

# Tropical Dermatology: Viral Tropical Diseases

# Tropical viruses with dermatologic findings

- RNA Viruses

- Arenavirus
- Filovirus
- Flavivirus
- Bunyavirus

- DNA Viruses

- Herpesvirus
- Poxvirus

# Importance

- Viruses are more dangerous than other pathogens because:
  - Greater ability to mutate
  - Easily cross species barriers
- Tropical viruses are becoming dangerous because:
  - Major ecological changes
  - Collapse of eradication programs
  - Travel and agriculture
- Biological Warfare

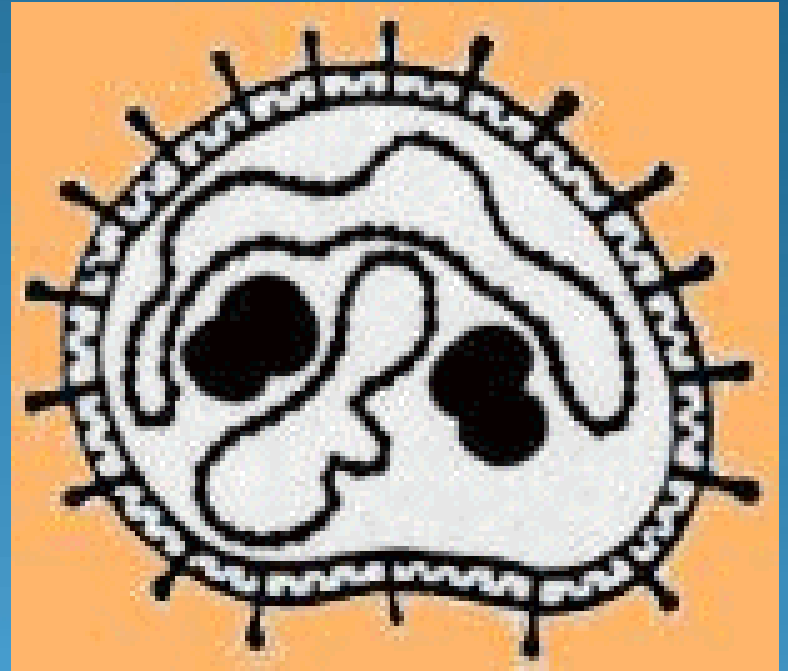
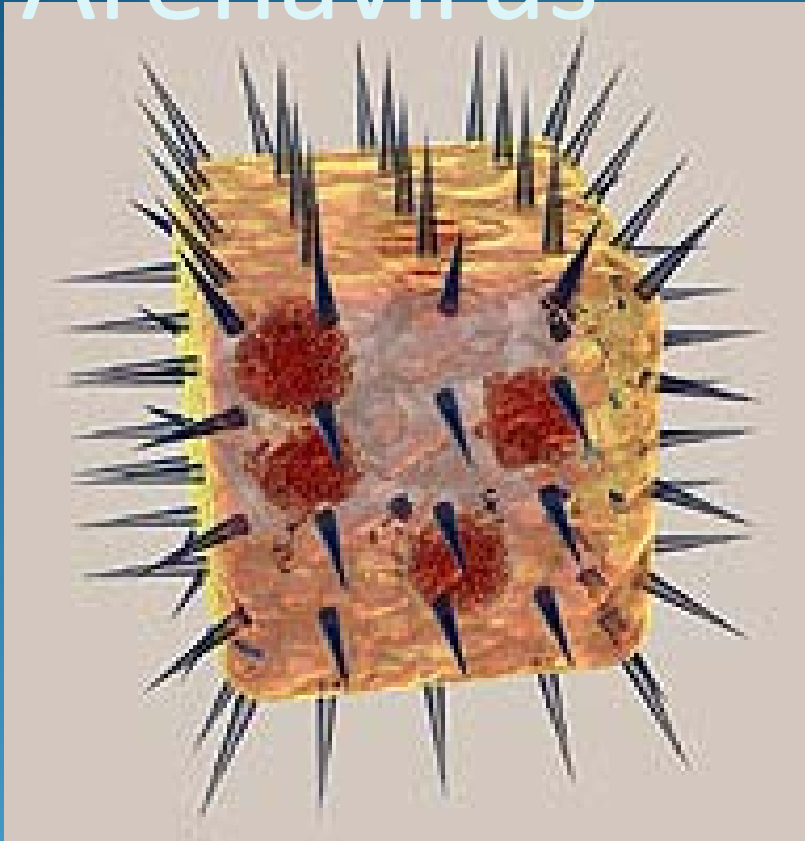
# Hemorrhagic Fever

- Zoonotic viral infection
- Four families of RNA viruses:
  - Arenavirus
  - Filovirus
  - Flavivirus
  - Bunyavirus
- Wide range of severity from mild febrile illness to multiorgan failure
- Most common in South America and Africa
- Cases in US

# Hemorrhagic fever

- In general, individual cases are hard to diagnose
- Death is not always from hemorrhage, but more often from capillary leakage syndrome (the virus replicates in the endothelial cell)
- Multisystem failure, as opposed to targeting one organ
- Non-specific, but severe flu-like symptoms
- Sequelae include alopecia, Beau's lines, deafness, retinitis, uveitis, encephalitis, pericarditis, renal insufficiency

# Arenavirus



# Arenavirus

- Old world

- LCM
- Lassa

- New World

- Tacaribe Complex Virus
  - Junin
  - Machupo
  - Guanarito
  - Sabia
- Less Common
  - Tamiami (Florida)
  - Whitewater Arroyo (California, NM)

# Arenavirus

- Rodents are the reservoir
- Benign infection in rodent host suggests symbiotic relationship
- Human infection plays no role in the life cycle of the virus



# Arenavirus

- All reported cases describe human interaction with rodent excrement (urine)
  - agriculture workers encountering rodents during crop harvesting (Pampas of Argentina)
  - Hunters encountering rodents in forests
- Portal of entry is unknown (probably aerosolized)

# Pampas of Argentina



# Arenavirus

- Spectrum of disease:
  - 70% are asymptomatic or cannot be distinguished from URI or gastroenteritis
  - 30% more serious disease
  - Recovery is the rule
- Cellular receptor has not been identified but is hypothesized to be widely distributed and highly conserved

# Lymphocytic Choriomeningitis Virus

- Prototype of Arenavirus
- Incidentally isolated 1934 when searching for the St. Louis encephalitis virus
- First recognized cause of aseptic meningitis in humans
- Only arenavirus that does not cause hemorrhagic fever

# LCM

- Occupies both Eastern and Western hemispheres (Old and New World)
- Reservoir is house mouse (*Mus Musculus*, *Mus domesticus*) and Syrian hamster (*Mesocricetus auratus*)
- These rodents are found in Europe, Asia and the Americas
- Virus has been found in pet mice and “lab rats”

# Arenavirus in America

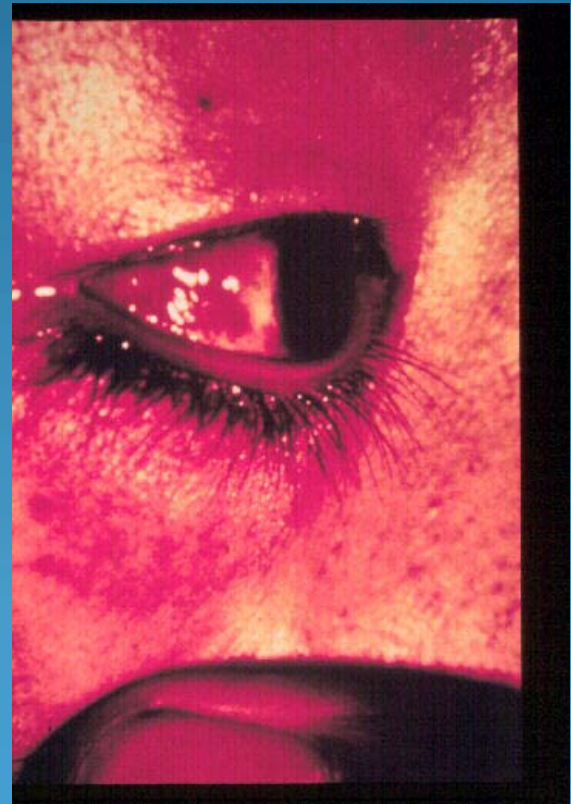
- Sabia virus in lab rats at Yale in 1996
- California 1999-2000: three female patients with ARDS, liver failure and death
  - Caused by Whitewater Arroyo virus that had been previously isolated from a white throated wood rat in New Mexico
  - *Neotoma* live all over US
- Tamiami Virus
  - Florida, in cotton rats

# Arenavirus: Hemorrhagic Fever

- Lassa and Tacaribe complex (not LCM)
  - Incubation period is two weeks
  - Malaise and fever over first five days of illness
  - Followed by headache, sore throat, cough, nausea/vomiting/abdominal pain, conjunctivitis
  - Dermatologic features of hemorrhagic fever are petechiae, purpura, ecchymoses and palatal hyperemia
- Lassa virus typically presents with significant edema and not severe hemorrhagic manifestations
- Tacaribe complex usually progress, leading to hemorrhagic complications and death in 15% of hospitalized patients.



# Junin: Argentine Hemorrhagic Fever





# Machupo: Bolivian Hemorrhagic Fever

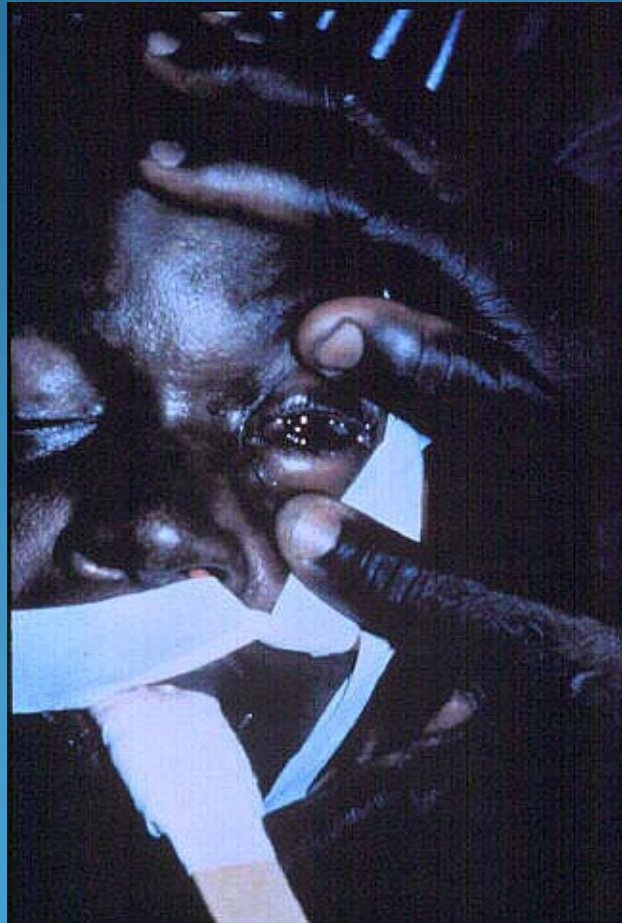


# Lassa Fever Outbreak

## Liberia, 1988



# Lassa Fever

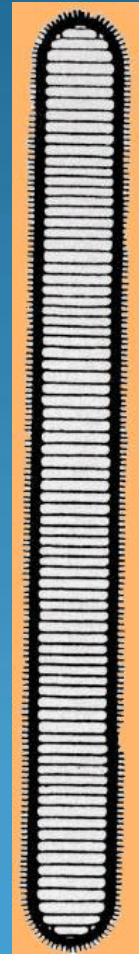


# Arenavirus: Prevention/Treatment

- Rodent control programs
- Vaccines under development
- Isolate hospitalized patients
- Ribavirin has been shown to be effective against only Lassa and Machupo viruses
  - May be used after exposure, or at any point during illness
- Plasma from convalescent patients
  - Does not work for Lassa virus because there are at least seven strains

# Filovirus

- Ebola
  - Zaire
  - Sudan
  - Reston
- Marburg



# Filovirus

- Indigenous to Africa
- Severe hemorrhagic fever
- Marburg Virus
  - isolated in 1967 in Marburg, Germany, from lab workers exposed to blood from African Green Monkeys
  - Sporadic cases in Africa



# Filovirus: Ebola

- Two major outbreaks with 88% mortality in Zaire and Sudan in 1976
- Reston virus found in 1989 in monkeys imported from the Philippines. The monkeys all died, but no humans became ill
- Two infected Cynomolgus monkeys are quarantined in Texas

# Filovirus

- Primary mode of infection is unknown, but secondary spread is via intimate contact among family members or among hospitalized patients
- Unknown natural reservoir, but likely an animal native to Africa (not the monkeys since they also died of hemorrhagic symptoms)



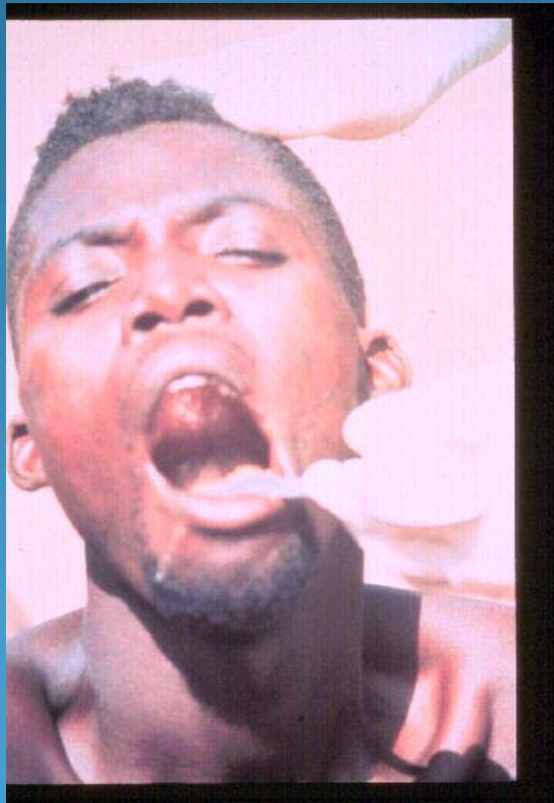
# Filovirus

- Incubation period of 4-15 days, followed by fever, transient rashes, myalgias, etc.
- Characteristic rash
  - First cutaneous sign is an enanthem, consisting of deep erythema of the hard and soft palate
  - Transient pin-head-sized papular exanthem on trunk, buttocks and arms
  - 24 hours later the papules coalesce into patches and plaques, possibly becoming hemorrhagic
  - Desquamation follows

# Filovirus

- Hemorrhagic manifestations
  - Petechiae and ecchymoses of skin and mucous membranes
  - Most commonly bleeding into GI tract, but also lungs, oropharynx, etc
    - Massive gingival bleeding heralds death
    - Patients die of hypovolemic shock
- The earlier the hemorrhagic manifestations, the higher the mortality (30-90%)

# Ebola Fever



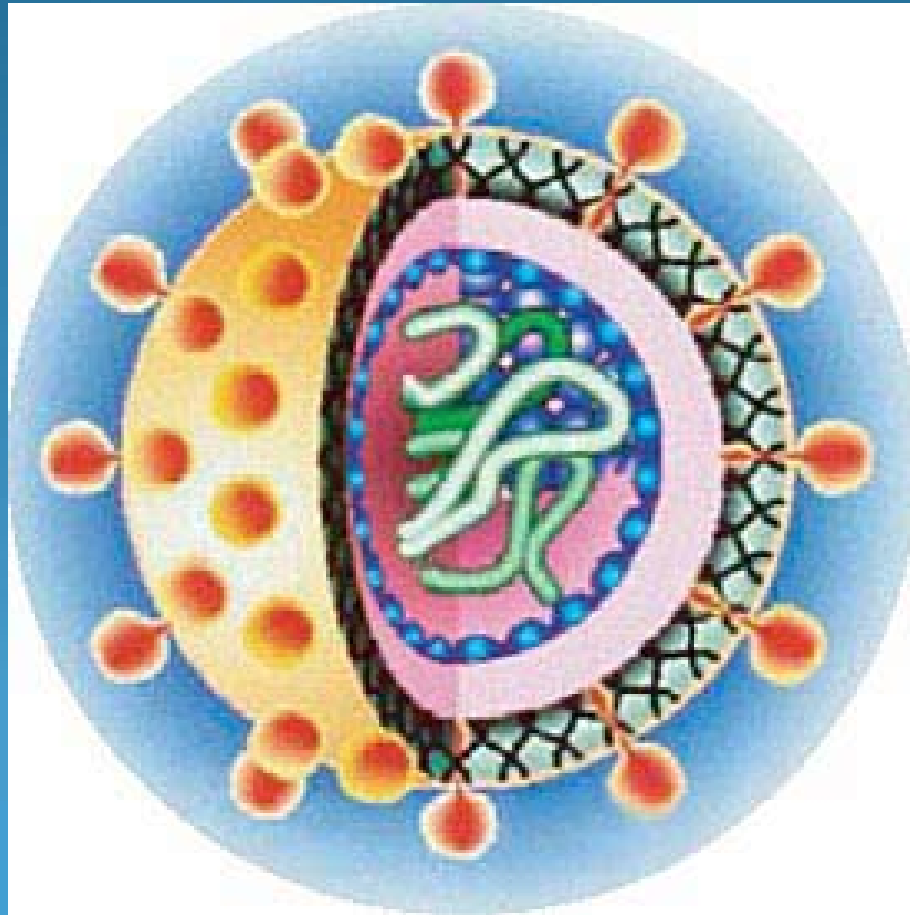
# Ebola



# Filovirus

- No treatment (supportive)
  - Ribavirin does not work
  - Interferon does not work
- No vaccines
- Prevention
  - Stay away from wild monkeys and quarantine them if you catch any
  - Isolate infected patients

# Flavivirus



# Flaviviruses

- Yellow Fever Virus
- Dengue
- West Nile Virus

# Flavivirus

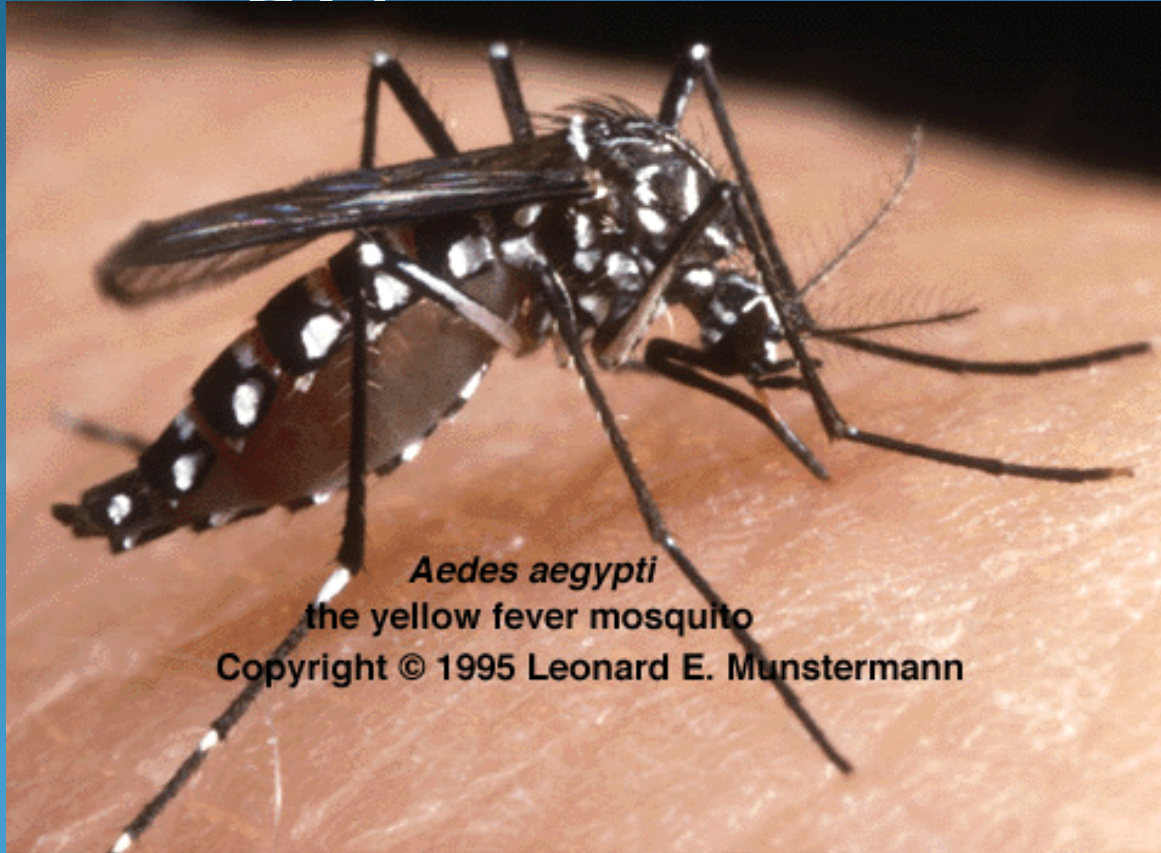
- Constellation
  - Acute febrile illness with arthropathy
  - CNS infection
  - Hemorrhagic fever
- Pathophysiology
  - Virus first replicates in lymph nodes, then spreads to spleen and bone marrow, followed by liver, lung and adrenals



# Dengue and Yellow Fever

- Large epidemics in Africa and the Americas for 400 years
- Mosquito is the vector...which one?
- Mosquito is also the reservoir as it passes infection to its eggs

# *Aedes Aegypti*



*Aedes aegypti*

the yellow fever mosquito

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Pupae of *Aedes aegypti*, the mosquito carrier of dengue virus (CDC).

# Dengue and Yellow Fever

- *Aedes Aegyptii* flourishes in urban and suburban environments, breeding in water storage containers of man-made materials such as plastic, earthenware, metal and concrete.
- A secondary vector, *Aedes albopictus*, emerged in Asia and has spread to the US, Latin America and Caribbean. The spread of this organism has been facilitated by the used-tire trade.

# Dengue: Epidemiology

- Breakbone Fever is not equivalent to Dengue Hemorrhagic Fever (DHF)
- Classically a disease of Asia and Africa, but spreading to the Caribbean, Central and South America
- One hundred million cases of Dengue per year ( $\frac{2}{5}$  of the world's population is at risk)
  - 2001: In Americas: 609,000 total cases; 15,000 DHF.  
In Brazil: 390,000 total cases, 670 DHF

- CDC**  
U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

# Dengue: Classifications

- 4 serotypes accounting for three major types of Dengue
  - Classic dengue
  - Dengue hemorrhagic fever
  - Mild dengue
- Dengue hemorrhagic fever is classified into four grades by the WHO, based on degree of thrombocytopenia, hemoconcentration and hemorrhage

# Classic Dengue Fever

- Febrile syndrome of sudden onset, with diffuse morbilliform pruritic rash that spares palms and soles and later desquamates
- Unlikely to affect children, who more often get DHF
- People new to the area (travelers), usually get classic dengue, while residents are more likely to get DHF



# Classic Dengue



# Dengue Hemorrhagic Fever

- Mostly occurs in children under age 15
- More severe course with 50% mortality
  - Vomiting, circumoral cyanosis, cool clammy extremities, bleeding
- The combination of thrombocytopenia and hemoconcentration is by definition DHF
- A person previously infected by (and thus immune to) one serotype who then becomes inoculated by a different strain is predisposed to DHF

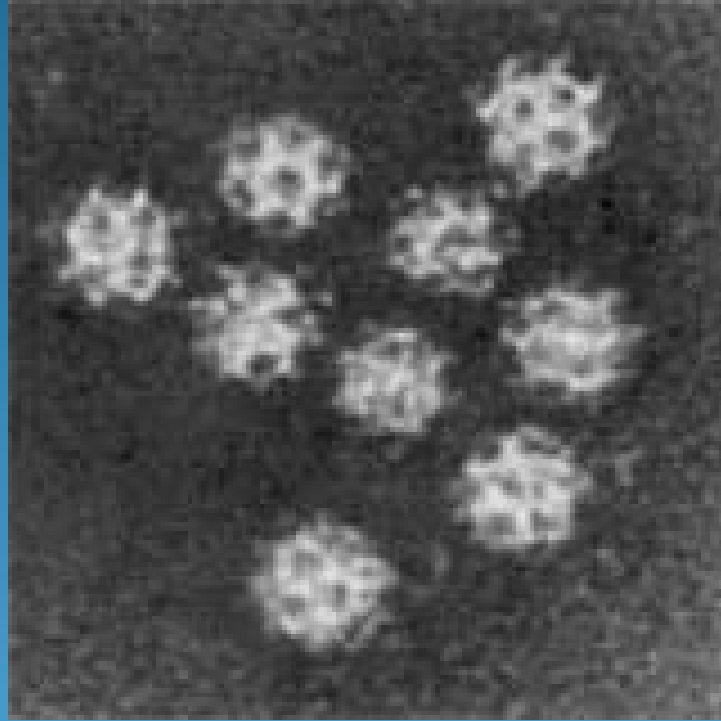
# Dengue Fever



# Dengue Hemorrhagic Fever



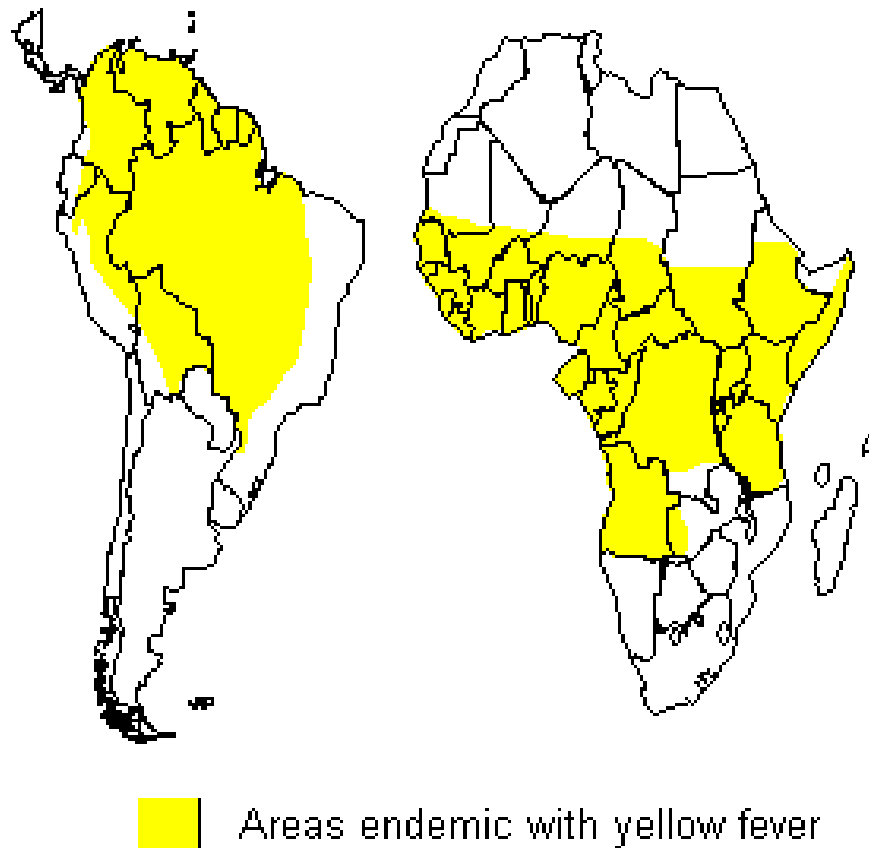
# Yellow Fever



# Yellow Fever: Epidemiology

- Constant low levels of infection in Africa and the Americas, but under the right environmental conditions, may cause major epidemics
- Transmitted by *Aedes* and *Haemogogus*
- Two transmission cycles
  - Sylvatic: mosquitoes bite humans who enter the forest
  - Urban: migrants bring disease to other areas
- Restricted geographic pattern

## Global Distribution of Yellow Fever, 1996



# Yellow Fever

- Flu-like illness
- High fever accompanied by low pulse
- Most cases resolve after four days
- 15% enter a “toxic phase,” with jaundice, severe abdominal pain, and 50% mortality
- Hemorrhage occurs from orifices; “black vomit”
- Hepatic damage leads to bleeding



# Prevention/Treatment:

## Dengue and Yellow Fever

- Control of mosquito vector: improved waste disposal and water storage practices. Insecticides, predatory fish.
- Vaccine for yellow fever is very successful
  - One dose provides ten years of protection
- Vaccine for Dengue challenging due to different strains and increased risk of DHF
- Ribavirin and Interferon in combination of limited benefit

# Yellow Fever Camp



A 1888 photo of a yellow fever detention camp in Florida. Persons traveling from yellow fever areas were required to remain in the camp for the incubation period (6-10 days) before proceeding elsewhere.

# West Nile Virus



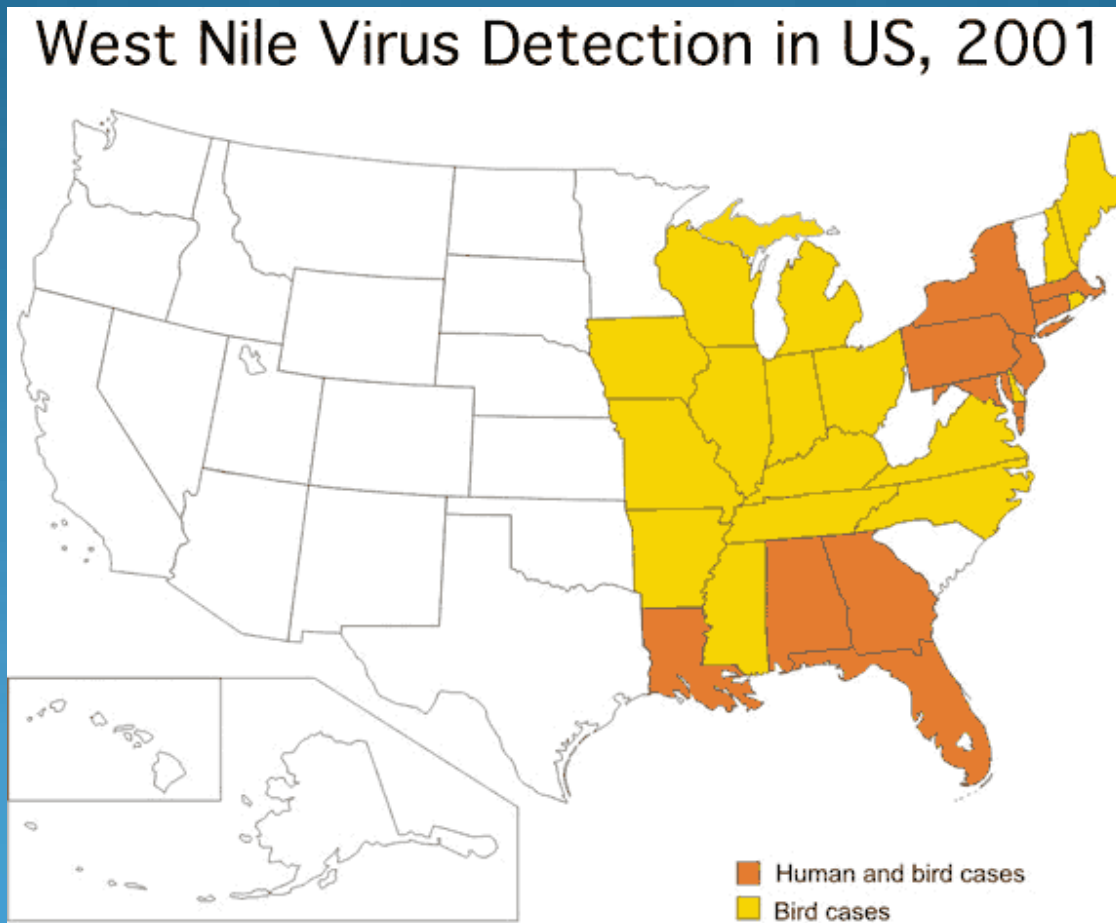
# West Nile Virus

- West Nile Encephalitis
  - Reservoir is birds of the crow family (including the Raven!)
  - Humans are an incidental, dead end host (virus is spread via mosquitoes—which ones?)
  - Endemic in East Africa, appearing in N. America in 1999

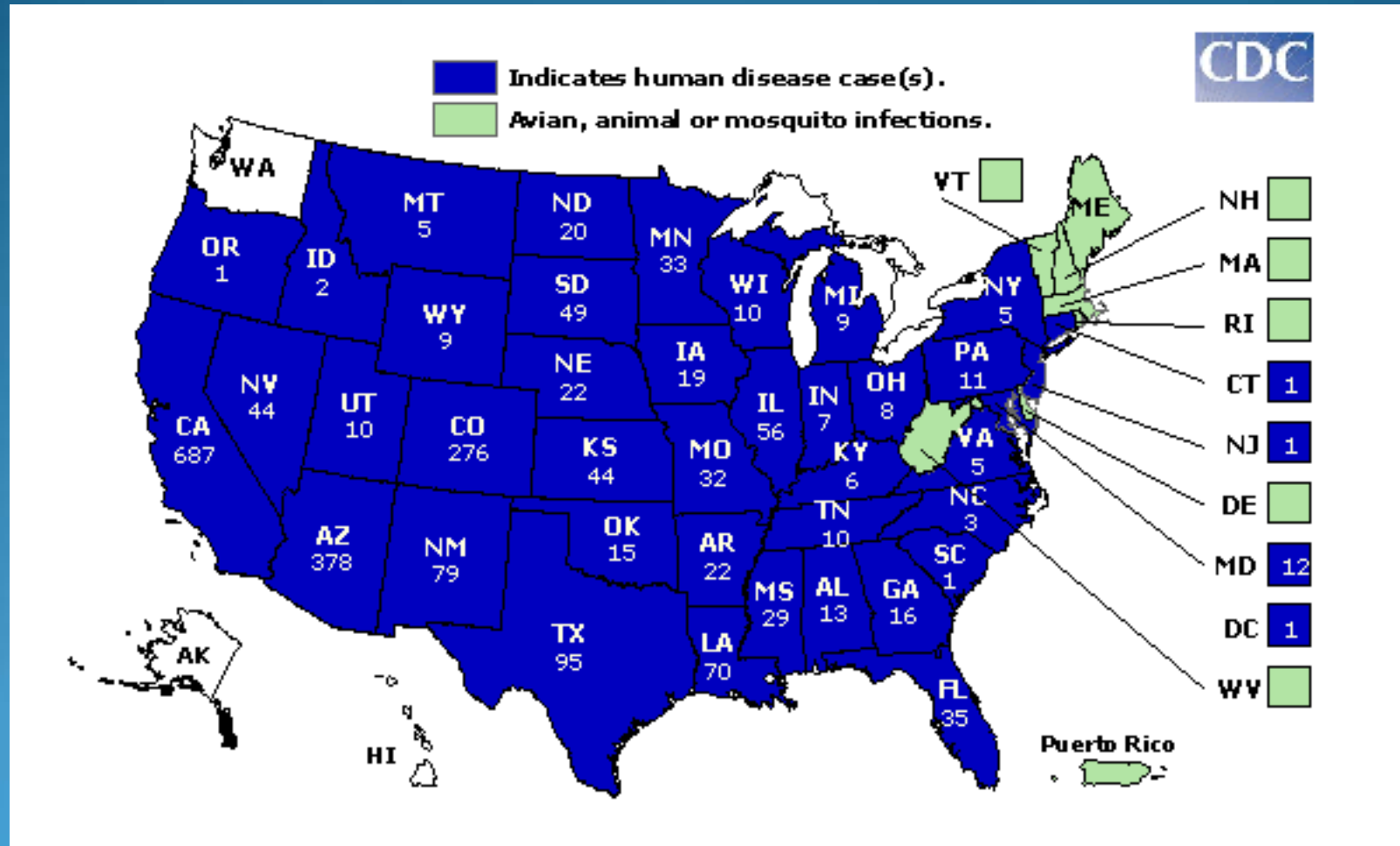
# Culex Mosquitoes: Salinarius and Tarsalis



# West Nile Virus: 2002



# West Nile Virus: 2004



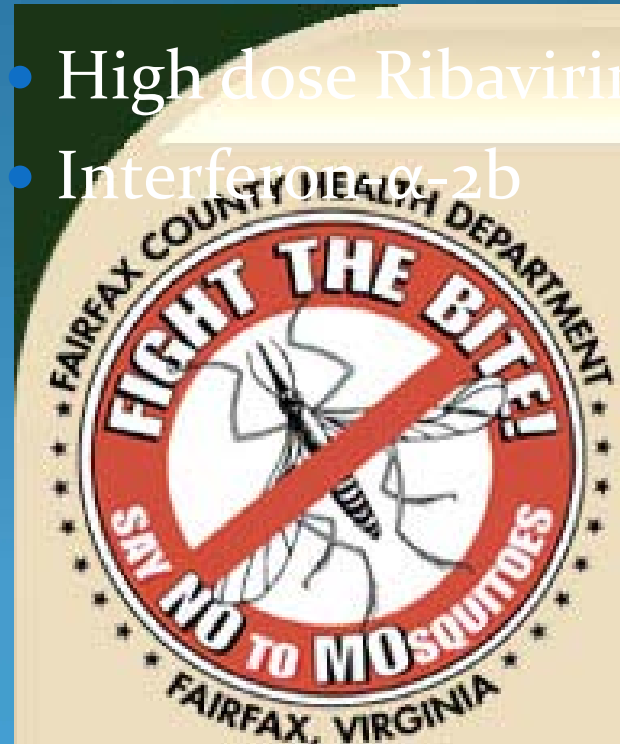
# West Nile Virus

- 80% of infections are asymptomatic
- Most are febrile illness, with non-specific symptoms
  - Incubation period is 3-14 days
  - 20% with maculopapular rash
- <1% develop severe disease
  - Ataxia, extrapyramidal signs, myelitis, seizures, optic neuritis, flaccid paralysis



# West Nile Virus: Prevention and Treatment

- Prevention
- Treatment
  - High dose Ribavirin
  - Interferon  $\alpha$ -2b



# Yellow Fever



# Bunyavirus



# Bunyavirus

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

# Crimean-Congo Hemorrhagic Virus

- Endemic in Africa, Europe and Asia
- First described in Crimea in 1944, then in Congo in 1956, followed by outbreaks (in Kosovo, Albania, Iran, Pakistan, S. Africa)
- Animal infection is common (domestic and wild), high mortality in humans
- Vector is tick of *Hyalomma* genus, but also may be transmitted through contact with infected blood or tissues from livestock

# *Hyalomma* Tick



# Crimean-Congo Hemorrhagic Fever

- 6 day incubation period, followed by typical symptoms
- May become aggressive with sharp mood swings, which evolves into depression and sleepiness
- Pulmonary and hepatorenal failure
- Petechial rash involving mucous membranes and skin
- Mortality is 30%

# Crimean-Congo Hemorrhagic Fever





# Crimean-Congo Hemorrhagic Fever



# Rift Valley Fever

- Isolated in 1930 in Kenya, now widespread in Africa and Egypt
- Major epidemics in 2000 in Yemen and Saudi Arabia (21% mortality)
- Epizootic cycle
  - After heavy rainfall, virus circulates among cattle and mosquitoes
- Interepizootic cycle
  - Virus persists in eggs of mosquitoes in floodwater

# Rift Valley Fever

- Vectors are *Aedes* and *Culex*
- Studies suggest that if transmitted to N. America, many of our mosquitoes would transmit it
- In animals, major manifestation is fetal loss
- Relative to CCHF, benign course in humans, with hemorrhagic fever in <1%, severe eye disease in <2%

# Rift Valley, Kenya



# CCHF and RVF: Treatment

- Ribavirin may benefit
- Plasma little help
- No Vaccine
- Isolation of hospitalized patients

# Hantavirus

- Worldwide distribution
- At least nine different viruses
  - Hemorrhagic fever with renal syndrome (HFRS), or Korean Hemorrhagic Fever, identified during Korean war near the Hantaan River
  - Hantavirus pulmonary syndrome (HPS) struck Navajo Indians in 1993
- Transmitted by aerosols of rodent excreta
- Ribavirin effective against HFRS but not HPS

# Hantavirus

- Two seasonal peaks
  - Small in spring, corresponding to farmer exposure to rodents during planting season
  - Large in fall, corresponding to harvest season as well as cool weather driving rodents into homes

# Hantavirus

- Hemorrhagic Fever Renal Syndrome
  - Incubation period 1-6 weeks
  - Non-specific symptoms followed by flushing of face and petechial rash
  - Severe albuminuria
  - Hemorrhagic symptoms
- Hantavirus Pulmonary Syndrome
  - Respiratory Failure, skin largely unaffected
  - Mortality 40-50%



# Korean Hemorrhagic Fever

## “sunburn flush”



# *Apodemus agrarius*: Vector of Korean Hemorrhagic Fever





*Peromyscus maniculatus*:  
Vector of Sin Nombre Virus

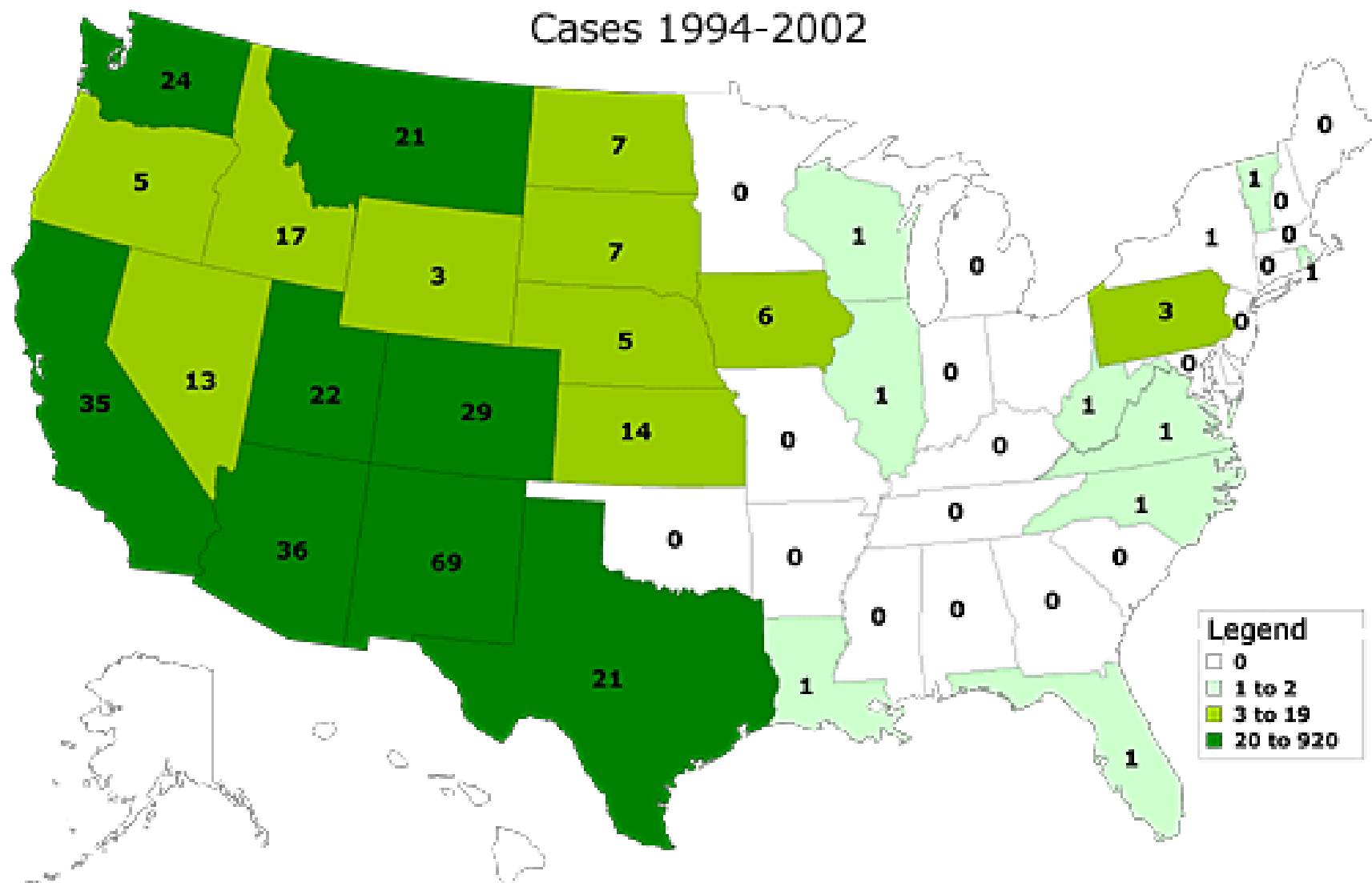


# *Peromyscus Maniculatus*

- Primary reservoir of Sin Nombre Virus, cause of Hantavirus Pulmonary Syndrome
- Very adaptable: live in and around homes
- Have spread from Four Corners Region to 31 US states

# Hantavirus

## Cases 1994-2002



# DNA Viruses

- Poxviruses
  - Monkeypox
- Herpesviruses
  - Herpesvirus Simiae

# Monkeypox

- Orthopoxvirus in rain forests of Africa
- Syndrome similar to smallpox: pustular rash, fever, respiratory symptoms
- Transmitted from squirrels and primates via contact with blood or bite
- Outbreaks in Africa are lasting longer, as person-to-person transmission is becoming more successful

# Monkeypox

- June 2003, monkeypox was reported in Wisconsin, Illinois and Indiana. These cases were contracted from pet prairie dogs, which had been caged in pet stores next to Gambian rats from Africa
- Good survival due to rapid diagnosis and good nutrition



# Sun Squirrel



# Prairie Dog



# Monkeypox

- Vaccination against small pox also gave protection against monkeypox
- End of vaccinations in 1970 could explain the increase in size of outbreaks
- Treatment of monkeypox includes small pox vaccination within 14 days of exposure, and Cidofovir

# Monkeypox



# Monkeypox



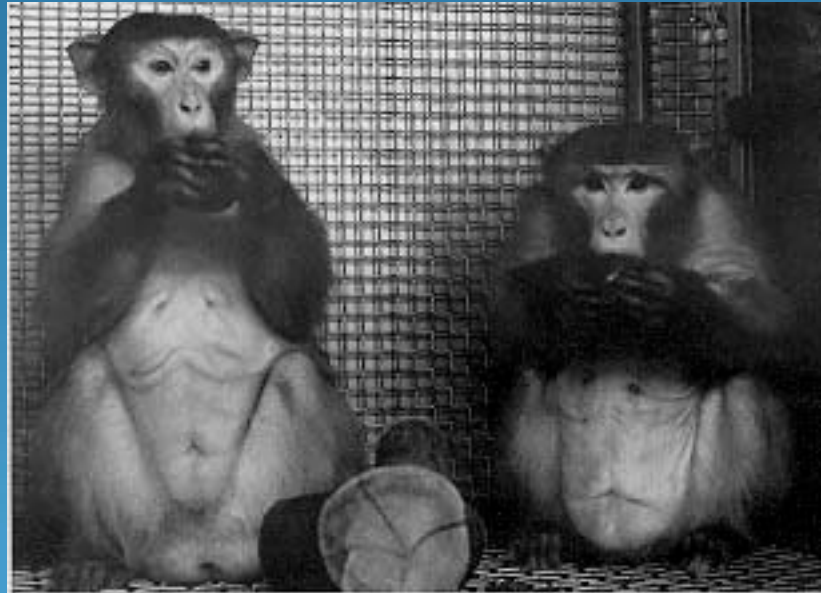
# Monkeypox



# Herpesvirus Simiae (Herpes B Virus)

- Enzootic to monkeys of *Macaca* genus used in biomedical research: rhesus, cynomolgus
- Present in 73-100% of captive adult monkeys
- Similar to HSV in humans, with lifelong infection and viral shedding in secretions during stress and illness

# Macaques: not good pets





# Herpes B

- Infection in humans due to macaque scratches or bites, mostly in lab workers
  - vesicular lesions at site of inoculation
  - may lead to encephalitis and death (rare)
  - One case of human-to-human transmission
  - Acyclovir may prevent progression of disease
- However, 48 cases of non-occupational macaque bites in US. Free ranging macaques in tourist destinations, as well as populations in Texas and Florida