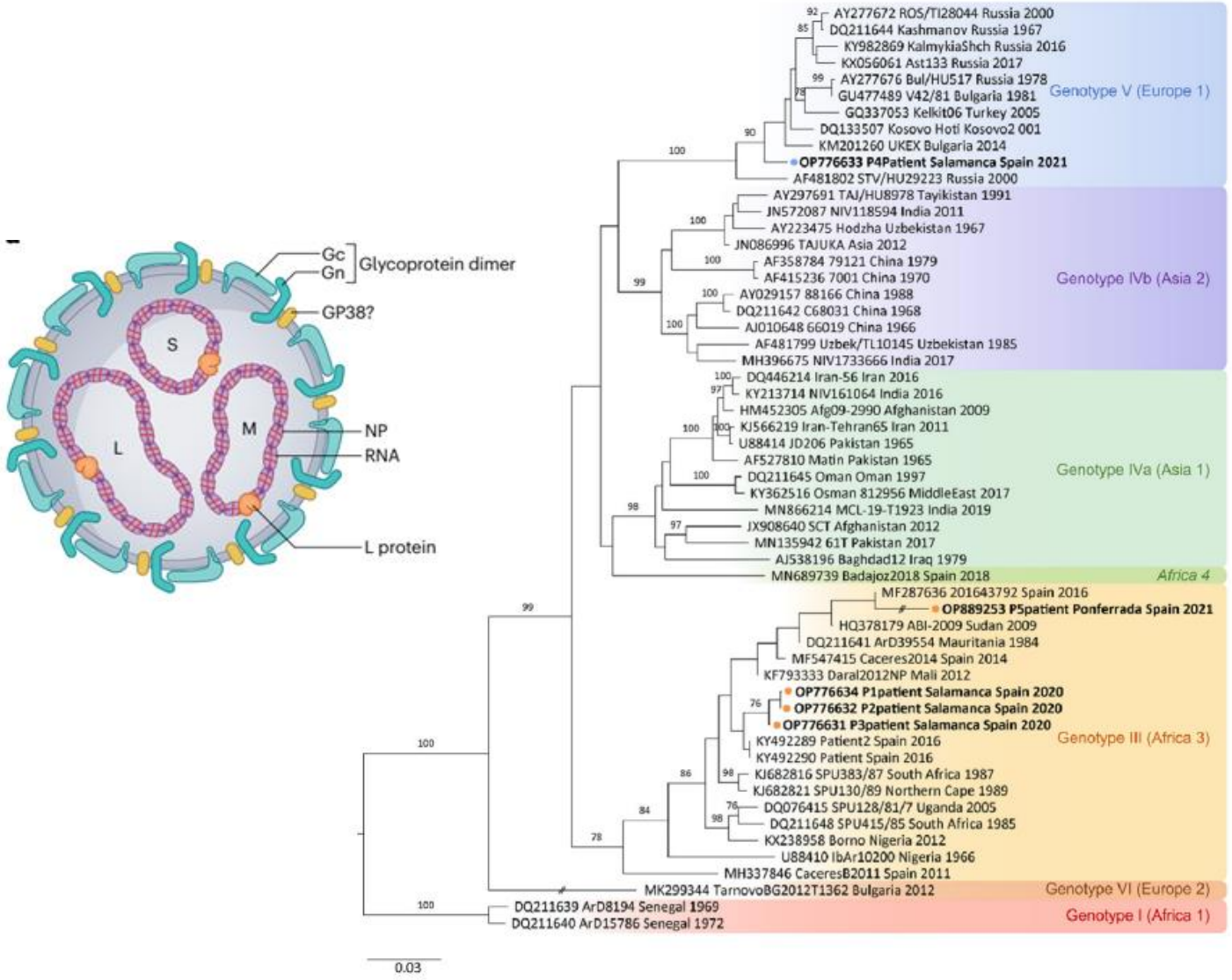
- CCHFV does not survive outside host, may persist in infected body fluids (blood, stool, vomit).



Bonnet SI, et al. PLoS Negl Trop Dis. 2022; https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever

CCHFV: structure

- Africa 1 (genotype I)
- Africa 2 (genotype II)
- Africa 3 (genotype III)
- Asia 1 (genotype IVa)
- Asia 2 (genotype IVb)
- Europe 1 (genotype V)
- Europe 2 (genotype VI)



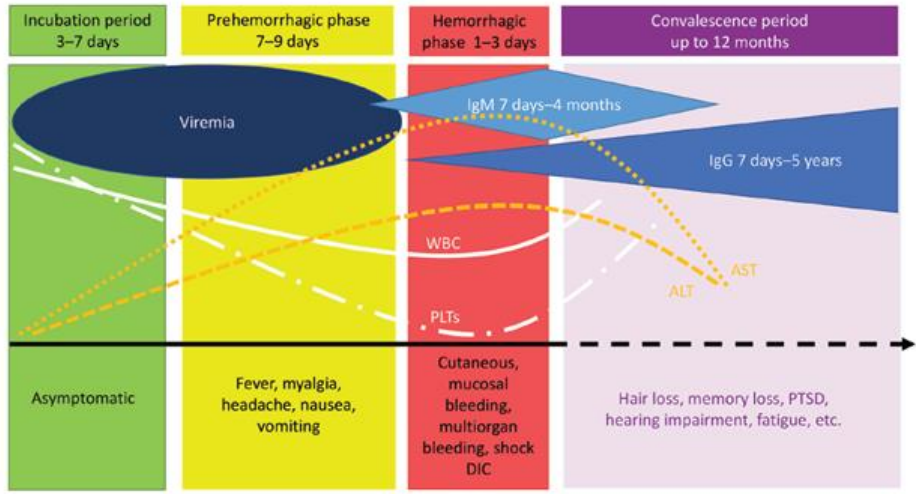
Different viral lineages and adaptation to regional hosts may determine disease severity in humans

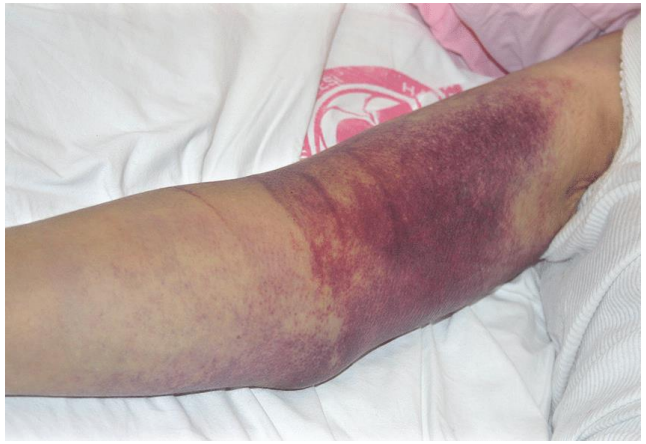
Febrer-Sendra B, et al. Int J Mol Sci. 2023; Frank MG, et al. Emerg Infect Dis. 2024; Hawman DW, et al. Nat Rev Microbiol. 2023

CCHFV: clinical manifestations

- Following tick bite: IP 1-3 days (max 9 days)—probably due to tick saliva-activated transmission (bioactive molecules causing antihemostatic, antiinflammatory, and immunomodulatory effects on the vertebrate host)
- Following contact with infected blood/tissues: IP 5-6 days (max 13 days).

- Subclinical illness (88 percent) ←→ **acute infection** with hemorrhage and multiorgan failure
- Sudden onset fever, headache, sore throat, conjunctivitis, photophobia, abdominal pain, nausea, and vomiting (up to 7 days)
- Followed by **recovery or progression to severe disease** (exaggerated proinflammatory "cytokine storm“: endothelial cell activation, increased vascular permeability, hypotension, shock, multiple organ failure, and death)
- **Convalescence** period weeks-months



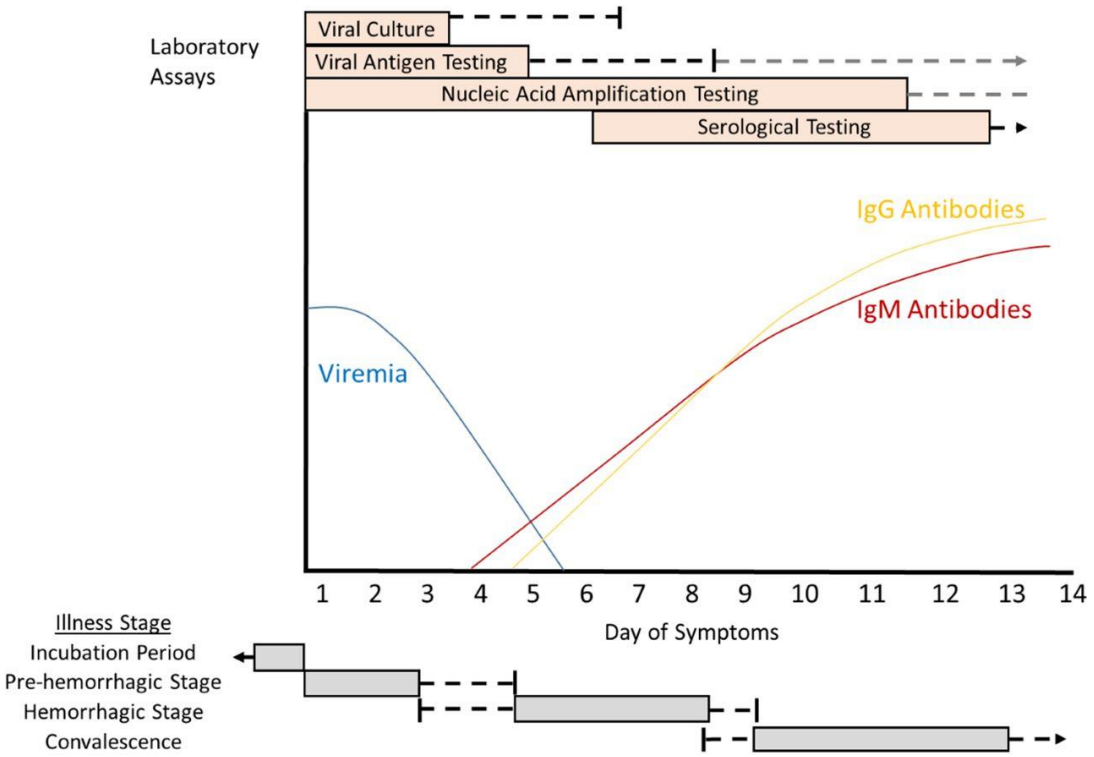


Frank MG, et al. Emerg Infect Dis. 2024

CCHFV: diagnosis

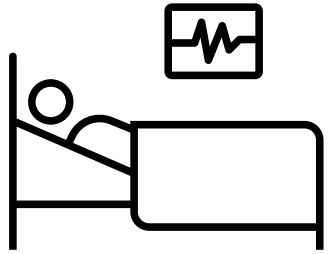
- **High index of suspicion!!**

- CCHFV RNA detection by RT-PCR
- Specific IgM and IgG 5 days from onset
- IgG can remain detectable <5 years
- CCHFV can be cultured—BSL- 4 (for research)



Raabe et al, J Clin Micro, 2020

CCHFV: case management

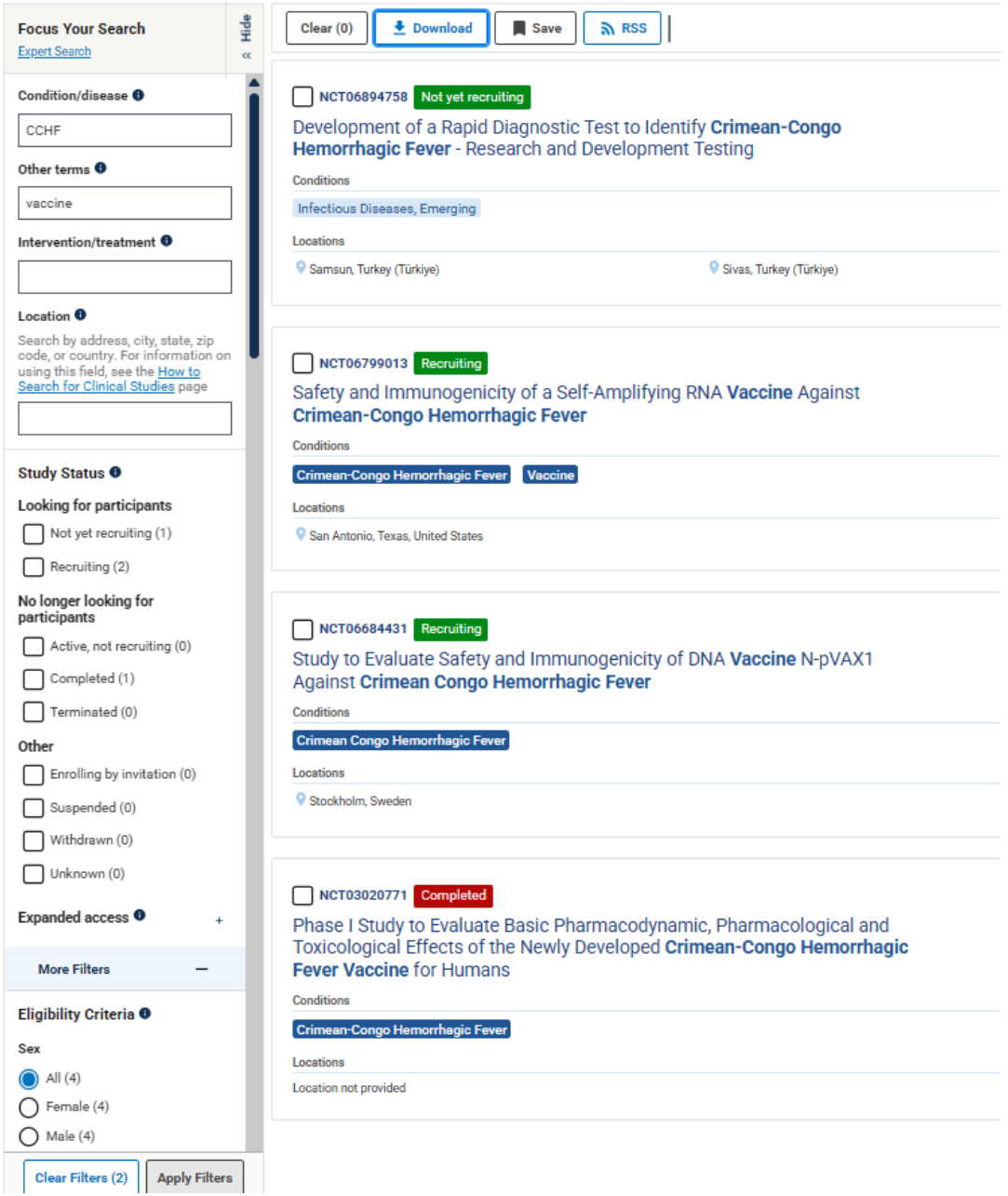


- No proven antiviral treatment
- Ribavirin studied in vitro, in animal models, and humans
  - **Not shown** to reduce viral load or mortality in humans
  - Clinical efficacy **controversial**
  - Limitations of **methodological flaws** of studies
  - Further study is needed
- Supportive care
- Insufficient data to support use of steroids, iv Ig, or plasma exchange
- Hyperimmunoglobulin (plasma of donors with CCHFV-Ab): further study
- Postexposure management:
  - two-week period of monitoring for symptoms or signs
  - role of ribavirin for prevention of clinical illness uncertain

Ceylan et al, Int J Inf Dis, 2013; Mardani et al, CID, 2003; Ascioglu et al, JAC, 2011; Kubar et al, Jpn J Inf Dis, 2011

CHFV: vaccine

- No approved vaccine for use in humans or animals.
- Inactivated suckling mouse brain-derived vaccine developed for CCHF used in Bulgaria (3 doses + booster), affords variable protection
  - virus-neutralizing activity low
  - repeated doses necessary for adequate neutralizing antibody levels
- Another vaccine based on CCHFV glycoproteins is under development



Hawman DW, et al. Nat Rev Microbiol. 2023; https://clinicaltrials.gov/ (access September 2025)

Recommended Reading

nature reviews microbiology

https://doi.org/10.1038/s41579-023-00871-9

Review article

Check for updates

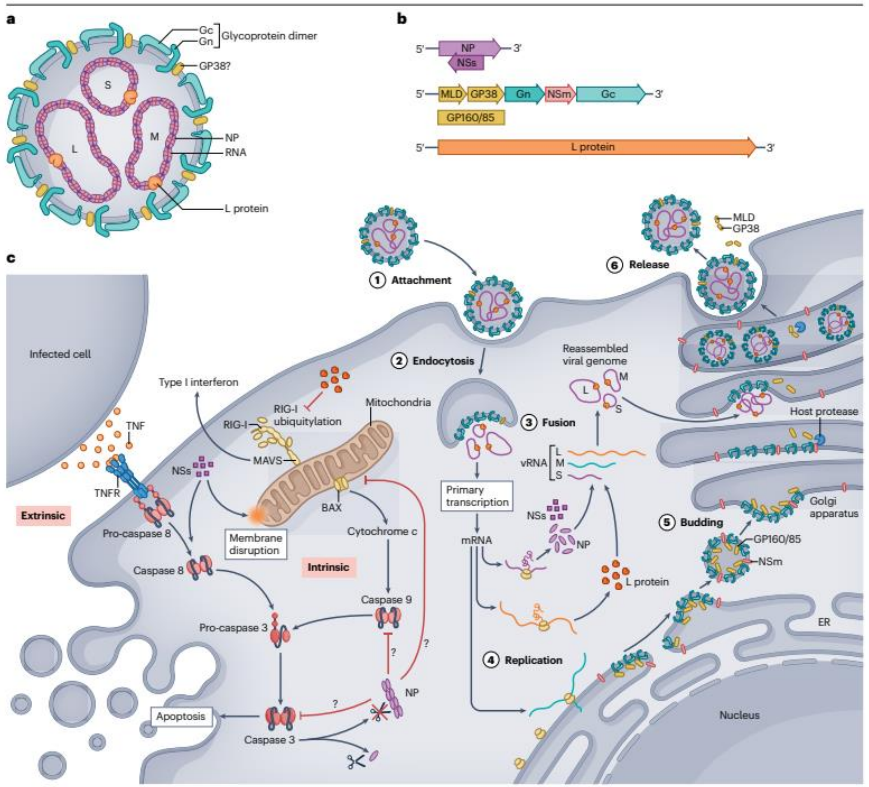
Crimean–Congo haemorrhagic fever virus

David W. Hawman & Heinz Feldmann

Abstract

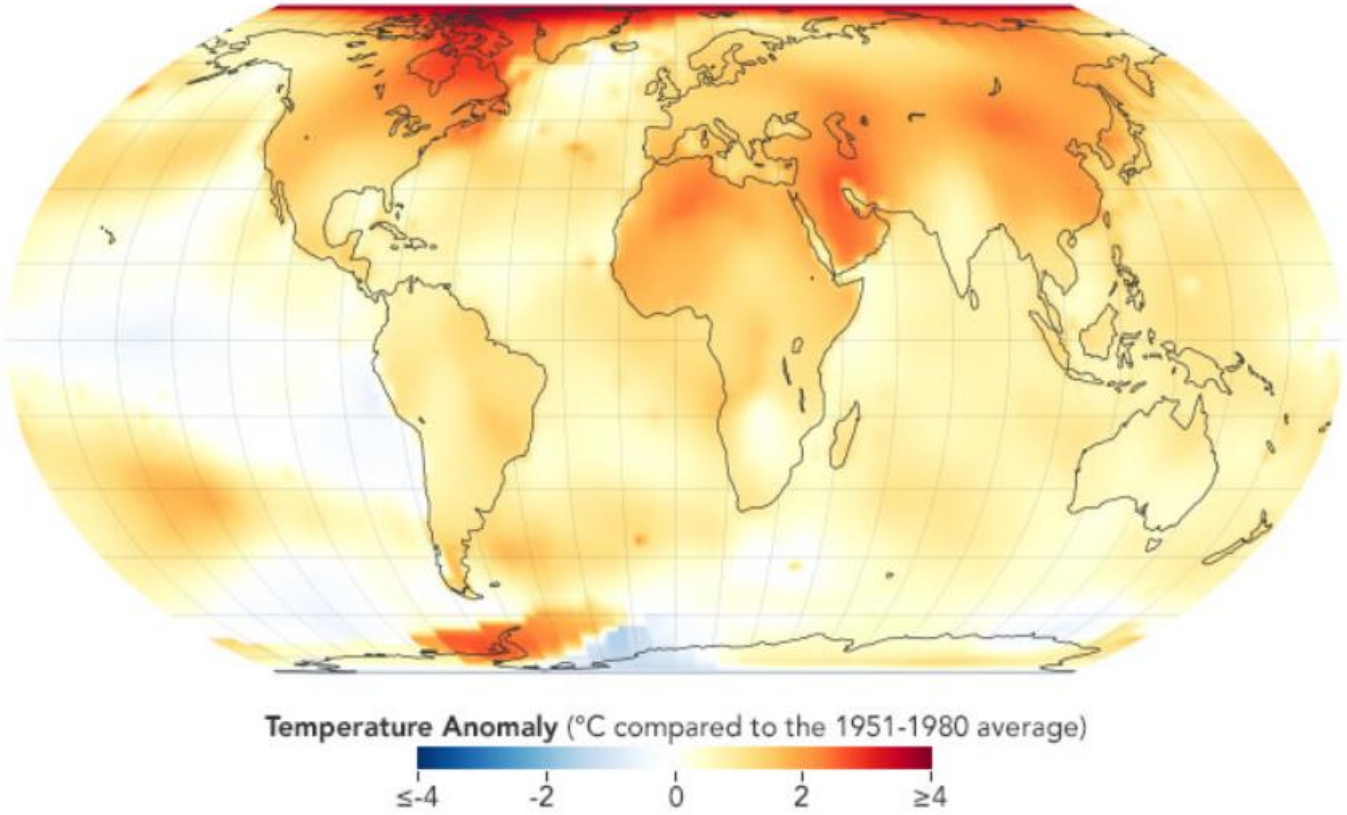
Crimean–Congo haemorrhagic fever (CCHF) is a severe tick-borne illness with a wide geographical distribution and case fatality rates of 30% or higher. Caused by infection with the CCHF virus (CCHFV), cases are reported throughout Africa, the Middle East, Asia and southern and eastern Europe. The expanding range of the *Hyalomma* tick vector is placing new populations at risk for CCHF, and no licensed vaccines or specific antivirals exist to treat CCHF. Furthermore, despite cases of CCHF being reported annually, the host and viral determinants of CCHFV pathogenesis are poorly understood. CCHFV can productively infect a multitude of animal species, yet only humans develop a severe illness. Within human populations, subclinical infections are underappreciated and may represent a substantial proportion of clinical outcomes. Compared with other members of the *Bunyavirales* order, CCHFV has a more complex genomic organization, with many viral proteins having unclear functions in viral pathogenesis. In recent years, improved animal models have led to increased insights into CCHFV pathogenesis, and several antivirals and vaccines for CCHFV have shown robust efficacy in preclinical models. Translation of these insights and candidate therapeutics to the clinic will hopefully reduce the morbidity and mortality caused by CCHFV.

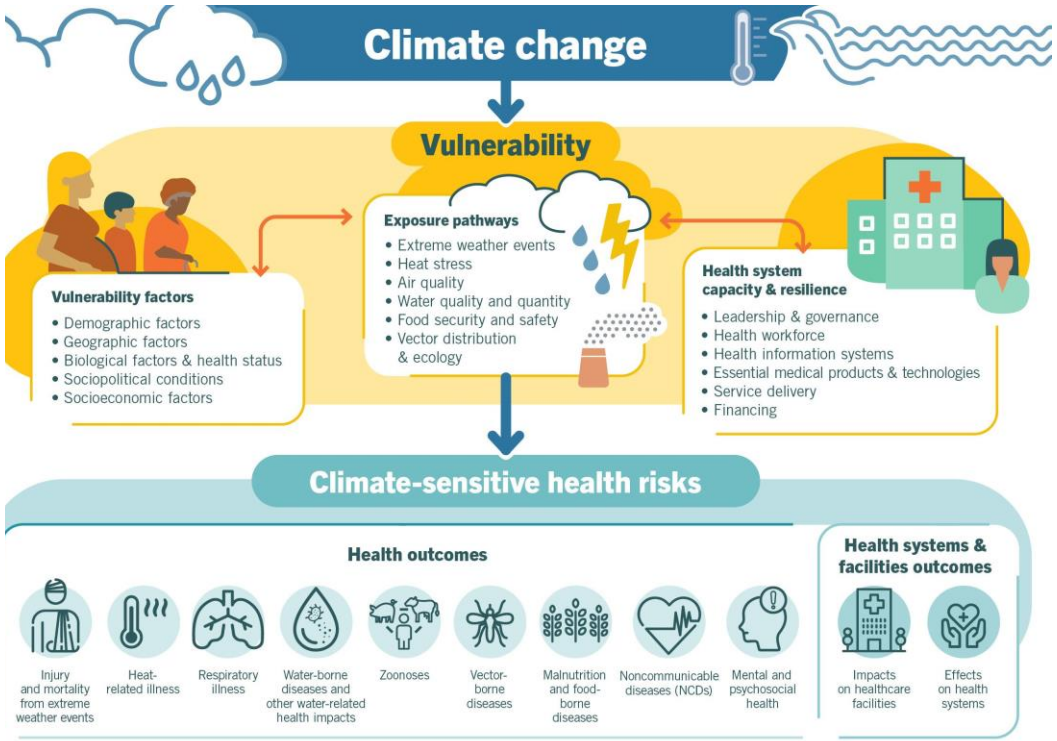
Sections



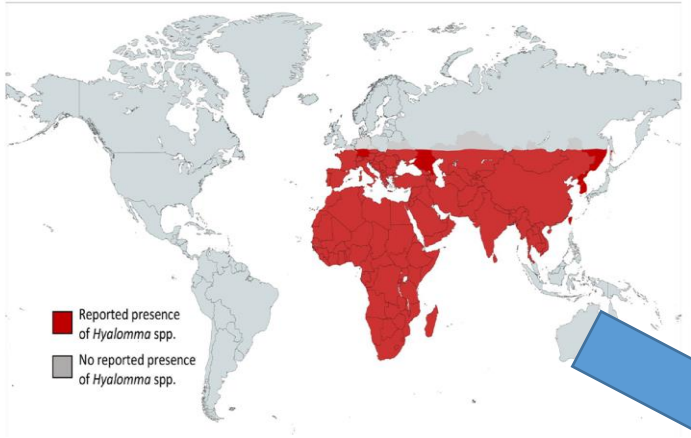

Challenges and Future
Perspective

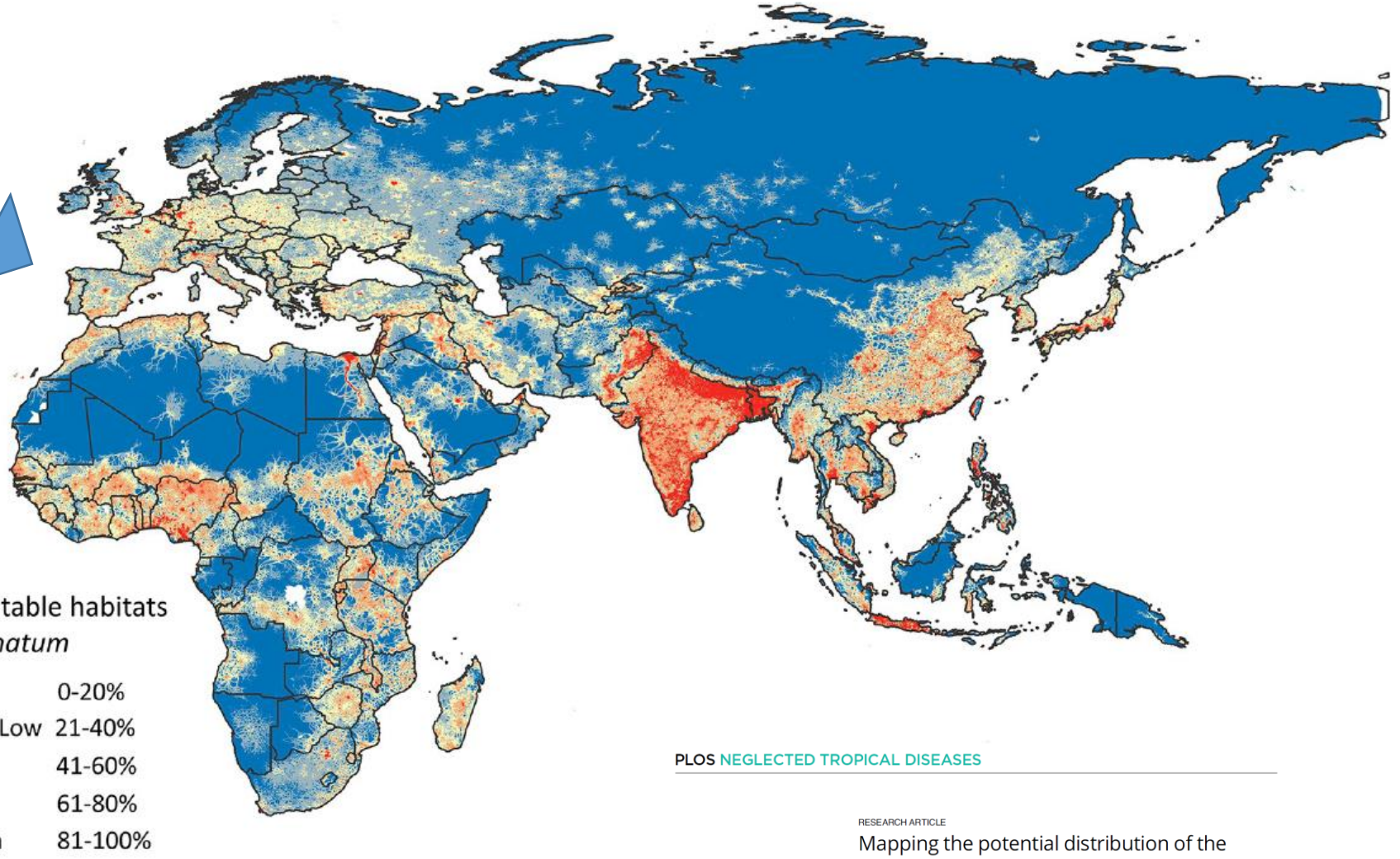
Climate change





Sources: Heat map showing temperature anomaly for 2021, compared to 1951-1980 average. Image: NASA: Earth Observatory, WHO





PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Mapping the potential distribution of the principal vector of Crimean-Congo haemorrhagic fever virus *Hyalomma marginatum* in the Old World

Seyma S. Celina[1*], Jiří Černý[1], Abdallah M. Samy[2,3*]

Bonnet SI, et al. PLoS Negl Trop Dis. 2022; Celina SS, et al. PLoS Negl Trop Dis. 2023

Risk of geographical expansion and introduction

One Health 13 (2021) 100290

Contents lists available at ScienceDirect

One Health

journal homepage: www.elsevier.com/locate/onehlt

Risk of Crimean Congo haemorrhagic fever virus (CCHFV) introduction and spread in CCHF-free countries in southern and Western Europe: A semi-quantitative risk assessment

Angela Fanelli *, Domenico Buonavoglia

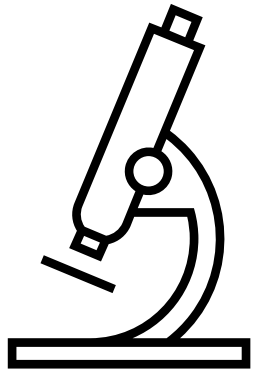
Table 2
Likelihood of occurrence of CCHF into EU free-countries.

Country	Likelihood of entry (Uncertainity)	Likelihood of exposure (Uncertainity)	Likelihood of occurrence
Austria	Medium (Medium)	Low (Low)	Low
Belgium	Low (Medium)	Low (Low)	Low
France	High (Medium)	Medium (Low)	Medium
Germany	Medium (Medium)	Medium (Low)	Medium
Italy	Medium (Medium)	High (Low)	Medium
Luxembourg	Low (Medium)	Low (Low)	Low
Netherlands	Medium (Medium)	Low (Low)	Low
Slovenia	Medium (Medium)	Low (Medium)	Low
Switzerland	Low (Medium)	Low (Low)	Low

Table 1
Factors used to assess the likelihood of entry of CCHFV into EU free-countries.

Factor	Explanation	Data Source
Number of CCHFV source countries within the main birds flyways (Supplementary material-Fig.S2)	Given the shapefile of the main flyways including the countries of interest, the number of source countries was evaluated using the geoprocessing tools in QGIS software [28]. These are used to establish the potential connections with CCHFV source countries.	The CMS Flyways Working Group [29]
Number of species of ground-feeding migratory birds[a] shared with CCHFV source countries	The ground-feeding migratory birds species shared with CCHFV source countries were extracted from Bird species distribution maps of the world using the geoprocessing tools in QGIS software [28]	http://datazone.birdlife.org/species/requestdis [30]
Number of neighbouring CCHFV source countries	The number of neighbouring CCHFV source countries were counted to assess the risk of wildlife cross-border movement.	
Number of live animals imported from CCHFV source countries	Total number of livestock and horses imported in 2019 (most recent information available) from CCHFV source countries	https://comtrade.un.org/ [31]
Number of CCHFV source countries as exporting trading partners	Total number of CCHFV source countries as exporting trading partners of live animals (livestock and horses) in 2019 (most recent information available)	https://comtrade.un.org/ [31]

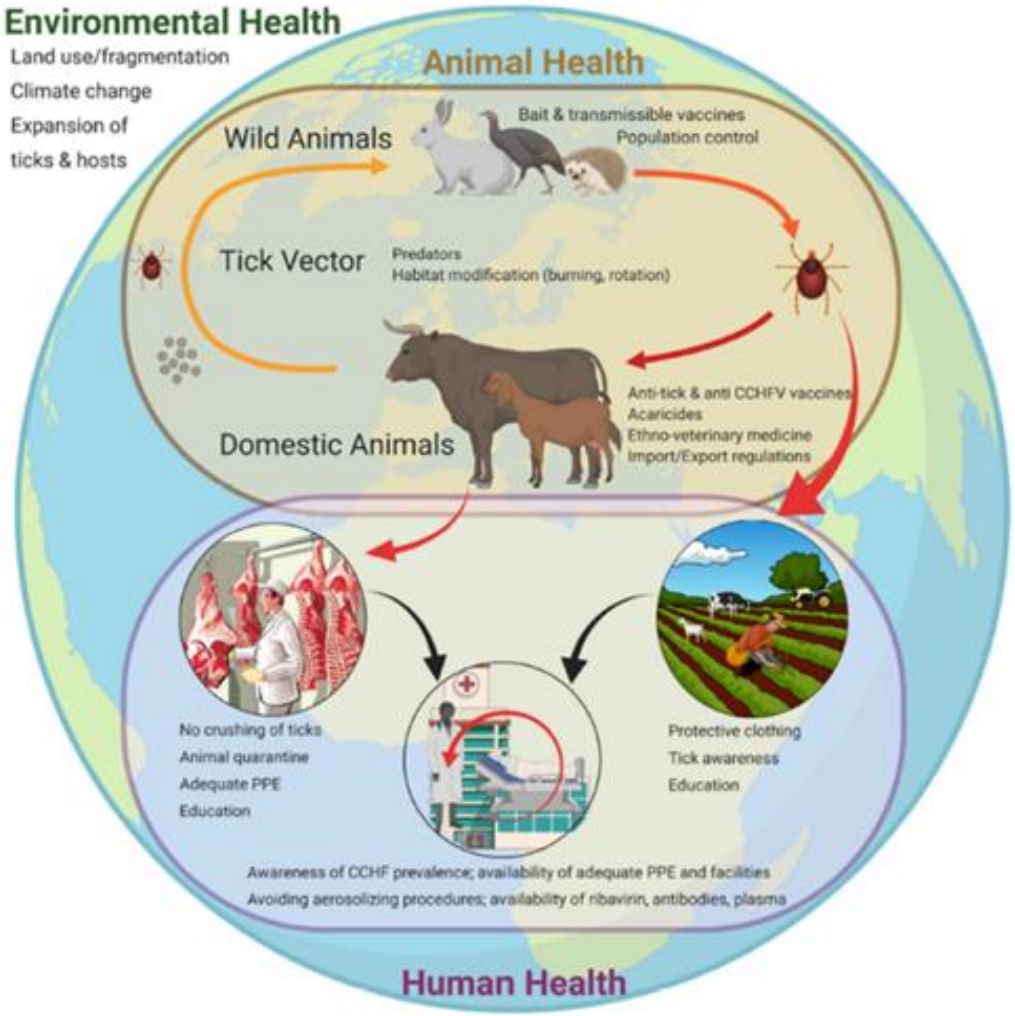
Diagnostic difficulties



- May have transient short-lived asymptomatic viremias in host
- Lack of “sentinel” animals to signal presence of outbreak
- Diagnostic delay (especially if new disease unrecognised in new area):
  - Hospitalisation and increased mortality
  - Increased possibility of nosocomial transmission
- Need BSL-3/4 laboratory support
- Development of rapid diagnostic tests for surveillance and detection of outbreaks

Key Points-VHFs

- Potential risk to close contacts→ isolation
- Official protocols/guidelines and alert systems for management
- Reference lab support with appropriate biosecurity level (warn the lab!)
- No specific treatment or vaccine (development)
- Investment in control strategies through a “One Health” approach



Thank you

ffnorman@gmail.com