Viral Hemorrhagic Fever

What is Viral Hemorrhagic Fever?

- Severe multisystem syndrome
- Damage to overall vascular system
- Symptoms often accompanied by hemorrhage
  - Rarely life threatening in itself
  - Includes conjunctivitis, petechia, echymosis

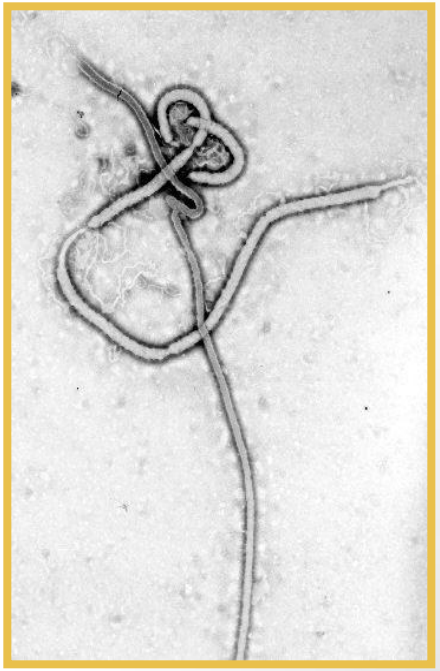
Overview

- Organism
- History
- Epidemiology
- Transmission
- Disease in Humans
- Disease in Animals
- Prevention and Control

The Organisms

Viral Hemorrhagic Fever

- Diverse group of illnesses caused by RNA viruses from 4 distinct families:
  - Arenaviridae, Bunyaviridae, Filoviridae, Flaviridae
  - Differ by geographic occurrence and vector/reservoir
  - Share certain clinical and pathogenic features
- Potential for aerosol dissemination, with human infection by respiratory route (except dengue)
- Target organ: vascular bed
- Mortality 0.5 - 90%, depending on agent
- RNA viruses
  - Enveloped in lipid coating
- Survival dependent on an animal or insect
- host, for the natural reservoir



Viral Hemorrhagic Fevers
Transmission

- Zoonotic diseases
  - Rodents and arthropods main reservoir
  - Humans infected via bite of infected arthropod, inhalation of rodent excreta, or contact with infected animal carcasses
- Person-to-person transmission possible with several agents
  - Primarily via blood or bodily fluid exposure
  - Rare instances of airborne transmission with arenaviruses and filoviruses
- Rift Valley fever has potential to infect domestic animals following a biological attack

Viral Hemorrhagic Fevers
Summary of Agents

Virus Family	Virus/Syndrome	Geographic occurrence	Reservoir or Vector	Human-human transmission ?
Arenaviridae	Junin (Argentine HF)	S.America	Rodents	Lassa Fever – yes, via body fluids; others – not usually
	Machupo (Bolivian HF)	S.America		
	Guanarito (Brazilian HF)	S.America		
	Sabia (Venezuelan HF)	S.America		
	Lassa (Lassa Fever)	West Africa		
Flaviridae	Yellow Fever	Tropical Africa,Latin America	Mosquitoes	Yellow Fever – blood infective up to 5d of illness; Others - No
	Dengue Fever	Tropical areas		
	Kyanasur Forest Disease	India	Ticks	
	Omsk HF	Siberia		

Viral Hemorrhagic Fevers
Summary of Agents

Virus Family	Virus/Syndrome	Geographic occurrence	Reservoir or Vector	Human-human transmission?
Bunyaviridae	Congo-Crimean HF	Crimea, parts of Africa, Europe & Asia	Ticks	Congo-Crimean Hemorrhagic Fever – yes, through body fluids; Rift Valley Fever, Hantaviruses – no
	Rift Valley Fever	Africa	Mosquitoes	
	Hantaviruses (Hemorrhagic Renal Syndrome/ Hantavirus Pulmonary Syndrome)	Diverse	Rodents	
Filoviridae	Ebola HF	Africa	Unknown	Yes, body fluid transmission
	Marburg HF	Africa		

Arenaviridae

Junin virus
Machupo virus
Guanarito virus
Lassa virus
Sabia virus

Arenaviridae History

- First isolated in 1933
- 1958: Junin virus - Argentina
  - First to cause hemorrhagic fever
  - Argentine hemorrhagic fever
- 1963: Machupo virus – Bolivia
  - Bolivian hemorrhagic fever
- 1969: Lassa virus – Nigeria
  - Lassa fever

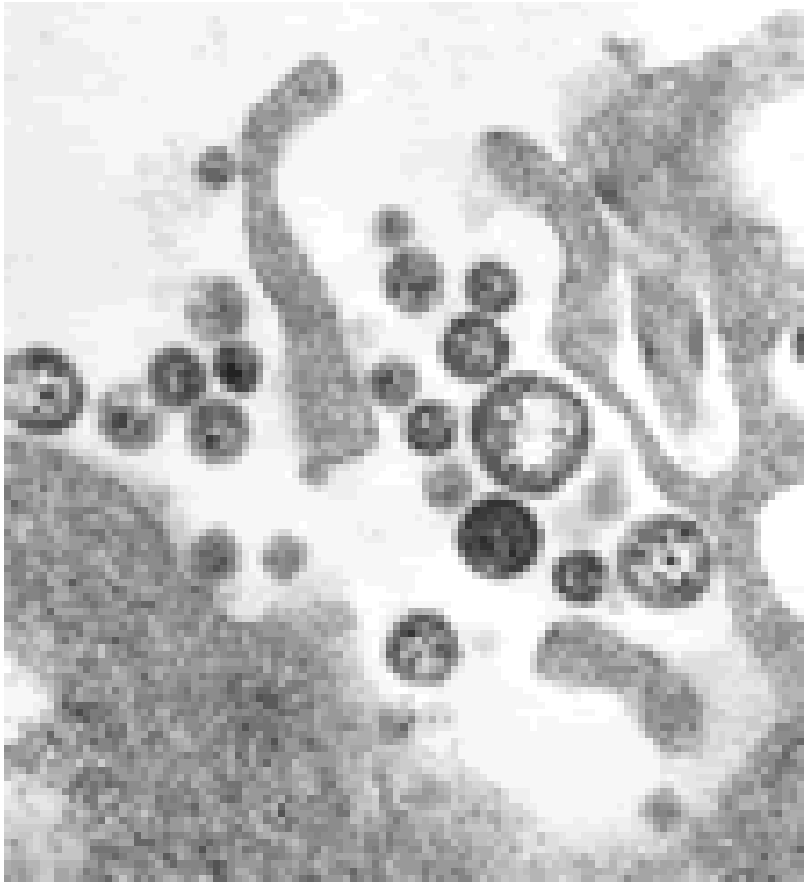
Arenaviridae Transmission

- Virus transmission and amplification occurs in rodents
- Shed virus through urine, feces, and other excreta
- Human infection
  - Contact with excreta
  - Contaminated materials
  - Aerosol transmission
- Person-to-person transmission

Arenaviridae Epidemiology

- Africa
  - Lassa
- South America
  - Junin, Machupo, Guanarito, and Sabia
- Contact with rodent excreta
- Case fatality: 5 – 35%
- Explosive nosicomial outbreaks with Lassa and Machupo

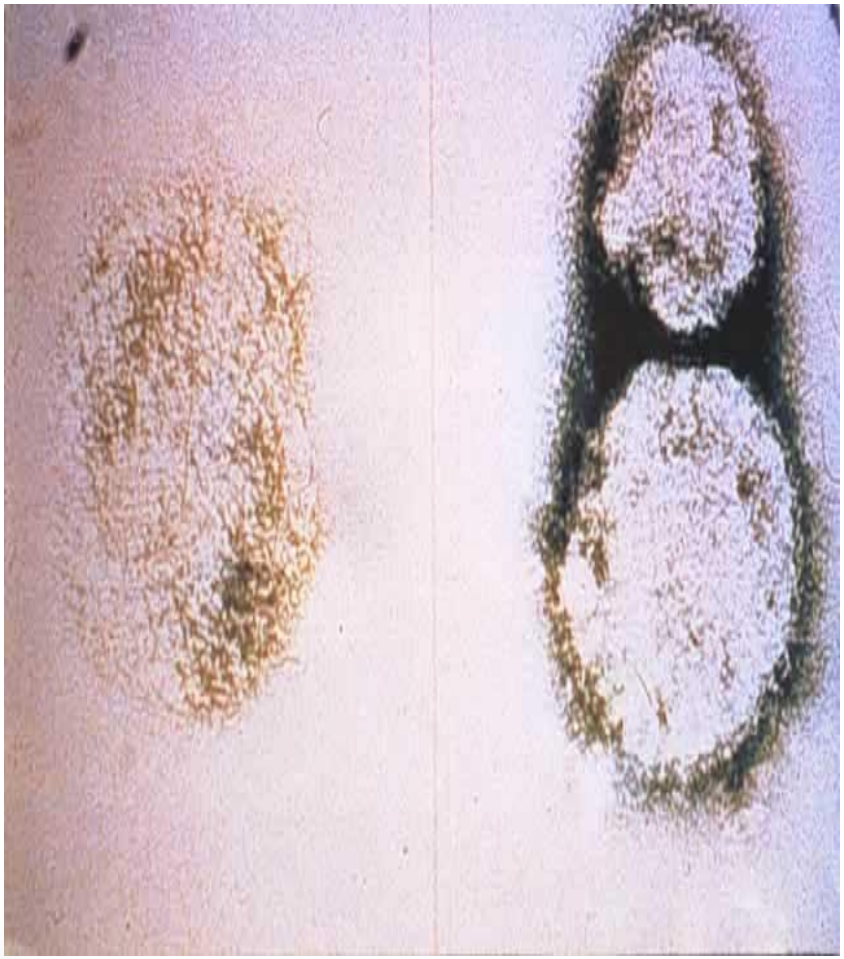
Lassa virus electron micrograph

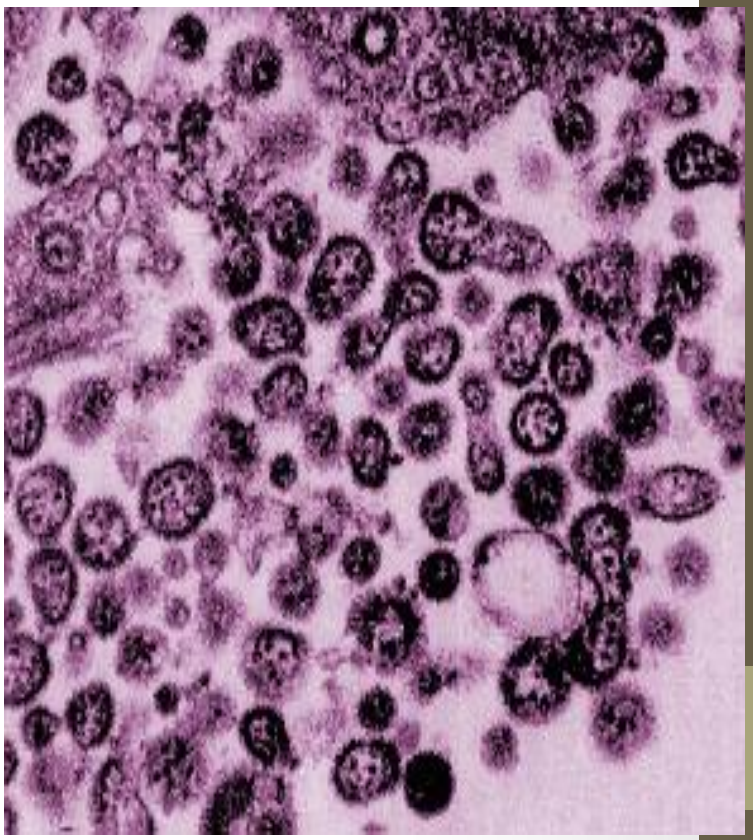


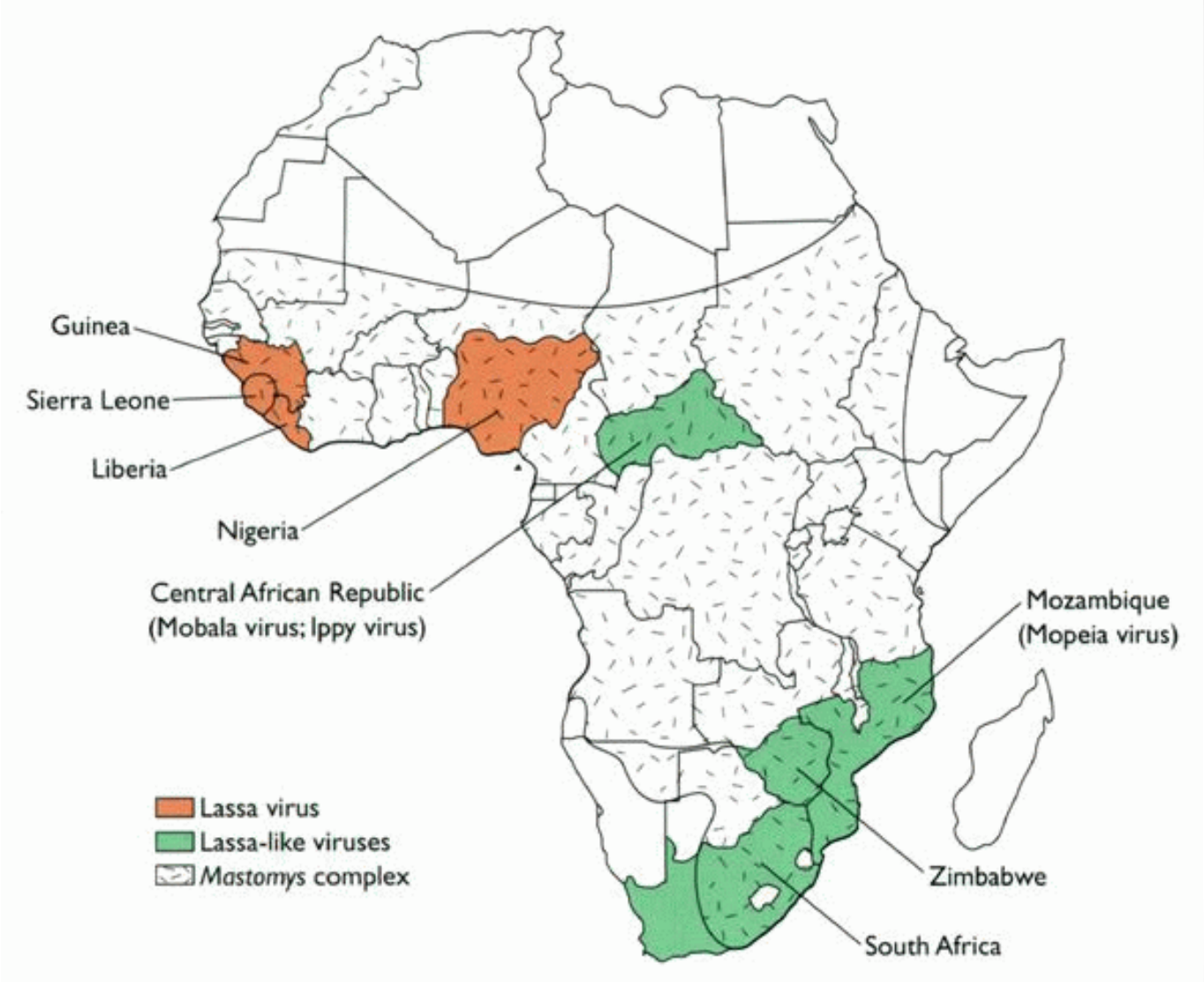
Lassa fever was first recognized in herdsmen's village in Nigeria in 1969. Lassa fever is known to be endemic in Guinea (Conakry), Liberia, Sierra Leone and parts of Nigeria, but probably exists in other West African countries as well.

It is fatal in almost half the cases. Some studies indicate that 300 000 to 500 000 cases of Lassa fever and 5000 deaths occur yearly across West Africa.

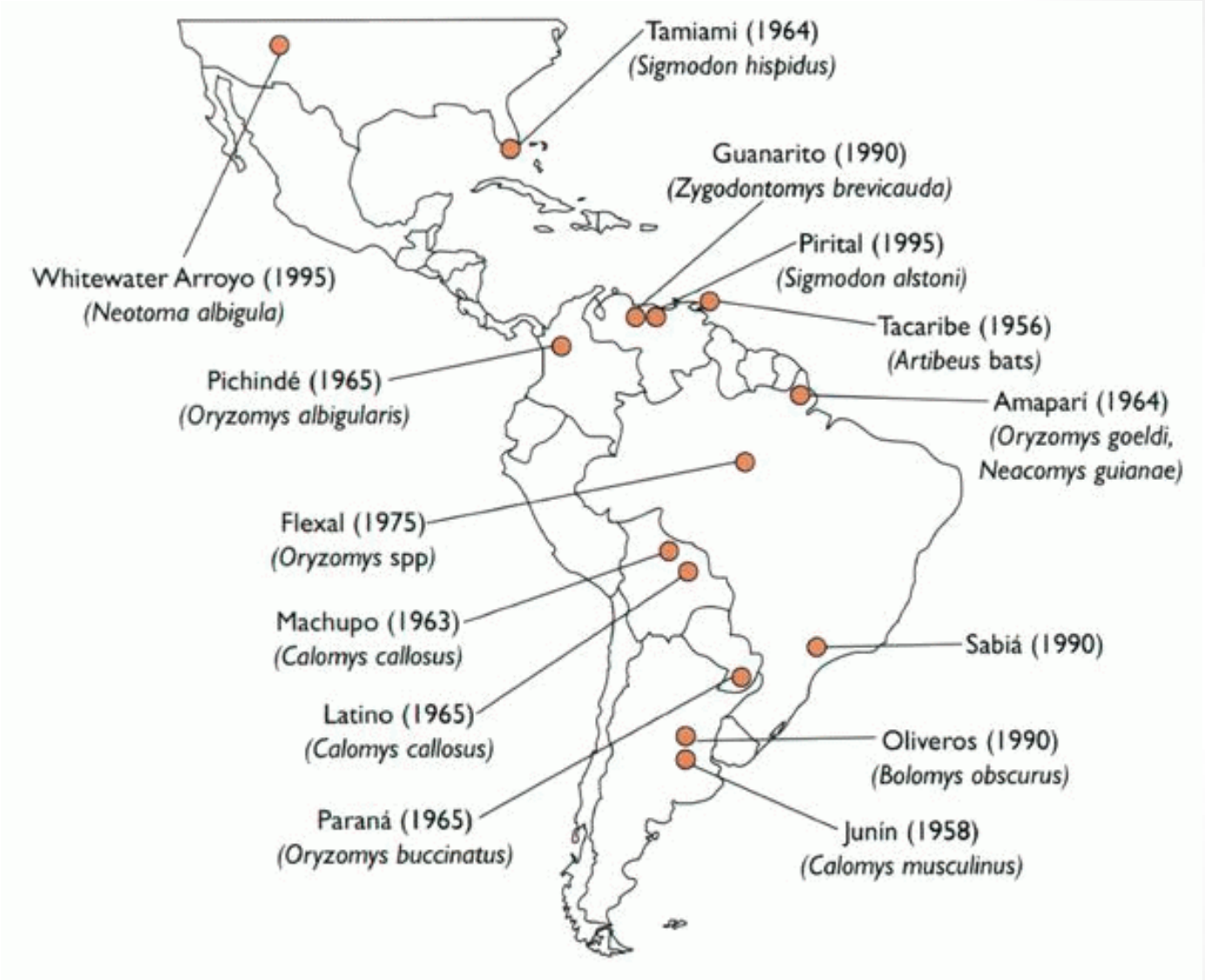
Arenavirus - Junin







Geographic distribution of arenaviruses in Africa.



Geographic distribution of arenaviruses in the Americas.

Arenaviridae in Humans

- Incubation period
  - 10–14 days
- Fever and malaise
  - 2–4 days
- Hemorrhagic stage
  - Hemorrhage, leukopenia, thrombocytopenia
  - Neurologic signs

Bunyaviridae

Rift Valley Fever virus
Crimean-Congo Hemorrhagic Fever virus
Hantavirus

Bunyaviridae History

- 1930: Rift Valley Fever – Egypt
  - Epizootic in sheep
- 1940s: CCHF - Crimean peninsula
  - Hemorrhagic fever in agricultural workers
- 1951: Hantavirus – Korea
  - Hemorrhagic fever in UN troops
- 5 genera with over 350 viruses

Bunyaviridae Transmission

- Arthropod vector
  - Exception – Hantaviruses
- RVF – *Aedes* mosquito
- CCHF – Ixodid tick
- Hantavirus – Rodents
- Less common
  - Aerosol
  - Exposure to infected animal tissue

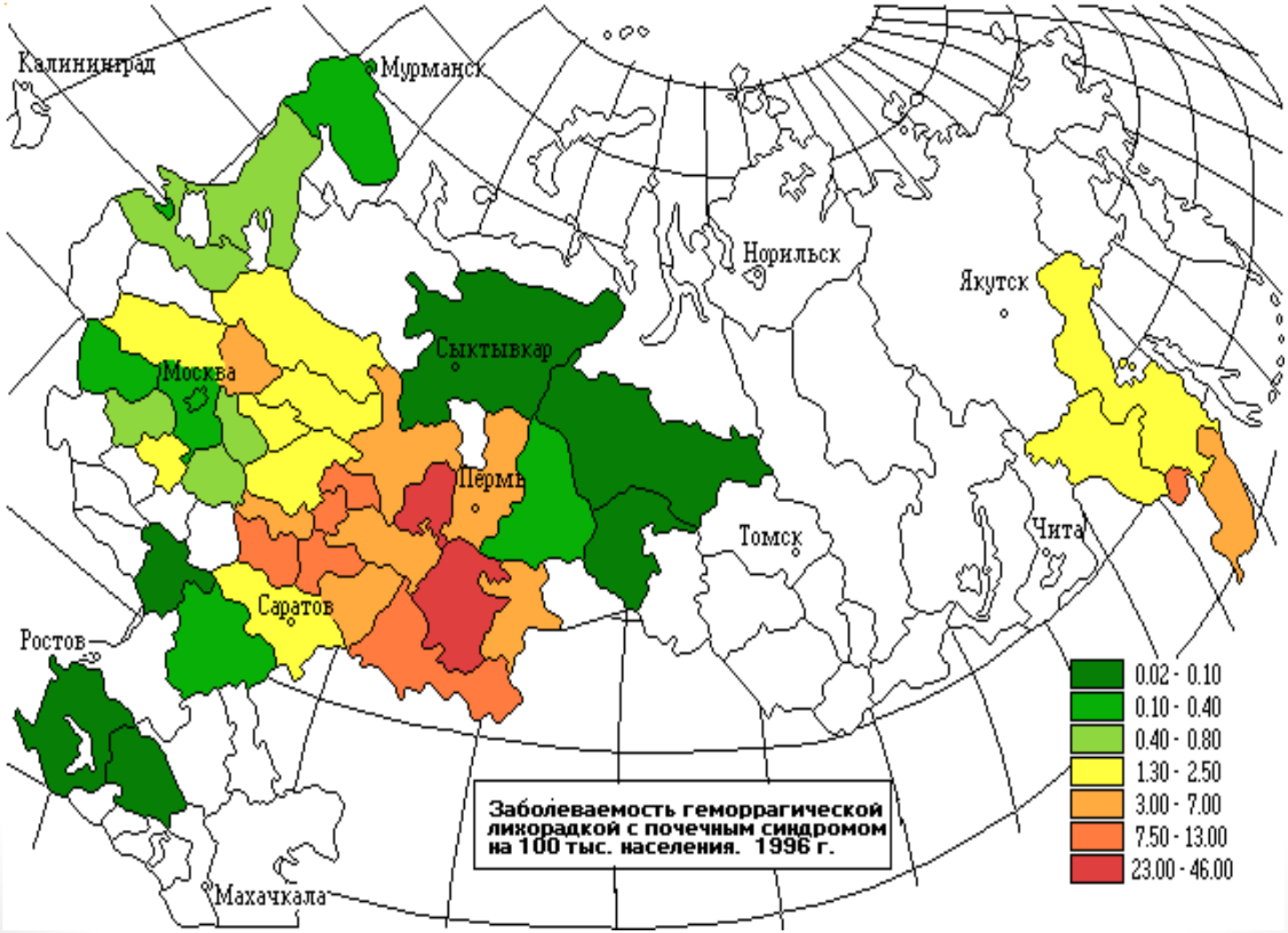
Bunyaviridae Epidemiology

- RVF - Africa and Arabian Peninsula
  - 1% case fatality rate
- CCHF - Africa, Eastern Europe, Asia
  - 30% case fatality rate
- Hantavirus - North and South America, Eastern Europe, and

Eastern Asia

  - 1-50% case fatality rate

HFRS distribuition



Bunyaviridae Humans

- RVF
  - Incubation period – 2-5 days
  - 0.5% - Hemorrhagic Fever
- CCHF
  - Incubation period – 3-7 days
  - Hemorrhagic Fever - 3–6 days following clinical signs
- Hantavirus
  - Incubation period – 7–21 days
  - HPS and HFRS

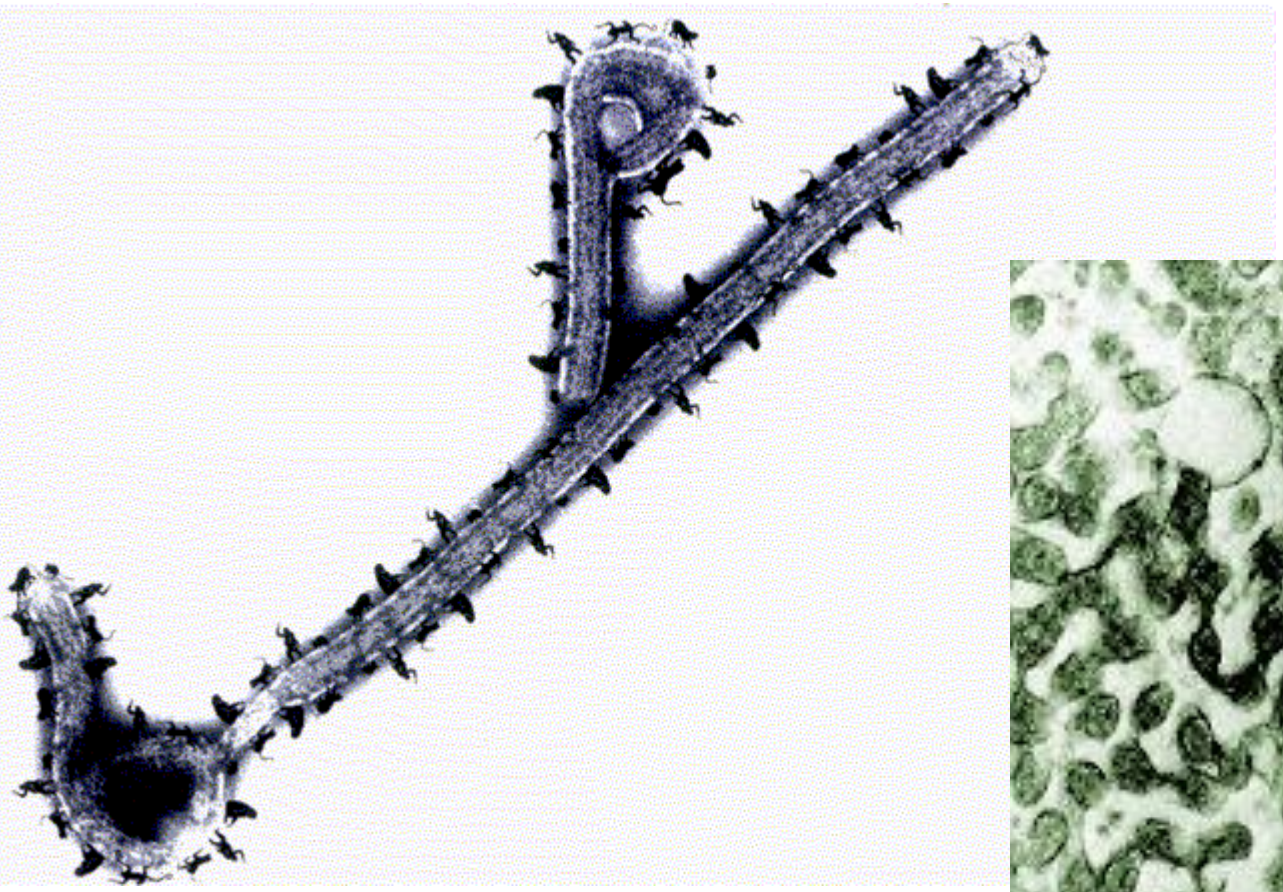
Bunyaviridae Animals

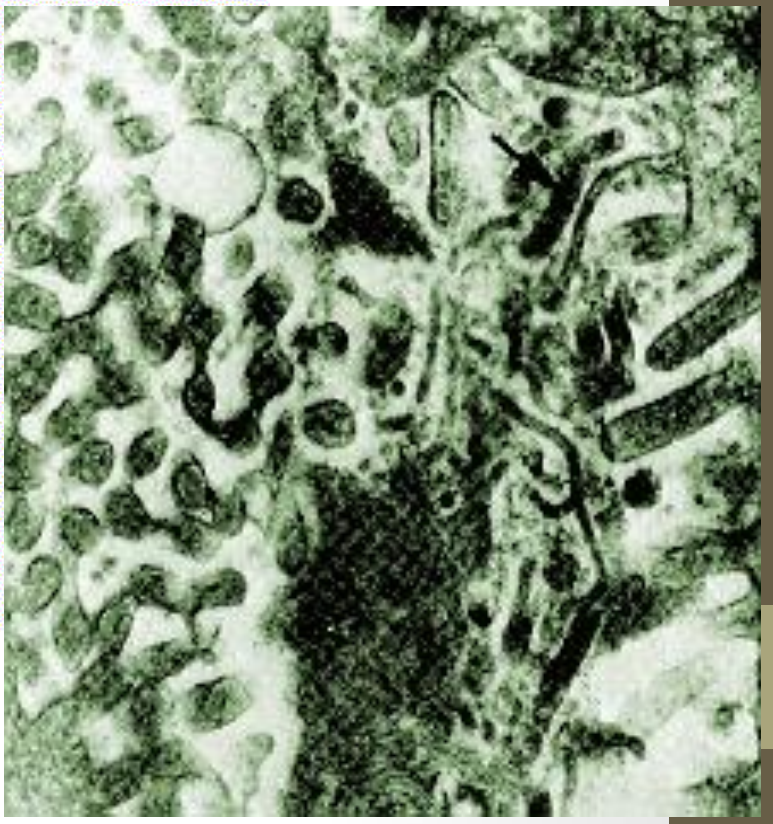
- RVF
  - Abortion – 100%
  - Mortality rate
    - >90% in young
    - 5-60% in older animals
- CCHF
  - Unapparent infection in livestock
- Hantaviruses
  - Unapparent infection in rodents

Filoviridae

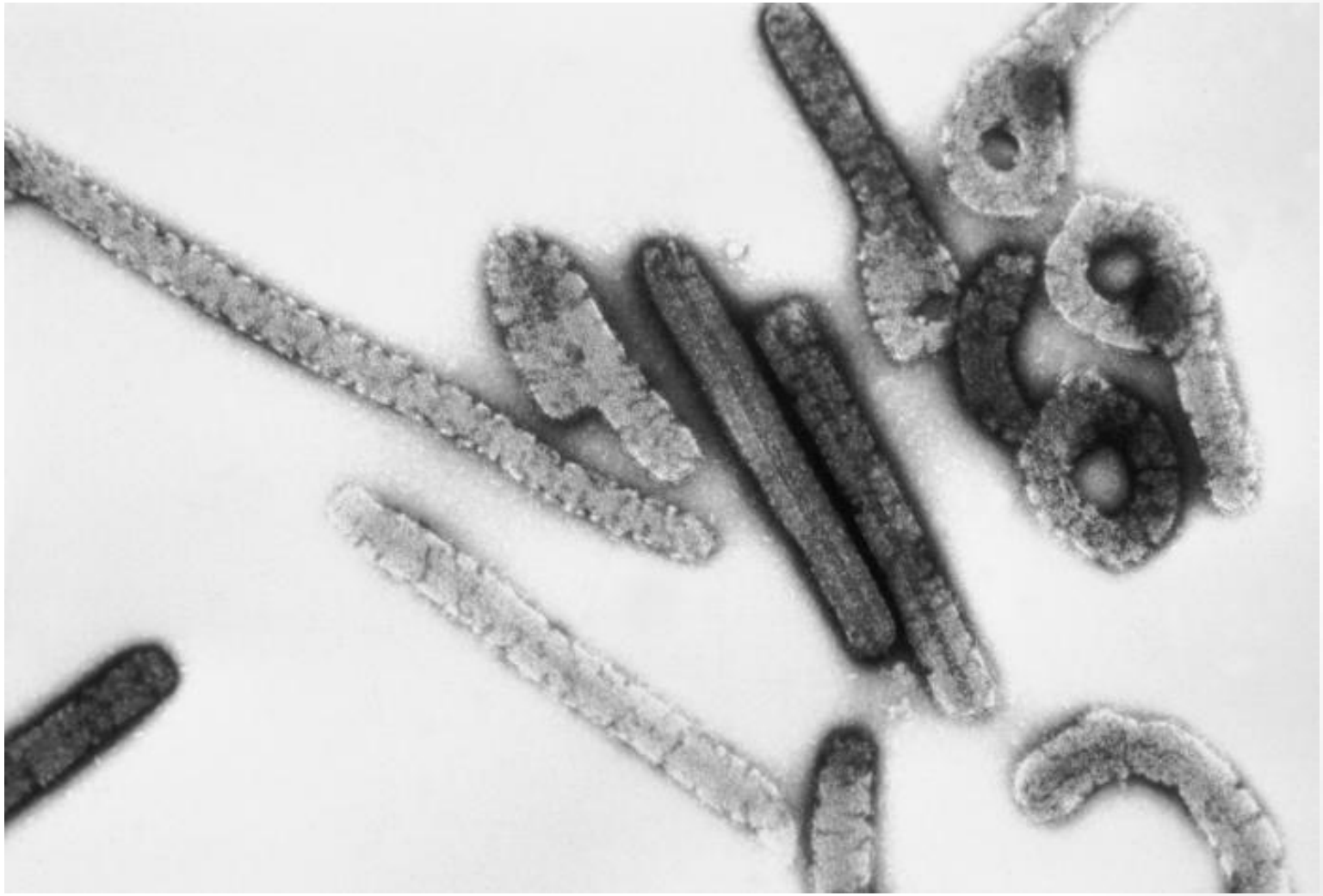
Marburg virus
Ebola virus

Ebola virus





This negative stained transmission electron micrograph (TEM) depicts a number of filamentous Marburg virions



Filoviridae History

- 1967: Marburg virus
  - European laboratory workers
- 1976: Ebola virus
  - Ebola Zaire
  - Ebola Sudan
- 1989 and 1992: Ebola Reston
  - USA and Italy
  - Imported macaques from Philippines
- 1994: Ebola Côte d'Ivoire

Filoviridae Transmission

- Reservoir is UNKNOWN
  - Bats implicated with Marburg
- Intimate contact
- Nosicomial transmission
  - Reuse of needles and syringes
  - Exposure to infectious tissues, excretions, and hospital wastes
- Aerosol transmission
  - Primates

Filoviridae Epidemiology

- Marburg – Africa
  - Case fatality – 23-33%
- Ebola - Sudan, Zaire and Côte d'Ivoire – Africa
  - Case fatality – 53-88%
- Ebola – Reston – Philippines
- Pattern of disease is UNKOWN

Filoviridae Humans

- Most severe hemorrhagic fever
- Incubation period: 4–10 days
- Abrupt onset
  - Fever, chills, malaise, and myalgia
- Hemorrhage and DIC
- Death around day 7–11
- Painful recovery

Filoviridae Animals

- Hemorrhagic fever
  - Same clinical course as humans
- Ebola Reston
  - High primate mortality - ~82%

Flaviviridae

Dengue virus
Yellow Fever virus
Omsk Hemorrhagic Fever virus
Kyassnur Forest Disease virus

Flaviviridae History

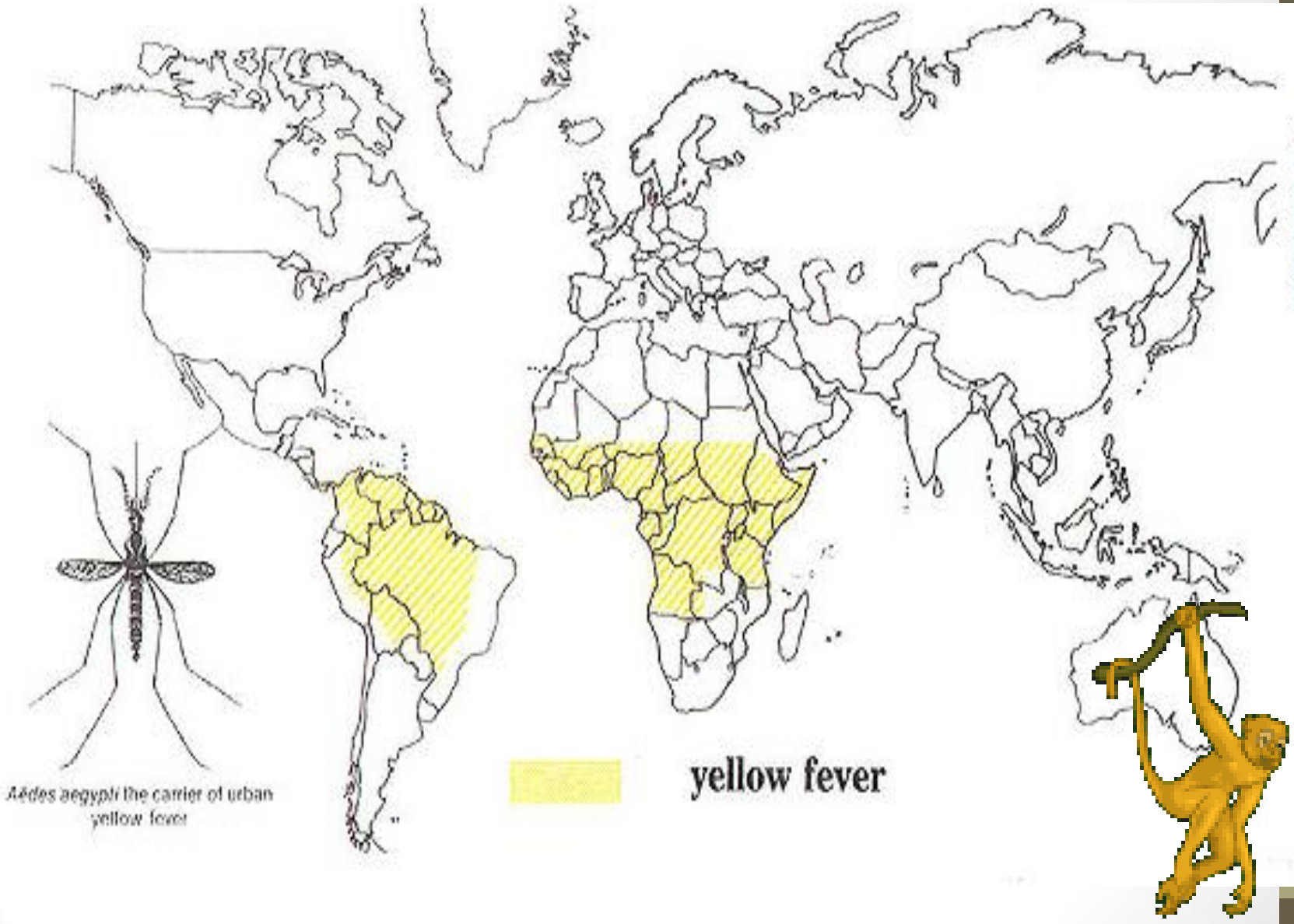
- 1648 : Yellow Fever described
- 17th–20th century
  - Yellow Fever and Dengue outbreaks
- 1927: Yellow Fever virus isolated
- 1943: Dengue virus isolated
- 1947
  - Omsk Hemorrhagic Fever virus isolated
- 1957: Kyasanur Forest virus isolated

Flaviviridae Transmission

- Arthropod vector
- Yellow Fever and Dengue viruses
  - *Aedes aegypti*
  - Sylvatic cycle
  - Urban cycle
- Kasanur Forest Virus
  - Ixodid tick
- Omsk Hemorrhagic Fever virus
  - Muskrat urine, feces, or blood

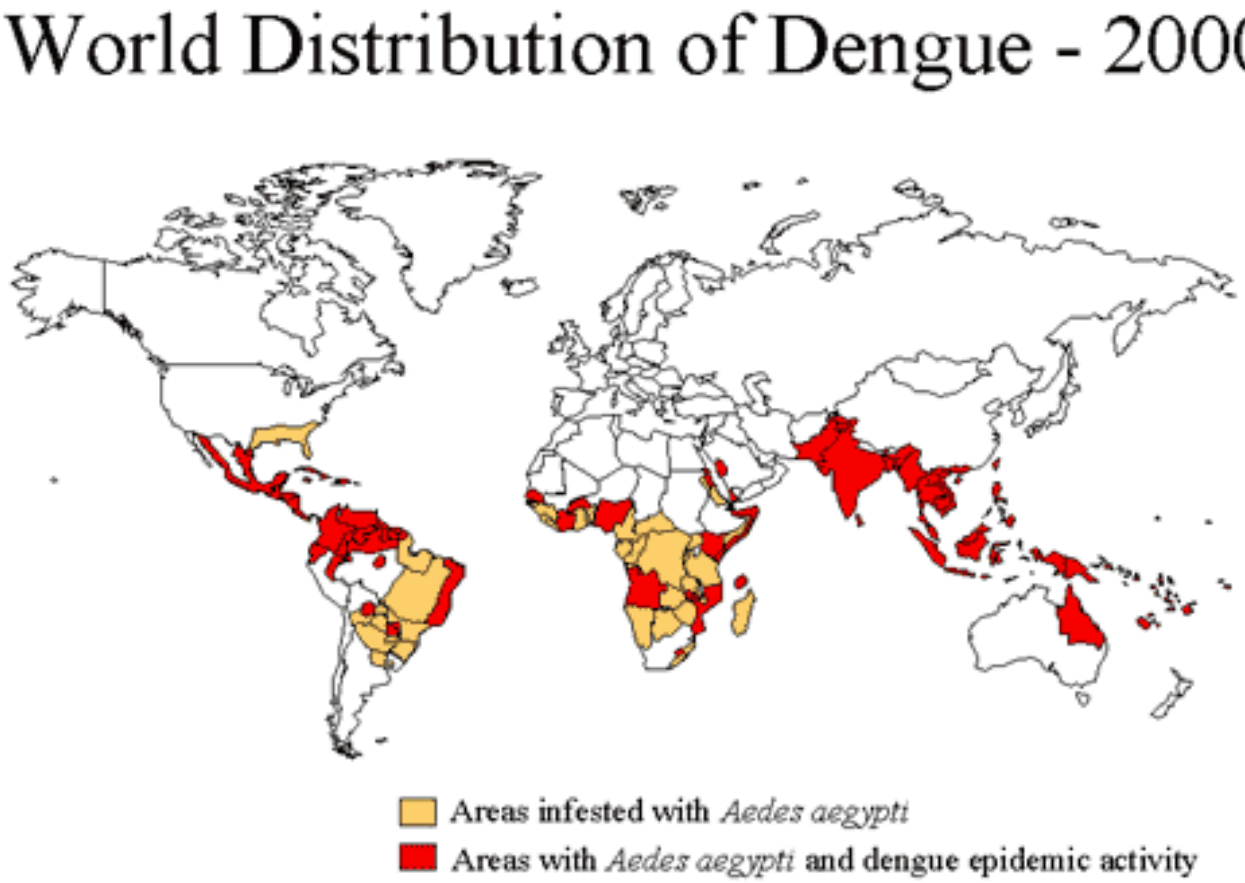
Flaviviridae Epidemiology

- Yellow Fever Virus – Africa and Americas
  - Case fatality rate – varies
- Dengue Virus – Asia, Africa, Australia, and Americas
  - Case fatality rate – 1-10%
- Kyasanur Forest virus – India
  - Case fatality rate – 3–5%
- Omsk Hemorrhagic Fever virus – Europe
  - Case fatlity rate – 0.5–3%



Aëdes aegypti the carrier of urban yellow fever

HF Dengue distribution



Dengue virus is transmitted to humans by bites of Aedes aegypti or Aedes albopictus

Yellow Fever

- Yellow Fever
  - Incubation period – 3–6 days
  - Short remission
- clinical manifestations - from mild to severe signs
- Severe Yellow Fever

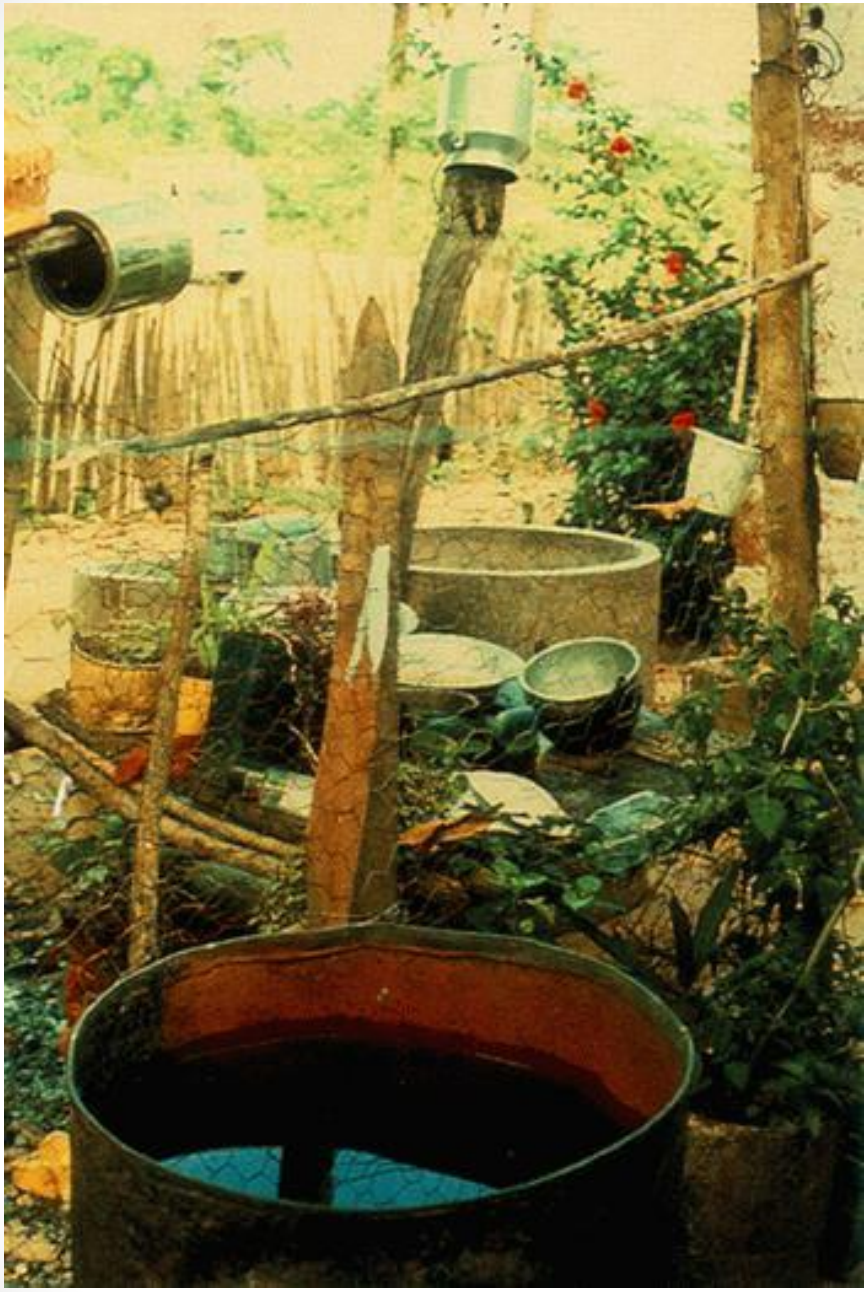
- begins abruptly with fever, chills, severe headache, lumbosacral pain, generalized myalgia, anorexia, nausea and vomiting, and minor gingival hemorrhages.
- A period of remission may occur for 24 hours followed by an increase in the severity of symptoms.
- Death usually occurs on day 7 – 10.

Flaviviridae Humans

- **Dengue Hemorrhagic Fever**
  - Incubation period – 2–5 days
  - a mild flu-like illness upon first exposure.
  - Infection with different serotype
  - quickly progress to a hemorrhagic syndrome and shock
- **Kyasanur Forest Disease**
- fever, headache, myalgia, cough, bradycardia, dehydration, hypotension, gastrointestinal symptoms, and hemorrhages.
- Recovery is uncomplicated with no lasting sequelae.
- **Omsk Hemorrhagic Fever**
  - Similar to Kyasanur +hearing loss, hair loss, neuropsychiatric complaints
  - Lasting sequela

Flaviviridae Animals

- Yellow Fever virus
  - Non-human primates – varying clinical signs
- Dengue virus
  - Non-human primates – No symptoms
- Kyasanur Forest Disease Virus
  - Livestock – No symptoms
- Omsk Hemorrhagic Fever Virus
  - Rodents – No symptoms



Outdoor water containers providing breeding sites for mosquitoes. Vector control through elimination of breeding sites can sometimes be a practical objective. The pictured containers in a Caribbean backyard are excellent for breeding by Aedes aegypti, which will reproduce only in relatively clean, still water.

Disease in Humans

Viral Hemorrhagic Fevers
Clinical Presentation

- Clinical manifestations nonspecific, vary by agent
- Incubation period 2-21 days, depending on agent
- Onset typically abrupt with filoviruses, flaviviruses, and Rift Valley fever
- Onset more insidious with arenaviruses

Viral Hemorrhagic Fevers

Initial Symptoms

Prodromal illness lasting < 1 week may include:

- High fever
- Headache
- Malaise
- Weakness
- Exhaustion
- Dizziness
- Muscle aches
- Joint pain
- Nausea
- Non-bloody diarrhea

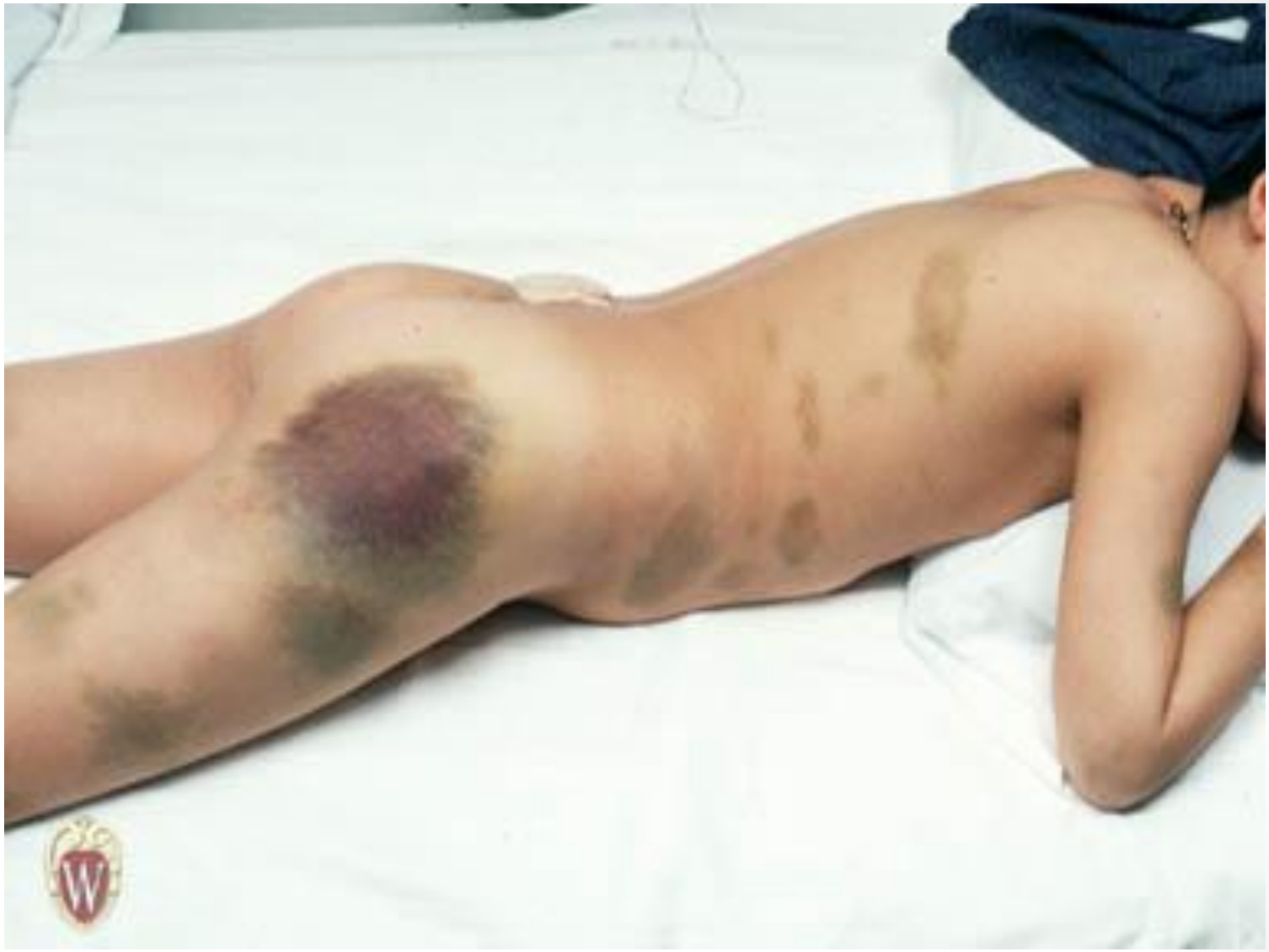
Viral Hemorrhagic Fevers
Clinical Signs

- Flushing, conjunctival injection (“red eye”)
- Pharyngitis
- Rash
- Edema
- Hypotension
- Shock
- Mucous membrane bleeding

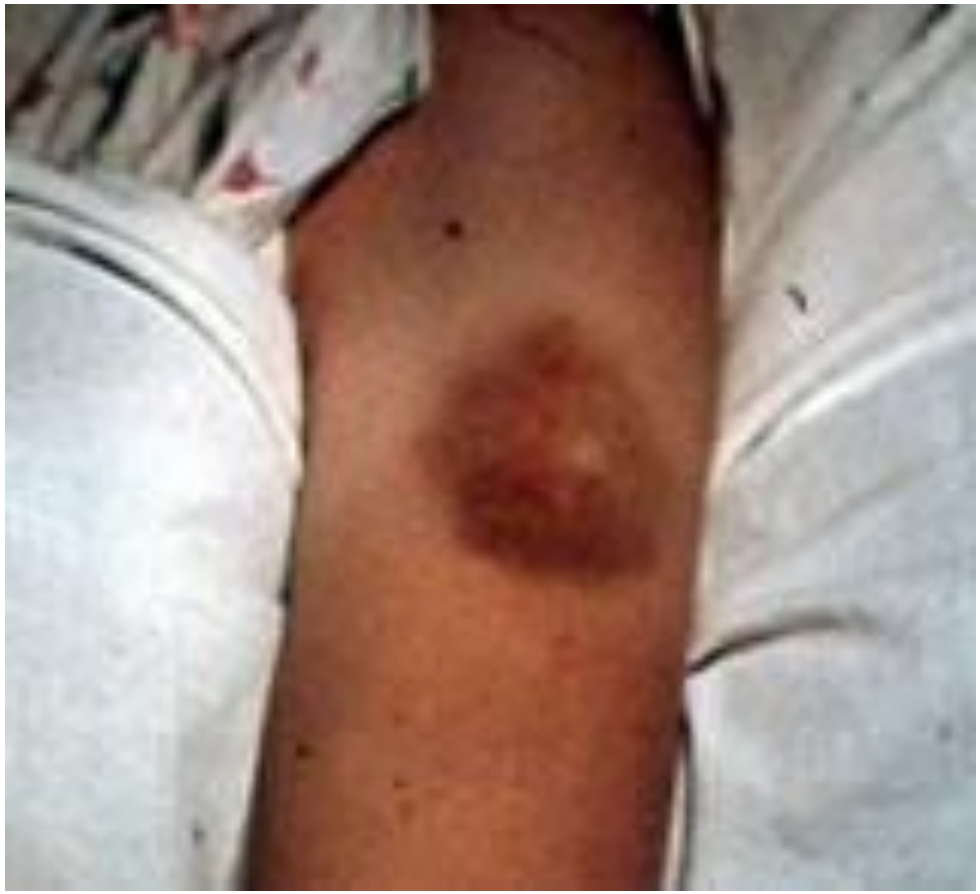
VHF Surveillance:

Clinical Identification of Suspected Cases

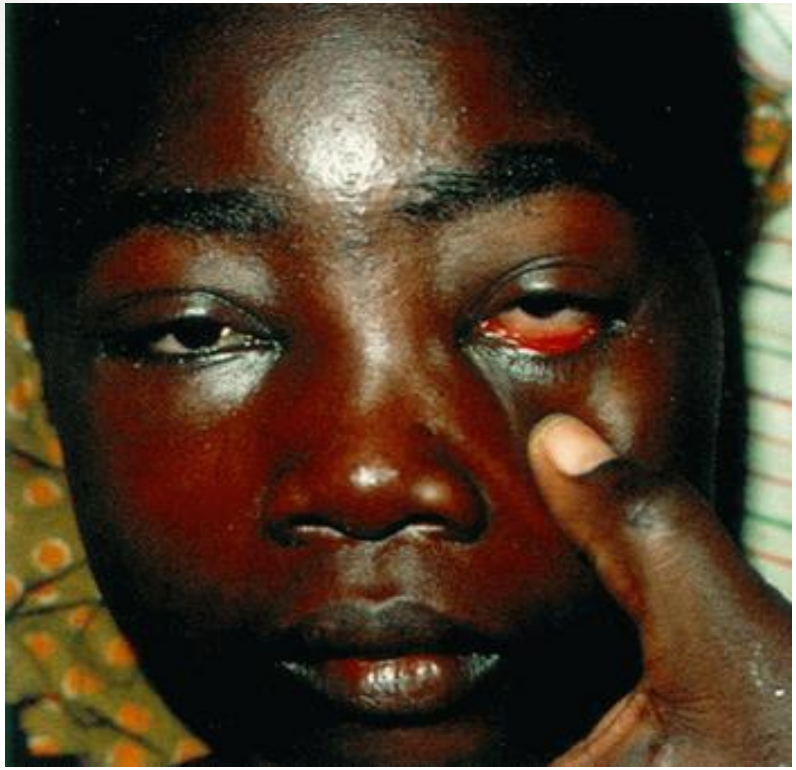
- Clinical criteria:
  - Temperature 101° F(38.3° C) for <3 weeks
  - Severe illness and no predisposing factors for hemorrhagic manifestations
  - 2 or more of the following:
    - Hemorrhagic or purple rash
    - Epistaxis
    - Hematemesis
    - Hemoptysis
    - Blood in stools
    - Other hemorrhagic symptoms
    - No established alternative diagnosis



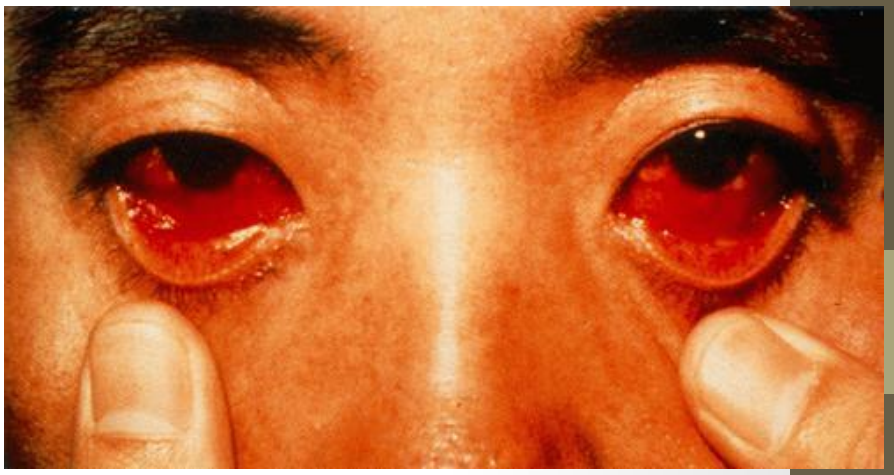
The child above suffers from Hemorrhagic Fever



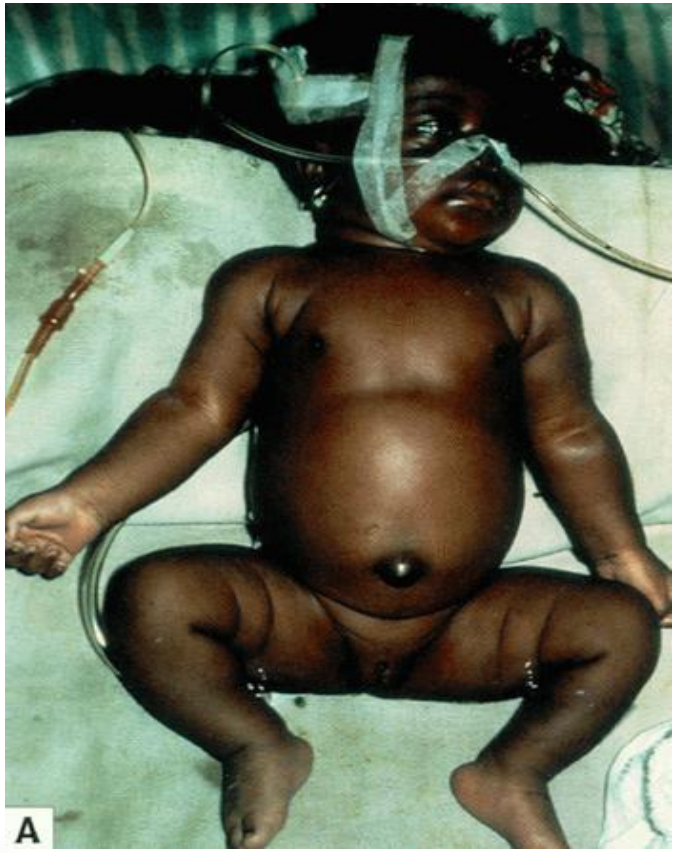
Hematoma on the site of injections in patients with hemorrhagic fever

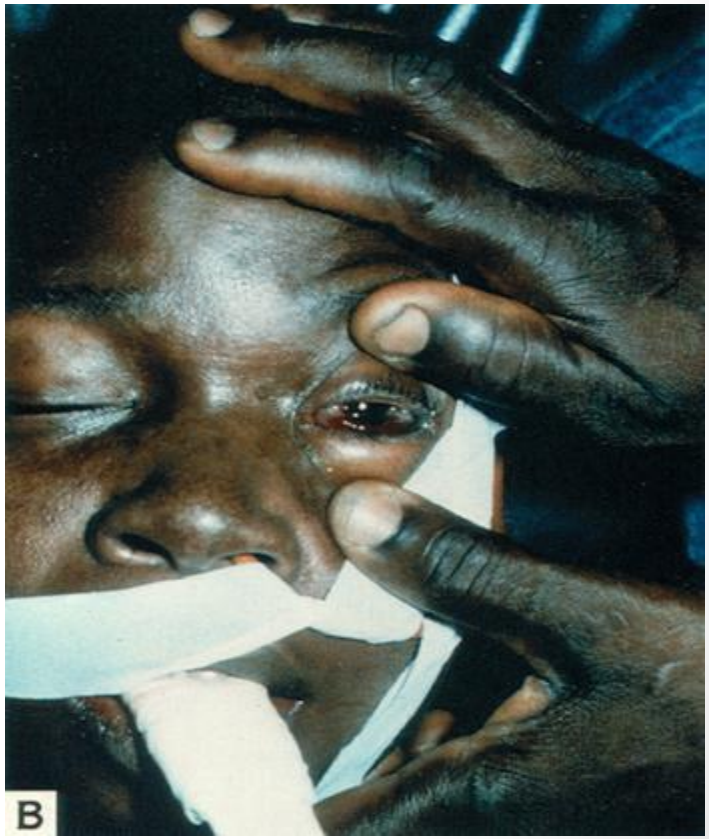


Conjunctival suffusion in hemorrhagic fever.
One of the early signs of abnormal vascular regulation is conjunctival suffusion, seen here in a patient with Lassa fever. This suffusion may be both bulbar and palpebral. Erythema of the oropharyngeal mucous membranes also may be noted.



A. In the more severe cases of hemorrhagic fever, vascular leakage leads to puffy eyes, cervical edema, and serous effusions, as seen in this child with Lassa fever. Such extensive and diffuse findings imply a poor prognosis.
B. Periorbital edema, chemosis, and subconjunctival hemorrhage are seen in another patient with Lassa fever.





Diagnosis

- Specimens must be sent to
  - Serology
  - PCR
  - Immunohistochemistry
  - Viral isolation
  - Electron microscopy of VHFs.

Treatment

- Supportive treatment
- Ribavirin
  - Not approved by FDA
  - Effective in some individuals
  - Arenaviridae and Bunyaviridae only
- Convalescent-phase plasma
  - Argentine HF, Bolivian HF and Ebola
- Strict isolation of affected patients is required
- Report to health authorities

Prevention and Control

Prevention and Control

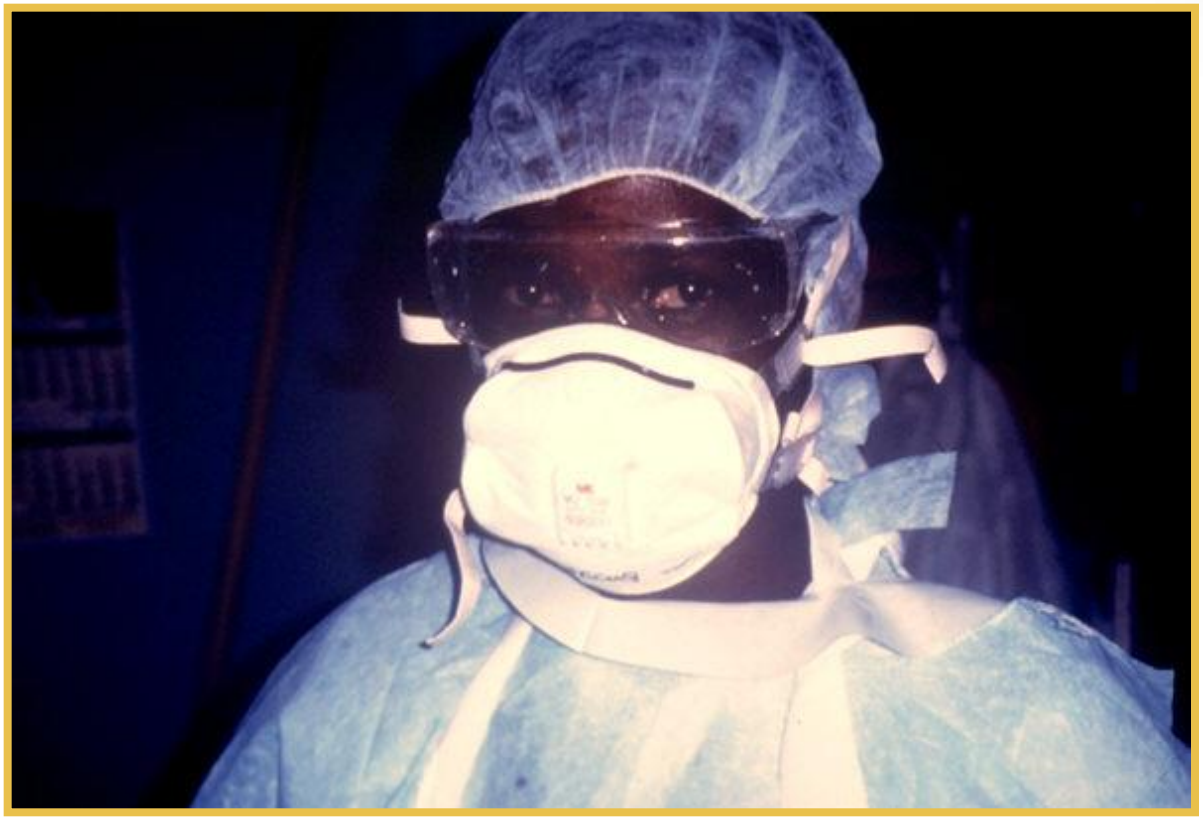
- Avoid contact with host species
  - Rodents
    - Control rodent populations
    - Discourage rodents from entering or living in human populations
    - Safe clean up of rodent nests and droppings
  - Insects
    - Use insect repellents
    - Proper clothing and bed nets
    - Window screens and other barriers to insects

Prevention and Control

- Vaccine available for Yellow fever
- Experimental vaccines under study
  - Argentine HF, Rift Valley Fever, Hantavirus and Dengue HF
- If human case occurs
  - Decrease person-to-person transmission
  - Isolation of infected individuals

Prevention and Control

- Protective clothing
  - Disposable gowns, gloves, masks and shoe covers, protective eyewear when splashing might occur, or if patient is disoriented or uncooperative
- WHO developed manual
  - “Infection Control for Viral Hemorrhagic Fevers In the African Health Care Setting”



Prevention and Control

- Anyone suspected of having a VHF must use a chemical toilet
- Disinfect and dispose of instruments
  - Use a 0.5% solution of sodium hypochlorite (1:10 dilution of bleach)

VHF Agents as Biological Weapons

- Outbreak of undifferentiated febrile illness 2-21 days following attack
  - Could include
    - Rash, hemorrhagic diathesis and shock
- Diagnosis could be delayed
  - Unfamiliarity
  - Lack of diagnostic tests
- Ribavirin treatment may be beneficial

VHF Agents as Biological Weapons

- Most are not stable in dry form
- Most have uncertain stability and effectiveness in aerosol form
  - Arenaviruses have tested effectiveness in aerosol form
- Marburg and Ebola have high case fatality rates
- Rift Valley is the most stable VHF in liquid or frozen state
- VHFs do pose a threat as aerosolized agents