

Emerging Infectious Diseases & Viral Hemorrhagic Fevers

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Emerging Infectious Diseases

- Newly evolved strains of pathogens
- Pathogens with recently increased human incidence or dramatic changes in their geographic host range
- Pathogens recently entering the human population

Burden of EID

- **Societal Costs**
 - Investigation
 - Increased hospitalizations
 - Additional/new diagnostics or therapeutic procedures
 - Additional antibiotic/antiviral use
 - Loss of productivity
 - Long-term disability
- **Containment Costs**
 - School closures
 - Closing of public places
 - Infection control and/or quarantine measures
- **Individual Costs**
 - Increased morbidity and mortality

Causes of Pathogen Emergence

• Human

- Changes in human demographics and society**
- Hospitals and medical procedures**
- International travel**
- Poor population health (e.g. HIV, malnutrition)**

• Pathogen

- Capacity to adapt to humans**
- Acquisition of virulence factors and antibiotic resistance**
- Failures of disease control programs**

• Environmental

- Land use and agricultural practices**
- Trade in animals and animal products**
- Production and supply of food and water**
- Climate Change**

Profile of an Emerging Pathogen

- **RNA virus**
- **Zoonotic**
- **Ability to use a receptor that is conserved across species**
- **Found in areas undergoing ecological, demographic, or social change**
- **Number of EID events has been steadily increasing**

Recent Novel EIDs

- **NIPAH (1999)**
 - **Disease: fever and encephalitis**
 - **Initial outbreak in Malaysia**
 - 265 human cases, 105 fatal
 - Case fatality rate ~ 40%
 - **Have been recurrent outbreaks with documented human to human spread**
 - **Virus originated: bats → pigs → humans**



Recent Novel EIDs

- **SARS (2003)**
 - First pandemic of the 21st century
 - Severe respiratory disease (~10% case fatality rate)
 - > 8000 cases in 28 countries
 - Pandemic was stopped primary through quarantine efforts and international collaborative efforts of public health personnel, clinicians, and laboratory scientists
 - Caused by a novel coronavirus, **SARS-CoV**, which originated in bats

ORIGINAL ARTICLE

Fever with Thrombocytopenia Associated
with a Novel Bunyavirus in China

N Engl J Med 2011;364:1523-32.

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Truly Emerging — A New Disease Caused by a Novel Virus

Heinz Feldmann, M.D.

**VIRAL
HEMORRHAGIC
FEVERS**

VHFs

- **Viruses**

- All enveloped viruses with single stranded RNA genomes
- Vary greatly in their morphology
- 4 families:
 - *Arenaviridae*
 - *Bunyaviridae*
 - *Filoviridae*
 - *Flaviviridae*

VHF

- **Clinical Syndrome**
 - Fever
 - bleeding diathesis
 - N/V/D
 - Circulatory shock
 - Multi-organ failure
 - High case-fatality rates
- **Laboratory Findings**
 - Thrombocytopenia
 - Leukopenia
 - Elevated LFTs
 - Prolonged PT, PTT, INR
 - Evidence of DIC

VHFs

- **Pathogenesis**

- Not fully understood
- Early target cells: dendritic cells, monocytes, macrophages, and vascular endothelial cells (but have a broad tissue tropism)
- Viruses evoke an intense cytokine response with severe inflammatory tissue damage
 - LN
 - Liver (decreased production of clotting factors)
 - Adrenal Gland (impaired synthesis of steroids)
- Failure of effective immune responses
 - Inhibition of IFN host responses
 - Depletion of lymphocytes
- Obtain quickly extremely high levels of viremia
- Can induce profound immunosuppression

Unregulated virus spread and replication



dysregulation of host immune responses



Coagulation abnormalities



Impairment of vascular system



hypotension



SHOCK & MULTI-ORGAN FAILURE

Table 1 Hemorrhagic fever viruses

Element or feature	Viral hemorrhagic fever ^a							
	EHF	MHF	AHF	BHF	Lassa fever	CCHF	RVF	Yellow fever
Virus family	Filoviridae	Filoviridae	Arenaviridae	Arenaviridae	Arenaviridae	Bunyaviridae	Bunyaviridae	Flaviviridae
Etiological virus	Ebola	Marburg	Junin	Machupo	Lassa	CCHF	RVF	Yellow fever
Natural distribution	Africa	Africa	South America	South America	West Africa	Africa, Central Asia, Europe, Middle East	Africa, Yemen, Saudi Arabia	Africa, tropical Americas
Source	Unknown	Unknown	Rodent	Rodent	Rodent	Tick	Mosquito	Mosquito
Incubation (days) ^b	2–21	2–14	7–14	9–15	5–16	3–12	2–6	3–6
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hypotension	Yes	Yes	Yes	Yes	Yes	Yes	NE	Yes
Hepatocellular necrosis (biochemical evidence)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bleeding ^c	Occasional	Occasional	Occasional	Occasional	Occasional	Occasional	Occasional	Occasional
Macular rash ^d	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vascular lesions	No	No	No	No	No	NE	NE	NE
Thrombocytopenia	Yes	Yes	Yes	Yes	Rare	Yes	Yes	Yes
DIC (biochemical evidence)	Yes	Yes	Some	Equivocal	No	Yes	Some	Yes
DIC (fibrin deposits)	Yes	Yes	Equivocal	Equivocal	Rare	NE	Some	NE
Lymphoid depletion	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lymphopenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lymphocyte apoptosis	Yes	Yes	NE	NE	NE	NE	NE	NE
Infection of lymphocytes	No	No	No	No	No	No	No	No
Infection of macrophages	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Infection of dendritic cells	Yes	Yes	Yes	NE	Yes	NE	NE	NE
Cytokines/chemokines (increased circulating levels)	IFN- α , IL-6, IL-10, IL-18, MIP-1 α , MIP-1 β , MCP-1, TNF- α	NE	IFN- α , IL-6, IL-8, IL-10, TNF- α	NE	IFN- γ , IL-8, IL-10, IP-10, TNF- α	NE	NE	IL-6, IP-10, MCP-1, TNF- α , IL-1RA
Other mediators (increased circulating levels)	TF, NO	NE	NE	NE	NE	NE	NE	NE

Ebola and Marburg

- **Filamentous, single-stranded, negative-sense RNA viruses**
- **First recognized in 1967**
- **Sporadic cases and outbreaks in equatorial Africa**
- **Causes severe disease in apes and humans**
- **Case fatality rate: 25-90% depending on strain**

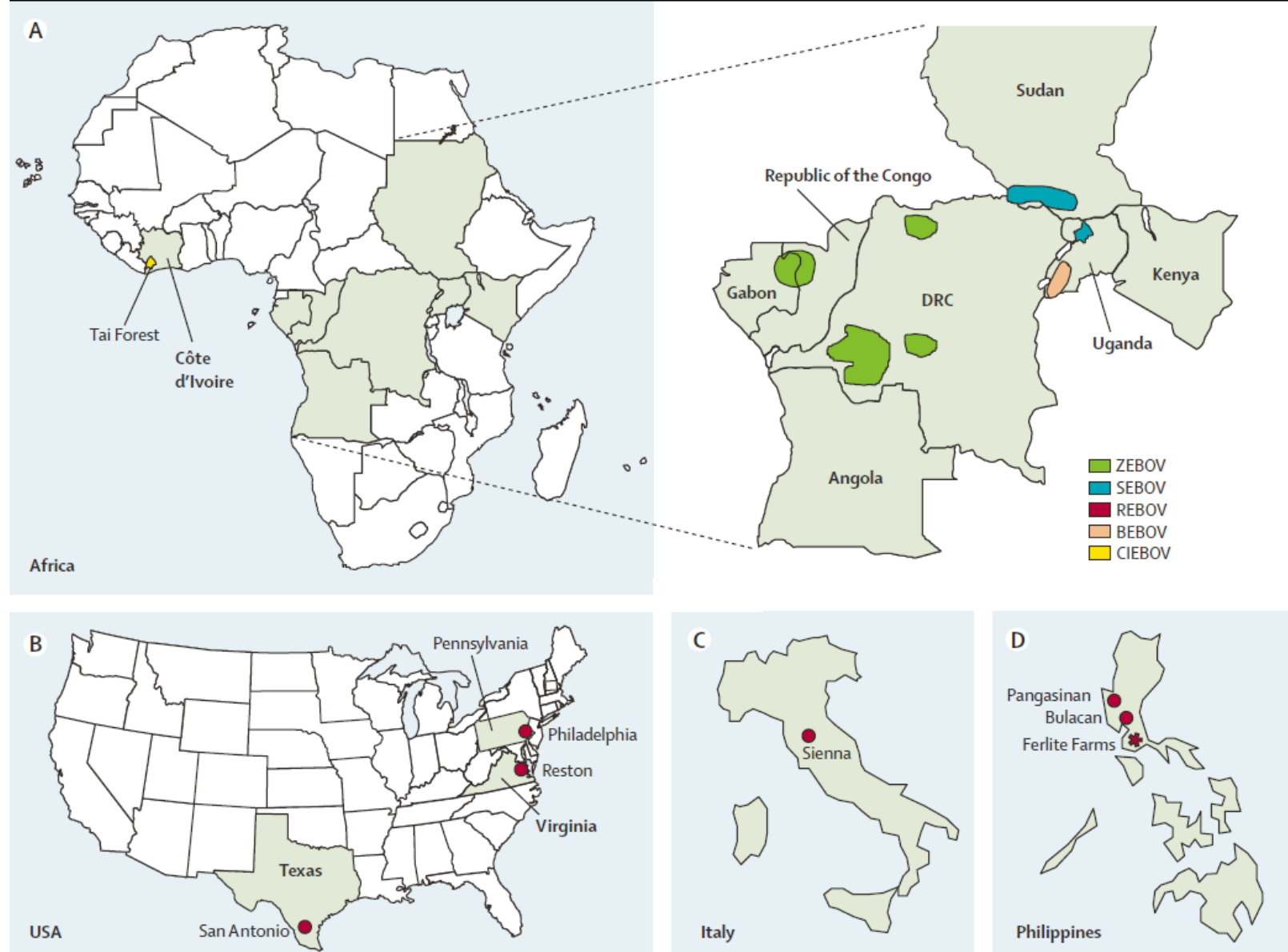


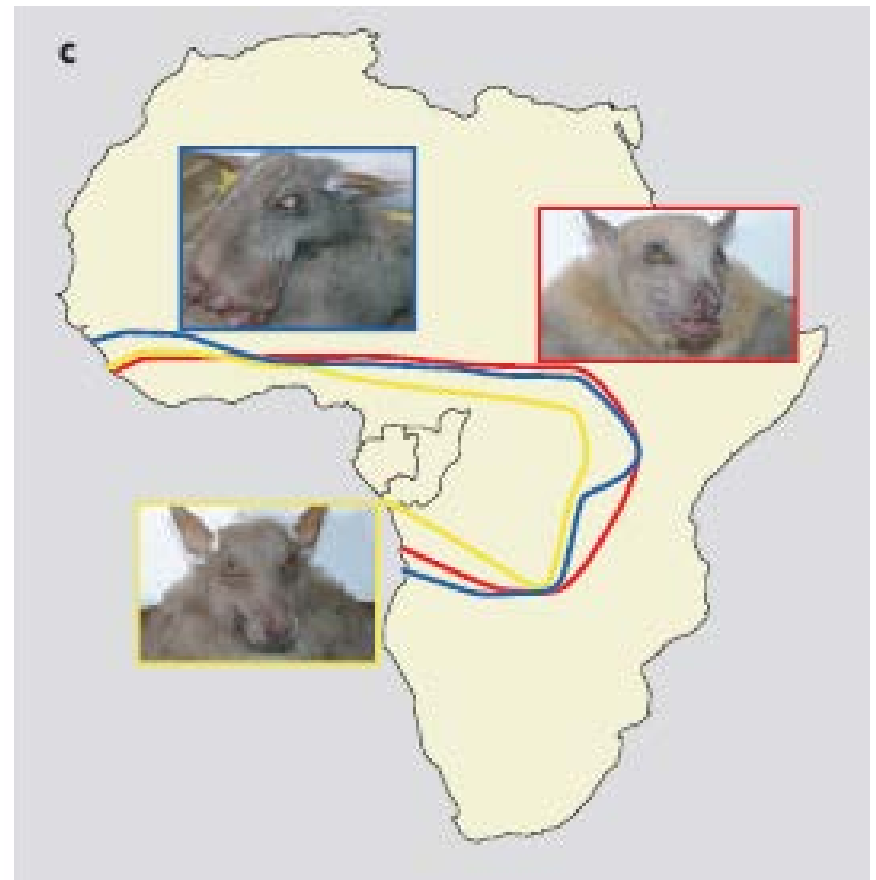
Figure 1: Locations of Ebolavirus infections and outbreaks

(A) Regions in Africa (approximate distribution 10° north and south of the equator) with reported outbreaks of Ebola haemorrhagic fever caused by the three central African species of Ebola virus, Zaire Ebola virus (ZEBOV), Sudan Ebola virus (SEBOV), and Bundibugyo Ebola virus (BEBOV). The Tai Forest region in Côte d'Ivoire reported the only case so far of Ebola virus in western Africa caused by the species Côte d'Ivoire Ebola virus (CIEBOV). (B) Reston ebolavirus REBOV has been introduced several times through imported macaques into USA from 1989 to 1996 (Philadelphia, PA; Reston, VA; San Antonio, TX) and into Italy (Siena) in 1992 (C). The source of the introduction in all cases of REBOV has been a primate export facility in the Philippines (Ferlite farm) (D). Animals of this farm have been diagnosed with REBOV infection several times in the 1990s. REBOV has been detected in pigs on two farms in the Philippines (Pangasinan, Bulacan). DRC=Democratic Republic of the Congo.

- **EBOLA**

Fruit bats as reservoirs of Ebola virus

Leroy EM, et al. *Nature* 2005;438:575.



• MARBURG

Marburg Virus Infection Detected in a Common African Bat

Jonathan S. Towner¹, Xavier Pourrut^{2,3}, César G. Albariño¹, Chimène Nze Nkogwe², Brian H. Bird^{1,4}, Gilda Grard², Thomas G. Ksiazek¹, Jean-Paul Gonzalez⁵, Stuart T. Nichol¹, Eric M. Leroy^{2,3*}



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Evidence for
Bats

PCR positive

Antibody positive

Figure 4. Geographic distribution (green shade) of *Rousettus aegyptiacus* in Africa. Red dots indicate the locations of all previous known Marburg virus outbreaks, as indicated in Figure 1, in addition to the locations of the Marburg-positive bats.

Isolation of Genetically Diverse Marburg Viruses from Egyptian Fruit Bats

Jonathan S. Towner¹, Brian R. Amman¹, Tara K. Sealy¹, Serena A. Reeder Carroll¹, James A. Comer¹, Alan Kemp², Robert Swanepoel², Christopher D. Paddock³, Stephen Balinandi⁴, Marina L. Khristova⁵, Pierre B. H. Formenty⁶, Cesar G. Albarino¹, David M. Miller¹, Zachary D. Reed¹, John T. Kayiwa⁷, James N. Mills¹, Deborah L. Cannon¹, Patricia W. Greer³, Emmanuel Byaruhanga⁸, Eileen C. Farnon¹, Patrick Atimmedi⁹, Samuel Okware¹⁰, Edward Katongole-Mbidde⁷, Robert Downing⁴, Jordan W. Tappero⁴, Sherif R. Zaki³, Thomas G. Ksiazek^{1*}, Stuart T. Nichol^{1*}, Pierre E. Rollin^{1*}

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Abstract

In July and September 2007, miners working in Kitaka Cave, Uganda, were diagnosed with Marburg hemorrhagic fever. The likely source of infection in the cave was Egyptian fruit bats (*Rousettus aegyptiacus*) based on detection of Marburg virus RNA in 31/611 (5.1%) bats, virus-specific antibody in bat sera, and isolation of genetically diverse virus from bat tissues. The virus isolates were collected nine months apart, demonstrating long-term virus circulation. The bat colony was estimated to be over 100,000 animals using mark and re-capture methods, predicting the presence of over 5,000 virus-infected bats. The genetically diverse virus genome sequences from bats and miners closely matched. These data indicate common Egyptian fruit bats can represent a major natural reservoir and source of Marburg virus with potential for spillover into humans.

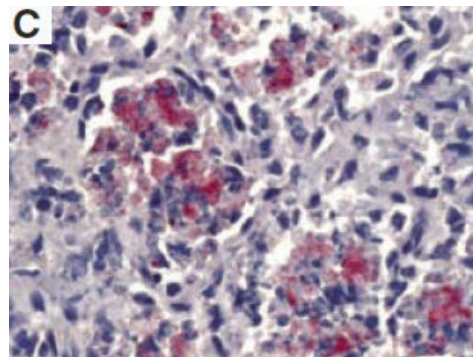
Citation: Towner JS, Amman BR, Sealy TK, Carroll SAR, Comer JA, et al. (2009) Isolation of Genetically Diverse Marburg Viruses from Egyptian Fruit Bats. *PLoS Pathog* 5(7): e1000536. doi:10.1371/journal.ppat.1000536

Editor: Ron A. M. Fouchier, Erasmus Medical Center, The Netherlands

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Discovery of Swine as a Host for the *Reston ebolavirus*

10 JULY 2009 VOL 325 SCIENCE www.sciencemag.org



Replication, Pathogenicity, Shedding, and Transmission of *Zaire ebolavirus* in Pigs

The Journal of Infectious Diseases 2011;204:200–8

Routes of Infection

- **Enters host via mucosal surfaces, breaks and abrasions in the skin, or by parenteral introduction**
- **Infectious virus particles have been detected in: blood, semen, genital secretions, skin, nasal secretions, and other body fluids**
- **Most human infections in outbreaks occur by direct contact with infected patients or cadavers**
- **Outbreaks associated with**
 - **Butchering of chimpanzees for food**
 - **Handling and consumption of freshly killed bats**
 - **Reuse of contaminated needles**

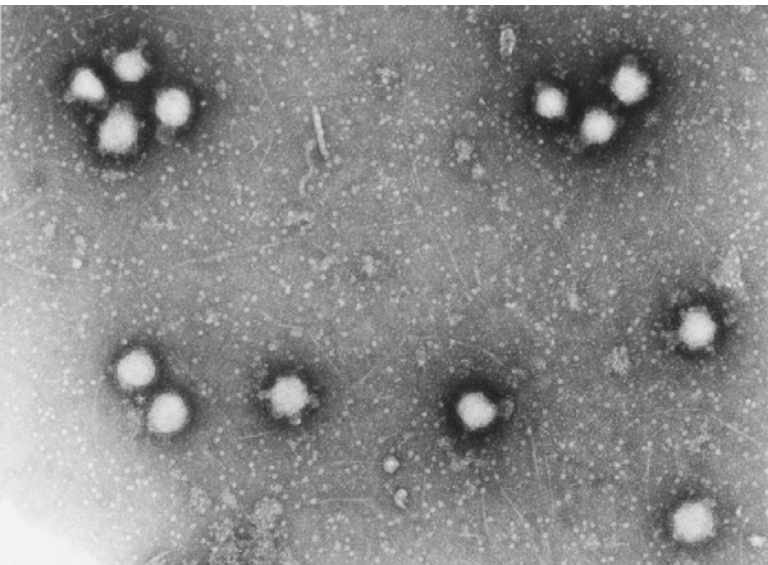
Clinical Disease

- **Incubation period: 2-21 days (mean 4-10 days)**
- **Abrupt onset: fevers, conjunctival injection, HA, myalgias, arthralgias**
- **Multisystem involvement:**
 - **GI: abd pain, N/V/D, anorexia**
 - **Resp: cough, chest pain, SOB, nasal discharge**
 - **CNS: HA, confusion**
 - **Derm: maculopapular rash common**
 - **Hemorrhagic manifestations (seen in about 1/2 of pts): petechiae, bruising, oozing from venopuncture sites, nosebleeds**
- **Around DOI 3-4 pts begin to deteriorate suddenly**
- **Around DOI 6-9 develop shock and multiorgan failure**
- **Asymptomatic infections (except for Ebola Reston) have not been reported**

Crimean-Congo Hemorrhagic Fever (CCHF)

genus: **Nairovirus**

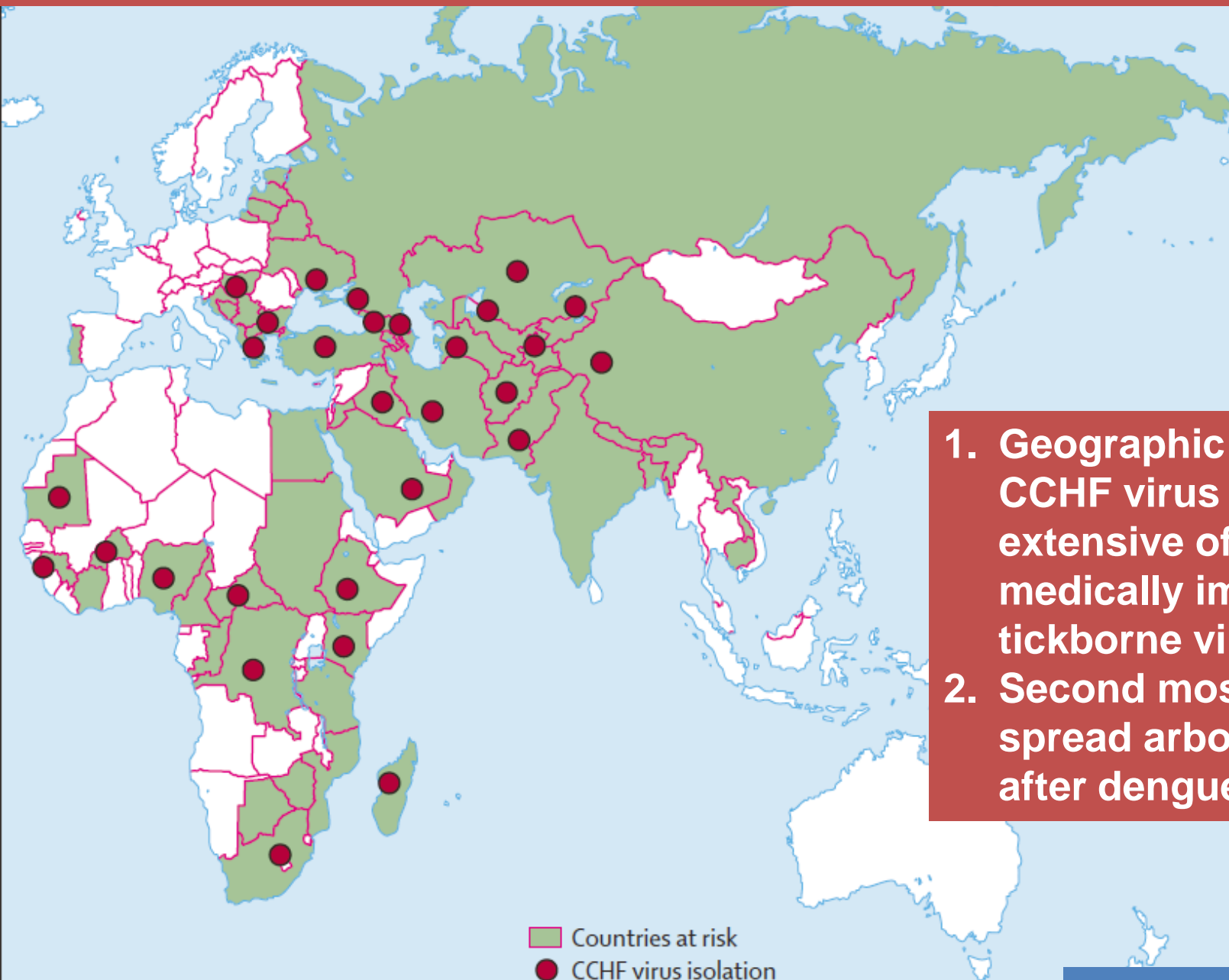
family: **Bunyavirus**



Epidemiology and Ecology

- **Single stranded, negative-sense, segmented RNA genome**
- **First recognized in Russia in 1945 and in the DRC in 1956**
- **Arbovirus**
 - **1^ovector = ticks of the Hyalomma genus**
 - **Ticks found throughout Africa, Middle East, eastern Europe, Asia, and Far East**
- **Main reservoirs: livestock (cattle, goats, sheep, horses, donkeys, pigs), small wild animals (hares, hedgehogs), small rodents, and birds (ostriches)**

Worldwide Distribution of CCHF



1. Geographic range of CCHF virus is the most extensive of all the medically important tickborne viruses
2. Second most widely spread arboviruses after dengue

Risk factors for Infection

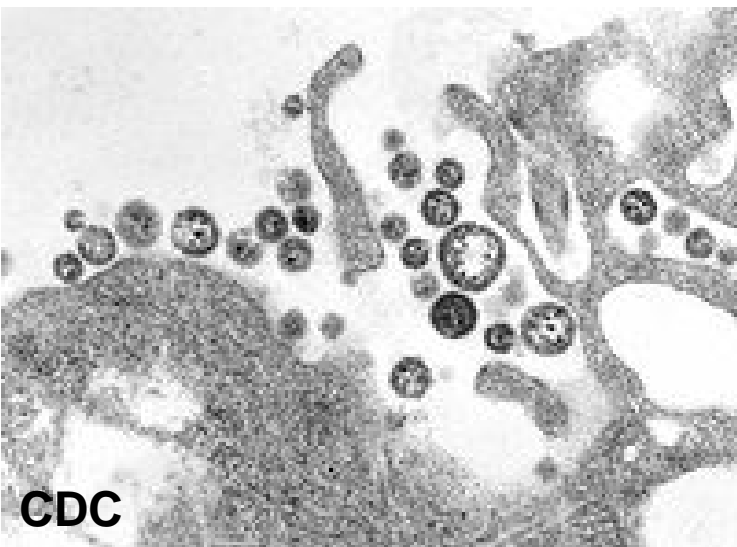
- **Natural routes of infection**
 - Direct contact of damaged skin with blood and tissues of infected animal
 - Inoculation by infected ticks
- **High risk groups/activities**
 - Farmers, herdsman, veterinarians, abattoir workers
 - Hiking, camping, rural recreational activities
- **Nosocomial human-human transmission**
 - Exposure to hemorrhages from nose, mouth, gums, vagina, injection sites
 - Needlestick injuries

CCHF – Clinical Disease

- **Incubation period: 1-13 days (mean 2-5 days)**
- **Abupt onset:** fevers, myalgias, HA, N/V/D, severe abdominal pain, conjunctivitis, eye pain, photophobia
- **Differs from other VHF – shorter clinical course, but has early-onset and extremely severe hemorrhage phase**
- **DOI 3-4: hemorrhagic phase begin (70% of pts) = petechial rash, bleeding from nose, GI system (haematemesis, melena), uterus, urinary tract (hematuria), and respiratory tract (hemoptysis)**
- **Case fatality rate ~ 30% (varies by strain)**
- **High seropositivity in endemic areas suggests mild illness occurs**

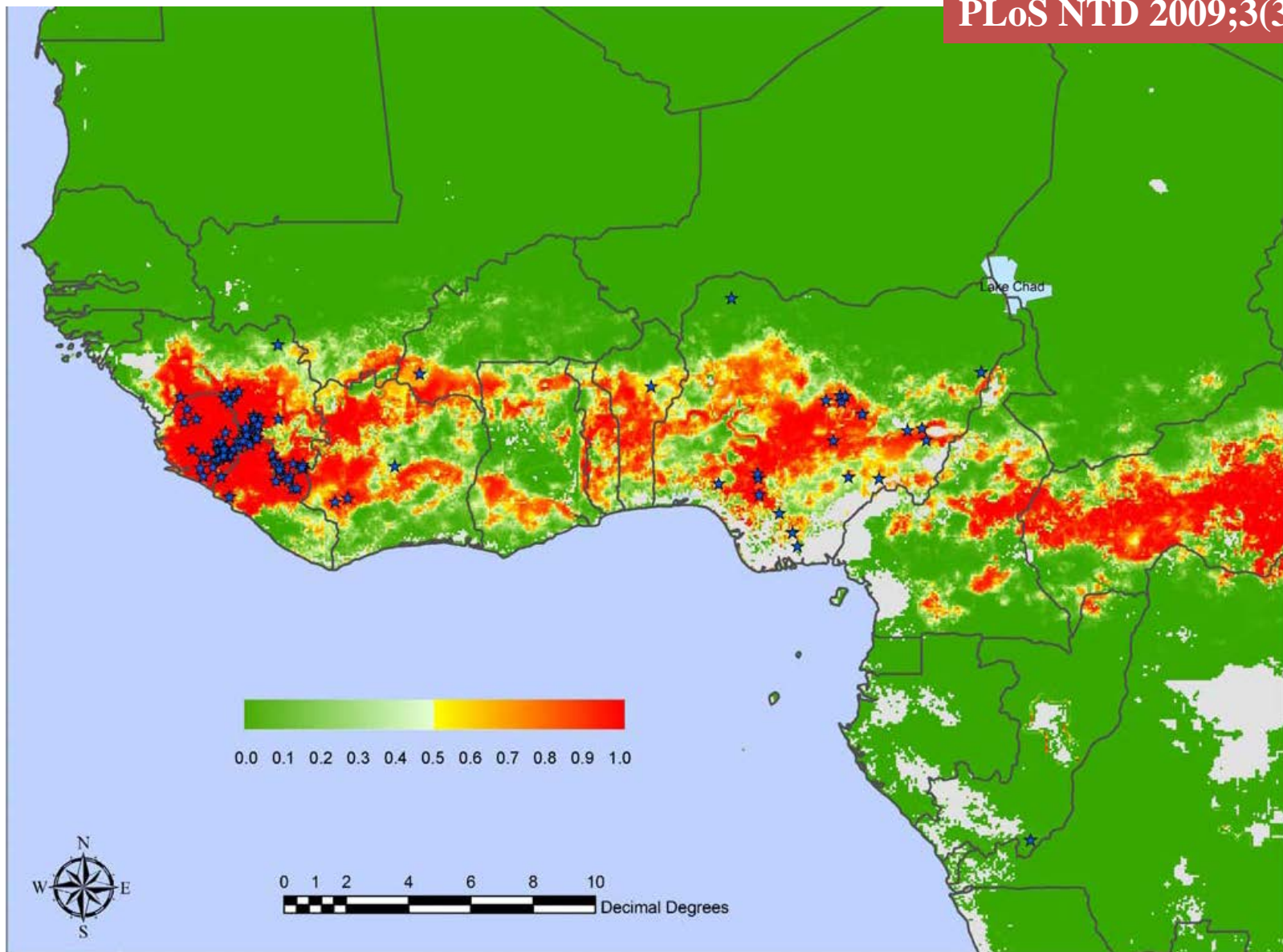
Lassa Fever Virus

family: Arenavirus



Epidemiology and Ecology

- **First recognized in 1969 in Lassa, Nigeria in several American missionary nurses**
- **Single stranded, negative-sense RNA genome**
- **Endemic in Western Africa**
- **Reservoir: multimammate **RATS** (*Mastomys natalensis*)**
 - **Breed frequently**
 - **Most common rodent in tropical Africa, distributed widely through west, central, and east Africa**
 - **Found predominately in rural dwellings**
 - **Persistently infected and shed virus in excreta**



Risk Map of Lassa Fever in West Africa

red = higher risk, stars = known outbreaks

Highest correlation of risk – associated with rainfall

Transmission

- **RAT to HUMAN**

- **African grain crops and stores are commonly contaminated with the virus and serve as a direct source of human infections**
 - **Inhalation of aerosolized virus**
 - **Direct contact and entry of virus through damaged skin**
 - **Ingestion of contaminated food**
- **Catching, preparing, and eating rats (considered a delicacy and eaten by 90% of people in some endemic areas)**

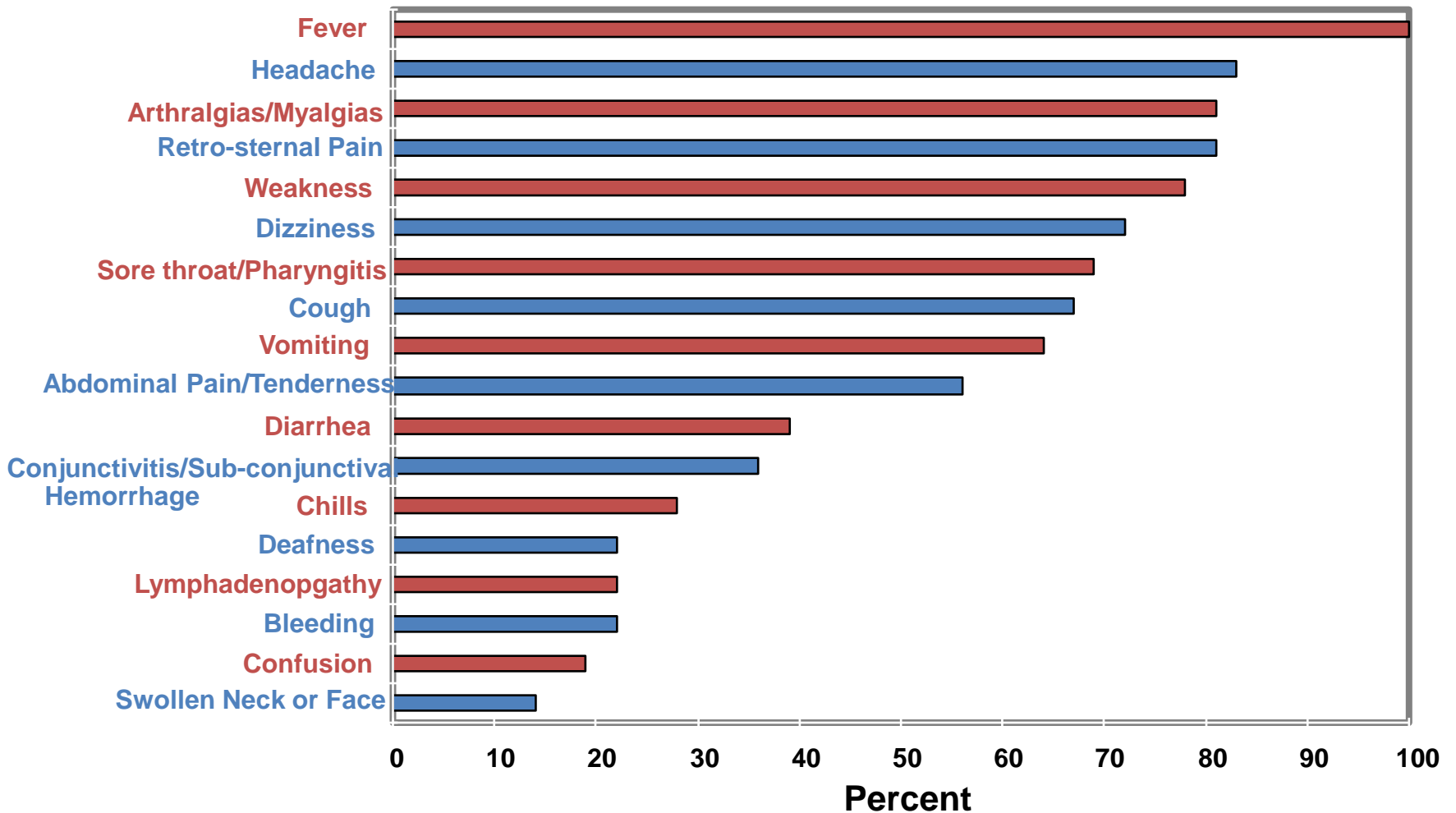
Transmission

- **HUMAN to HUMAN**
 - **Direct contact with blood, tissues, secretions or excretions of infected humans**
 - **Needle stick or cut**
 - **Inhalation of aerosolized virus**
 - **Spread during traditional burial ceremonies of infected corpses**

Clinical Disease

- **Incubation period: 3-21 days (mean 5-10 days)**
- **Gradual onset: fever, HA, myalgias, N/V/D, abdominal pain**
- **Distinguishing features: Sore throat with exudative tonsillitis, cough, retro-sternal pain**
- **80% of people infected have asymptomatic or mild disease; 20% have severe disease**
- **More severe in pregnancy**
- **Case fatality rate < 2% overall, but ~20% for untreated hospitalized cases**
- **Long term complication: deafness**
 - **30% of patients, not related to severity of illness**

Clinical Signs and Symptoms



Clinical Stages of Lassa Fever

Other Old and New World HF Arenaviruses

Virus	Origin of name	Reservoir	Year	Distribution
Lassa	Town, Nigeria	Rodents	1969	West Africa
Junin	Town, Argentina	Rodents	1957	South America
Machupo	River, Bolivia	Rodents	1962	South America
Guanarito	Area, Venezuela	Rodents	1989	South America
Sabia	Town, Brazil	Rodents	1990	South America
Chapare	River, Bolivia	Rodents	2004	South America
Lujo	Towns in Zambia and South Africa	Rodents	2008	Southern Africa

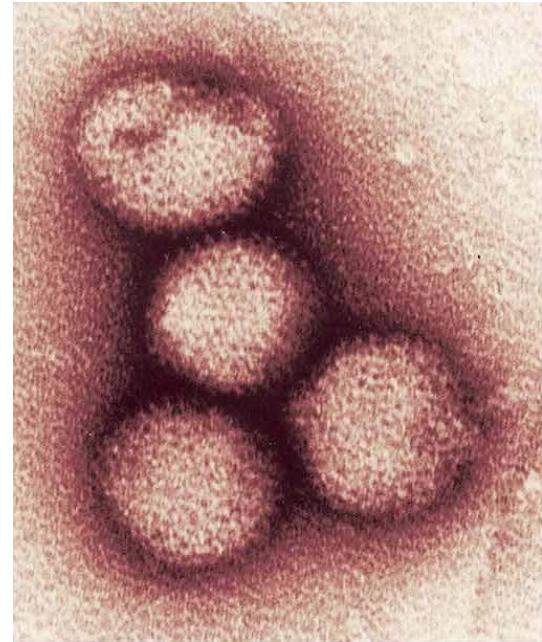
Not a cause of VHF, but most well known arenavirus:

LCMV	Clinical disease	Rodents	1933	worldwide
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Rift Valley Fever Virus

genus: **Phlebovirus**

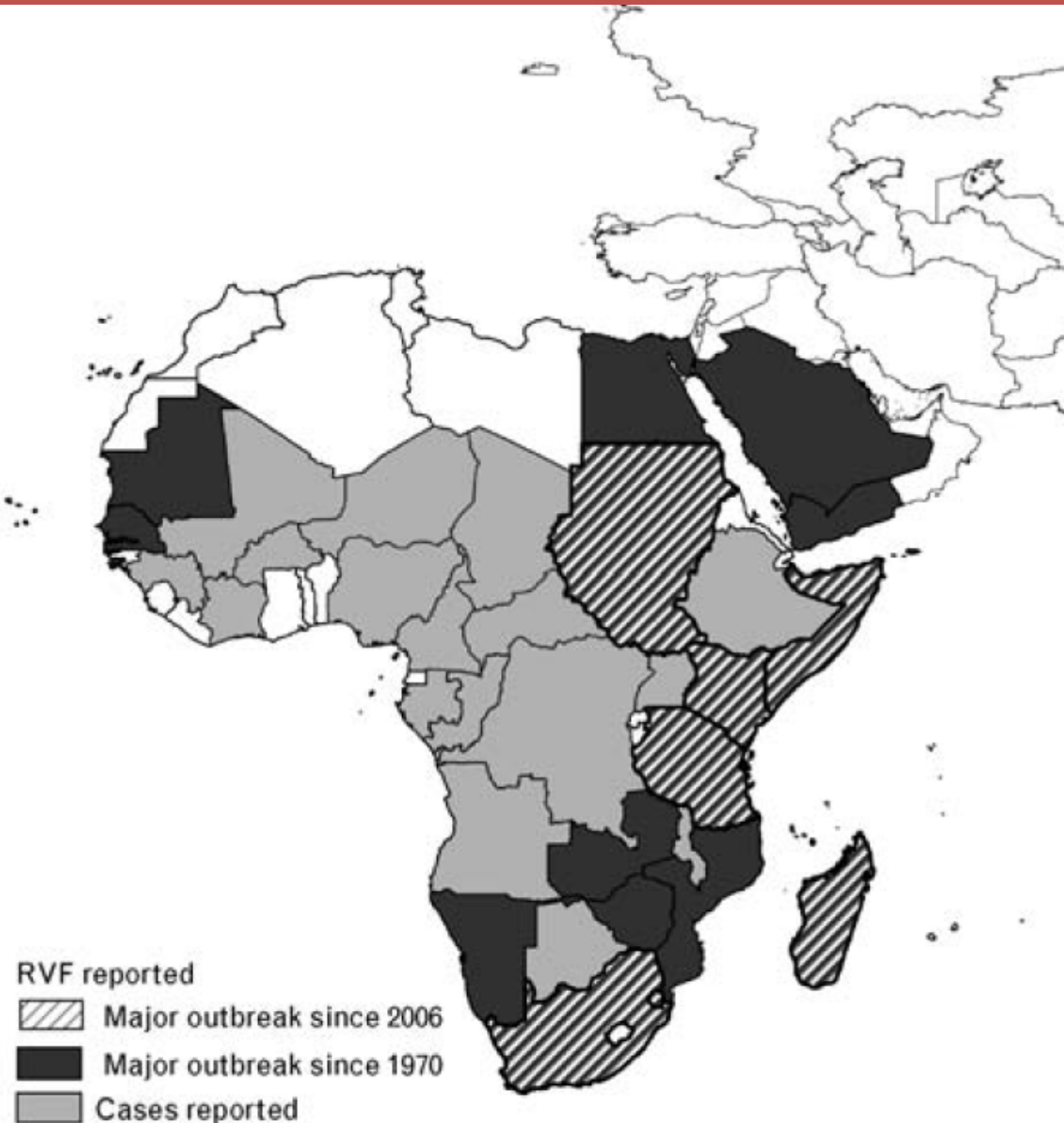
family: **Bunyavirus**



Epidemiology and Ecology

- **First recognized as a viral zoonosis in Kenya in 1930**
- **Endemic in Africa (primarily Eastern Africa)**
- **In 2000 – spread for first time beyond African continent to Saudi Arabia and Yemen**
- **Concerns regarding further geographic spread**

Current World Distribution of RVFV



Epidemiology and Ecology

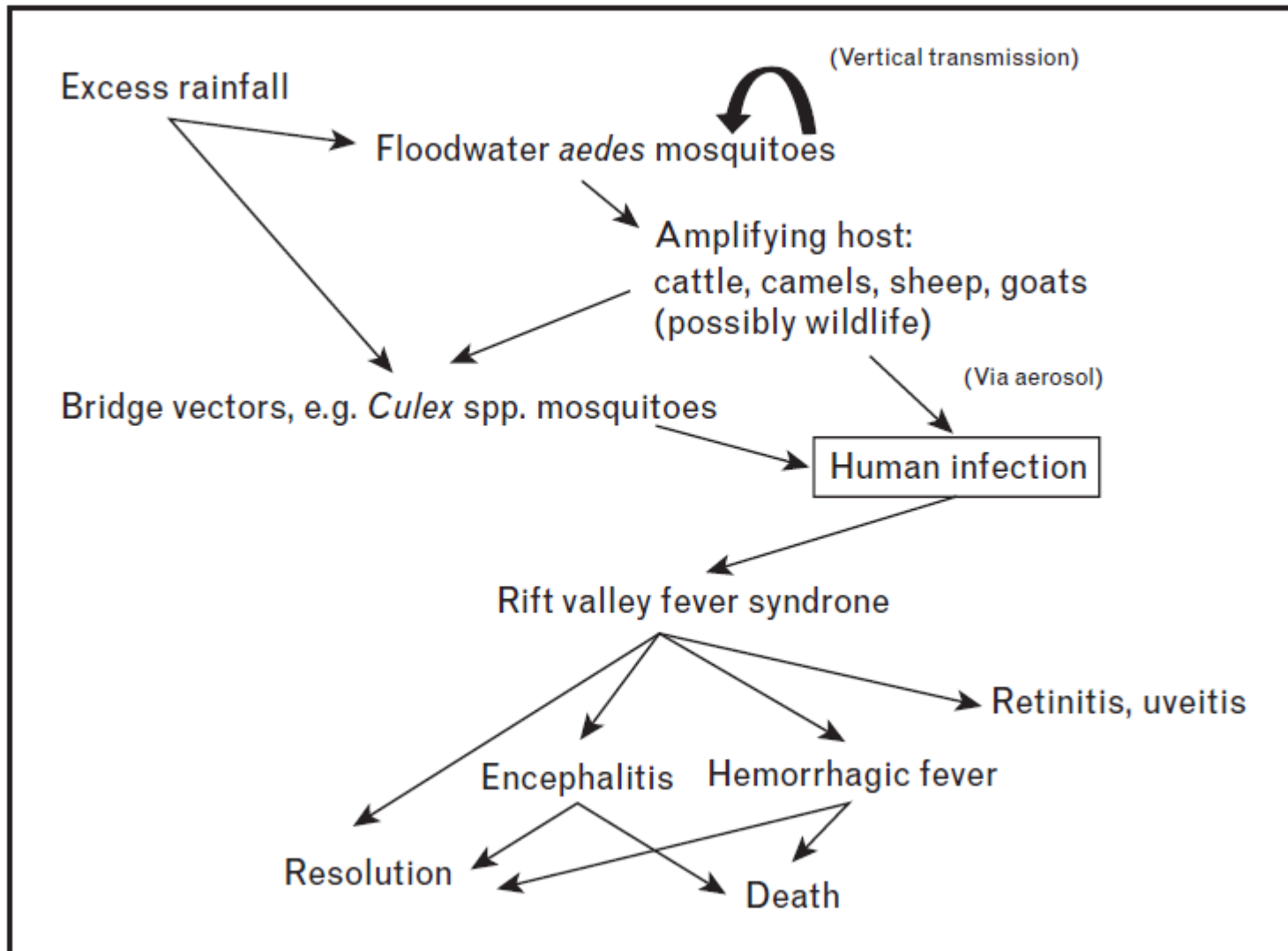
- **Outbreaks tend to follow heavy rainfalls and floods**
- **Pathogenic to both livestock and humans**
- **1^o vector = *aedes* mosquito**
 - **Other vectors = *culex* mosquitoes**
- **Amplifying hosts = animals, primarily livestock (cattle, sheep, goats, camels)**

Transmission

- **Direct or indirect contact with blood or organs of infected animals**
 - handling of animal tissue during slaughtering or butchering
 - assisting with animal births
 - conducting veterinary procedures
 - disposal of carcasses or fetuses.
- **Modes of transmission**
 - **Inoculation: contact through broken skin, wound from infected knife**
 - **Inhalation: aerosols produced during slaughter**
- **Drinking of unpasteurized milk**
- **Directly from mosquitoes or blood-feeding flies**
- **NO human to human transmission has been reported**

Clinical Disease

- **Incubation period: 2-6 days**
- **Abrupt onset, usually lasts 4-7 days**
- **Majority of human infections are asymptomatic or have a “flu-like” illness: fever, HA, myalgias, photophobias**
- **Severe disease**
 - **Occular (2-10%)**
 - 50% can develop blindness
 - **Meningoencephalitis (1-8%)**
 - **Hemorrhagic fever (~1%)**
 - Case-fatality rate ~ 50%



**DIAGNOSIS
&
TREATMENT**

Diagnosis

- **Antigen detection ELISA**
- **Serology**
- **RT-PCR**

- **Diagnosis is generally done in national or international reference labs**
- **For any suspected case contact them immediately regarding proper advice on sampling, sample preparation, and sample transport**

Treatment

- **Supportive Care (ICU)**
- **Ribavirin (IV better than PO)**
 - **YES: Lassa and CCHF**
 - [for Lassa – best results if given before DOI 6]
 - **NO: filoviruses, flaviviruses**
 - **NO: CNS dz -- does not cross blood-brain barrier**
- **Passive immunization – benefits correlate with level of neutralizing antibody**
- **Treatment of coagulation problems**
 - **Nematode-derived anticoagulation protein rNAPc2 (33% efficacy in EBOV primate studies)**
 - **Activated protein C**

Box 1: recommended dosage regimens for treating CCHF or Lassa fever with ribavirin

Intravenous regimen (preferred)

Loading dose: 33 mg/kg by infusion in normal saline

Continuation dose: begin 6 h after loading dose and give 16 mg/kg 6 h for four days

Completion dosing: 8 mg/kg 8 h for a further six days

Oral regimen (commence if intravenous ribavirin is not available)

Loading dose: 2 g

Continuation dose: begin 6 h after loading dose and give 1 g 6 h for four days

Completion dosing: 0.5 g 6 h for a further six days

Observe for adverse reactions:

Nausea, sleeplessness, intrusive dreams

Dose-related haemolytic anaemia, which may require blood replacement

Jaundice, transaminaemia, rare pancreatitis

Differential Diagnosis

- **Difficult to recognize during first 3-7 days of illness b/c present with influenza like syndromes (fever and myalgias)**
- **At initial stages of disease, pts may not look that ill or have significant bleeding until severe disease develops abruptly**
- **Diseases to consider (common things being common):**
 - Malaria
 - Dengue
 - Meningococcal bacteremia
 - Gram-positive and Gram-negative bacteremia
 - Rickettsial infections
 - Leptospirosis
 - Brucellosis
 - Salmonella
 - Q fever
 - Influenza

Consider a VHF diagnosis...

- **Epidemiological Risk Factors**
 - Consider incubation period
 - Consider areas of exposure and “high risk” factors
 - Generally no risk in cities or modern hotels
 - Travel without stops for rural excursions is usually safe
- **Clinical warning signs**
 - Failure to improve on antimalarial and/or antibiotic therapy
 - Failure of “dengue” fever to improve after 7 days
 - Rapid rise in AST
 - Rapid fall in platelet count
 - Onset of epistaxis or bloody diarrhea

Infection Control

- **Put suspected patient with VHF in a separate room, cubicle, or resuscitation area**
- **Use available PPE**
 - Water repellent gown and/or apron
 - Disposable gloves
 - Surgical face mask
 - Wrap-around eye protection
- **Have appropriate sharp containers and waste containers nearby for direct disposal**
- **Immediately notify local infection specialist and infection control team of any suspected case**

Infection Control

- **Casual contact, household contact, sharing public transport – not shown to carry any risk of infection**
- **Can be spread by percutaneous exposure, mucosal splash, or inadvertent ingestion of infected body fluids**
- **Aerosol transmission has not been confirmed outside of a laboratory setting**

Table 3 Managing risk from suspected VHF cases assessments and responses in healthcare facilities.

Type of risk	Risk level	Specific measures for worker	Infection control for patient
Casual contact, receptionist tasks, sharing a sitting area or public transport with a feverish ambulant, self-caring patient, taking temperature and blood pressure observations.	None recognized	None required	Single room isolation; standard personal protective equipment (PPE); prepare for transfer to specialist unit if rapid VHF test results are positive
Close face-to-face contact with a feverish ambulant or self-caring patient, taking or examining diagnostic specimens	Low	Healthcare worker should report the onset of fever, if within the incubation period, and have a full clinical review, other community-acquired infections should be considered	As above

Type of risk	Risk level	Specific measures for worker	Infection control for patient
Caring, taking diagnostic specimens or having close face-to-face contact, without appropriate PPE, with a patient who is coughing or vomiting, has nosebleeds, or who has diarrhoea	Moderate	Healthcare worker should check their temperature each day, and to report any elevation above 38°C, and should have a full clinical review: with consideration of early diagnostic testing for the VHF.	Single room isolation; negative pressure or airflow ventilation to dilute droplets; standard PPE with face and eye protection; expect to transfer to specialist unit (may wait for VHF test results, discuss with specialist)
Percutaneous, needlestick or mucosal exposure to virus-contaminated blood, body fluids, tissues or laboratory specimens in a severely ill or known positive patient; accidental aerosol exposure in a laboratory setting.	High	Do baseline blood tests and VHF tests; for CCHF, consider post-exposure treatment with immune plasma or oral ribavirin; for Lassa fever, consider post-exposure prophylaxis with oral ribavirin.	Send specimens for VHF diagnostic tests immediately; patient should be transferred without waiting for results, to a specialist unit; discuss with specialist unit whether to commence antiviral treatment, and treat for malaria or bacterial infections.

For moderate and high risk VHF exposures healthcare worker should report temperature daily to the appropriate safety officer (extend the reporting period to 4 weeks if post-exposure prophylaxis is given). If fever develops, do diagnostic tests, admit to specialist unit and commence treatment, if appropriate, until the result is known.