Viral Hemorrhagic Fevers

Epidemiology, Clinical Presentation and Control

JOHNS HOPKINS
MEDICINE

JOHNS HOPKINS BAYVIEW MEDICAL CENTER

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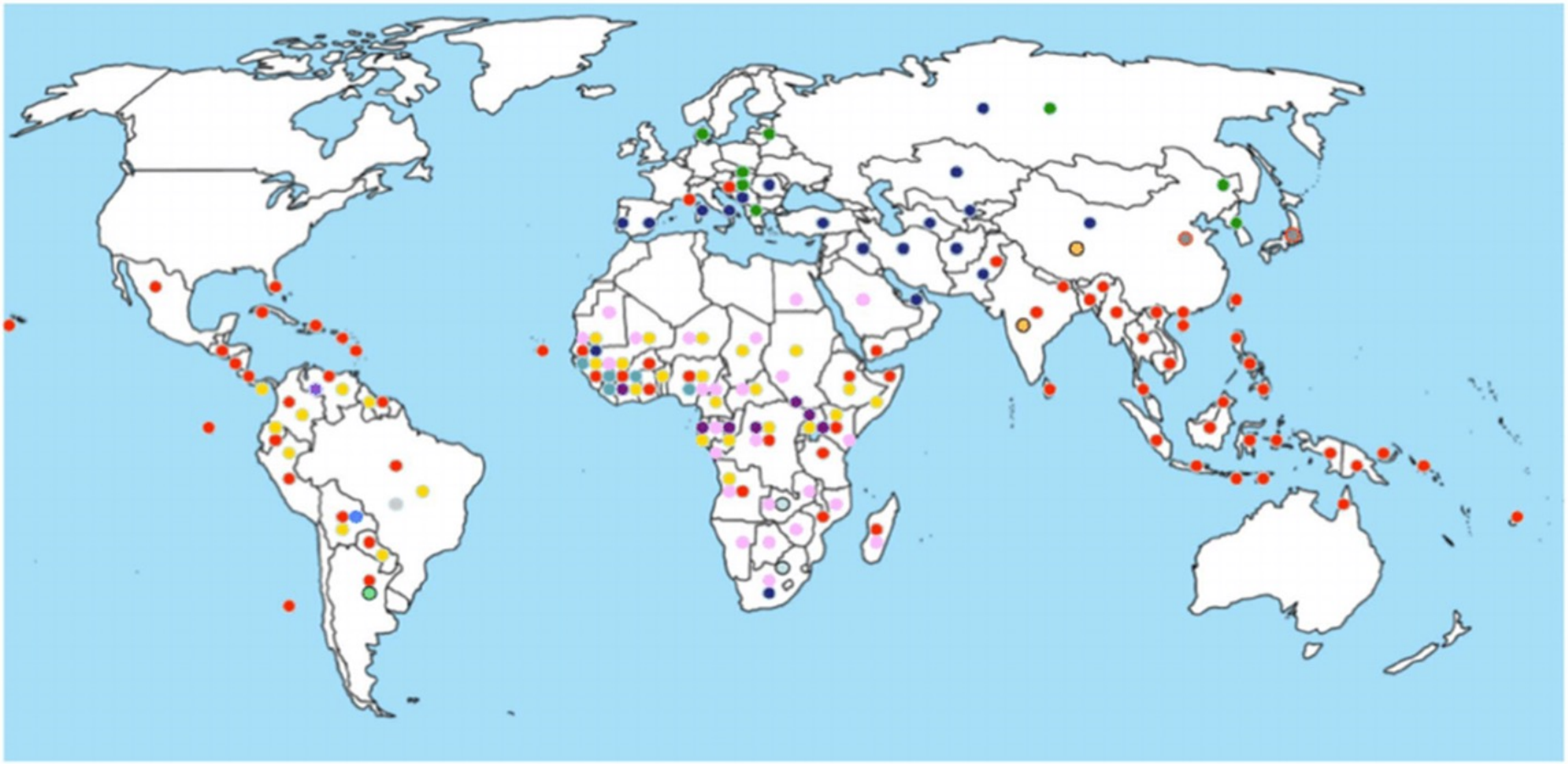
Dec 7, 2023

Geographic Distribution



Flaviviridae

- Dengue virus
- Yellow fever virus
- Kyasanur forest disease

Bunyaviridae

- CCHF virus
- Hantavirus HFRS
- Rift valley fever virus
- SFTS virus

Arenaviridae

- Lassa virus
- Lujo virus
- Junin virus
- Machupo virus
- Guaranito virus
- Sabiá virus

Filoviridae

- Ebola and Marburg

Definitions

Viral hemorrhagic fever (VHF) is a term historically used to define an acute, **febrile**, multi-systemic illness characterized by malaise, myalgia, and prostration, with a tendency for bleeding diathesis.

Caused by lipid-enveloped, single-stranded, **RNA viruses** in ***Filoviridae***, ***Arenaviridae***, ***Bunyaviridae***, and ***Flaviviridae*** families.

Over view of Agents

Family	Genus	Species
Filoviridae	*Ebolavirus*	Zaire, *Sudan*, *Tai Forest Reston, Bundibugyo (“Uganda”)*
	Marburgvirus	*Marburg marburgvirus*
Arenaviridae	*Arenavirus*	*Lassa* (“Old World”) *Junin, Machupo, Guanarito, Sabia* (“New World”)
Bunyaviridae	*Nairovirus*	*Crimean-Congo hemorrhagic fever*
	Phlebovirus	*Rift Valley fever*
(Old syndrome Hantavirus	*Hantavirus*	*Hantaan*, *Seoul*, *Puumala, Dobrava-Belgrade* World) - cause Hemorrhagic fever with renal (HFRS) *Sin Nombre*, Andes (New World) – cause Pulmonary Sydrome
Flaviviridae	*Flavivirus*	*Omsk HF* *Kyasanur forest disease* *Dengue, Yellow fever*

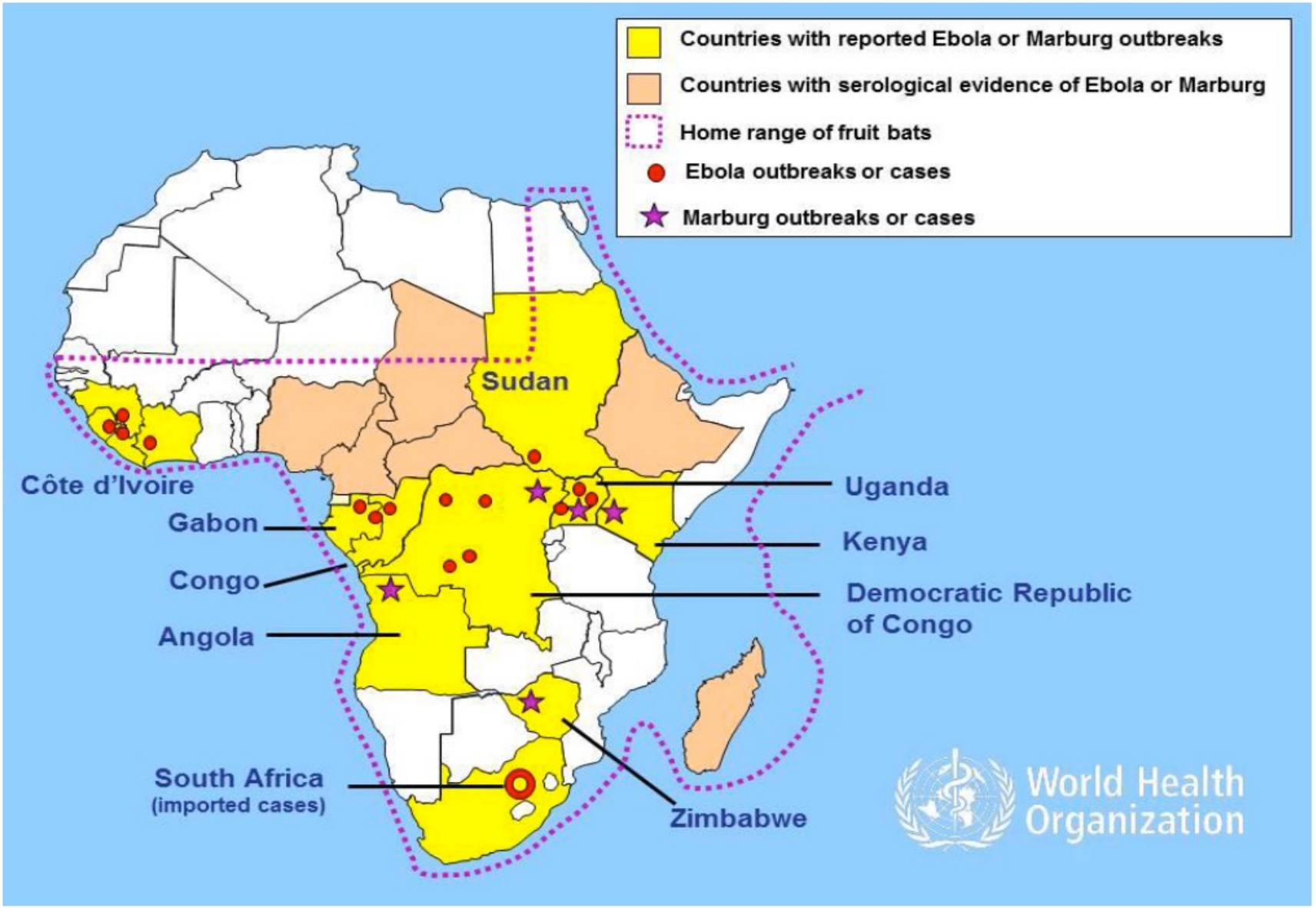
Potential Distinguishing Features

- Prominent Jaundice/Icterus: Yellow Fever
- Prominent Renal Failure: HFRS, Yellow Fever
- Hemorrhage:
  - Filoviruses: Not early, usually late. May manifest as overt bleeding, but often it is only minimal and sometimes solely internal
  - CCHF: Hemorrhagic period is usually short (2–3 days, but it can be up to 2 weeks), develops rapidly, and usually begins between the third and fifth days of disease
- Onset:
  - CCHF and Filoviruses more sudden
  - Lassa fever typically has a more indolent presentation; patients feel fatigued and “feverish” for a few days
- Swollen face and neck:
  - Classic signs in Lassa fever but occur in only about 10% of cases; these signs are not seen in Ebola/Marburg

Potential Distinguishing Features

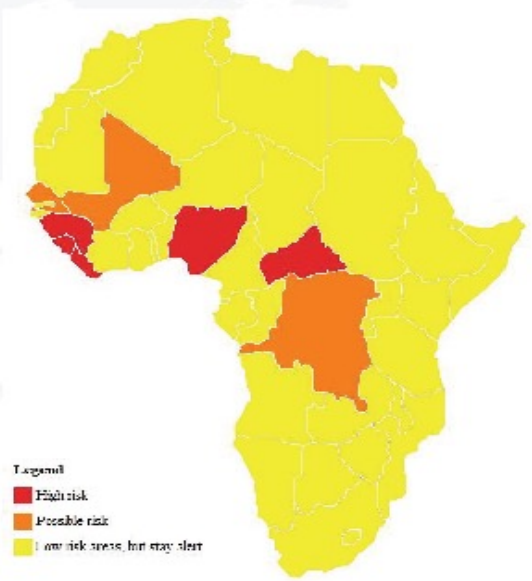
- Sore throat occurs in Filoviruses and Lassa but **exudative pharyngitis** and **convalescent hearing loss** suggest **Lassa**
- Pericarditis: Lassa
  - Best predictor of **Lassa** fever found to be the combination of **fever, pharyngitis, retrosternal pain, and proteinuria**
- Ocular:
  - RVF early (retinitis)(4 to 15 days (mean, 8.8 days), 1-15% depending on series
  - Filoviruses in convalescence (Uveitis)

Figure 1. Geographical distribution of Ebola and Marburg outbreaks in Africa (1967-2014)



Distribution in Africa

Lassa Virus



Ebola Virus

Marburg Virus

Photos courtesy of Travel Approved (for Lassa and Ebola), Mehedi et al. 2011 (for Marburg)

THE MENTOR initiative

DEVOTED TO REDUCING **MALARIA DEATHS & SUFFERING IN HUMANITARIAN CRISES**

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Ebola Virus Ecology and Transmission

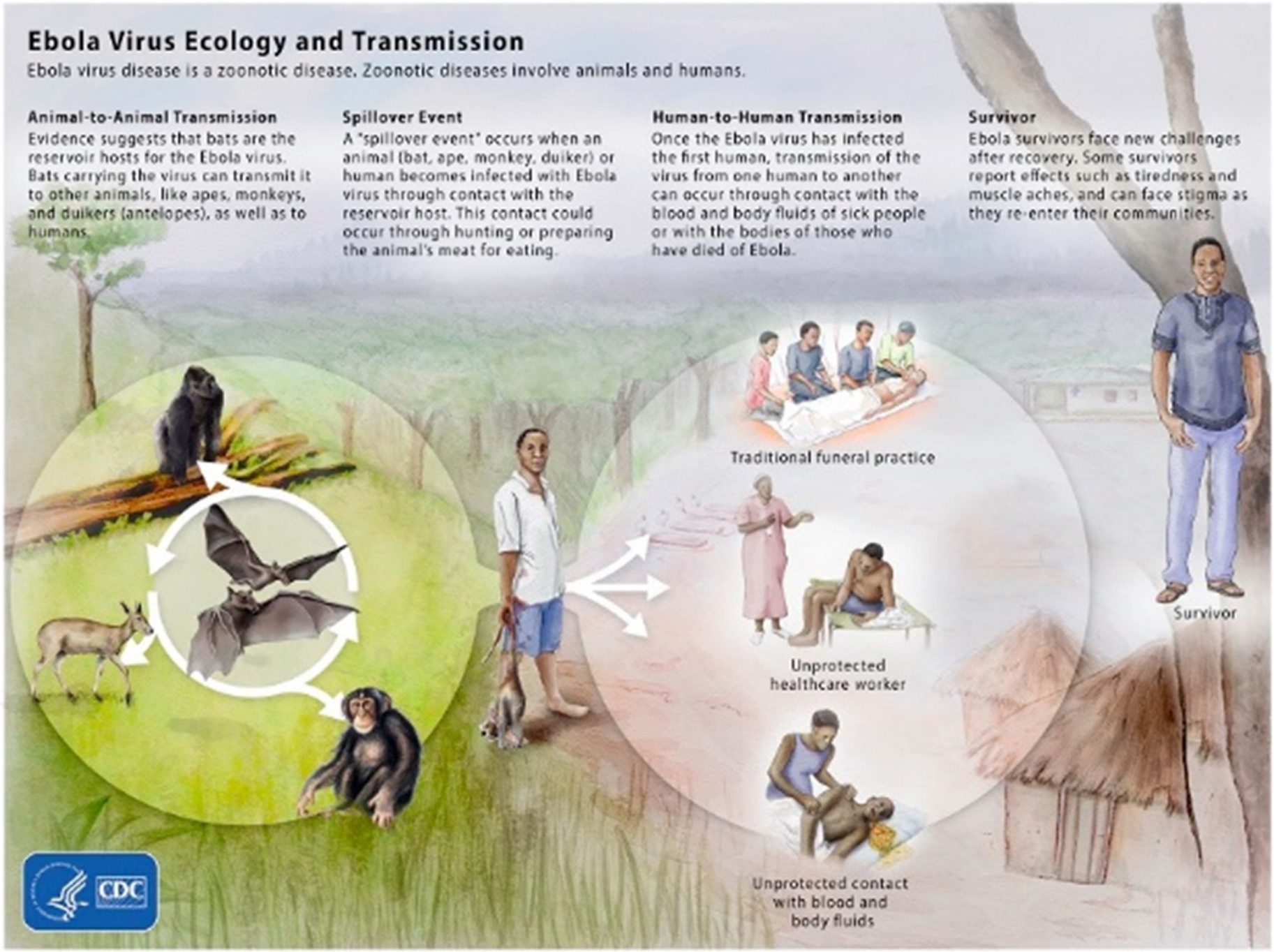
Ebola virus disease is a zoonotic disease. Zoonotic diseases involve animals and humans.

Animal-to-Animal Transmission
Evidence suggests that bats are the reservoir hosts for the Ebola virus. Bats carrying the virus can transmit it to other animals, like apes, monkeys, and duikers (antelopes), as well as to humans.

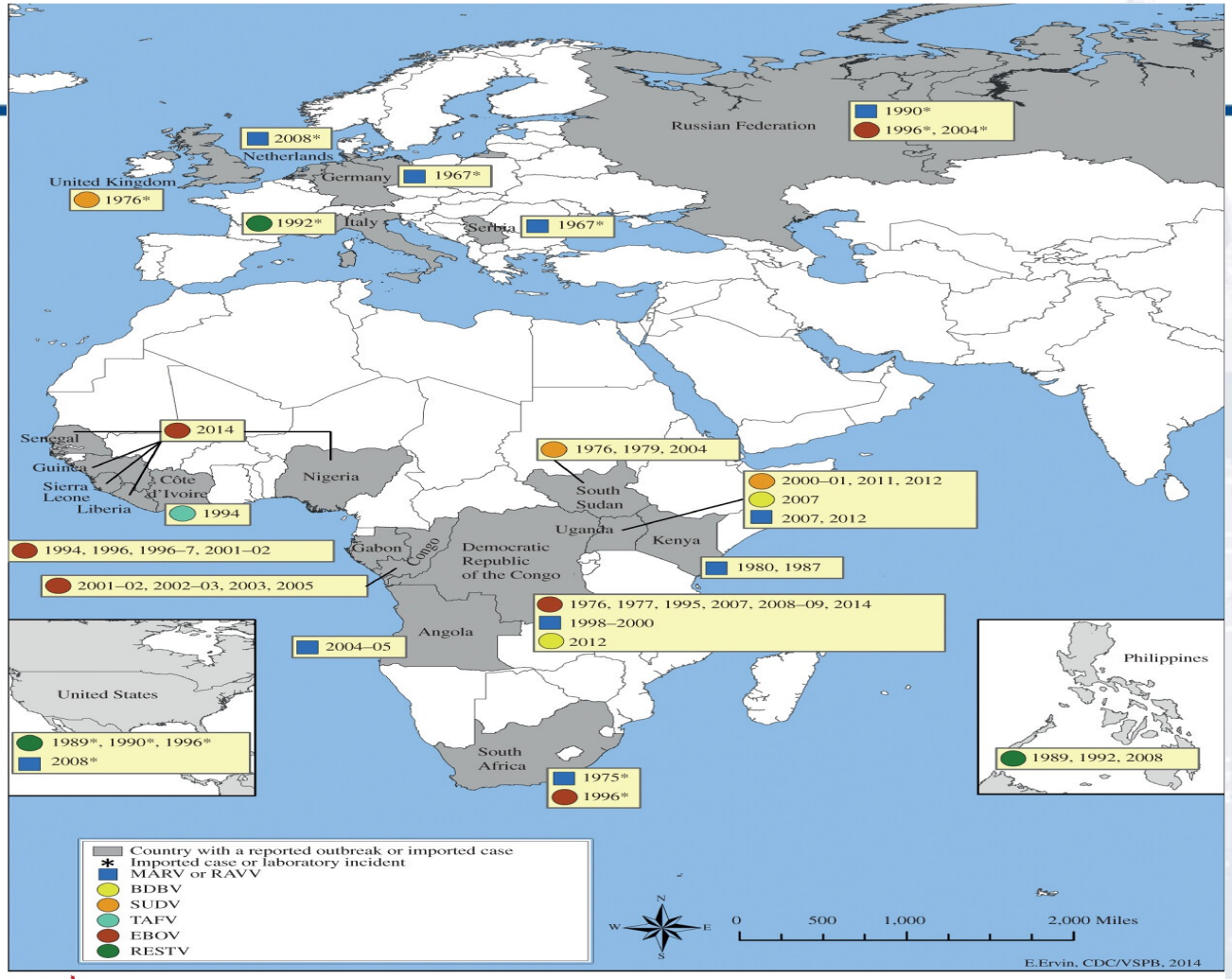
Spillover Event
A "spillover event" occurs when an animal (bat, ape, monkey, duiker) or human becomes infected with Ebola virus through contact with the reservoir host. This contact could occur through hunting or preparing the animal's meat for eating.

Human-to-Human Transmission
Once the Ebola virus has infected the first human, transmission of the virus from one human to another can occur through contact with the blood and body fluids of sick people or with the bodies of those who have died of Ebola.

Survivor
Ebola survivors face new challenges after recovery. Some survivors report effects such as tiredness and muscle aches, and can face stigma as they re-enter their communities.



Worldwide geographic distribution of filovirus haemorrhagic fever cases, 1967–2014.



Understanding Disease

The Journal of Pathology, Volume: 235, Issue: 2, Pages: 153-174, First published: 09 October 2014, DOI: (10.1002/path.4456)

Ebola Vaccine (Not commercially available)

- ERVEBO® (Ebola Zaire Vaccine, Live)
- Single dose
- ERVEBO does not provide protection against other species of Ebolavirus or Marburgvirus.
- Eligibility: Outbreak responders, Laboratory and support staff, Healthcare personnel.

Deadly Marburg virus detected in bats in West Africa

The Impact of a Single Case!

Duncan

Lab supervisor isolated on cruise ship

120 healthcare workers

48 people in contact including fiancee

Nina Pham

Amber Joy Vinson

1 person monitored

16 close contacts In Ohio

Bridal store- 1 person

1000+ Frontier Airline passengers

153 Passengers Dallas to Cleveland

132 passengers Cleveland to Dallas

750 passengers on 5 other flights that used same plane

6 schools closed in Texas and Ohio

6 crew members on paid leave

Ebola isn't the only problem

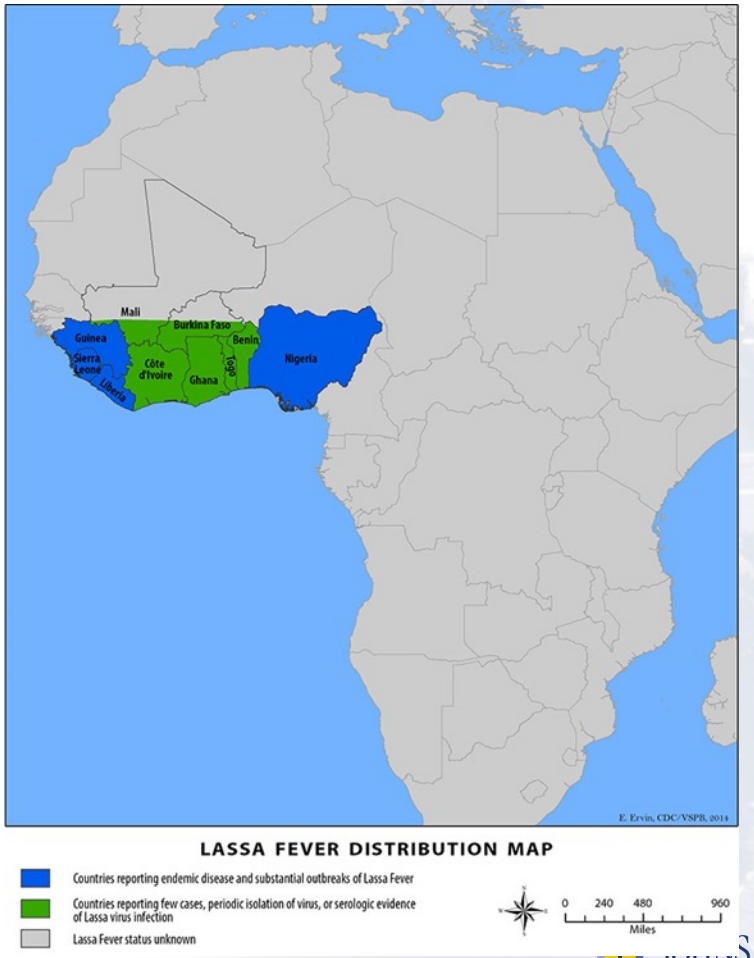
Health Care Response to CCHF in US Soldier and Nosocomial Transmission to Health Care Providers, Germany, 2009[1]

Nicholas G. Conger, Kristopher M. Paolino, Erik C. Osborn, Janice M. Rusnak, Stephan Günther, Jane Pool, Pierre E. Rollin, Patrick F. Allan, Jonas Schmidt-Chanasit, Toni Rieger, and Mark G. Kortepeter

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 21, No. 1, January 2015

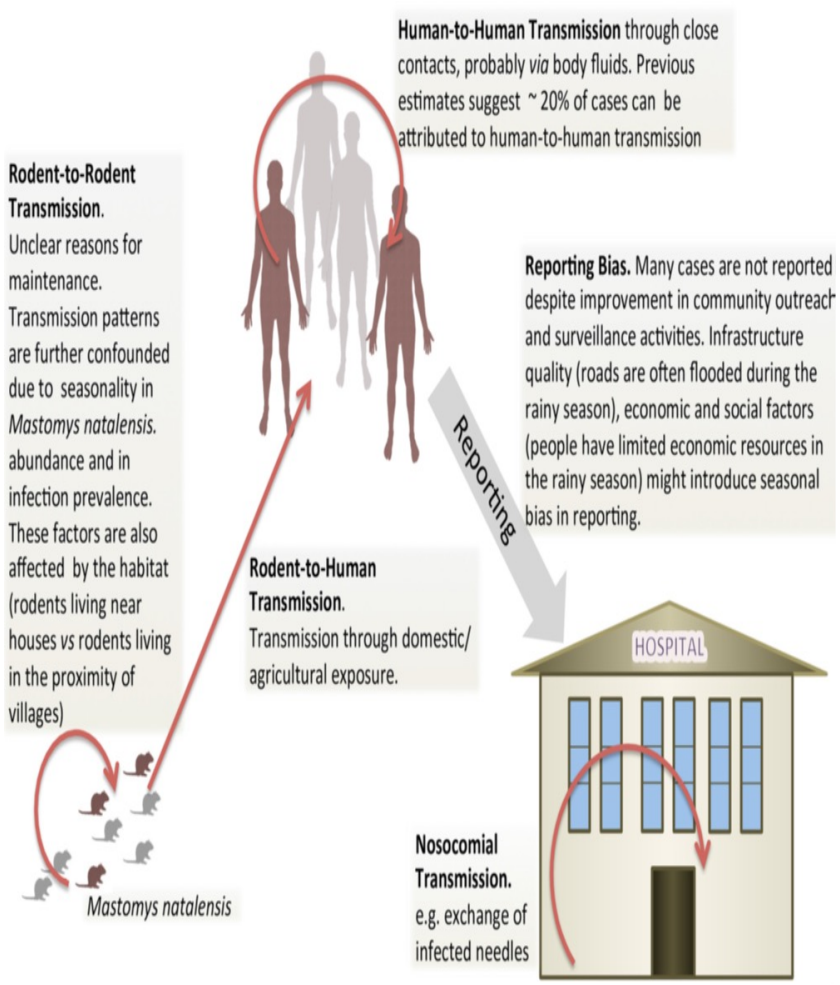
Lassa

- Lassa fever is an acute viral illness, discovered in 1969 in Nigeria.
- In 2009, the first case from Mali was reported in a traveler living in southern Mali
- Ghana reported its first cases in late 2011.
- There is serologic evidence of Lassa virus infection in Togo and Benin.




LASSA FEVER
Fresh Outbreak Hits Nigeria

Lassa Virus Transmission- Control



Patients with imported Lassa fever hospitalized in the US

Patient no.	Year of import	From	To	Clinical manifestations
1	1969	Nigeria	New York, NY	Fever, malaise, headache, nausea, sore throat, epigastric/right upper quadrant tenderness, pleural effusion, facial/cervical edema, dysphagia, elevated transaminases, cough, dyspnea, pulmonary infiltrates, epiglottal edema, lethargy, nystagmus, lightheadedness, dizziness without vertigo, ataxia, alopecia (*2*)
2	1975	Sierra Leone	Washington, DC	Abdominal pain, diarrhea, fever, headache, myalgia, arthralgia, conjunctival injection, lymphadenopathy, weight loss, pleuritic chest pain, pleural effusion, unilateral deafness
3	1976	Sierra Leone	Washington, DC	Abdominal cramps, nausea, vomiting, diarrhea, fatigue, headache, retroorbital pain, neck/back pain, paresthesias, right ear pain, fever, vertigo, syncope, dysmorphopsias, alopecia, weight loss, ecchymoses, insomnia, depression, hypotension, left-sided facial weakness, right-sided Babinski reflex, Weber test lateralized to the left (*3*)
4	1989	Nigeria	Chicago, IL	Shaking chills, fever, sore throat, myalgia, headache, dysphagia, bloody diarrhea, elevated transaminases, hypotension, adult respiratory distress syndrome, death (*4*)
5	2004	Sierra Leone and Liberia	Trenton, NJ	Chills, fever, sore throat, diarrhea, back pain, adult respiratory distress syndrome, death (*1*)

*Patients 1–4 are US citizens; patient 5 is a Liberian national.

Abe M. Macher, et al. Historical Lassa Fever Reports and 30-year Clinical Update. Emerg Infect Dis. 2006 May; 12(5): 835–837.

Patients with imported Lassa fever, worldwide, 1969-2004

Year of import	From	To	Occupation	Clinical outcome
1969	Nigeria	United States	Nurse	Survived
1971	Sierra Leone	United Kingdom	Nurse	Survived
1971	Sierra Leone	United Kingdom	Physician	Survived
1972	Sierra Leone	United Kingdom	Nurse	Survived
1974	Nigeria	Germany	Physician	Survived
1975	Nigeria	United Kingdom	Physician	Died
1975	Sierra Leone	United States	Aid worker	Survived
1976	Sierra Leone	United States	Aid worker	Survived
1976	Nigeria	United Kingdom	Engineer	Survived
1980	Upper Volta	Netherlands	Aid worker	Survived
1981	Nigeria	United Kingdom	Teacher	Survived
1982	Nigeria	United Kingdom	Diplomat	Survived
1984	Sierra Leone	United Kingdom	Geologist	Survived
1985	Sierra Leone	United Kingdom	Nurse	Survived
1987	Sierra Leone/Liberia	Israel	Engineer	Survived
1987	Sierra Leone	Japan	Engineer	Survived
1989	Nigeria	Canada	Agricultural specialist	Survived
1989	Nigeria	United States	Engineer	Died
2000	Cotê d'Ivoire/Burkina Faso/Ghana	Germany	Student	Died
2000	Sierra Leone	United Kingdom	Peacekeeper	Died
2000	Nigeria	Germany	Unknown	Died
2000	Sierra Leone	Netherlands	Physician	Died
2003	Sierra Leone	United Kingdom	Peacekeeper	Survived
2004	Sierra Leone/Liberia	United States	Businessman	Died

*A fully referenced version of this appendix table is available online from http://www.cdc.gov/ncidod/EID/vol12no05/05-0052_app.htm

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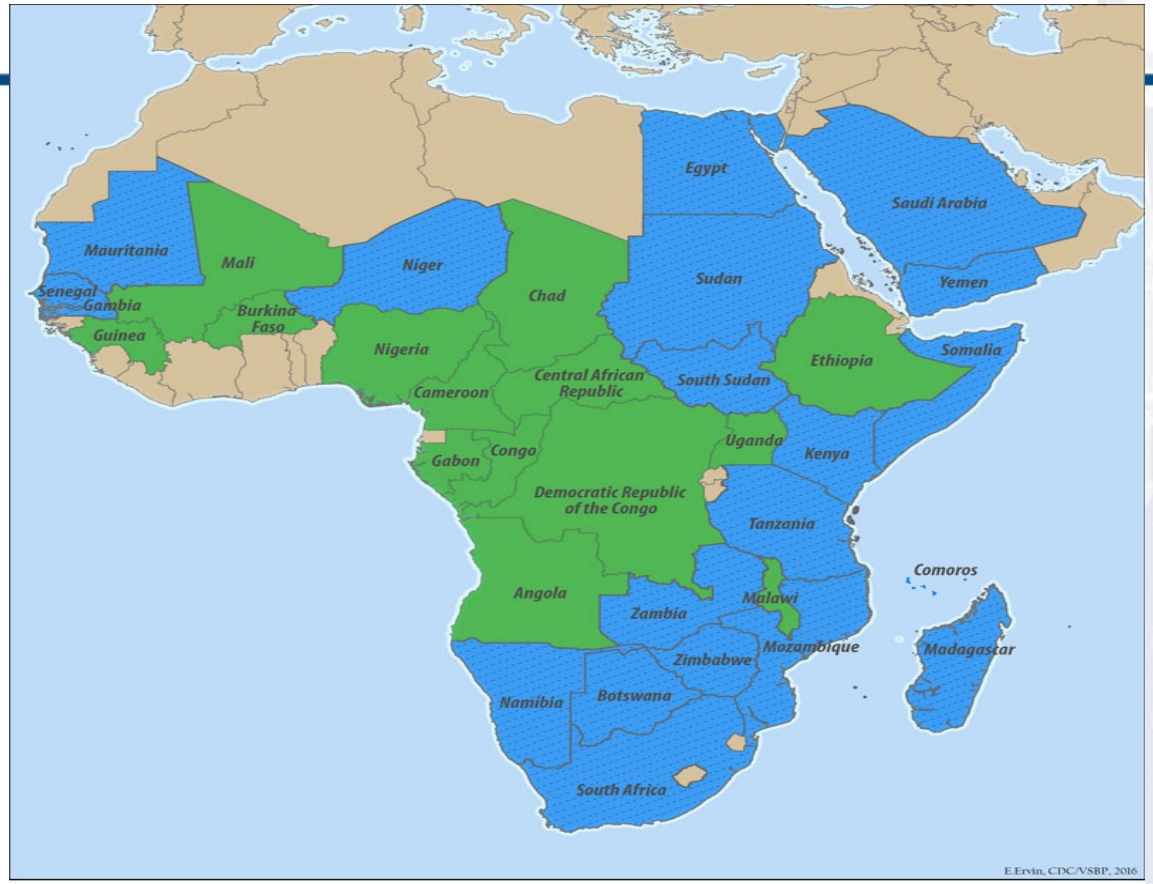


Rift Valley Fever Distribution Map

Countries reporting endemic disease and substantial outbreaks of RVF

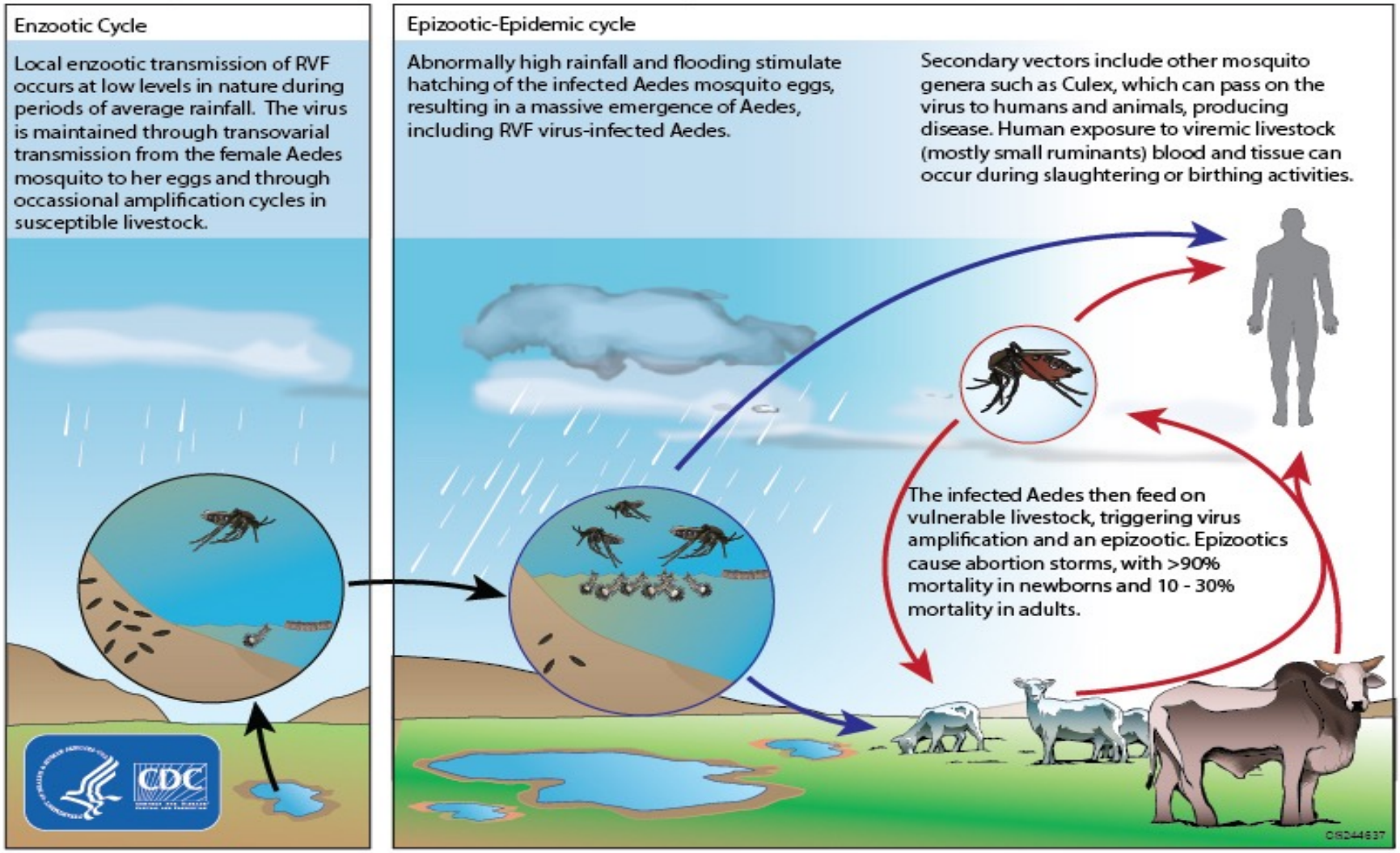
Countries reporting few cases, periodic isolation of virus, or serologic evidence of RVF infection

RVF status unknown

0 250 500 1,000 Miles

0 375 750 1,500 Km

Rift Valley Fever (RVF) virus ecology



More Recent Outbreaks of Rift Valley Fever

- **Sudan 2007-2008:** A cumulative total of **698 cases (222 deaths)** reported from 6 states yielding a case fatality rate of **32.4 per cent**
- **South Africa: Feb 2010**
  - Department of Health of South Africa reported 172 cases since 1st incident on 13 Feb 2010; **15 deaths**
  - majority of those affected were people working on farms, veterinary workers, and workers in abattoirs

. Mauritania 2022: A total of **47 confirmed cases including 23 deaths (CFR 49%)**—mostly among animal breeders— have been reported from nine of Mauritania's 15 districts.

History & Epidemiology Rift Valley Fever (Bunyaviridae)

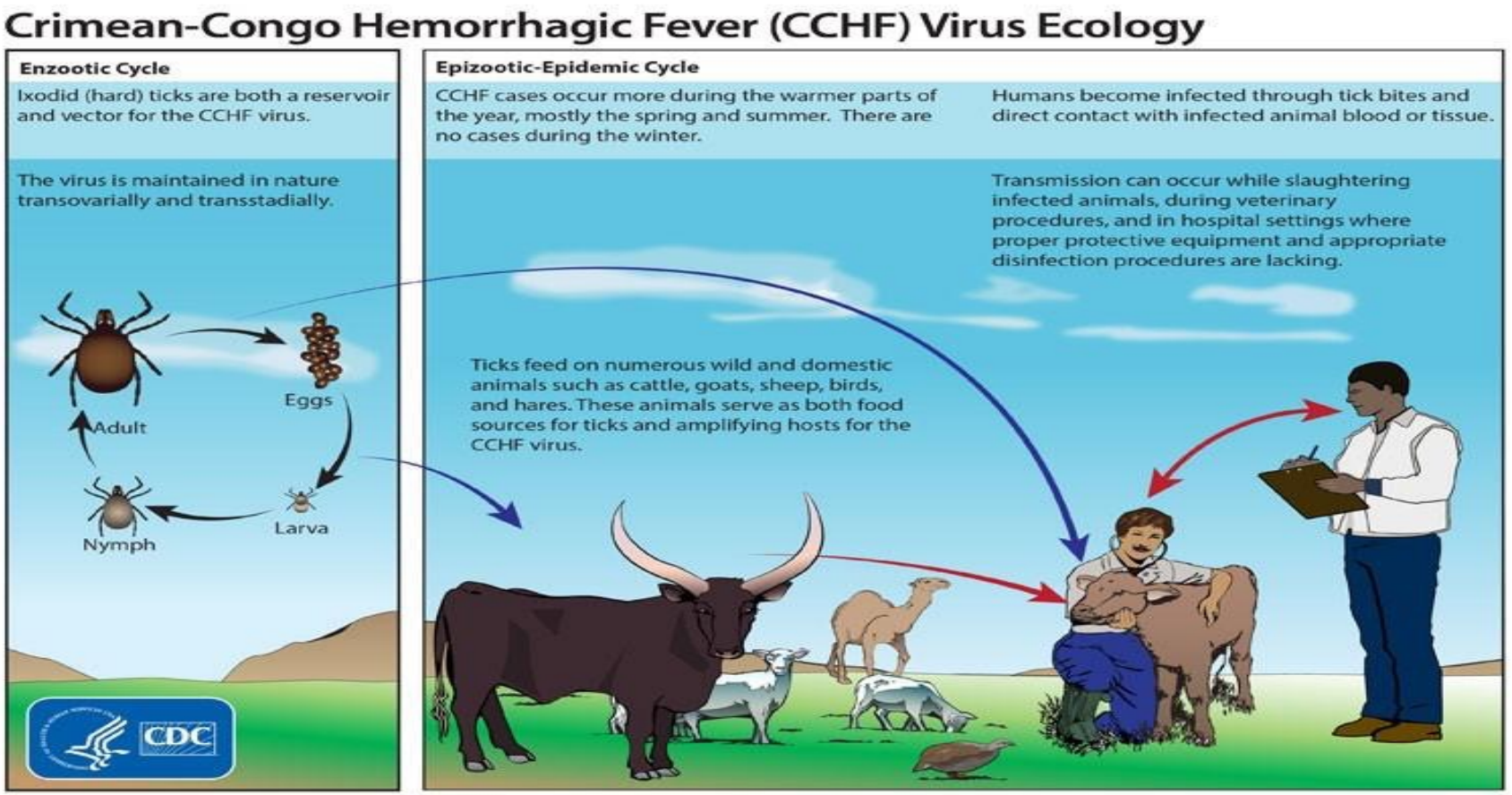
- First isolated in the Rift Valley, Kenya in 1930 during an investigation into a disease epidemic in sheep
- Livestock (sheep, cattle, camels, and goats) **Abortions**
- Human infection: **mosquito bites**, handling infected tissues (**animal slaughter**), **ingestion** of raw milk.
- **Aerosol** transmission has also led to infection in laboratory workers.
- In humans, no symptoms to mild illness but can progress to hemorrhagic fever (1% fatality rate)
- **Retinitis leading to blindness is the most common complication associated with RVF in humans (1-10%)**

RVFV causes significant disease in sheep, cattle, camels, and goats

Rift Valley Fever Prevention/ Vaccine

- Protect yourself against mosquitoes and other bloodsucking insects.
- Avoid contact with blood, body fluids, or tissues of infected animals.
- Use only safe animal products.
- RVF (live attenuated) vaccines for animals are available in endemic areas and is known to cause birth defect and abortion in animals
- A safe and efficacious vaccines for pregnant animals remains important.
- The new live-attenuated MP-12 vaccine (single dose) is attenuated and efficacious for both animals and humans, and is conditionally licensed for animal use in the U.S.
- Effective control of a RVF outbreak should be considered using suitable RVF vaccines in different scenarios.

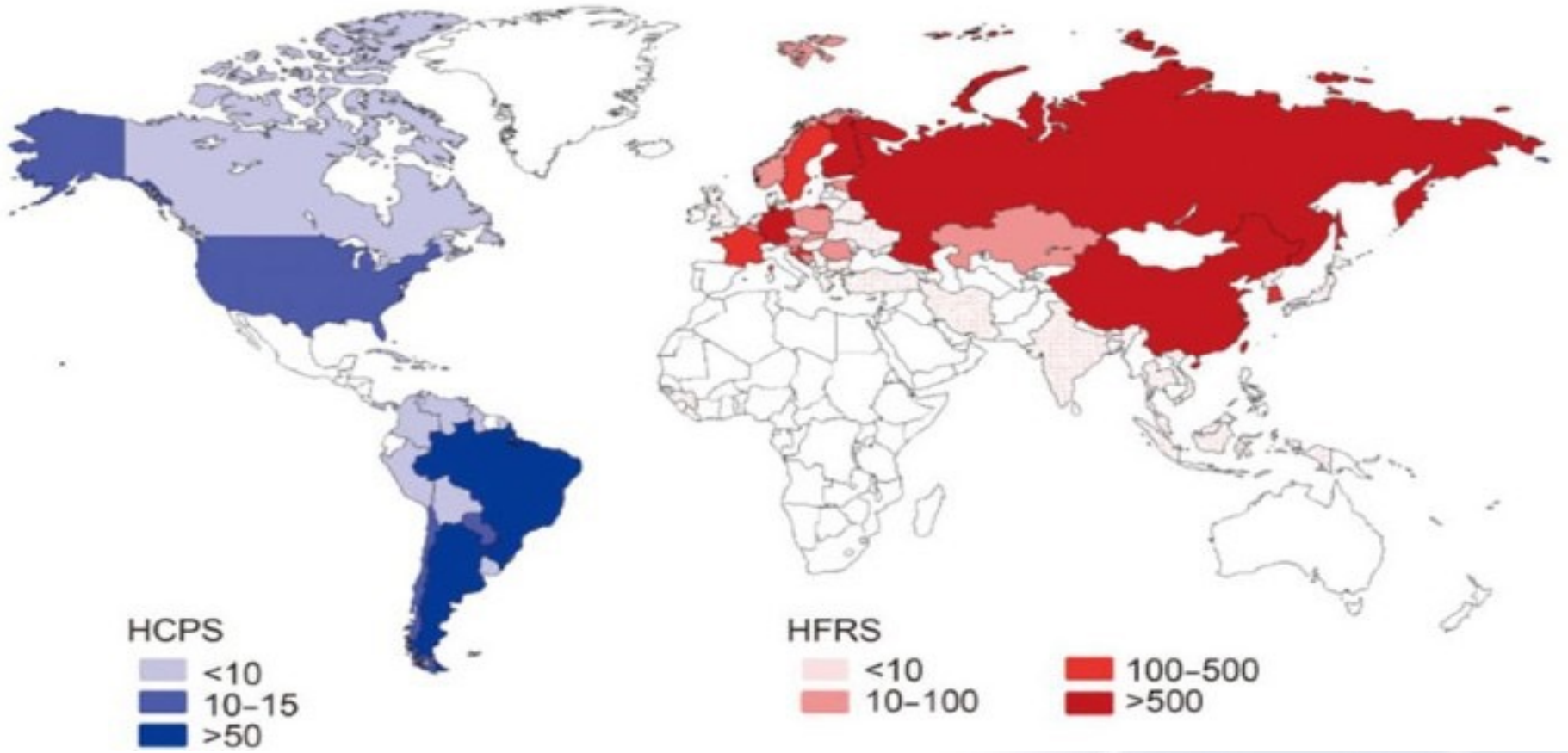
CCHFV Ecology



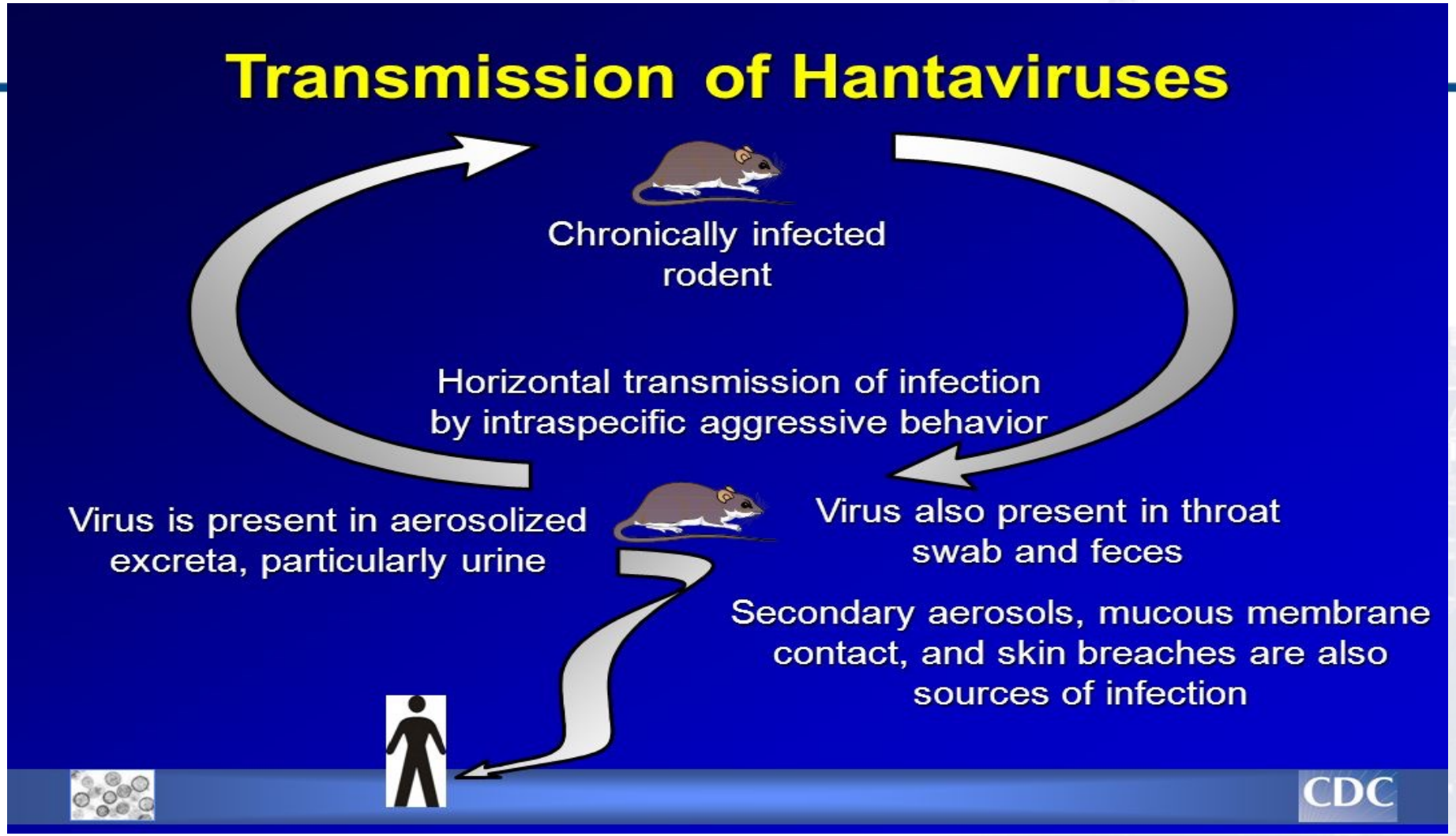
History & Epidemiology
Crimean Congo HF (bunyaviridae)

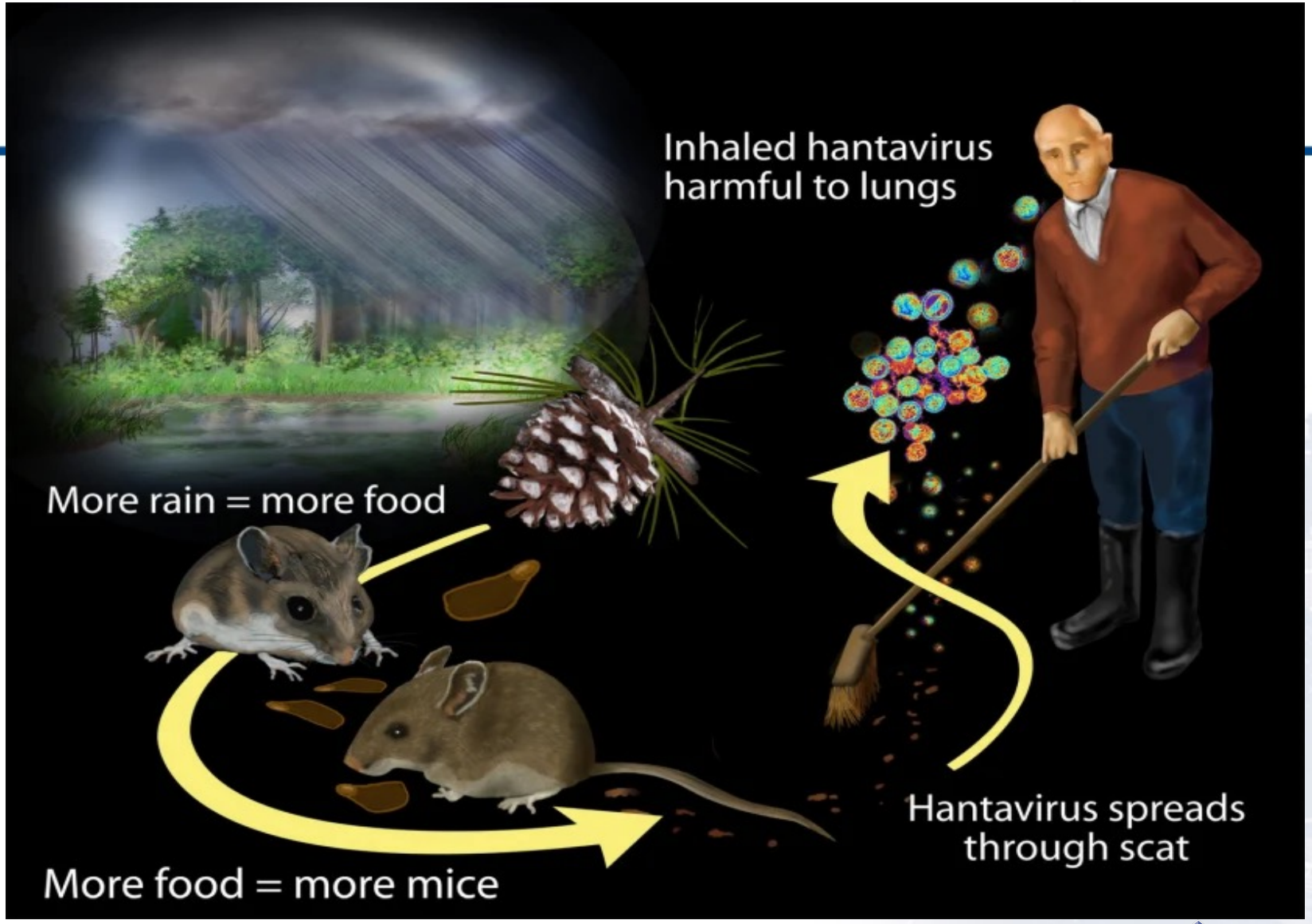
- CCHF was first brought to modern medical attention in 1945, when it was recognized as an acute febrile illness, accompanied by fever and severe bleeding in over 200 Soviet military personnel and local inhabitants supporting war devastated Crimea.
- Its viral etiology was identified in 1947 through experiments which included the inoculation of psychiatric patients and human "volunteers" with ultra-filtrates of patient serum and/or extracts of pooled ticks

Hantavirus Cardiopulmonary Syndrome (HCPS)
Hemorrhagic fever with renal syndrome (HFRS)



Hantavirus Transmission



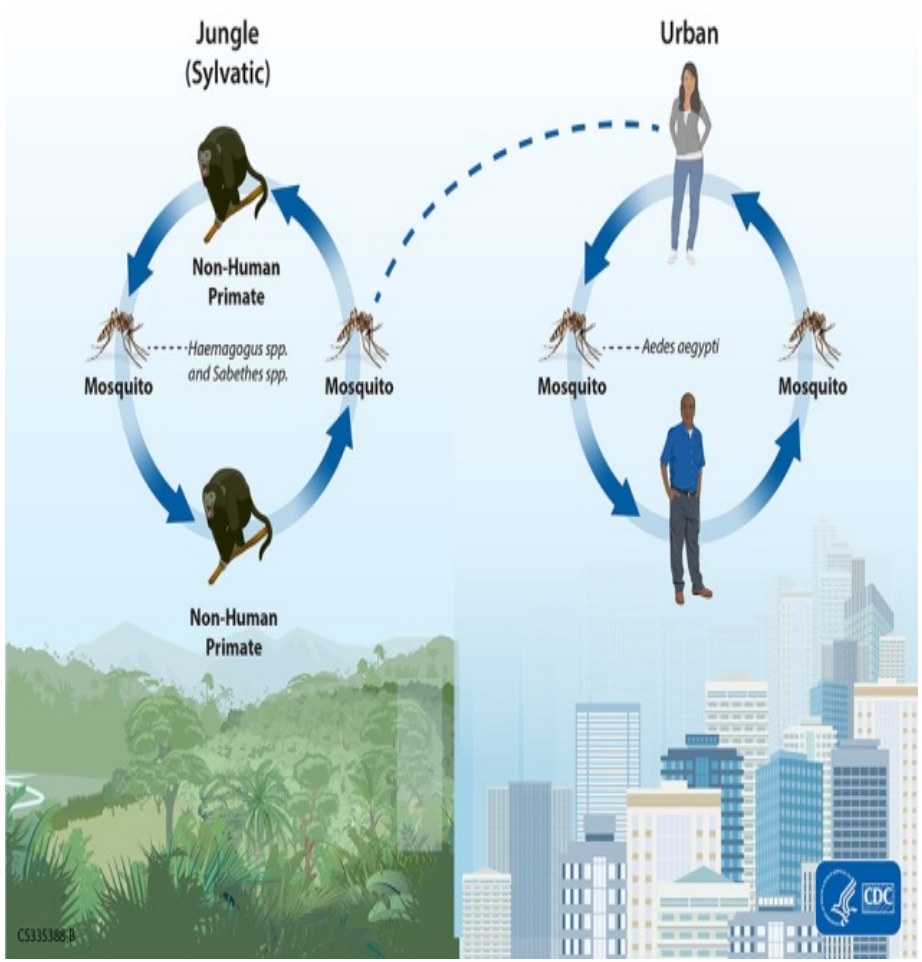

Inhaled hantavirus
harmful to lungs
More rain = more food
Hantavirus spreads
through scat
More food = more mice

Hantavirus Vaccine

- No licensed vaccine that can be used widely.
- Inactivated hantavirus vaccines are licensed for human use in China and South Korea.
- In 1990, the Korean HFRS vaccine Hantavax was put into commercial production.
- Since 2008, the Chinese government has implemented an expanded immunization program targeting HFRS.
- At present, DNA vaccines are the most popular method and have progressed to clinical trials (Phase 2).

Yellow fever vaccine recommendations for Africa and South America

Yellow fever endemic in Africa and South America



Yellow Fever Vaccine

- Live attenuated
- Safe and effective
- A single dose provides lifelong protection for most people.
- Single shot.
- Aged 9 months or older
- Traveling to or living in areas at risk for yellow fever virus in Africa and South America.
- Yellow fever vaccine may be required for entry into certain countries.

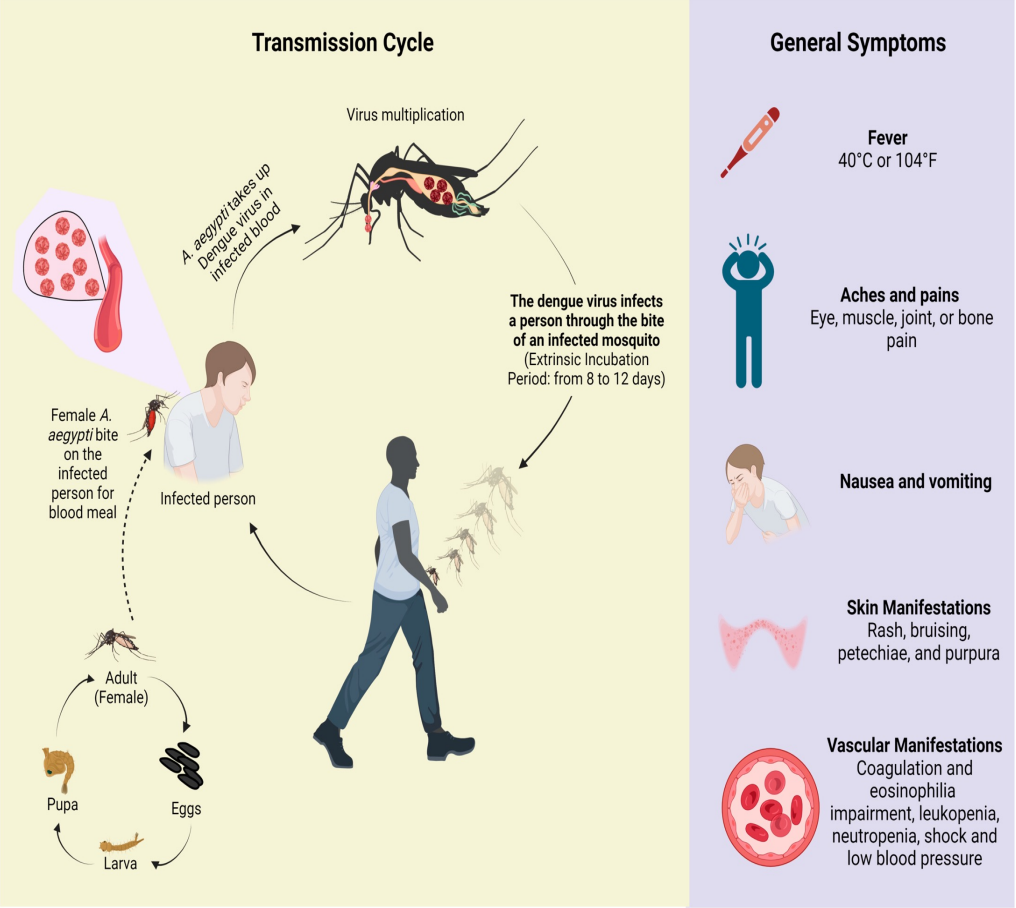
Dengue fever

Dengue transmission cycle and symptoms

- The transmission system of the dengue virus begins when the mosquito bites an infected person.

- The virus multiplies in the gut of the insect and passes into other organs, finally reaching the salivary glands.

- The virus eventually exits through the bite into the bloodstream of another person not yet infected.



Dengue fever vaccine (Dengvaxia)

- Dengue Vaccine for those living in endemic areas.
- The vaccine is not approved for use in travelers.
- (tetravalent, live-attenuated dengue vaccine), U.S. FDA approved
- Three-dose series, given 6 months apart, SQ, 0.5 ml per dose
- Eligibility : laboratory-confirmed previous dengue virus infection and living in an endemic area.
- At least 6 months after the first infection

Dengue fever Vaccine

- DO NOT vaccinate a person without laboratory evidence of previous dengue virus infection.
- If you vaccinate a person who has never been infected with dengue virus, they skip the first natural infection.
- If the person is then infected after vaccination, they will experience an infection that is similar to the second dengue virus infection, which poses the highest risk for severe disease.
- The mechanism: **Antibody-dependent enhancement, which can lead to plasma leakage and severe disease**.

VHF Vaccines

- Yellow fever 17D is a currently licensed, available vaccine, single dose, lifelong protection
- Dengue fever vaccine licensed for only previously infected individuals living in endemic regions.
- ERVEBO® (Ebola Zaire Vaccine) is licensed for the prevention of Zaire ebolavirus).
- Utility for post-exposure vaccination?

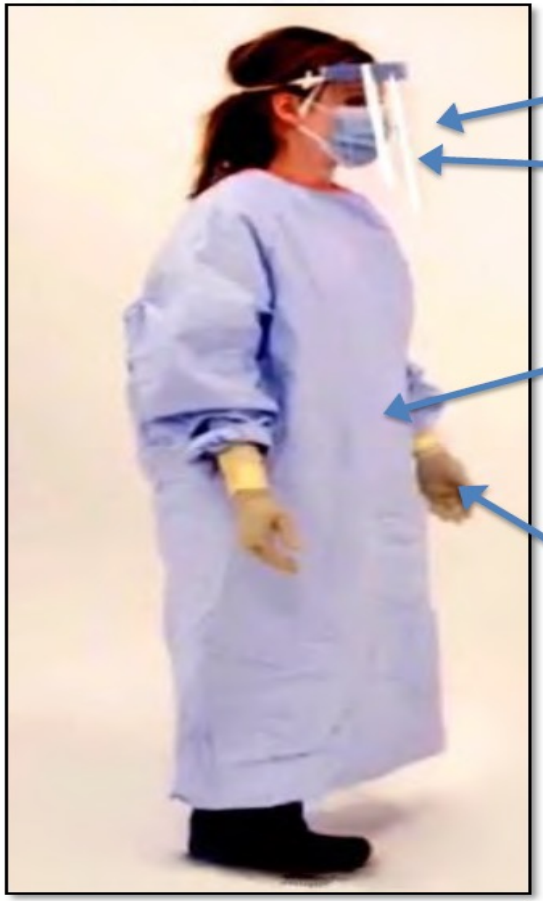
VHFs With Known Nosocomial Spread

- Arenaviruses – Lassa, Junin/Machupo (rare)
  - **Lassa – most common imported VHF (if dengue not included)**
- Filoviruses – Ebola and Marburg
- Bunyaviruses – CCHF, Andes virus (a cause of hantavirus pulmonary syndrome)
- Flaviviruses – dengue (rare – from blood splash or needlestick)

Wherever patient care occurs:

- Care must be deliberate
- Every procedure must be practiced and follow risk/benefit analysis
- Anyone can and should call a safety stop
- Care must be deliberate
- Training is as (or more) important as PPE
- Healthy respect (not fear) for what the virus can do

Persons Under Investigation (PUIs) for VHF Who Are Clinically Stable and Do Not Have Bleeding, Vomiting, or Diarrhea



Single Use (Disposable) Face Shield

Single Use (Disposable) Surgical Mask

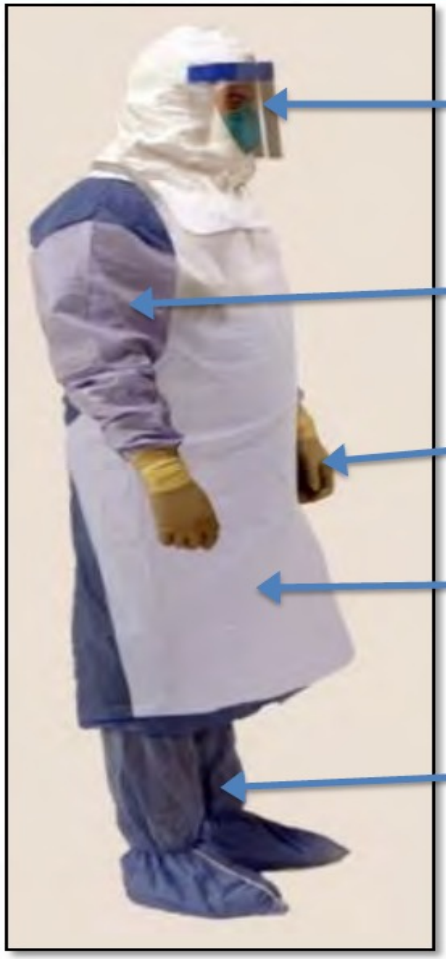
Single use (disposable) fluid-resistant gown that extends to at least mid-calf or coverall without integrated hood

Single use (disposable) gloves with extended cuffs. Two pairs of gloves should be worn.

At a minimum, outer gloves should have extended cuffs and must completely cover the gown cuff.

http://www.cdc.gov/vhf/ebola/healthcare-us/ppe/

Patients with Confirmed VHF or Persons under Investigation (PUIs) for VHF who are Clinically Unstable or Have Bleeding, Vomiting, or Diarrhea



Single use face shield, surgical hood extending to shoulders, and N95 Respirator **OR** PAPR with a full face shield, helmet, shroud (not shown)

Single use fluid-resistant or impermeable gown that extends to at least mid-calf **OR** coverall without integrated hood (not shown)

Two pairs of single use, disposable gloves. At a minimum, outer gloves should have extended cuffs.

Single use fluid-resistant **OR** impermeable apron that covers the torso to the level of the mid-calf

Single use fluid-resistant or impermeable boot covers that extend to at least mid-calf **OR** single-use fluid-resistant or impermeable shoe covers, which are acceptable only if used with a coverall with integrated socks (not shown)

http://www.cdc.gov/vhf/ebola/healthcare-us/ppe/