

# Viral hemorrhagic fevers (VHFs)

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# Overview

- Viral hemorrhagic fevers (VHFs) are a group of illnesses caused by four families of viruses. *Arenaviridae* , *Bunyaviridae*, *Filoviridae* and *Flaviviridae*
- Diffuse Damage to overall vascular system.
- Symptoms often accompanied by hemorrhage
- Some VHFs cause mild disease, but some, like Ebola or Marburg, cause severe disease and death.

# Quick Overview: Who are they?

- **Arenaviridae**

- Lassa Fever
- Argentine HF (Junin)
- Bolivian HF (Machupo)
- Brazilian HF (Sabia)
- Venezuelan HF (Guanarito)

- **Bunyaviridae**

- Rift Valley Fever (RVF)
- Crimean Congo HF (CCHF)
- Hantavirus (Hemorrhagic Fever with Renal Syndrome (HFRS))
- Hantavirus Pulmonary Syndrome (HPS)

- **Filoviridae**

- Marburg
- Ebola

- **Flaviviridae**

- Yellow Fever
- Dengue Fever
- Omsk HF
- Kyasanur Forest Disease

# Quick Overview: How do we get infected?

- **Rodents & Arthropods, both reservoir & vector**
  - Bites of infected mosquito or tick
  - Inhalation of rodent excreta
  - Infected animal product exposure
- **Person-to-Person**
  - Blood/body fluid exposure
  - Airborne potential for some arenaviridae, filoviridae

# Common features

- **Enveloped Lipid-encapsulated**
- **Single-strand RNA**
- **Zoonotic (animal-borne)**
- **Geographically restricted by host**
- **Persistent in nature (rodents, bats, mosquitoes, ticks, livestock, monkeys, and primates)**
- Survival dependent on an animal or insect host, for the natural reservoir

# Arenaviridae

- Junin virus : Argentine hemorrhagic fever
- Machupo virus : Bolivian hemorrhagic fever
- Guanarito virus : Venezuelan hemorrhagic fever
- Lassa virus : Lassa fever- Nigeria
- Sabia virus : Brazilian hemorrhagic 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



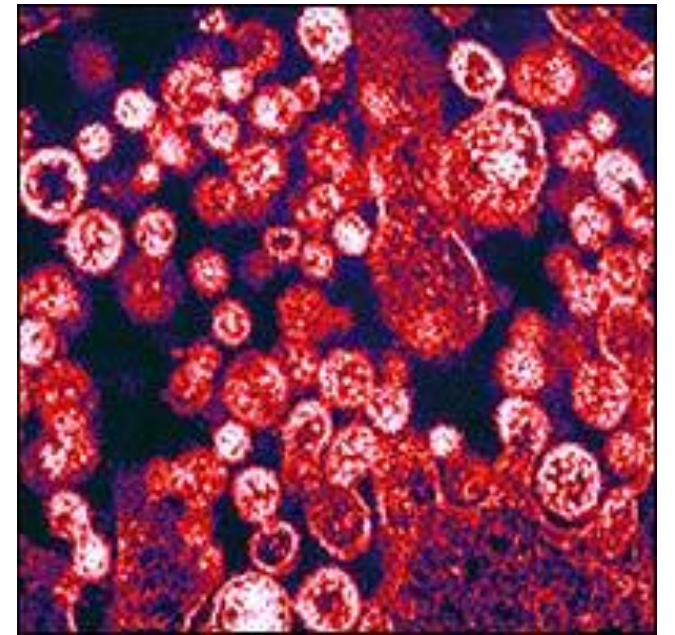
# Arenaviridae in Humans

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



# Arenaviridae: Lassa Fever

- First seen in Lassa, Nigeria in 1969.
- Now in all countries of West Africa
  - 5-14% of all hospitalized febrile illness
- Rodent-borne (*Mastomys natalensis*)
- Interpersonal transmission
  - Direct Contact
  - Sex
  - Breast Feeding



# Lassa Fever

- Distinguishing Features
  - Gradual onset
  - Retro-sternal pain
  - Exudative pharyngitis
  - Hearing loss in 25% may be persistent
  - Spontaneous abortion
- Mortality 1-3% overall (up to 50% in epidemics)
- Therapy: Ribavirin

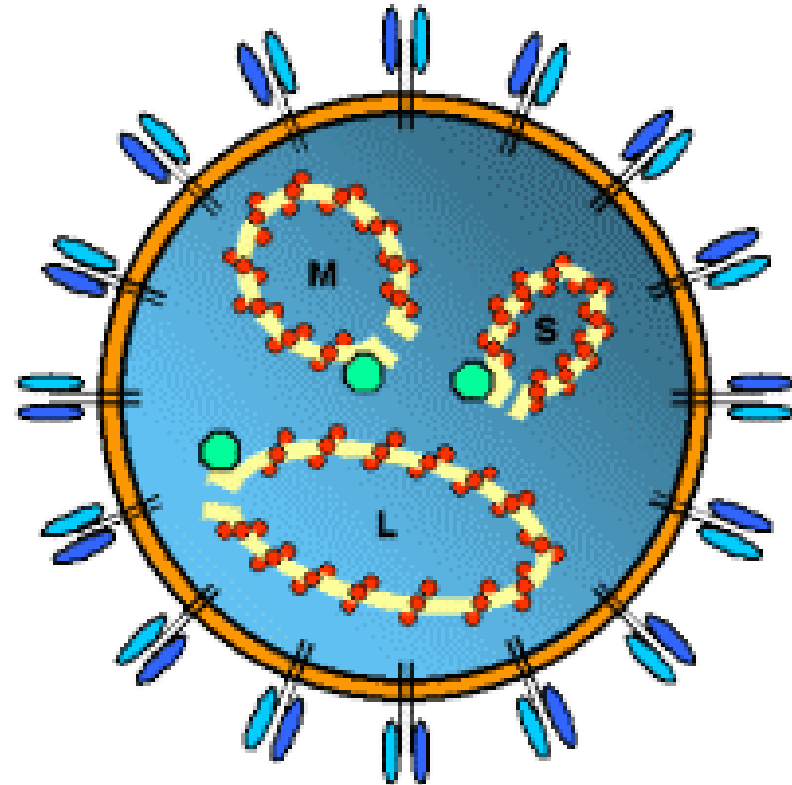
# Bunyaviridae

- Rift Valley Fever virus
- Crimean-Congo Hemorrhagic Fever virus
- Hantavirus

**L-segment** codes for an L-protein (the RNA dependent RNA polymerase);

**M segment** codes for two surface glycoproteins G1 and G2 which form the envelope spikes;

**S segment** codes for an N-protein (nucleocapsid protein).



# Bunyaviridae Transmission

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



# Bunyaviridae

- **Transmission to humans**
  - Arthropod vector (RVF, CCHF)
  - Contact with animal blood or products of infected livestock
  - Rodents (Hantavirus)
  - Laboratory aerosol
  - Person-to-person transmission with CCHF

# Rift Valley Fever

- Asymptomatic or mild illness in humans
- Distinguishing Characteristics
  - Hemorrhagic complications rare (<5%)
  - Vision loss (retinal hemorrhage, vasculitis) in 1-10%
- Overall mortality 1%
- Therapy: Ribavirin?

# Crimean-Congo Hemorrhagic Fever

- Distinguishing features
  - Abrupt onset
  - Most humans infected will develop hemorrhagic fever
  - Profuse hemorrhage
- Mortality 15-40%
- Therapy: Ribavirin

# Bunyaviridae: Hantaviruses

- Transmission to humans:
  - Exposure to rodent saliva and excreta
    - Inhalation
    - Bites
    - Ingestion in contaminated food/water (?)
    - Person-to-person (Andes virus in Argentina)



# Hemorrhagic Fever with Renal Syndrome (HFRS)

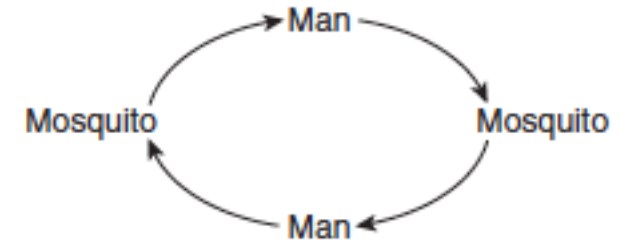
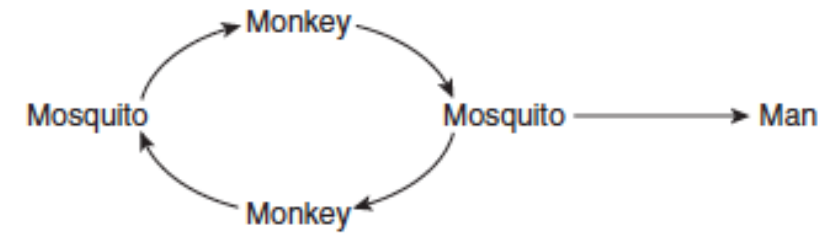
- Distinguishing Features
  - Insidious onset
  - Intense headaches,
  - Blurred vision
  - kidney failure
    - (causing severe fluid overload)
- Mortality: 1-15%

# Flaviviridae

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

# Flaviviridae Transmission

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



# Yellow Fever

- Distinguishing features
  - Biphasic infection
  - Common hepatic involvement & jaundice
- Mortality: 15-50%

# Flaviviridae: Dengue

- Dengue Fever (DF) /Fatality: <1%
- Dengue Hemorrhagic Fever (DHF)/ Fatality: 5-6%
- Dengue Shock Syndrome (DSS) /Fatality 12-44%
- Four distinct serotypes
  - DEN-1, DEN-2, DEN-3, DEN-4
- Distinguishing Features
  - Sudden onset
  - Eye pain
  - Rash
  - Complications/sequelae uncommon
- Illness is severe in younger children

# Omsk Hemorrhagic Fever

- Distinguishing Features
  - Acute Onset
  - Biphasic infection
  - Complications
    - Hearing loss
    - Hair loss
    - Psycho-behavioral difficulties
  - Mortality: 0.5 – 3%

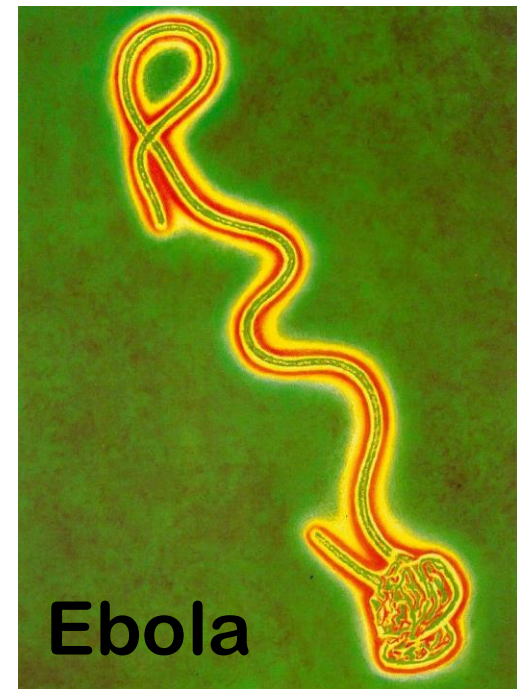
# Flaviviridae: Kyanasur Forest

- Distribution: limited to Karnataka State, India
- Haemaphysalis vector
- Distinguishing Features
  - Acute onset
  - Biphasic
- Case-fatality: 3-5% (400-500 cases annually)



# Filoviridae

- Ebola
  - Ebola-Zaire
  - Ebola-Sudan
  - Ebola-Ivory Coast
  - Ebola-Bundibugyo
  - (Ebola-Reston)
- Marburg





# Filoviridae Transmission

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

# Filoviridae: Ebola

- Rapidly fatal febrile hemorrhagic illness
- Transmission:
  - bats implicated as reservoir
  - Person-to-person
  - Nosocomial
- Five subtypes
  - Ebola-Zaire, Ebola-Sudan, Ebola-Ivory Coast, Ebola-Bundibugyo, Ebola-Reston
  - Ebola-Reston imported to US, but only causes illness in non-human primates
- Human-infectious subtypes found only in Africa

# Filoviridae: Ebola

- Distinguishing features:
  - Acute onset
  - GI involvement / Weight loss
  - 25-90% case-fatality

# Filoviridae: Marburg

- Distinguishing features
  - Sudden onset
  - Chest pain
  - Maculopapular rash on trunk
  - Pancreatitis
  - Jaundice
- 21-90% mortality

# 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

# Common Pathophysiology

- Small vessel involvement
  - Increased vascular permeability
    - Multiple cytokine activation
  - Cellular damage
  - Abnormal vascular regulation:
    - Early -> mild hypotension
    - Severe/Advanced -> Shock
- Viremia
  - Macrophage involvement
    - Inadequate/delayed immune response

# Common Clinical Features: Early/Prodromal Symptoms

- Fever
- Myalgia
- Malaise
- Fatigue/weakness
- Headache
- Dizziness
- Arthralgia
- Nausea
- Non-bloody diarrhea

# Common Clinical Features: Progressive Signs

- Conjunctivitis
  - Facial & thoracic flushing
  - Pharyngitis
  - Exanthems
  - Periorbital edema
  - Pulmonary edema
- Hemorrhage
    - Subconjunctival hemorrhage
    - Ecchymosis
    - Petechiae
    - But the hemorrhage itself is rarely life-threatening.



# Common Clinical Features: Severe/End-stage

- Multisystem compromise
- Profuse bleeding
- Consumptive coagulopathy/DIC
- Encephalopathy
- Shock
- Death

# Lab studies

- Complete Blood Count
  - Leucopenia, leucocytosis, thrombocytopenia, hemoconcentration, DIC
- Liver enzymes
- Proteinuria universal
- Serological tests – Ab not detected acute phase; Direct examination blood/tissues for viral Ag enzyme immunoassay.
- Immunohistochemical staining liver tissue
- Virus isolation in cell culture
- RT-PCR sequencing of virus
- Electron microscopy specific and sensitive

# Treatment

- Supportive care:
  - Fluid and electrolyte management
  - Hemodynamic monitoring
  - Ventilation and/or dialysis support
  - Steroids for adrenal crisis
  - Anticoagulants, IM injections,
  - Treat secondary bacterial infections

# Treatment

- Manage severe bleeding complications
  - Cryoprecipitate (concentrated clotting factors)
  - Platelets
  - Fresh Frozen Plasma
  - Heparin for DIC
- Ribavirin in vitro activity vs.
  - Lassa fever
  - New World Hemorrhagic fevers
  - Rift Valley Fever
  - No evidence to support use in Filovirus or Flavivirus infections

# Prevention

- Nosocomial: Complete equipment sterilization & protective clothing
- House to house rodent trapping
- Better food storage & hygiene
- Cautious handling of rodent if used as food source
- If human case occurs
  - Decrease person-to-person transmission
  - Isolation of infected individuals

# Vaccination

- Argentine and Bolivian HF
  - PASSIVE IMMUNIZATION
    - ✓ Treat with convalescent serum containing neutralizing antibody or immune globulin
- Yellow Fever
  - ACTIVE IMMUNIZATION
    - ✓ Travelers to Africa and South America
- Experimental vaccines under study
  - Argentine HF, Rift Valley Fever, Hantavirus and Dengue HF

# Why do VHFs make good Bioweapons?

- Disseminate through aerosols
- Low infectious dose
- High morbidity and mortality
- Cause fear and panic in the public
- No effective vaccine
- Available and can be produced in large quantity
- Research on weaponization has been conducted

The END