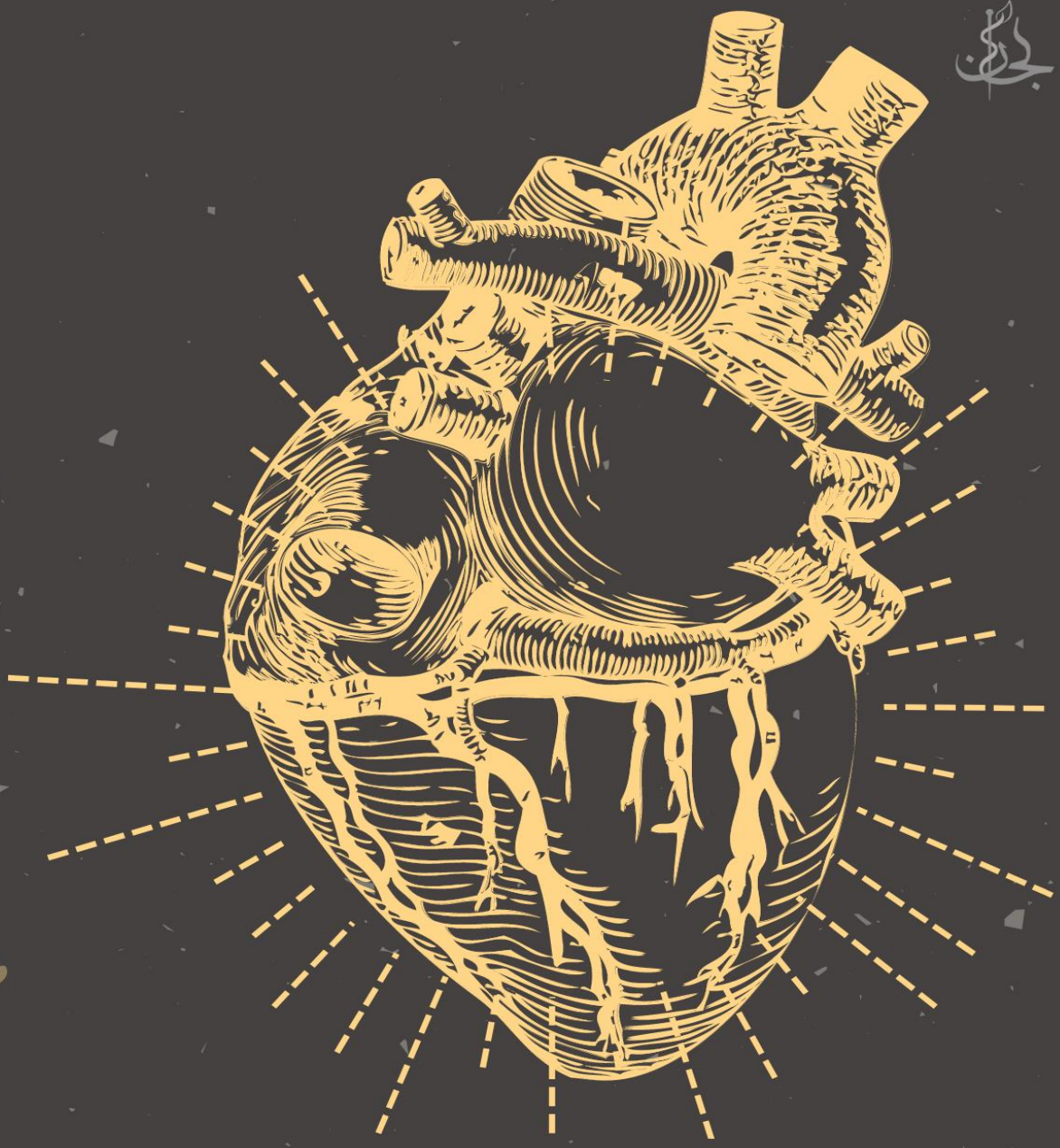

MICROBIOLOGY

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Viral hemorrhagic fevers (VHFs)

Overview

Viral hemorrhagic fevers (VHFs) are a group of febrile illnesses that sometimes associated with hemorrhage caused by four families of viruses: ***Arenaviridae***, ***Bunyaviridae***, ***Flaviviridae,*** *and* ***Filoviridae****.(all of them are biosafety level 4 viruses -dangerous viruses)*

They don't have a specific or clear pathophysiology rather than they are **marked** by Diffuse Damage to overall -small & large- vascular system also immune response (cytokines production) that lead to viral hemorrhagic fever and the patient might end up with shock and death.

-Symptoms often accompanied by hemorrhage (some of them only end by fever).

-Some VHFs cause mild disease, but some, like Ebola or Marburg, cause severe disease and death . **in all of the cases patient needs supportive treatment**

Common features between the four groups:

- Enveloped (glycoprotein,hemagglutinin& lipoprotein) \Lipid-encapsulated.
- Single-stranded RNA.
- Zoonotic (animal-borne-infect animal) (important).
- The geographical distribution of these viruses is restricted to the geographic distribution of the host (+the vector if it is an arbovirus).
- Persistent in nature (rodents, bats, mosquitoes, ticks, livestock, monkeys, and primates).
- Handling with animals increases the chance of infection.
- All of them replicate in the cytoplasm except Flaviviridae in the nucleus

VHFs are classified according to the involvement of an arthropod vector in their transmission cycle into 2 groups:

1. Arboviruses (Arthropod-borne): viruses which one of their main routes of transmission is an arthropod (such as mosquitoes, flies and ticks). Examples include: Flaviviridae and Bunyaviridae -except Hantaviruses- .

2. Non-Arboviruses zoonotic: viruses that are not transmitted by arthropods. Examples include: Arenaviridiae and Filoviridae & hantavirus

Quick Overview: How do we get infected?

Rodents & Arthropods, both reservoir & vector

-For Arboviruses by Bites of infected mosquito or tick.

- Inhalation of rodent excreta or by Infected animal product exposure .

Person-to-Person : through Blood/body fluid exposure mainly filovaridae or Airborne potential for some arenaviridae (especially lassa fever) & filoviridae

There are two types of transmission between the infected rodents:

1. Horizontal transmission: when it infect young and old age animals (adults) and lead to their death

2. Vertical transmission: It means the transmission of viruses from the mother to its fetus (intrauterine & perinatal)the fetus will have viremic phase. So, if an infected rodent transmits the virus to its fetus, then the transmission cycle continues and they infect the human . That is why vertical transmission is much more dangerous compared to horizontal transmission.

Quick Overview: Who are they?

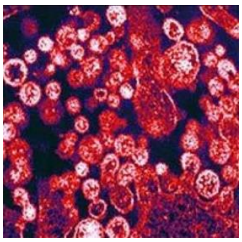
Arenaviridae	Filoviridae	Flaviviridae	Bunyaviridae
Lassa fever	Marburg	Yellow Fever	Rift Valley Fever (RVF) •
Argentine HF (Junin)	Ebola	Dengue Fever	Crimean Congo HF (CCHF)
Bolivian HF (Machupo)		Kyasanur Forest Disease	• Hantavirus Pulmonary Syndrome (HPS)
Brazilian HF (Sabia)		Omsk HF	• Hantavirus (Hemorrhagic Fever with Renal Syndrome (HFRS))
Venezuelan HF (Guanarito)			
The different names within each family of these viruses are dependent on the first geographic region they were isolated from.			

The Arenaviridae

Non-Arboviruses, their replication takes place in the cytoplasm, and they carry RNA dependent-RNA polymerase.

They have taken their specific name from the “Arena” (The place of competition); because these viruses acquire the host’s ribosomal subunits in their virion state.

This feature appears under the electron microscope as a “Sandy Cytoplasm”.

 : **electromicrograph of lasssa fever (sandy cytoplasm)**

The Arenaviridiae family is classified into 2 groups according to the geographical distribution:

1. **West African:** such as Lassa fever (in Nigeria) This one has the highest mortality rate in this family.
2. **South American:** Argentine hemorrhagic fever (caused by the Junin virus), Bolivian HF (caused by the Machupo virus), Brazilian HF (caused by the Sabia virus), Venezuelan HF (caused by the Guanarito virus).
   -Usually, they are mild. Mortality rate for South Americans (less than 3%) is milder than the Africans (5 – 40 %)

Arenaviridae Transmission: NO arthropods are involved as vectors here (nonArboviruses).

Virus transmission and amplification occurs in rodents, they shed the virus through urine, feces blood ,tissues , and other excreta. Humans can be infected by contact with a rodent's excreta, contaminated materials and aerosol transmission(inhalation).

- ✓ Person-to-person transmission has been documented in arenaviridae , Feco-oral root a bit controversial

• Incubation period 10–14 days , after one week the patient will show constitutional symptoms from the viremic phase (fever , headache , myalgia , arthralgia and malaise and within 2-4 patient will show post fever symptoms (the hemorrrhagic signs) usually mild hemorhhage as simple as petechiae and macular rash sometimes accompanied with neurological signs and leukopenia, thrombocytopenia and hypotension

Arenaviridae: Lassa Fever

First seen in Lassa, Nigeria in 1969. Now in all countries of West Africa , in Jordan between soldiers of united nations peacekeeping in West Africa قوات حفظ السلام.

• 5-14% of all hospitalized febrile illness

• Rodent-borne (Mastomys natalensis)(remember : nonArbo : so direct contact with rodent needed for infection to occur don't need Arthropod)

• Interpersonal transmission (person to person) through body fluids :Direct Contact (saliva) ,Sex & Breast Feeding.

• Distinguishing Features

- Gradual onset Marked by constitutional symptoms: Fever, headache, myalgia and malaise also they exhibit Myocarditis, hepatitis & marked by chest pain. Exudative **pharyngitis** &

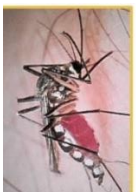
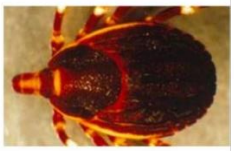
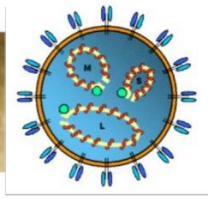
Retro-sternal pain also Hearing loss in 25% may be persistent even after treatment and cause Spontaneous abortion

- Mortality 1-3% overall (up to 50% in epidemics)

- Therapy: Ribavirin antiviral is an effective treatment (documented), although supportive (fluid & blood) treatment is considered as the main therapeutic approach .

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

Bunyaviridae

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

The RNA of this family is segmented (genes that encode for a certain function are present on different segments). There are 3 segments:: L-segment (large) codes for an Lprotein (the RNA dependent RNA polymerase) M segment (medium) codes for two surface glycoproteins G1 and G2 which form the envelope spikes , S segment (small)codes for an Nprotein (nucleocapsid protein).

Transmission : Arthropod vector Except Hantaviruses (the arthropods transmit the virus from an infected animal usually rodents)

- RVF arthropod is Aedes mosquito while CCHF arthropod is Ixodid tick (Hyalomma) , remember : Hantavirus is transmitted by Rodents
- Contact with animal blood or products of infected livestock
- Less common : laboratory Aerosol or Exposure to infected animal tissue
- Person-to-person transmission with CCHF

Bunyaviridae : Rift Valley Fever

Caused by the simplest virus in this family with the lowest mortality rate (less than 1- 5%). It is an asymptomatic or mild illness in humans However, it has hemorrhagic complications, but they are rare (< 5%) it also cause **Vision loss "blindness"** (due to retinal hemorrhage, vasculitis) in 1-10% of patients.
The arthropod vector that transmits RVF is the Aedes aegypti mosquito.
Treatment: Supportive therapy only. However, Ribavirin is documented treatment but doesn't have a great result (the disease is mild so we don't need a specific antiviral treatment).

• Crimean-Congo Hemorrhagic Fever (CCHF)

The virus causing CCHF is an arbovirus, and the vector that transmits the virus is the Ixodid tick (Hyalomma/Haemaphysalis).

- Person to person transmission is an effective mode of transmission for CCHF, in addition to aerosols inhalation from laboratories .

-Distinguishing features: Abrupt (acute) onset, profuse hemorrhage, and most humans infected will develop hemorrhagic fever.

-Mortality rate of CCHF is much higher (15-40%) than RVF.

-Treatment: Ribavirin is an effective documented treatment for CCHF.

• Hantaviruses

They are non-arboviruses (The only exception for Bunyaviridae family).

We have two serotypes of Hantaviruses 2 distinct outcomes:

1.New-world Hantavirus (Nombre virus): which causes Hantavirus Pulmonary Syndrome (HPS). THIS TYPE IS OUT OF THE SCOPE OF THIS LECTURE to be discussed in the Respiratory System

2.Old-world Hantavirus (puumal virus): which causes Hemorrhagic Fever with Renal Syndrome (HFRS).

-Hemorrhagic Fever with Renal Syndrome (HFRS) :

I. Distinguishing Features: Insidious (gradual) onset, intense headaches, **blurred vision**, kidney failure (due to capillary leakage causing severe fluid overload).
II. Mortality rate: 1-15%

Transmission to humans:

1. Direct contact or exposure to rodents through: saliva, excreta, inhalation, bites.
2. Ingestion of contaminated food/water: This route of transmission is still controversial and is not evidence-based yet as a well-established route of transmission.
3. Person-to-person transmission: only found in Andes virus in Argentina member of Nombre family.

Flaviviridae

-They are arboviruses, and their replication takes place inside the cytoplasm.

-We will talk about 4 viruses: **Dengue virus** (dengue fever ,dengue hemorrhagic fever or dengue shock syndrome), **Yellow Fever virus**, **Omsk Hemorrhagic Fever virus**(in eastern Europe **), Kyasanur Forest Disease virus** (India)

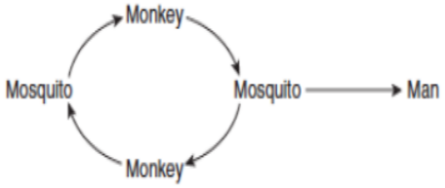
ALL Flaviviridae are characterized by the “Biphasic clinical presentation”:

1. Viremia phase: It is characterized by a high viral load in the blood and high secretion of cytokines. It includes constitutional signs and symptoms; for example: marked fever. ¬ In between the 2 phases, there is a window period, in which signs and symptoms disappear.
2. Toxemia phase (complications phase , sequelae phase): Fever returns along with the constitutional symptoms + Hemorrhagic signs and symptoms appear.

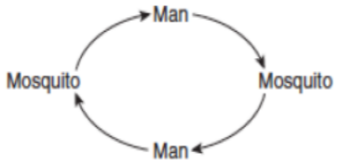
Flaviviridae Transmission : Arthropod vector
-vector for RVF virus is the same as the vector for yellow fever virus and dengue virus, which is the **Aedes aegypti**
-Kyasanur Forest Virus vector is: Ixodid tick
- additional : Omsk Hemorrhagic Fever virus vectors are : the Dermacentor reticulatus tick **D. marginatus**, Ixodes persulcatus.
Omsk Fever has Lasting sequela • Muskrat urine, feces, or blood

Both Yellow Fever and Dengue have two cycles :

• Sylvatic cycle the human isn't the primate rather there is a cycle between nonhuman primates like monkeys (natural host) and the vector. Humans are considered accidental hosts



• Urban cycle : between humans and the vector without the need of an intermediate host (the virus is directly transmitted from the mosquito to the human and vice versa).



Flaviridae :Yellow fever

- Distinguishing features :biphasic infection with a window period lasts for 1-2 days Common hepatic involvement it has lytic effect in vertebrate host which cause necrosis of the hepatocyte & jaundice.
- Mortality rate: high (15-50%) but still low compared to Filoviruses.

Flaviridae :Dengue

Dengue fever has 4 distinct serotypes (DEN 1, DEN 2, DEN 3, DEN 4), all are known to cause diseases in humans. 1 Dengue Fever (DF) /Fatality: <1% 2. Dengue Hemorrhagic Fever (DHF): Fatality rate: 5-6% 3. Dengue Shock Syndrome (DSS): has a higher fatality rate (12-44%).

- Onset of dengue fever infections is sudden (acute).
- Remember the vector is Aedes aegypti.
- Illness of dengue infection (dengue fever & DHF) are very severe in younger children (well-documented).

- Treatment: supportive treatment only.
- Distinguishing Features: Eye pain, maculopapular Rash.
- Complications: sequelae hemorrhage is uncommon

Omsk Hemorrhagic fever

Distinguishing Features :

- Acute Onset
- Biphasic infection (window of improvement > 2 days)
- Complications • Hearing loss • Hair loss • Psycho-behavioral difficulties (in phase 2)
- Mortality: 0.5 – 3%

Flaviviridae: Kyanasur Forest

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

Filoviridae

Filoviridae family has the highest mortality rate between all of VHF families (before covid-19 scientists had fears about a filoviridae outbreak). They are the family with the highest mortality rate (up to 90%), fatality, and morbidity rates, compared to all the previous hemorrhagic fever viruses in humans (Most severe hemorrhagic fever)

They are non-Arboviruses, that have **a sudden (acute) onset of the disease** Abrupt onset : Fever, chills, malaise, and myalgia **with rapidly fatal febrile hemorrhagic illness.**

- Incubation period: 4–10 days

*Reservoir is UNKNOWN, but it is zoonotic. However, bats are a possible reservoir.

They include Ebola and Marburg viruses

Transmission:

1. Person-to-person (Intimate contact) is an effective route of transmission through the body fluids (well documented)

2. Nosocomial: a. Reuse of needles and syringes. b. Exposure to infectious tissues, excretions, and hospital wastes.

3. Aerosol transmission: Primates has been documented to be transmitted in labs while working with specimen

- **Ebola & Marburg specific characteristics:**

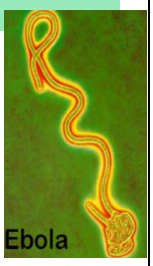
- often the death occur in the second week (Death around day 7–11)usually due to DIC (**Disseminated intravascular coagulation) consumption of clotting factors**
- If the patient survives after the second week, he is considered to be recovering. However, this **recovery is "painful "**during which the patient does not feel that he is getting well, but the lab results say that everything is getting better.

❖ **Common Pathophysiology** (remember :there isn't a specific pathophysiology):

-"Viremia phase (Early/Prodromal Symptoms)": high viral overload ,Macrophage involvement , and thare is an inadequate (delayed) immune response may include cytokine storm (excessive cytokines production) which leads to Cellular damage also there is small & large vessels involvement which may lead to vascular ,capillary leakage (small vessels involvement increases vascular permeability) and this involvement cause all the hemorrhagic sequelae that result from infection with these viruses the abnormal vascular regulation in the early phase leads to mild hypotension while in severe and advanced cases leads to shock .

Common Clinical Features: **Early/**Prodromal Symptoms (before hemorrhagic sequele - small & large vessels involvement-)	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 (under the skin) . However, in this stage the hemorrhage itself is rarely lifethreatening.
Common Clinical Features: Severe/End-stage	Multisystem compromise , Profuse bleeding , Consumptive coagulopathy/DIC , Encephalopathy , may end with hypotension Shock & Death. Filoviridae patients may also bleed from external orifices so (internl & external bleeding)

Filoviridae : Ebola


Ebola

■ Ebola serotypes: ■ Ebola-Zaire ■ Ebola-Sudan ■ Ebola-Ivory Coast ■ Ebola-Bundibugyo ■ (Ebola-Reston)

First 4 serotypes cause disease in humans (Ebola hemorrhagic fever), whereas the fifth serotype (Ebola-Reston) causes illness mainly in nonhuman primates , Ebola-Reston

imported to US, but only causes illness in nonhuman primates. On the other hand, Human-infectious subtypes found only in Africa.

•Distinguishing features: Acute onset ,GI involvement (the mechanism is unknown),Weight loss ,25-90% case-fatality

Filoviridae: Marburg

Distinguising features: •Sudden onset • Chest pain (retro-sternal) • Maculopapular rash on trunk • Pancreatitis • Jaundice
21-90% mortality rate

Lab tests

In order to diagnose patients with VHF, we can use many tests:

1) Complete Blood Count: **Leukopenia**, leukocytosis, **thrombocytopenia**, hemoconcentration, DIC.
   - **hypotention**
2) Liver function test: can be used to detect yellow fever(**high liver enzymes**)
3) Kidney function test: can be used to detect HFRS
4) Proteinuria universal (**Albuminuria)**
5) Serological tests –**Abs are not detected** during the acute phase- : Direct examination of blood/tissues in viral Ag enzyme immunoassay .
6) Immunohistochemical staining for liver tissue.
7) Virus isolation in cell culture.
8) **RT-PCR sequencing of the virus**.
9) **Electron microscopy** specific and sensitive: can be used to show Lassa fever sandy cytoplasm.

❖ Biosafety level 4 (in labs) is required to prevent infections (And always remember they aren't easy to deal with , those tests are only done by governments and after notifying the WHO).

Treatment for VHF in general

- **Supportive care & symptoms treatment:** Fluid and electrolyte management, Hemodynamic monitoring, Ventilation and/or dialysis support, Steroids for adrenal crisis, Anticoagulants, IM injections and the Treatment of secondary bacterial infections.
  - Suppurative ABC : Airway , Bleeding , Circulation (fluids)
- **Manage severe bleeding complications:** Cryoprecipitate (concentrated clotting factors), Platelets, Fresh Frozen Plasma and Heparin for DIC.

- Ribavirin shows activity in vitro (in labs, outside the body) against Lassa fever, New and Old World Hanta-hemorrhagic fevers and the Rift Valley Fever.

➢ No evidence to support using Ribavirin in Filovirus or Flavivirus infections.

Prevention

1) The first step of prevention is by isolation of the patient once diagnosed with one of the VHFs. Decrease person-to-person transmission.
2) The second step is dependent on the type of the VHF. If it is an arthropod-borne virus, then this step is about arthropod control. If it is a non-arthropod-borne, then it is about controlling the natural host (Rodents control-House to house rodent trapping).
3) Nosocomial: Complete equipment sterilization & protective clothing
4) Better food storage & hygiene , Cautious handling of rodent if used as food source وصحتين وعافية

Vaccination : There is **only one active vaccine** that is approved for VHF and it is against the **yellow fever** as other vaccines are experimental(Experimental vaccines under study :Argentine HF, Rift Valley Fever, Hantavirus and Dengue HF). It is given for travellers before visiting Africa and South America. There are also passive vaccines for the Argentine and Bolivian HF. Active immunization is better than passive if there is enough time. However, passive immunization is a good choice for immunocompromised patients for therapeutic purposes not for prevention. (Remember: Active Immunization is the administration of a pathogen to the body in order for the immune system to develop an immune response that forms a long- lasting immunity against that pathogen. On the other hand, passive immunization is Treat with convalescent serum containing neutralizing antibody or immune globulin (giving antibodies from previously infected person) Because of that, passive immunization doesn't confer a long-lasting immunity, it merely functions as a therapeutic approach not a preventive one)

-All VHF viruses can be used as bioweapons; because they are available and can be produced in large quantity transmission can be through aerosol, they need a low infectious dose, no vaccine, as well as they have high mortality and morbidity rates and can cause fear and panic in the public.

✓ 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).

- VHFs 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 VHFs 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	-

Thank you