

# Viral hemorrhagic fevers (VHFs)

Edited by: Ahmad AlHurani

GOOD LUCK!

Black is original, Red is what was added in the lecture

By : Assis. Prof Nader Alaridah MD, PhD

# 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 **and fever**
- Some VHFs cause mild disease, but some, like Ebola or Marburg, cause severe disease and death.
- **Doctor doesn't care about the percentages of mortality that you'll find in this lecture as they vary, BUT we have to understand that THE HIGHEST MORTALITY RATE (can reach 90% with or without treatment) is found in EBOLA and MARBURG.**

All of these viruses are ssRNA, enveloped and zoonotic.  
All are -ve sense except Flaviviridae, they're +ve sense viruses.

Remember that:

-ve sense viruses are only found in the cytoplasm

+ve sense viruses can be found in the nucleus (Flaviviridae)

All are zoonotic viruses (Transmitted from Animals to humans)

We have to know 3 levels of transmission:

1. Animal to human **directly**, usually by rodents, so people in close contact to that animal can get the virus through the animal's bite, inhalation of aerosols, animal's body fluids; saliva urine, feces, tissue during slaughter)

2. Animal to human through a tick/mosquito/fly **without close direct contact** with that animal (**Arboviruses**)

3. Interpersonal transmission (human to human) only in :

1. Ebolavirus
2. Marburgvirus
3. Lassa fever
4. Crimean Congo HF

Non of these viruses have available vaccines, except for the "Yellow fever" which has a live attenuated vaccine.



"Ebola Armor"

# Quick Overview: Who are they?

- **Arenaviridae** **Non arboviruses**

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

- **Bunyaviridae** **Arboviruses**

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

Non arboviruses



- **Filoviridae** **Highest mortality**

- Marburg **Non arboviruses**
- Ebola

- **Flaviviridae** **Arboviruses**

- Yellow Fever
- Dengue Fever
- Omsk HF
- Kyasanur Forest Disease
- **Hepatitis C is also a member**

# 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** **Only the mentioned 5 viruses**
  - Blood/body fluid exposure
  - Airborne potential for some arenaviridae, filoviridae

**Between animals, there's what we call "horizontal transmission", where an infected animal infects another:**

- 1) Infecting an adult, this animal dies immediately.**
- 2) Transovarial transmission; the transmission of an infectious agent from parent to offspring, the newly born animal will stay viremic throughout his life (dangerous).**

# 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**

You'll not be asked about the country of origin for these, but you'll have to memorize them if you're preparing for USMLE steps.

# Arenaviridae

- Junin virus : Argentine hemorrhagic fever
- Machupo virus : Bolivian hemorrhagic fever
- Guanarito virus : Venezuelan hemorrhagic fever
- Lassa virus :Lassa fever- Nigeria **West African, higher mortality**
- Sabia virus : Brazilian hemorrhagic fever

# Arenaviridae Transmission **non arboviruses**

(only directly, no invertebrate arthropod (tick, fly, mosquito))

- 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  
Only **Lassa fever** in this family can be transmitted interpersonally





# Arenaviridae in Humans

As we said, west African lassa virus is more severe (up to 50% mortality rate) compared to south American viruses of this family

flu like symptoms are present in all of today's lecture's viruses

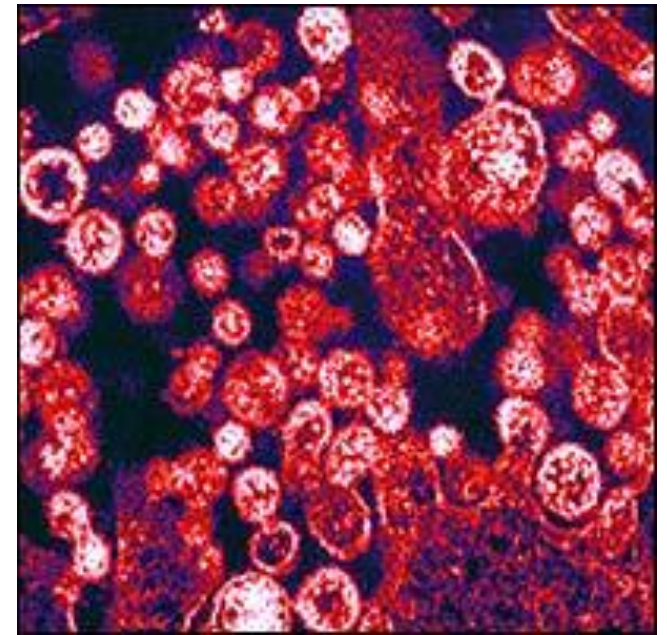
- Incubation period 10–14 days
- Fever and malaise 2–4 days
- Hemorrhagic stage
  - Hemorrhage, leukopenia, thrombocytopenia
  - Neurologic signs
  - **psycho-behavioral changes**

# 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



Arenaviridae are named due to their morphology under the microscope; Soil like ~ Arena they form viroids around each ribosome in the host cell



# Lassa Fever

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

When talking about therapy, we first make sure to apply the ABC (Airway, Breathing, Circulation) as supportive management so if patient lost blood, we give him blood, liquids also same thing, cannot breath? use a ventilator. This approach is used in patients of all families, but some antiviral therapies such as Ribavirin can reduce mortality if used. So ABC for all, Ribavirin only in some viruses where it's mentioned.

# Bunyaviridae

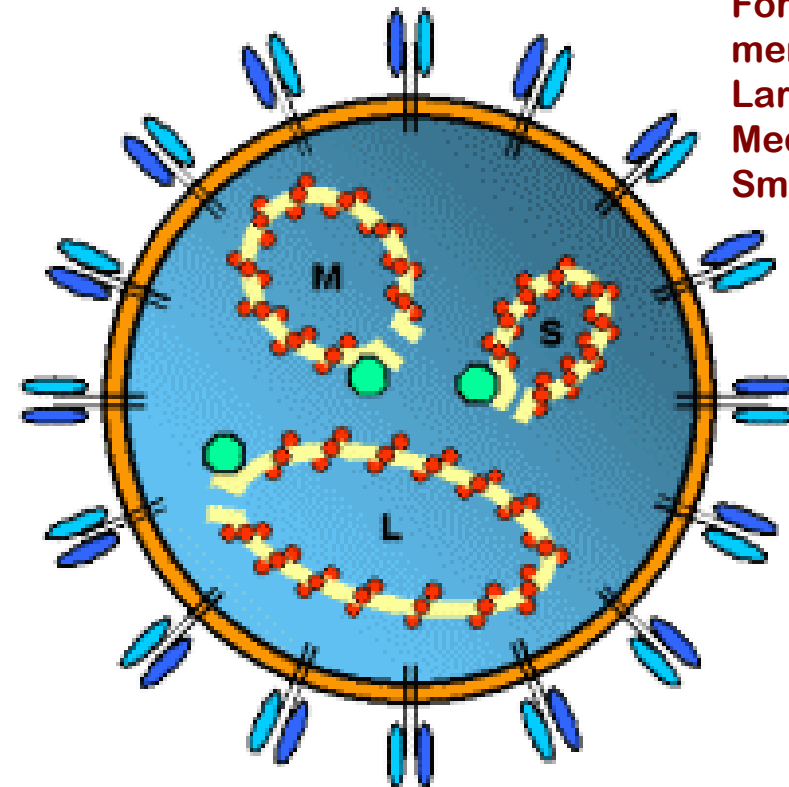
Arboviruses, except Hantavirus

- 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).



For easier  
memorization:  
Large,  
Medium,  
Small segments

# Bunyaviridae Transmission

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

**Aedes Mosquito**



**Hyalomma**

# 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 mildest one, least mortality percentage

- 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? The use of Ribavirin is controversial, as it's usually a very mild illness anyway thus not usually given here.

# Crimean-Congo Hemorrhagic Fever

Remember, interpersonal transmission is possible

- Distinguishing features
  - Abrupt onset, **sudden**
  - Most humans infected will develop hemorrhagic fever
  - Profuse hemorrhage hematemesis+melena
- Mortality 15-40%
- Therapy: Ribavirin



# Bunyaviridae: Hantaviruses non-arbovirus

- Transmission to humans:
  - Exposure to rodent saliva and excreta
  - Inhalation
  - Bites
  - Ingestion in contaminated food/water (?)  
Still debatable, as an example, if saliva of an infected animal contaminated water.
  - Person-to-person (Andes virus in Argentina)

# Hemorrhagic Fever with Renal Syndrome (HFRS)

## Old world Hantavirus

(New world Hantaviruses cause Hantavirus pulmonary syndrome(HPS)  
(discussed in Respiratory system))

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

# Flaviviridae

Arboviruses

- Dengue virus aka "break bone fever"
- Yellow Fever virus +effect on hepatocytes, causes Jaundice hence the name
- Omsk Hemorrhagic Fever virus
- Kyassnur Forest Disease virus

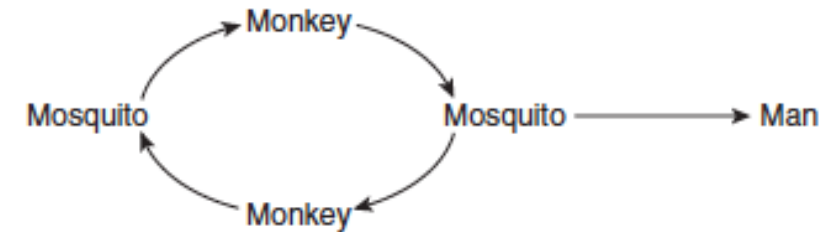
# Flaviviridae Transmission

Hepatitis C is also a member

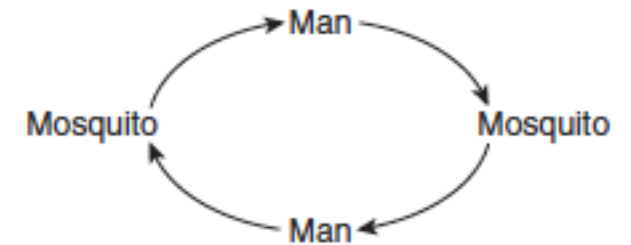
- Arthropod vector
- Yellow Fever and Dengue viruses
  - *Aedes aegypti* (mentioned for the third time already, summary in the last slides)
  - Sylvatic cycle
  - Urban cycle
- Kasanur Forest Virus
  - Ixodid tick
- Omsk Hemorrhagic Fever virus : Fever Lasting sequela
  - Muskrat urine, feces, or blood



**Sylvatic cycle** aka Jungle cycle, where there's a subhuman primate in the cycle; monkeys



In both cycles, the disease was transmitted to the human as "vector borne"



**Urban cycle** where the vector transmits the disease to human (the primate) (Human&Mosquito)

# Yellow Fever

- Distinguishing features
  - Biphasic infection a fever that **remits** for a day or a week, then **viremic/toxic** phase again
  - Common hepatic involvement & jaundice
- Mortality: 15-50%
- Active immunization through a **live attenuated** vaccine is available (Cannot be given for Children/Pregnant /Immunocompromised)

# Flaviviridae: Dengue "Break bone fever"

- Dengue Fever (DF) /Fatality: <1% *Only fever, very limited vascular damage, no signs of bleeding*
- Dengue Hemorrhagic Fever (DHF)/ Fatality: 5-6% *marked vascular damage*
- Dengue Shock Syndrome (DSS) /Fatality 12-44% *D.I.C (Disseminated intravascular coagulation)*
- 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
  - Dengue fever is **very severe in kids!**
  - Infection of DEN-1 as an example, gives life time immunity against DEN-1 itself BUT, the problem is that now any infection with **another serotype** will actually be **more severe** due to antigenic cross-reactivity.

# Omsk Hemorrhagic Fever

- Distinguishing Features

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

Reservoir host is muskrat

Additional info: Vector of Omsk fever is *Dermacentor reticulatus*



# Flaviviridae: Kyanasur Forest

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





Highest mortality

Very similar

Both have GI involvement with hematemesis and melena

# Filoviridae

Filament like morphology under the microscope

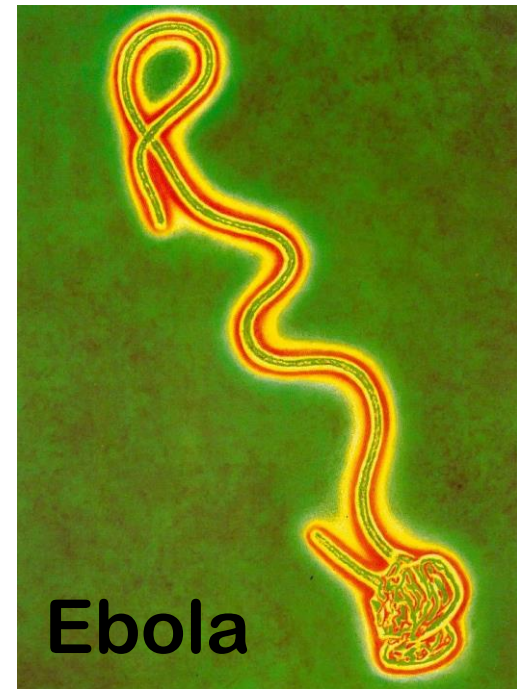
## ■ Ebola Africa

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

Doesn't affect humans "RESTon")

Other than humans  
Subhuman primates

## ■ Marburg Germany



Ebola



Marburg

# Filoviridae Transmission

Non arboviruses, only direct contact with an animal and interpersonal transmission

- Reservoir is UNKNOWN
  - Bats implicated with Marburg
- Intimate contact
- Nosocomial transmission
  - Reuse of needles and syringes **in hospital (healthcare personnel)**
  - Exposure to infectious tissues, excretions, and hospital wastes
- Aerosol transmission
  - Primates
  - Mortality usually after second week
  - Painful course, painful recovery!

# 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 - hematemesis+melena
  - 25-90% case-fatality even with treatment!

# 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 (such as necrosis of hepatocytes in yellow fever)
  - Abnormal vascular regulation:
    - Early -> mild hypotension
    - Severe/Advanced -> Hypovolemic Shock
- During Viremia:
  - Macrophage involvement
    - Inadequate/delayed immune response  
(Inadequate antigen presentation by macrophages and dendritic cells is well documented) ~  
(Either by not recognizing them, or treating them as super antigens causing cytokine storm)

# Common Clinical Features: Early/ Prodromal Symptoms **Stage 1**

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

Stage 1 has no Bleeding, not internally nor externally!



# Common Clinical Features: Progressive Signs **Stage 2**

mild forms of hemorrhage  
never life threatening

- 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 **Stage 3**

- Multisystem compromise
- Profuse bleeding bleeding from all orifices  
of the body, even the ears
- Consumptive coagulopathy/DIC
- Encephalopathy
- Shock
- Death

# Lab studies

- Complete Blood Count
  - Leucopenia, leucocytosis, thrombocytopenia, hemoconcentration, DIC (hemoconcentration is increased hematocrit(compensatory))
- Liver enzymes are all distorted in yellow fever
- Proteinuria is universal not only Hantavirus with renal syndrome
- 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 is highly specific and highly sensitive if available

# Treatment

Useful in the following conditions:

- 1) Lassa fever
- 2) Crimean-Congo HF
- 3) Rift valley fever (controversial and not used if mild, which is the usual case)

## ■ Supportive care:

- Fluid and electrolyte management
- Hemodynamic monitoring
- Ventilation and/or dialysis support
- Steroids for adrenal crisis
- Anticoagulants, IM injections,
- Treat secondary bacterial infections **Superimposed infections**
- **Give heparin if D.I.C occurs**

# Treatment

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

# Prevention

Prevention depends on whether the virus is an arbo or a non-arbovirus. If it's an arbovirus we also have to focus on getting rid of the vector.

- 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

Active immunization: we give a vaccine to stimulate antibody production by the immune system

Passive immunization: we give already formed antibodies from a previously infected patient through transferring their serum

# 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



# From 018 sheet

## Quick recap of the most important information mentioned throughout this lecture:

**Documented** person-to-person route of transmission is found in all of the following:

- 1) Lassa fever.
- 2) CCHF.
- 3) Andes virus in Argentina (the only one from the Hantaviruses).
- 4) Filoviridae (Ebola + Marburg).

- VHF that are transmitted by Aedes aegypti vector are:
- 1) RVF
  - 2) Yellow fever
  - 3) Dengue fever

Ixodid tick (*Hyalomma/Haemaphysalis*) is the main vector that transmits:

- 1) CCHF.
- 2) Kyasanur fever.

Biphasic clinical presentation is found in:

1. Arenaviridae
2. Filoviridae
3. Flaviviridae (mainly).

Ribavirin is considered an effective (well-documented) treatment -in vivo- only for:

1. Lassa fever
2. CCHF

Number of serotypes for:

- A. Ebola : five
- B. Dengue : four
- C. Hantaviruses : two
- D. Marburg: one

Lassa fever patients keep shedding the virus from their urine for at least 2 weeks after recovery, so you must isolate the patient for 2 weeks.

Filoviridae (Ebola +Marburg) have the highest mortality, fatality and morbidity rates compared to all other VHFs.

Sandy cytoplasmic appearance under the EM is found in: Arenaviridae (Lassa virus mainly).

DIC or Consumptive Coagulopathy is mainly found in Filoviridae (Ebola +Marburg).

All VHF's are zoonotic

- Lassa fever is transmitted by : (*Mastomys natalensis*)
- Omsk fever natural reservoir is: Muskrat.

Illness of dengue infection is very severe in younger children (well-documented).

Arboviruses	Non-arboviruses
Bunyaviridae ( except Hantaviruses)	Arenaviridae
Flaviviridae	Filoviridae

Hearing loss (deafness)	Vision loss (blindness)
Lassa fever	RVF
Omsk	-

Acute (sudden) onset	Chronic (insidious)/ gradual onset
Filoviridae (Ebola +Marburg)	HFRS, caused by old-world hantavirus
Dengue fever	Lassa fever
Omsk fever	-
Kyasanur fever	-

True about Dengue fever:

1. Caused by a DNA virus
2. It's caused by a non enveloped virus
3. It causes a very severe illness in children

Ans: 3

21-The Filoviridae family of viruses, one is incorrect :

- a. Most pathogenic of the hemorrhagic fever viruses .
- b. Human-to-human transmission via body fluids and respiratory droplets .
- c. Virus primarily infects liver cells, resulting in fever, jaundice, and hemorrhage .
- d. Enveloped, nonsegmented, single-stranded, RNA viruses .
- e. The natural animal reservoir has never been determined.

Ans: C

13-The dengue virus, one is correct :

- a. The virus is limited to Karnataka State, India .
- b. A live attenuated vaccine is available for dengue .
- c. Infection with one serotype confers immunity only to the infecting serotype .
- d. Dengue virus has five serotypes that cause a variety of clinical manifestations .
- e. Is the least prevalent arbovirus in the world.

Ans: C

Disease	Vector
RVF	Aedes aegypti
Yellow fever	Aedes aegypti
Dengue fever	Aedes aegypti
CCHF	Ixodid tick (Hyalomma)
Kasanur Forest Virus	Ixodid tick (Hyalomma)
Omsk HFV	Dermacentor Reticulatus
Omsk HFV	RODENT: Muskrat
Lassa fever	RODENT(non arbo): (Mastomys natalensis)