Lecture 16: VHF s
Biosafety Level IV
( BSL IV )
Viral Hemorrhagic Fevers (VHFs)

- Group of diseases in humans and animals characterized by bleeding disorders and fevers
- Sometimes mild, sometimes fatal
- Humans are not the natural reservoir, but secondary transmission can occur
- 5 families of RNA viruses (designation and classification seems a bit under debate):
  - Arenaviridae
  - Bunyaviridae
  - Filoviridae
  - Flaviviridae
  - (Togaviridae)

Source: CDC – 4 families
Sample family members

Arenaviridae:
   Lassa fever, Argentine, Bolivian, Venezuelan HF

Bunyaviridae:
   *Hantavirus* genus:
      HF with renal syndrome (HFRS)
   *Nairovirus* genus:
      Crimean-Congo HF (CCHF)
   *Phlebovirus* genus:
      Rift Valley Fever (RVF)

Filoviridae:
   Ebola and Marburg
Sample family members

- **Flaviviridae:**
  - *Flavivirus* genus:
    - Dengue HF
- **Two tick-borne encephalitis that go VHF:**
  - Omsk HF
  - Kyasanur Forest disease

- **Arteriviridae:**
- **Simian hemorrhagic fever virus (SHFV)**
  - Identified in US and Russian labs in 1964
  - Patas monkey thought to be natural host – 50% wild population test for antibodies, asymptomatic;
  - also found at low levels (~10%) in vervets and baboons
  - In macaques, highly infectious, highly fatal (10-15 days)
50% SHFV
Filoviruses

• The filoviridae family was discovered in 1967
  – 31 people were infected with the Marburg virus in Marburg, Germany after working with imported Ugandan monkey tissue
  – Seven died.

• Ebola was named after Ebola River Valley in DRC (Zaire, 1976)
  – 4-5 current subtypes or strains:
    • Zaire ebolavirus
    • Sudan ebolavirus
    • Reston ebolavirus
    • Ivory Coast (Tai) ebolavirus
    • Bundibugyo ebolavirus
Filoviruses

• Three ‘original’ human outbreaks of Ebola
  – The first two, in 1976 in Zaire (90% case fatality) and in western Sudan (50% case fatality) were large outbreaks that resulted in more than 550 cases and 340 deaths.
    – The third outbreak, in 1979 in Sudan, was smaller, with 34 cases and 22 deaths.

• In each of these outbreaks, most cases occurred in hospitals where medical supplies were inadequate and where needles and syringes were re-used.

• The outbreaks were quickly controlled by isolating sick patients in a place requiring the wearing of mask, gown, and gloves; sterilizing needles and syringes; and disposing of wastes and corpses in a sanitary way.
RESTON: lab monkey Ebola

- 1989 – Ebola Reston
  - Monkeys shipped to Reston, Virginia from Mindano, Philippines
  - The Hot Zone by Richard Preston – read it!!
  - No-one actually got HF, but some people seroconverted
Kikwit, 1995

- In 1995, an outbreak in Kikwit and surrounding areas in Bandundu Province, Zaire, caused 316 deaths.
  - Outbreak was amplified in a hospital by staff with poor nursing techniques.
  - At the request of health officials in Zaire, medical teams from CDC and the World Health Organization, and from Belgium, France, and South Africa, collaborated to investigate and control the outbreak.

- When people showed up, they found a few health workers abandoned in a back room of the hospital, dying of Ebola
  - Inspired the CDC Special Pathogens Branch to produce a health worker’s manual for VHF:
    http://www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm
Ebola Tai and Gabon outbreaks

• Two isolated cases of Ebola hemorrhagic fever were identified in Cote d'Ivoire in 1994-1995.
  – Tai Forest is home to the Tai chimps – they have Ebola
  – A Swiss researcher caught it from a chimp necropsy, and survived

• Two more outbreaks in rural Gabon, 1994 and 1996.
  – 1996: Young boys found a dead chimp in the forest
  – Brought it back for a bushmeat dinner
  – 68% mortality rate
  – A patient from the 1996 Gabon outbreak traveled to Johannesburg, South Africa, and fatally infected a health-worker there as well.
Sudan Ebola again
2000/2001 (53% mortality); May 2004, 20 cases, 5 deaths

Source: CDC and wikicommons
January 2008
should the McGill field course go to Uganda?

• *Riots in Kenya notwithstanding*
• November 30, 2007: Uganda Ministry of Health confirmed an outbreak of Ebola in the Bundibugyo District
• After confirmation of samples tested by the US National Reference Laboratories and the CDC, the WHO confirmed a new species of Ebola.
• The epidemic came to an official end on February 20, 2008. 149 cases were reported and 37 deaths.
• Scary property – longer incubation.
Natural reservoir?

- Not gorillas – they are being decimated by it
- Not chimps – same story
  - Red colobus – not likely, but the potential source for the Tai chimps
- Fruit bats – cave source of viruses, asymptomatic carriers ?? Possible
- What does this mean for control?

http://www.youtube.com/v/RP5IZd1rooQ&hl=en
Bunyaviridae:

*Hantavirus* genus:
HF with renal syndrome (HFRS)

*Nairovirus* genus:
Crimean-Congo HF (CCHF)

*Phlebovirus* genus:
Rift Valley Fever (RVF)
Bunyaviruses - Hantavirus

• The Hantaan, Puumala, and Seoul viruses found mostly in Asia and Europe. They cause a group of illnesses called hemorrhagic fever with renal syndrome (HFRS).

• HFRS - kidneys may not function properly, so the body is not as able to produce urine.

• People with severe cases of HFRS may have circulatory problems, including shock, bleeding, and fluid buildup in the lungs, and abnormal liver function is sometimes seen.

• < 10% death rate

Source: CDC.gov
Bunyaviruses – Hantavirus in the USA

• Hantavirus (Sin Nombre Virus) is transmitted to humans from rodent feces
• First recognised in 1993 – mysterious “Four Corners” (NM, AZ, CO, UT) outbreak in the Southwest
  – Previous healthy adults had respiratory illness, then collapsed (50% mortality)
• Found throughout the United States (about ½ the states)
  – Don’t shake out a rug in your summer cabin without wearing a facemask
  – Clean your camping stoves very carefully
  – Store your camping food in bear bins
• Probably occurred in the Four Corners for a long time; cases defined as early as 1959 in retrospect
• 1993 outbreak thought to be caused by a large increase in rodent population due to good rains
• HPS – Hanta Pulmonary Syndrome, rare, but potentially deadly
• The Black Creek Canal virus, carried by the cotton rat, was found in Florida,
• Bayou Virus, carried by the rice rat, was found in Louisiana
• New York, the New York-1 virus was linked to the white-footed mouse

Source: CDC.gov
Bunyaviruses - Crimean-Congo HF

- Tick-borne *Nariovirus* first recognized in 1944 in the Crimea
  - 1969 – same illness emerged in the Congo
- Distribution:
  - Eastern Europe, particularly in the former Soviet Union
  - throughout the Mediterranean
  - northwestern China
  - central Asia
  - southern Europe
  - Africa, the Middle East
  - Indian subcontinent
- Ixodes ticks – hard bodied ticks
- Wild and domestic animals (cattle, goats, sheep, hares) are amplifying hosts
- Humans get it from ticks or infected animal body fluids
  - Peticheae, bruising, nosebleeds follow from joint aches, headaches, fever, vomiting
  - Fatality rates from 9-50%
  - Only supportive care (fluids)

Source: CDC.gov
Bunyaviruses - Rift Valley Fever

- Current outbreak: Madagascar (CDC travel)
- Mosquito-borne epidemic in rainy years
  - *Aedes* mosquitoes
- Eastern Africa has had multiple outbreaks
  - cattle, domestic livestock, and people
- First reported early 1900s by vets in Kenya
  - Around 1% of humans die of RVF
  - Around 100% of pregnant livestock abort
- People tend to have low levels of symptoms
  - liver problems, low-grade fever.
  - 1-10% of people have vision loss, because RVF manifests as a retinal inflammation
Arenaviruses

- Lassa (Nicole’s presentation)
- Argentine, Bolivian, Venezuelan, etc. HFs
- Junin virus, isolated in 1958, was the first identified (mortality 20-30%)
  - Argentine hemorrhagic fever in limited agricultural area of the pampas
- 1963, remote savannas of Beni province, Bolivia, Machupo virus isolated
- Lassa virus in Africa in 1969.
- Most recently, Guanarito (Venezuelan – 1989 – 30% fatality) and Sabia (Brazilian) viruses were added.
- Transmitted by rodents – urine and feces
  - Consumption or aerosolized
  - Tacaribe complex viruses (New World) – NW rats and mice
  - LCM/Lassa complex (Old World) – OW rats and mice
- Lassa and Machupo viruses can have secondary human-human transmission

Source: CDC special pathogens branch

http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/arena.htm
Figura 1
Distribución geográfica de los Arenavirus en América y sus reservorios

Figure swiped from uncited web source: http://www.stanford.edu/group/virus/arena/2005/SabiaVirus.htm
Flaviviridae:

*Flavivirus* genus:

- Dengue HF, yellow fever

Two tick-borne encephalitis that go VHF:
- Omsk HF
- Kyasanur Forest disease
Dengue HF

Classic Dengue – 6-7 days Historically not a severe disease, a “mild tropical fever”

– DHF emerged in the Pacific and Americas with multiple serotypes (4 major DEN currently) around WWII
– SE Asia 1950s, first DHF epidemic emerged
– 1980s – today, multiple epidemics of DHF in Asia, Africa, Middle East – everywhere with people and Aedes mosquitoes

WHO definition of DHF:

1. Fever, bladder problem, constant headaches, severe dizziness and loss of appetite.
2. Hemorrhagic tendency (spontaneous bruising, bleeding from muscosa, gingiva, injection sites, etc.; vomiting blood, or bloody diarrhea)
3. Thrombocytopenia (<100,000 platelets per mm³)
4. Evidence of plasma leakage

Can lead to DSS (Dengue Shock Syndrome)

– Weak rapid pulse,
– Narrow pulse pressure (less than 20 mm Hg)
– Cold, clammy skin and restlessness.

Current ongoing outbreak in Brazil – travel warnings (CDC)
CDC: 2.5 billion people live where local Dengue exists
Two tick-borne encephalitis that go VHF: Omsk HF & Kyasanur Forest disease

- Omsk, Siberia
  - Rodents – water voles and introduced muskrats are the reservoir
    - Tick-borne disease for humans
  - Described in 1945 and 1947 in Omsk
    - Also occurs in Novosibirsk, Kurgan and Tyumen
  - 3-8 day incubation
    - Fevers, chills, conjunctival suffusion (bloody eyes), nosebleeds, gastrointestinal hemorrhage – recovery from first stage
    - Biphasic – 1-2 weeks later there can be another set of symptoms, including encephalitis
      - 1-10% fatality
  - Survives in water, so can be a contaminant!
  - Also transmitted through sheep and goats milk
  - Quite stable virus for a VHF – not a good thing

Source: CDC and CWBInfo.com – a site for bioweapons safety. Ha.
Two tick-borne encephalitis that go VHF: Omsk HF & Kyasanur Forest disease

• Kyasanur Forest Disease (KFDV) also known as Monkey Disease
  – Epizootic in Kyasanur Forest, Karnataka, India in 1957, killed monkeys, local villagers reported a ‘prostrating disease’
  – Very local disease, but increase in cases between 1999-2005 suggest increased contact with reservoir
  – Reservoirs: Porcupines, forest birds, rats and mice. Ticks bite people, infecting them.
  – Initial disease 2 weeks, but several months of convalescence afterwards
• A variant arose in Saudia Arabia in 2005
  – Alkhurma haemorrhagic fever virus (AHFV)

Source: CDC and http://www.histopathology-india.net/kyasanur_forest_disease.htm
BSL4: fine in a lab, hard outside!