Emerging viruses

Lecture 22

Biology 3310/4310

Virology

Spring 2017

Nothing endures but change
HERACLITUS

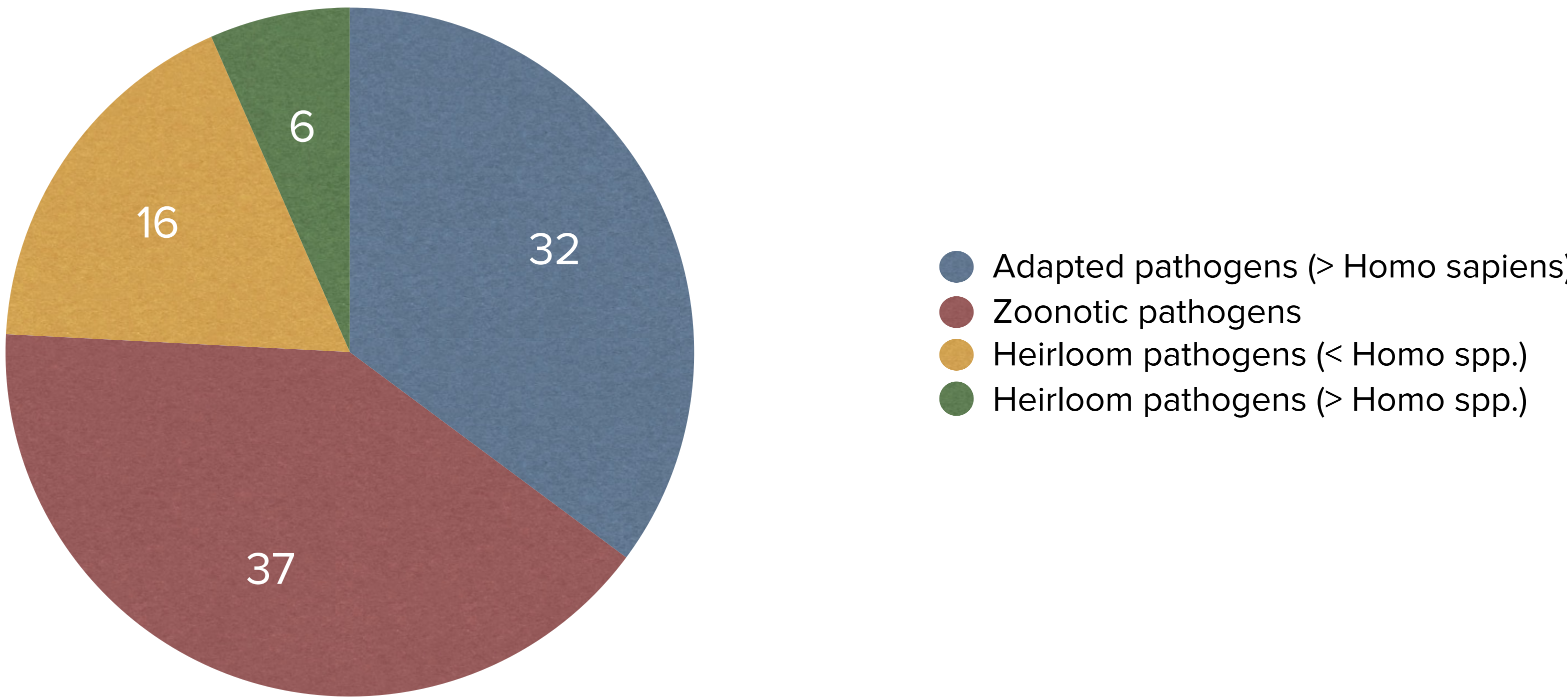
Emerging viruses

- *Emerging virus* - causative agent of a new or previously unrecognized infection
- The term became popular in 1990s, but emerging viruses are not new
- Since the rise of agriculture - 11,000 years ago - new infectious agents have invaded human populations because they can be sustained by numbers that were unknown before agriculture and commerce
- Only recently have we become good at detecting emerging viruses

Emerging viruses

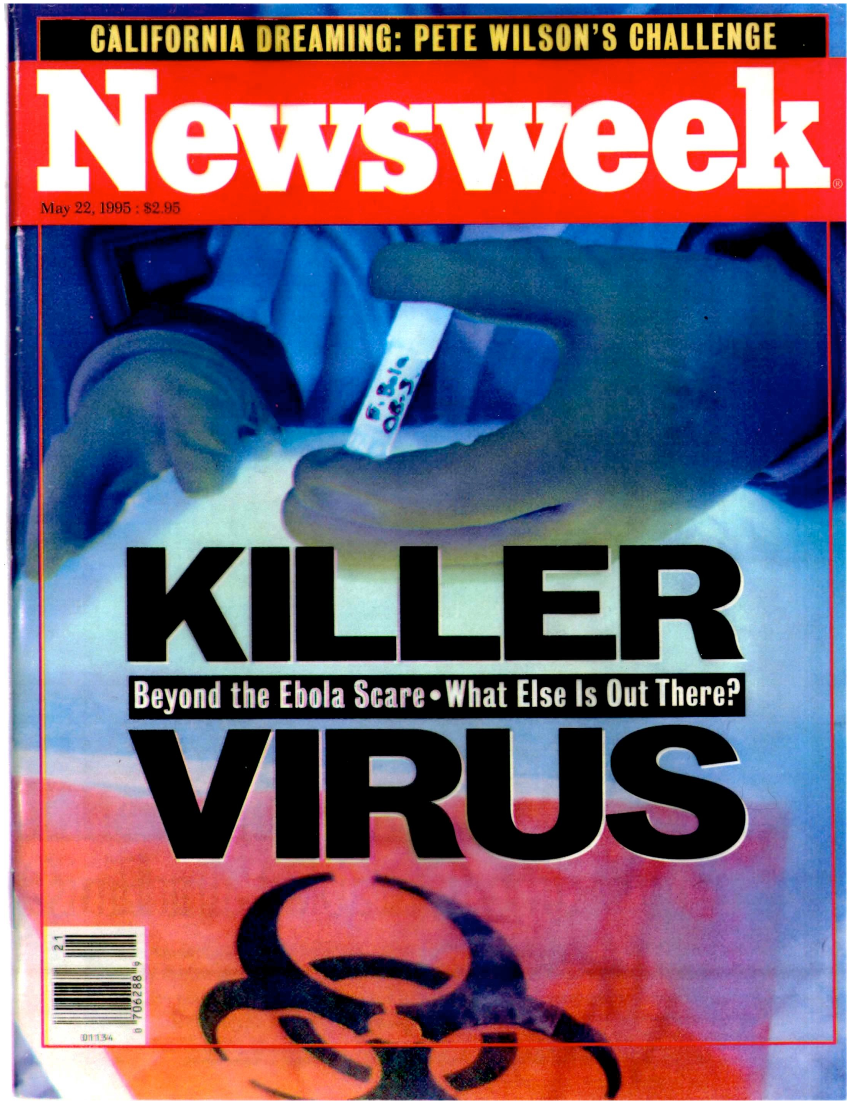
- Expanded host range with an increase in disease not previously obvious
- Transmission of a virus from a wild or domesticated animal to humans - *zoonosis*
- Cross-species infection may establish a new virus in the population (SIV moving from chimps to humans)
- Often cross-species infection cannot be sustained (e.g. Ebola and Marburg from bats to humans)

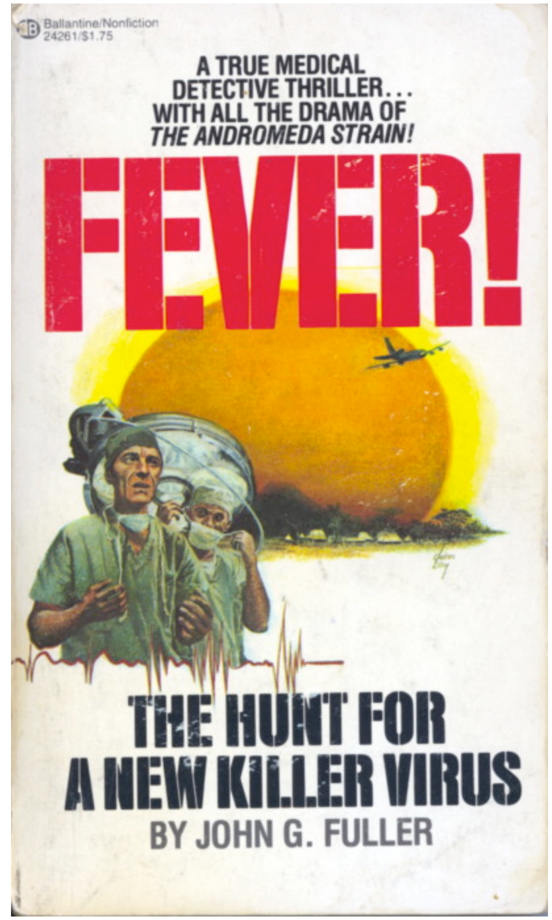
Human - animal interface



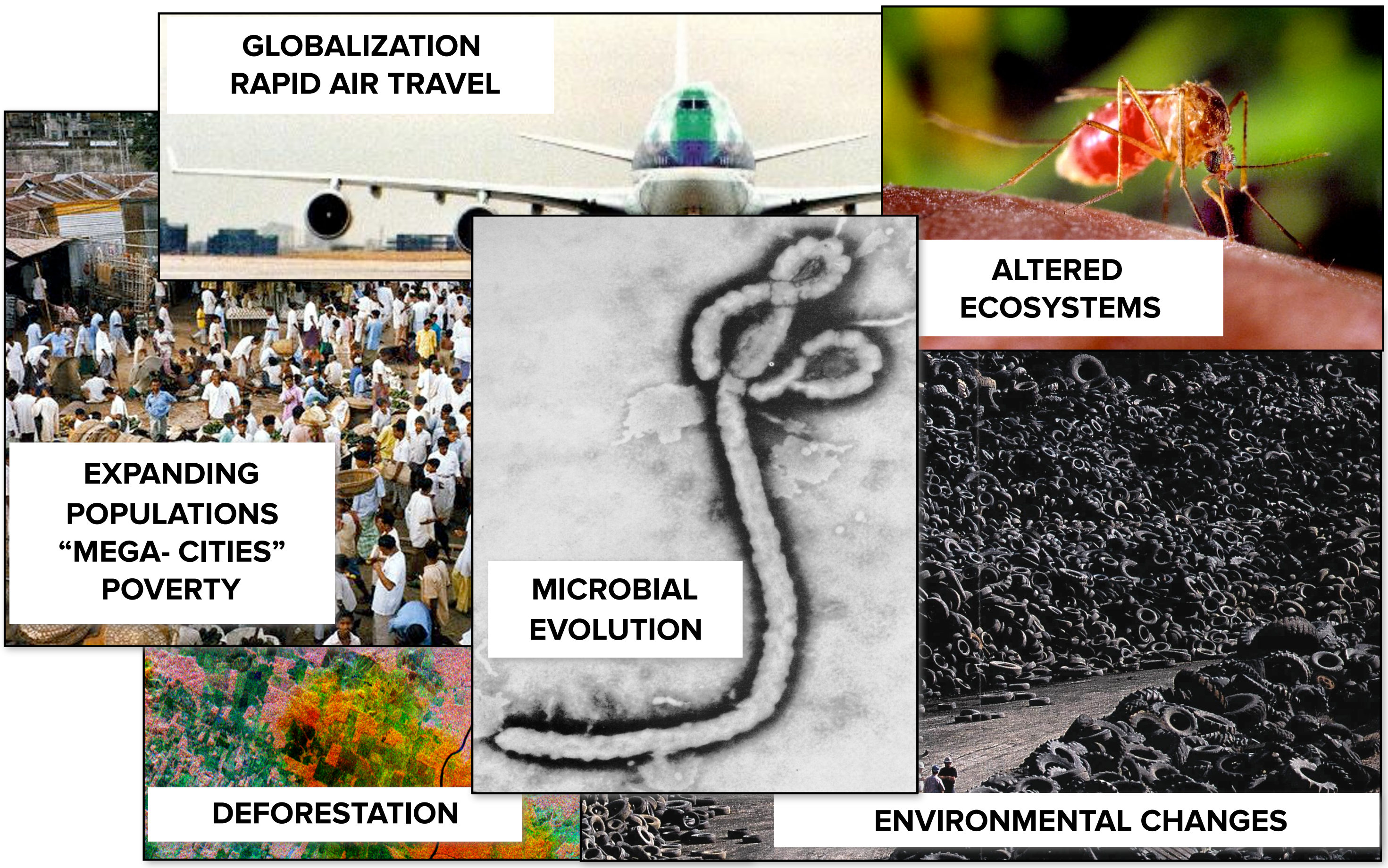
Viruses belonging to # of genera

One Health, ASM Press


CALIFORNIA DREAMING: PETE WILSON'S CHALLENGE
Newsweek
May 22, 1995 : $2.95
KILLER
Beyond the Ebola Scare • What Else Is Out There?
VIRUS

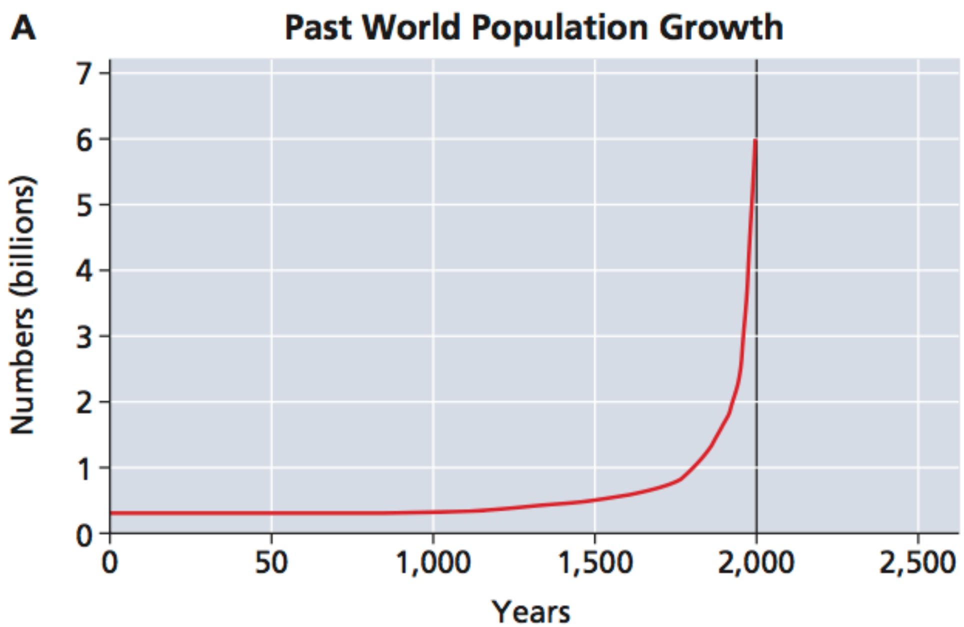

Ballantine/Nonfiction
24261/$1.75
A TRUE MEDICAL DETECTIVE THRILLER . . . WITH ALL THE DRAMA OF THE ANDROMEDA STRAIN!
FEVER!
THE HUNT FOR A NEW KILLER VIRUS
BY JOHN G. FULLER

Convergent forces of disease emergence



Over-riding factors driving the emergence of infectious diseases of humans and animals:

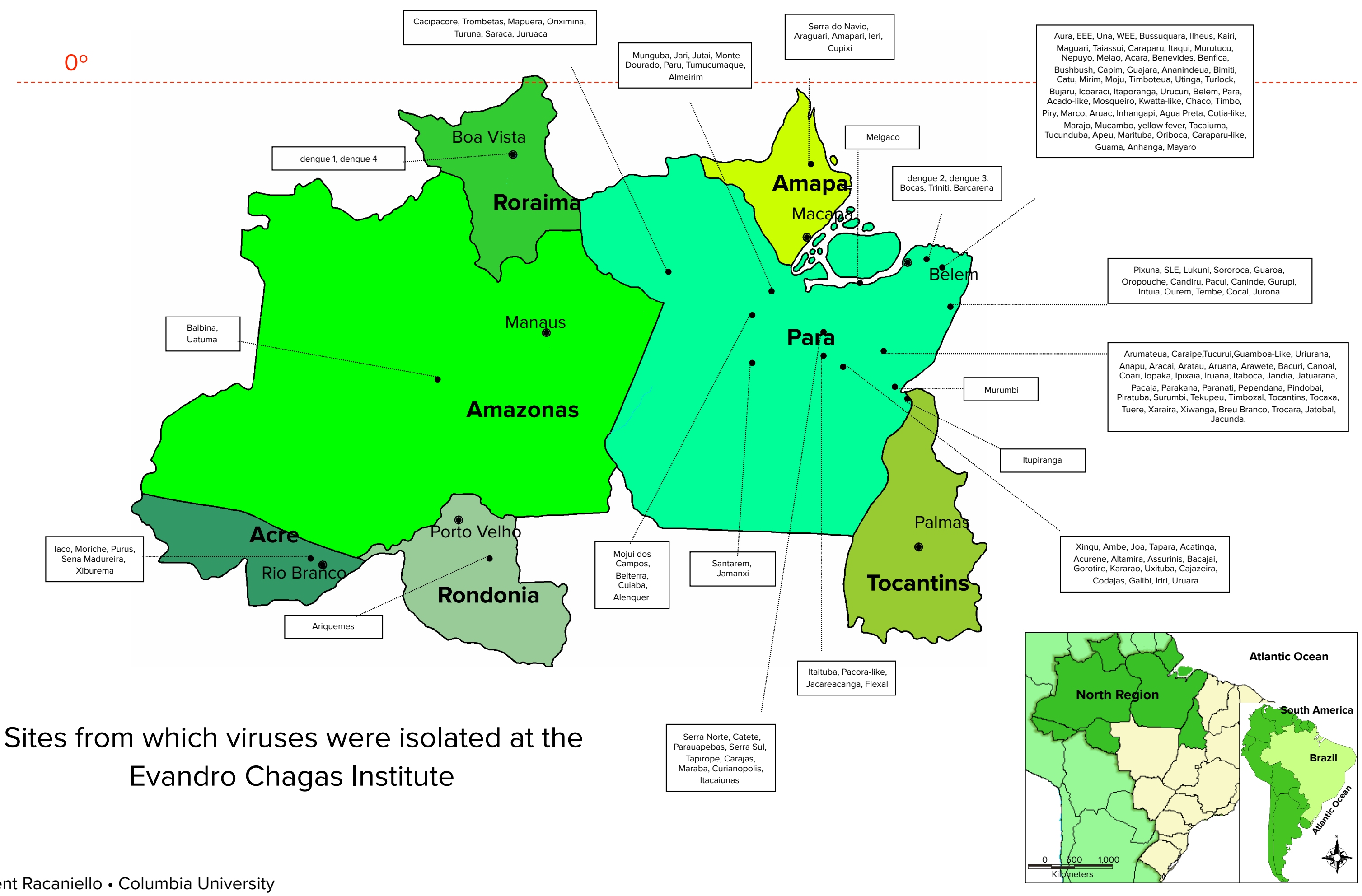
Human population growth and incredible change occurring in all ecosystems brought about by human occupation of almost every corner of the planet



Principles of Virology, ASM Press

The Amazon North Region of Brazil

Home to 183 Arthropod-borne and Other Vertebrate Viruses



Sites from which viruses were isolated at the Evandro Chagas Institute

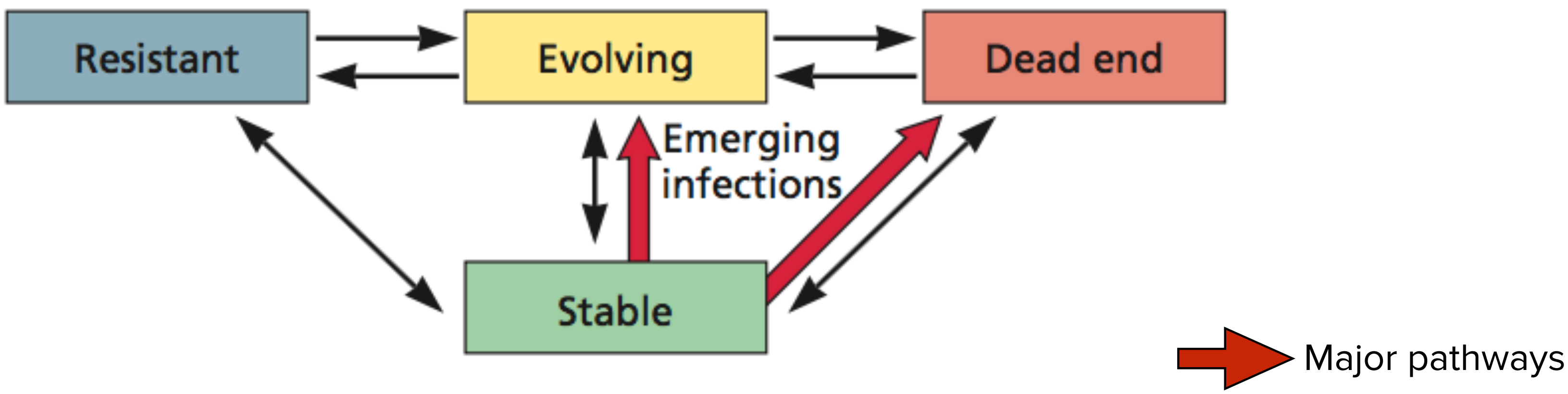
Virus	Family	Drivers of Emergence
Dengue virus	*Flaviviridae*	Urban population density, mosquito breeding
Ebolavirus	*Filoviridae*	Human contact with natural host; bushmeat
Hantaan virus	*Bunyaviridae*	Agriculture: human/rodent contact
Hendra virus	*Paramyxoviridae*	Bats to horses to stable workers
HIV	*Retroviridae*	Bushmeat trade
Influenza virus	*Orthomyxoviridae*	Pig/bird agriculture
Junin virus	*Arenaviridae*	Agriculture: human/rodent contact
Nipah virus	*Paramyxoviridae*	Bats to pigs to humans
Machupo virus	*Arenaviridae*	Agriculture: human/rodent contact
Rift Valley virus	*Bunyaviridae*	Dams, irrigation
Sin Nombre virus	*Bunyaviridae*	Weather, human/rodent contact
West Nile virus	*Flaviviridae*	Mosquito

Principles of Virology, ASM Press

Roles of Evolution

- Leads to the biodiversity of pathogens existing in nature (*quasispecies*)
- Adaptation to new hosts and environments (through variation and selection)

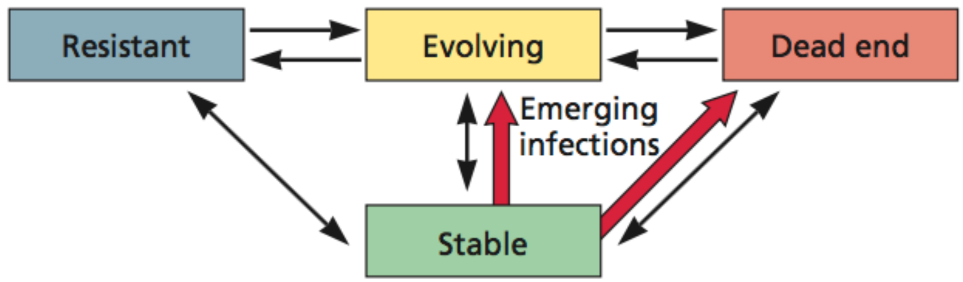
The general interactions of hosts and viruses



- Stable: maintains virus in ecosystem
- Evolving: passage of virus to naive population (same or different host)
- Dead-end: one way passage to different species
- Resistant host: infection blocked

Principles of Virology, ASM Press

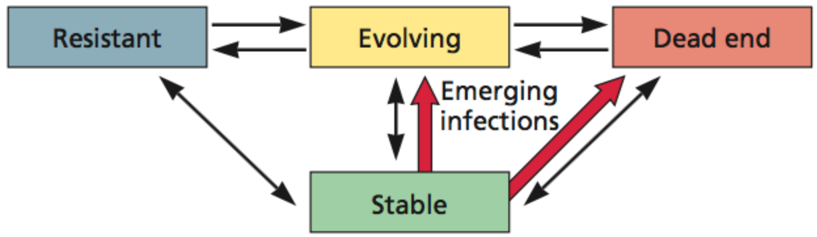
Stable host-virus interactions



- Both participants survive and multiply
- Some are effectively permanent
  - *Humans are sole natural host for measles virus, herpes simplex virus, HCMV, smallpox*
- May include infection of more than one species
  - *Influenza A virus, flaviviruses, togaviruses*

Principles of Virology, ASM Press

Evolving host-virus relationship



- Hallmarks are instability and unpredictability
- Outcome of infection may range from benign to death
  - Introduction of smallpox and measles to natives of Americas by Old World colonists and slave traders
  - Introduction of West Nile virus into Western Hemisphere, 1999
  - Introduction of rabbits into Australia

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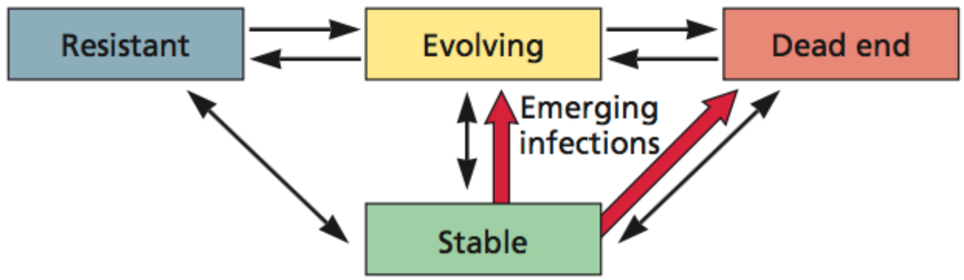
Dead-end interaction

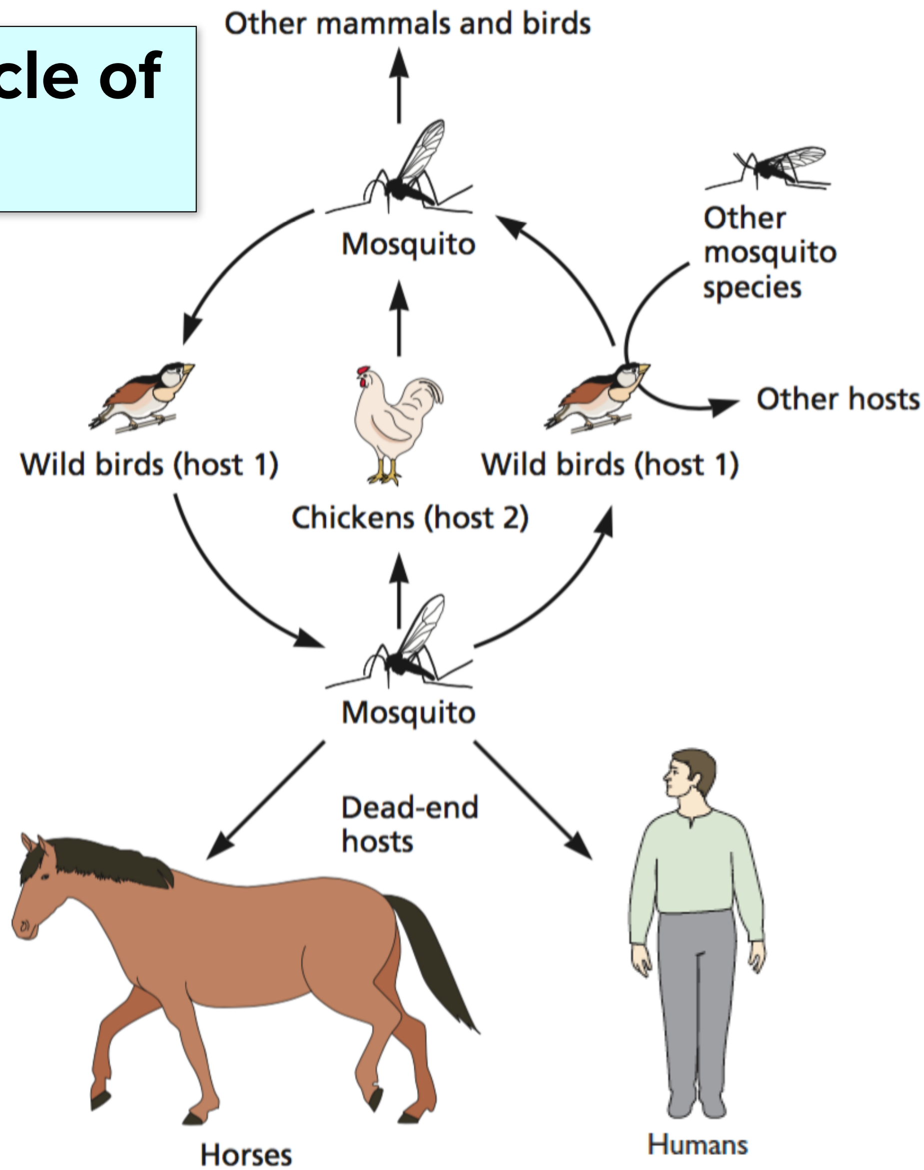


- Frequent outcome of cross-species infection
- No sustained transmission from new infected host to others of the same species
- Ebolavirus: humans, chimps, gorillas
- H5N1
- Contribute little to the spread of a natural infection

Principles of Virology, ASM Press

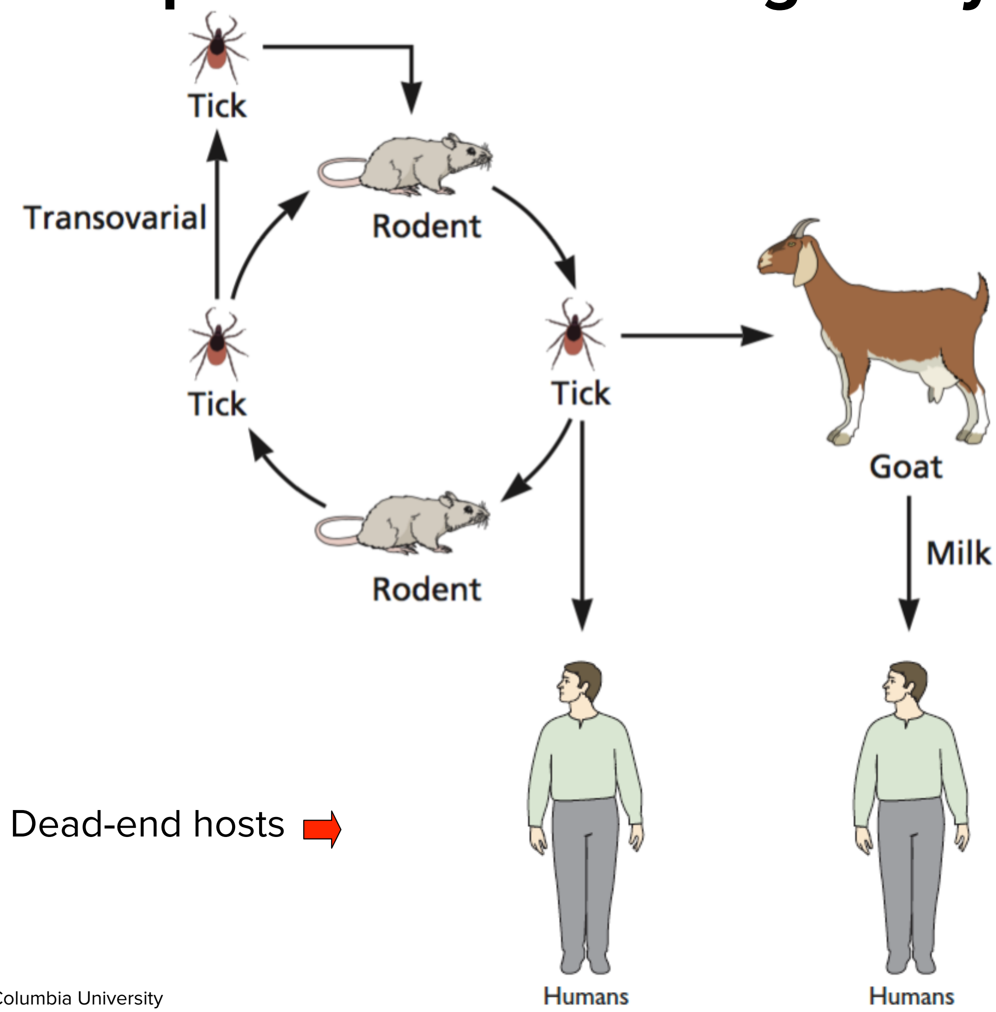
The complex life cycle of an arbovirus

Stable host-virus interactions



Principles of Virology, ASM Press

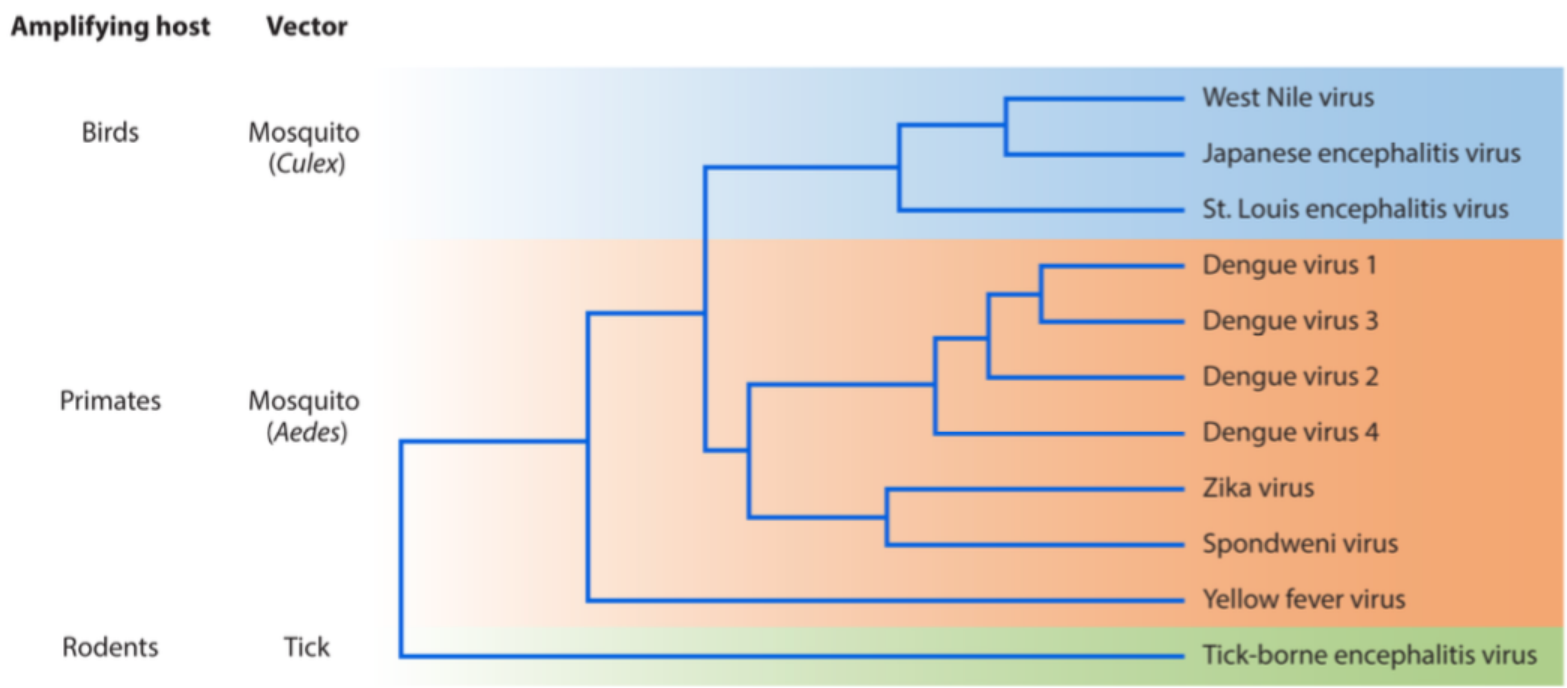
Rodents and insect vectors move European tick-borne encephalitis virus among many hosts



Dead-end hosts

Principles of Virology, ASM Press

Flaviviruses: Human pathogens



Emerging infections: Two steps

- Introduction
- Establishment and dissemination

Human are constantly providing new ways to meet viruses

Dams and water impoundments

Irrigation

Massive deforestation

Rerouting of wildlife migration patterns

Wildlife parks

Long distance transport of livestock and birds

Air travel

Uncontrolled urbanization

Day care centers

Hot tubs

Air conditioning

Millions of used tires

Blood transfusion

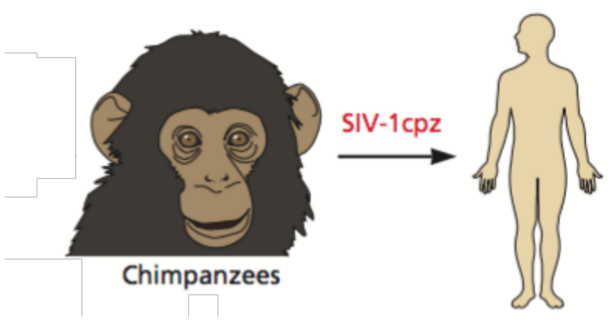
Xenotransplantation

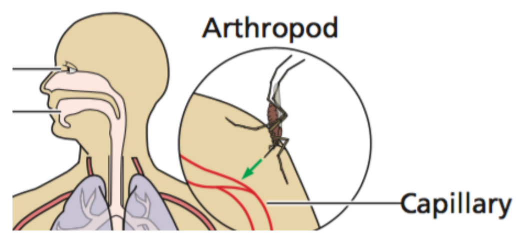
Societal changes with regard to drug abuse and sex

Principles of Virology, ASM Press

Encountering new hosts

- Rare chance encounters of viruses with new hosts may never be detected
- Single-host infections are not transmitted among humans for many reasons





horses, pigs, chickens

Principles of Virology, ASM Press

Expanding viral niches

- Successful encounters require access to susceptible and permissive cells
- Population density and health are important factors
- Virus populations will endure in nature only because of *serial infections* (a chain of transmission)

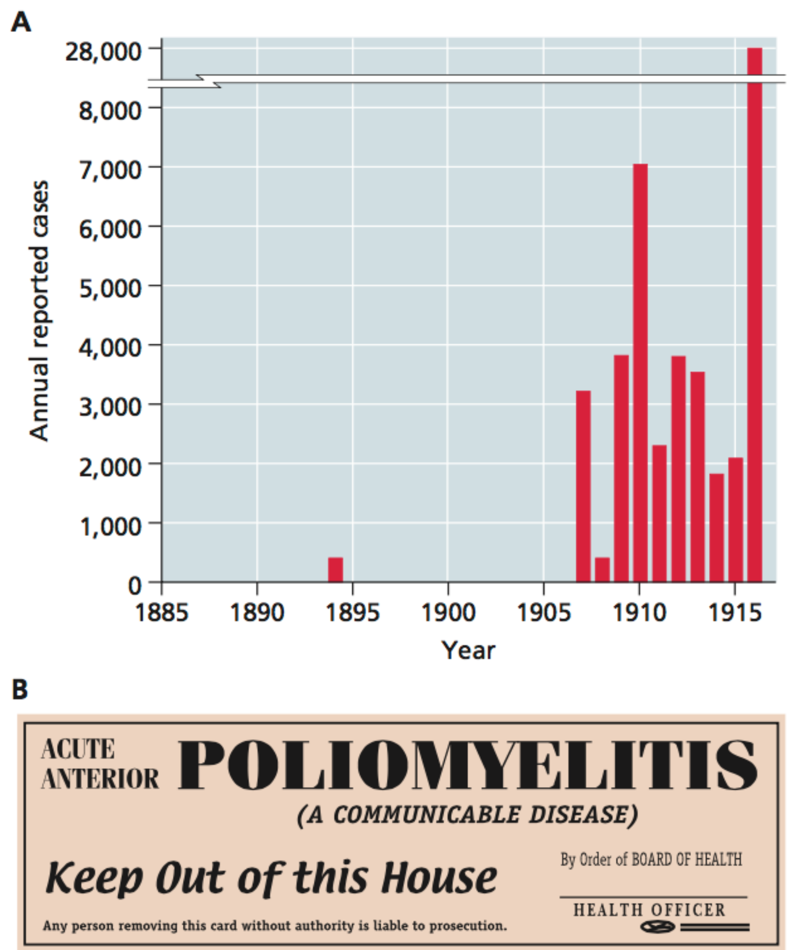
Diseases of exploration and colonization

- Explosive epidemic spread may occur when a virus enters a naive population
- Smallpox reached Europe from the Far East in 710 AD, attained epidemic proportions
- Smallpox changed the balance of human populations in the New World - killed 3.5 million Aztecs in 2 years (1520 - spread from Hispaniola), allowing conquest by Cortez

Changes in human populations and environments

- Emergence of epidemic poliomyelitis in the beginning of the 20th century: improved sanitation delayed transmission
- Known since 4,000 years ago, stable host-virus relationship

Poliomyelitis: A disease of modern sanitation



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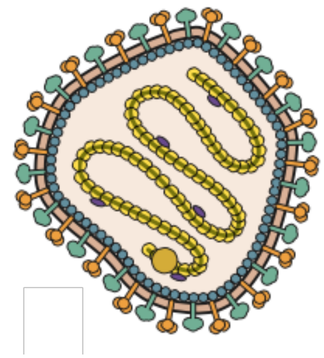
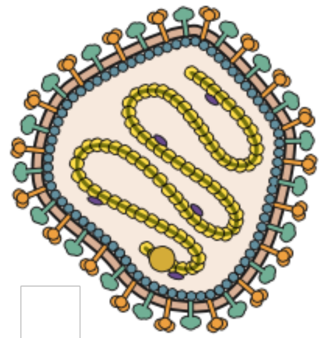
Bats: A source of zoonotic infections



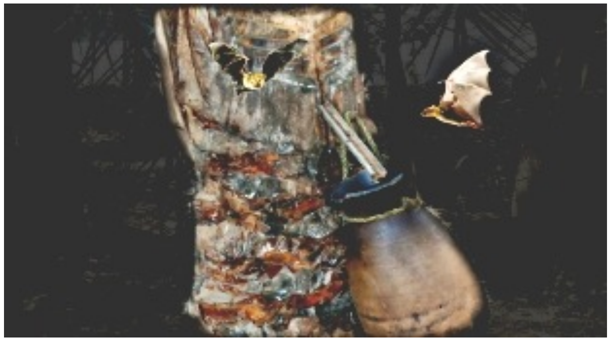
- Many new paramyxoviruses found in flying foxes since 1995, including Nipah and Hendra viruses
- Cause severe disease in domestic animals (horses and pigs) and infect humans

Principles of Virology, ASM Press

Nipah virus

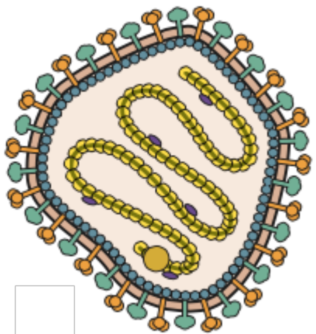


- First outbreak Malaysia 1998
  - *Outbreak of respiratory and neurological disease on pig farms*
  - *105 human deaths, 1 million pigs culled*

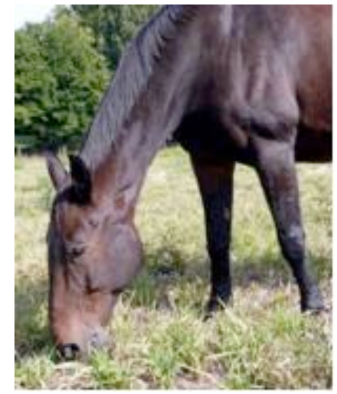


- Fruit bats are unaffected, excrete virus in urine
- Pig farmers plant mangoes near pigpens
- Pigs spread infection to humans
- Subsequently humans infected by consuming date palm sap contaminated by bats (India, Bangladesh)
- Human to human transmission; infections continue

Principles of Virology, ASM Press



Hendra virus

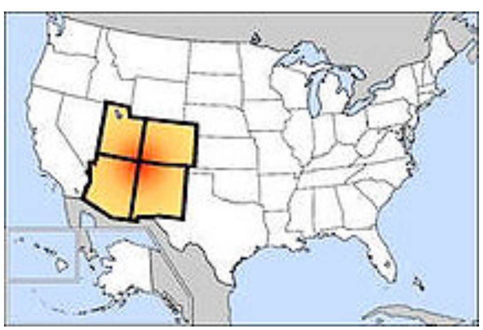


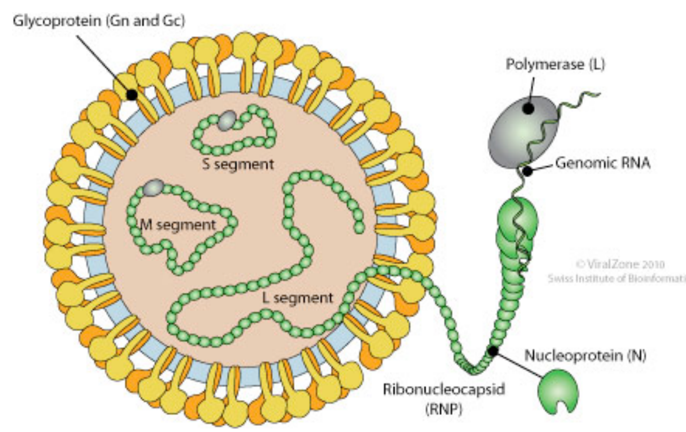
- Discovered in Hendra, Australia, September 1994
  - *Outbreak killed 14 racehorses and a trainer*
- Spread from flying foxes to horses, then to humans
- Horses continue to acquire infection
- Vaccine for horses: One World health

Principles of Virology, ASM Press

Changing climate and animal populations

- Hantavirus pulmonary syndrome - first noted in Four Corners area of New Mexico, 1993
- Disease is caused by Sin Nombre virus, endemic in the deer mouse (*Peromyscus maniculatus,* 30% virus positive)
- Originally called Muerto Canyon virus, but residents objected

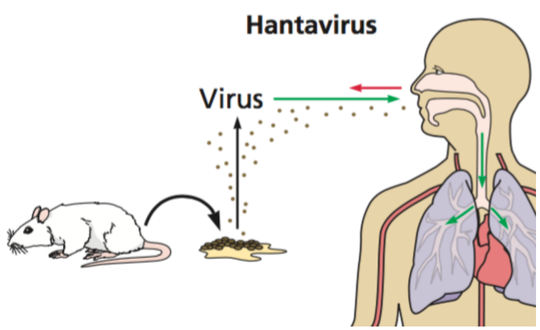




Bunyaviridae

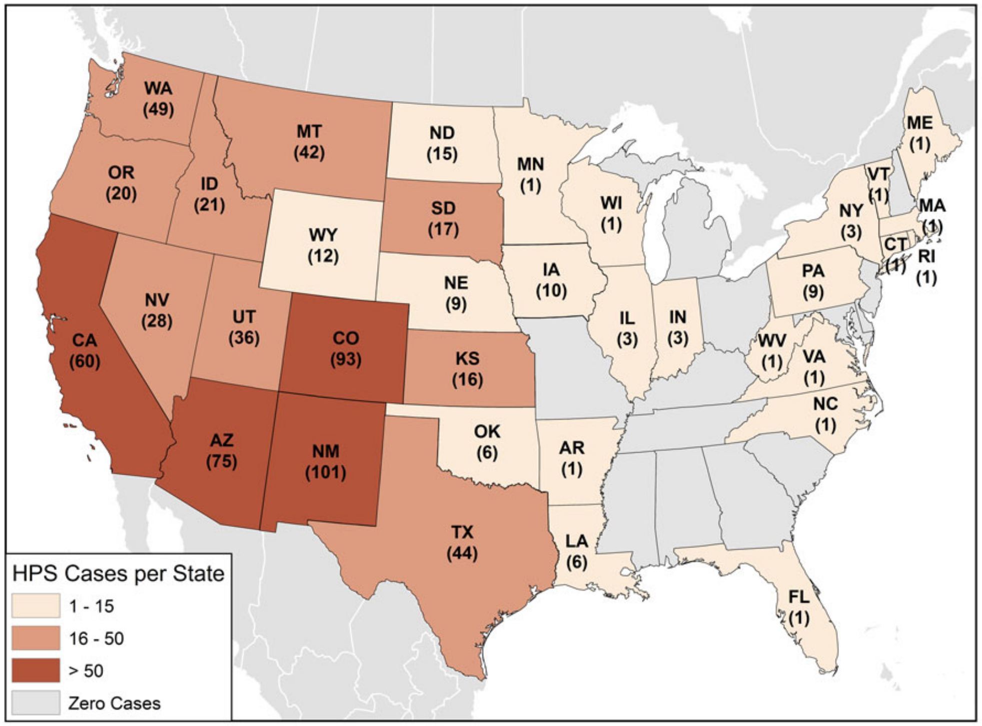
Changing climate and animal populations

- In 1992-93, abundant rainfall produced a large crop of piñon nuts, food for humans and the deer mouse. Mouse population rose, contact with humans increased.
- Virus is excreted in mouse feces; contaminated blankets or dust from floors provided opportunities for human infection
- Humans not the natural host for Sin Nombre virus, human disease is rare
- Not new - earliest known case 1959



Principles of Virology, ASM Press

HPS by State, January 2016
n=690



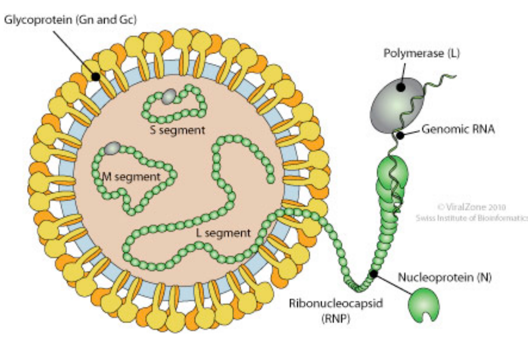
https://www.cdc.gov/hantavirus/surveillance/reporting-state.html

Range of *P. maniculatus*

Deer mouse, white-footed mouse, rice rat, cotton rat

Heartland virus disease

- 2012 - new phlebovirus identified in two farmers in Missouri
- Six subsequent cases identified, tick vector?
- How long had it been infecting people?

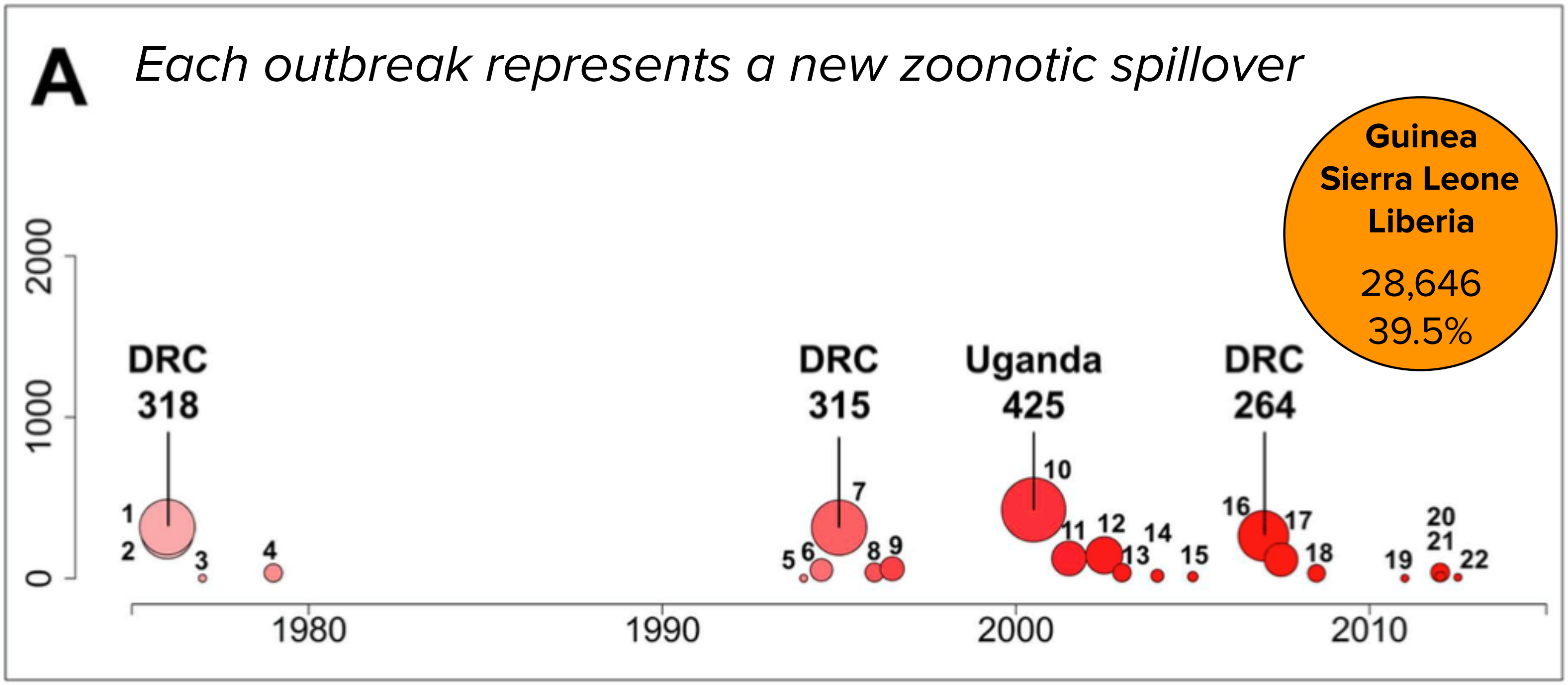


Bunyaviridae

Ebola hemorrhagic fever

- Simultaneous outbreaks in 1976 in DRC (318, 88%) and Sudan (284, 53%)
- Sudan index case: cotton factory workers
- Spread by use of contaminated needles, among family members
- Named after small river in northwestern DRC

Outbreaks of Ebolavirus disease

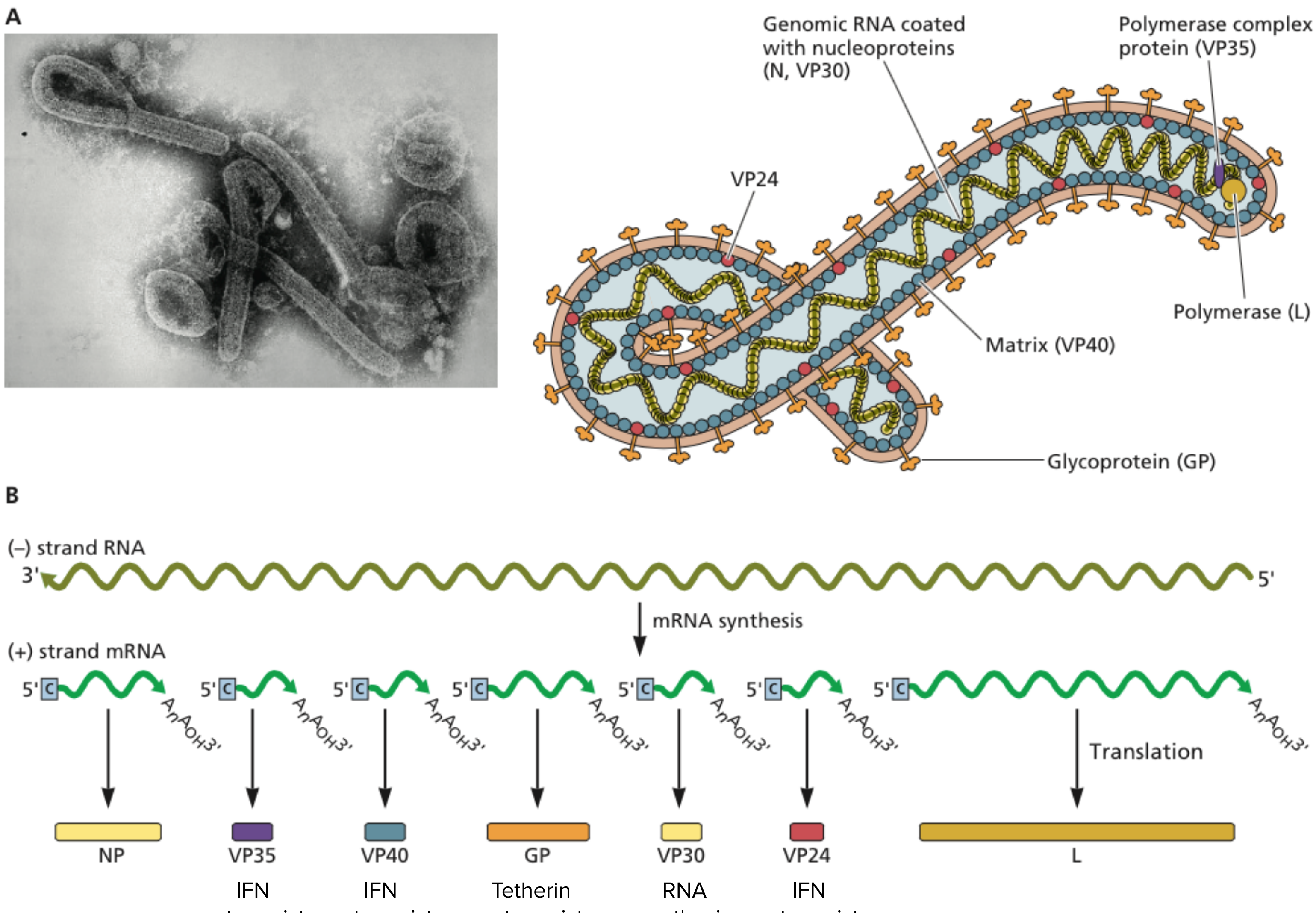


Pigott *et al.* eLife 2014;3:e04395. DOI: 10.7554/eLife.04395

Biosafety level 4 (BSL-4)

- High mortality
- Person to person transmission
- No approved vaccine or antiviral

Threading the NEIDL https://youtu.be/tqAjkjGq8Ug



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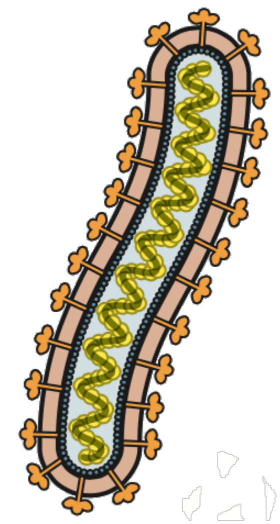
How are humans infected?



- A classic zoonosis
- Index case: contact with animal carcass* (bushmeat)
- Transmitted to other humans by close contact with infected fluids
- Chains of human infections short
- $R_0 = 2$

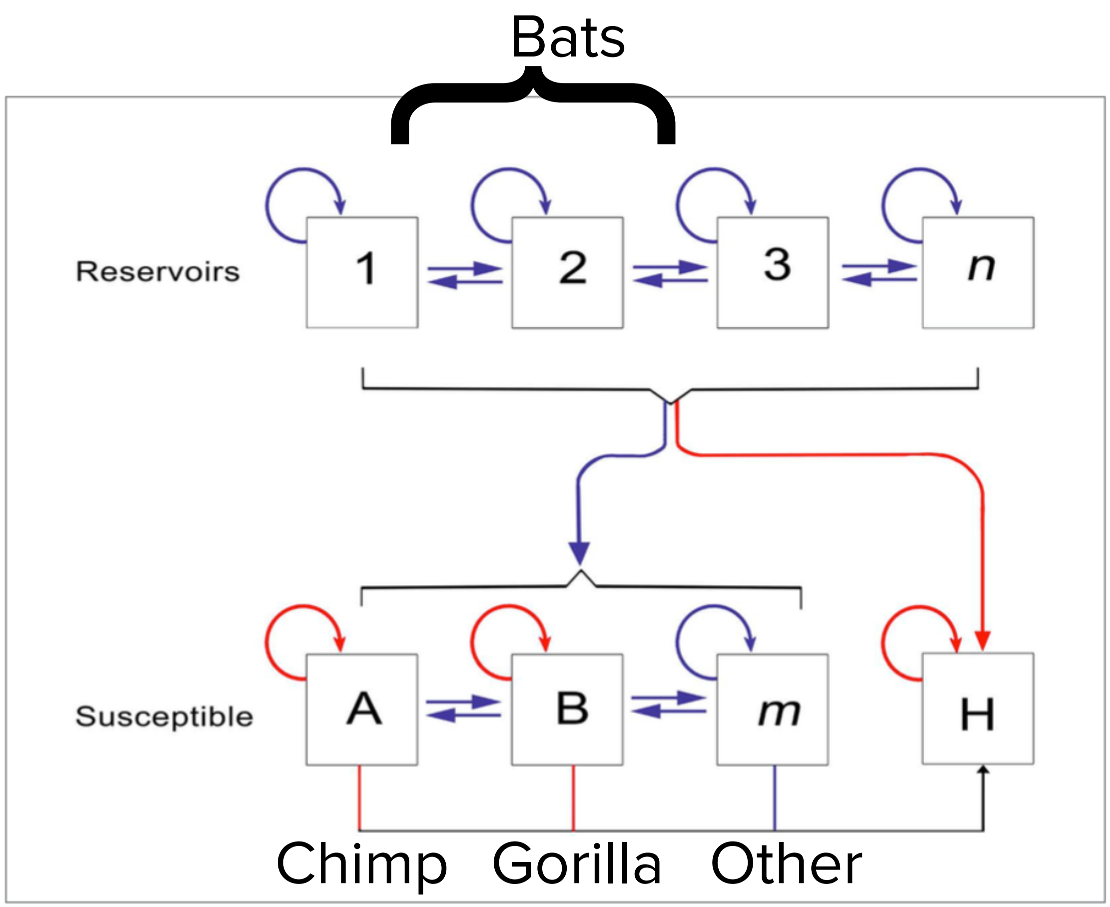
*not always identified

Filovirus ecology

- Marburg virus has been isolated from cave-dwelling fruit bat (*Rousettus aegyptiacus*)
- Zaire Ebolavirus RNA, antibodies found in three tree-roosting bats (but not infectious virus)
- Humans, gorillas, chimpanzees are dead-end hosts

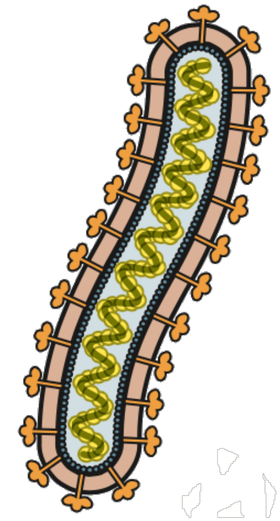
http://commons.wikimedia.org/wiki/File:Rousettus_aegyptiacus_Tel_Aviv_250504.jpg

What is the origin of Ebolaviruses?



Pigott *et al.* eLife 2014;3:e04395. DOI: 10.7554/eLife.04395

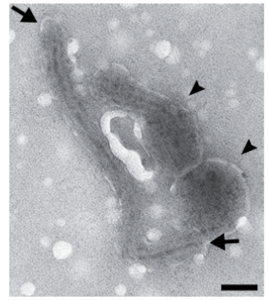
Ebolavirus outbreak examples



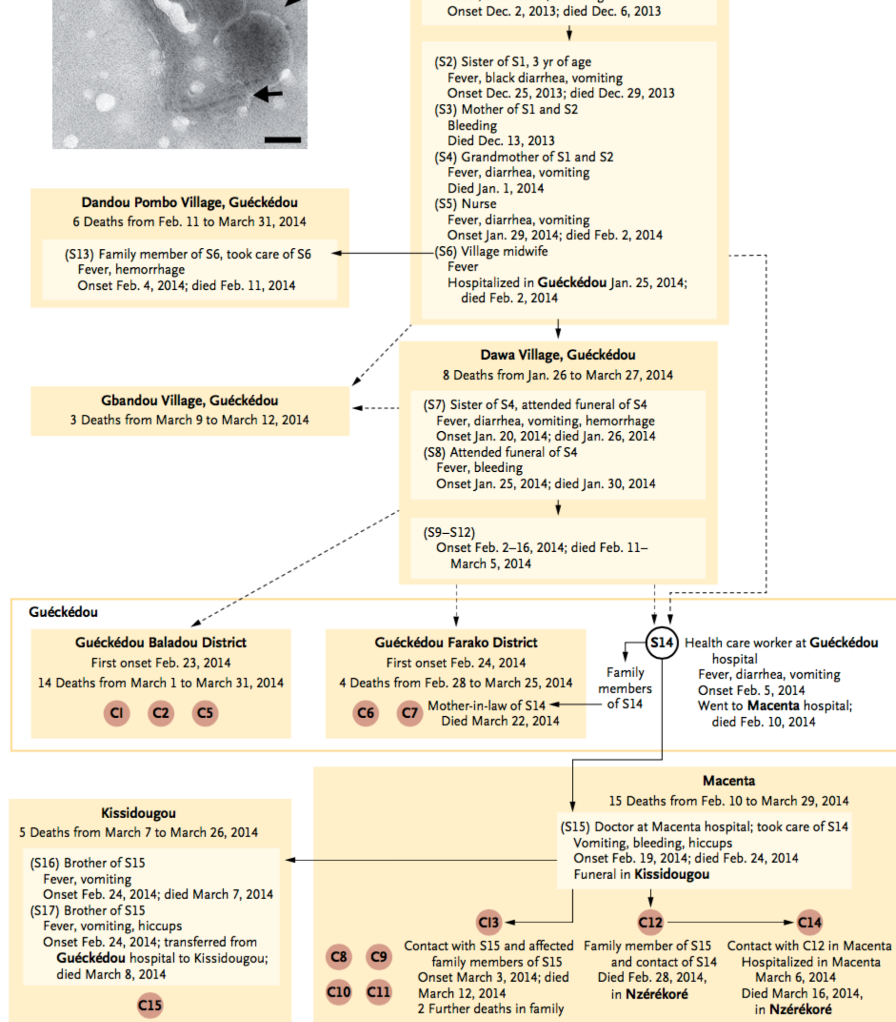
- Gabon, 1996 (Zaire ebolavirus, 37 cases) A chimpanzee found dead in the forest was eaten by people hunting for food. Eighteen people who were involved in butchering the animal became ill. Ten other cases occurred in their family members.

- Gabon, 1996-97 (Zaire ebolavirus, 60 cases) The index case was a hunter who lived in a forest camp. A dead chimpanzee found in the forest at the time was infected with Ebola virus.

Ebolavirus emergence in Guinea

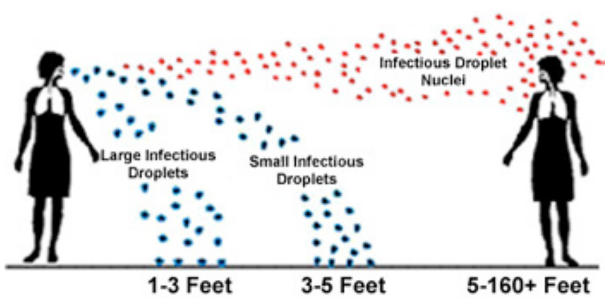


N Engl J Med 2014; 371:1418-1425

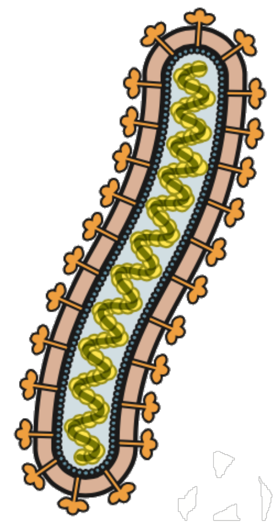


Human-human transmission

- Contact with infected blood or body fluids (urine, saliva, sweat, feces, vomit, breast milk, semen) from someone who is sick or has died
- Contact with contaminated objects (needles, syringes)
- Not by insects, water, food, or aerosol

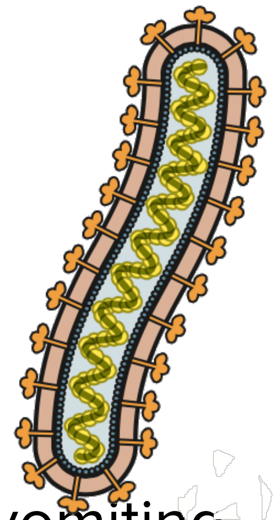


Host entry



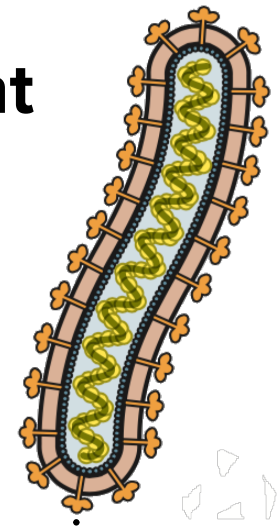
- Mucosal surfaces
- Breaks or abrasions in skin
- Parenteral (e.g. contaminated needles)
- Virus detected in skin, body fluids, nasal secretions, blood, semen

Ebolavirus disease: Clinical features



- Incubation period 2-21 days (not contagious)
- Early symptoms: fever, headache, muscle pain, diarrhea, vomiting, stomach pain
- Peak illness: rash, hemorrhage, convulsions, severe metabolic disturbances, diffuse coagulopathy
- 30-90% case fatality ratio in Africa

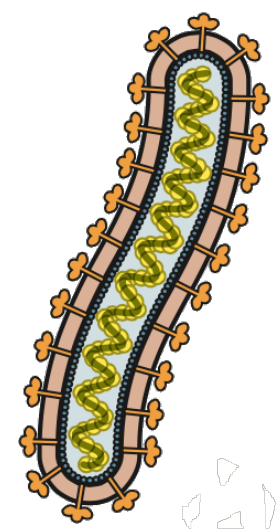
Clinical features: Multisystem involvement



- Systemic (prostration)
- Gastrointestinal (anorexia, nausea, vomiting, abdominal pain, diarrhea)
- Respiratory (chest pain, shortness of breath, cough)
- Vascular (conjunctival injection, postural hypotension, edema)
- Neurological (headache, confusion, coma)

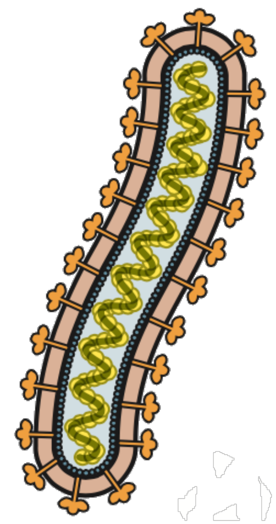
Pathogenesis

- Extensive necrosis in parenchymal cells of many organs (liver, spleen, kidney, gonads)
- Broad cell tropism: Monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, epithelial cells
- Elevation of liver enzymes, shock (adrenal)
- Massive lymphocyte death but not infected



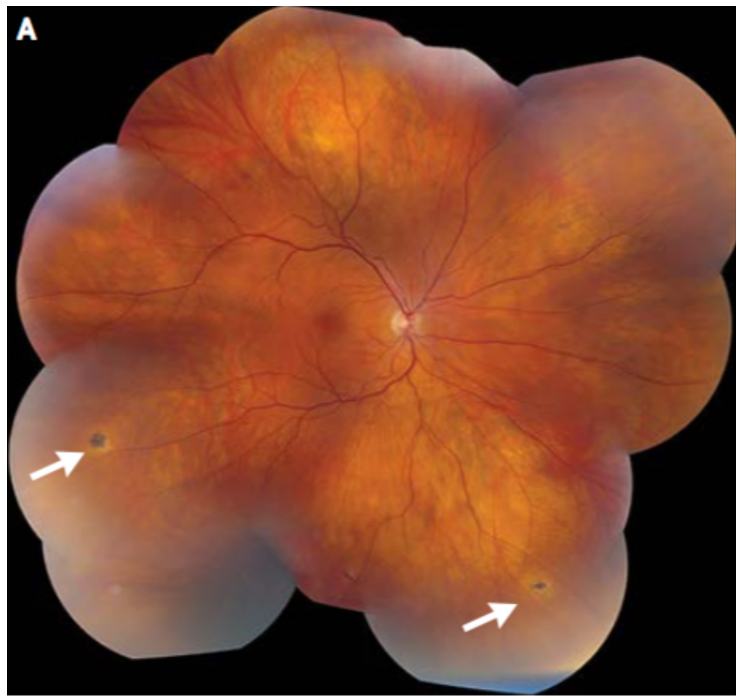
Immunopathogenesis

- Many inflammatory mediators produced, especially by infection/activation of monocytes/macrophages
- Imbalanced cytokine production => disease
- Impairment of vascular and coagulation systems



An acute infection?

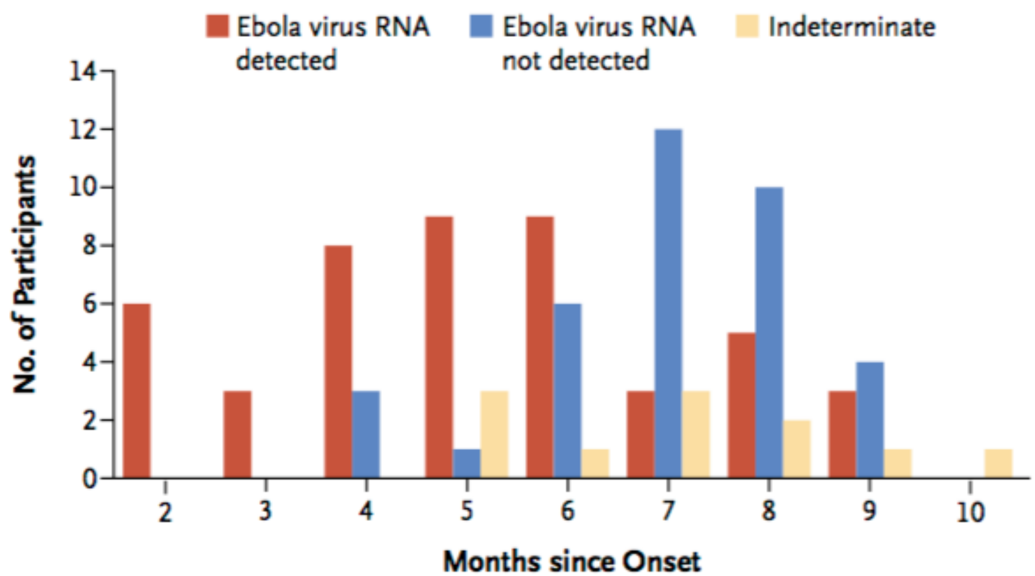
Persistence of Ebolavirus in ocular fluid during convalescence
9 weeks after clearance of viremia



http://www.nejm.org/doi/pdf/10.1056/NEJMoa1500306

An acute infection?

Evidence of sexual transmission
Presence of viral genome in semen

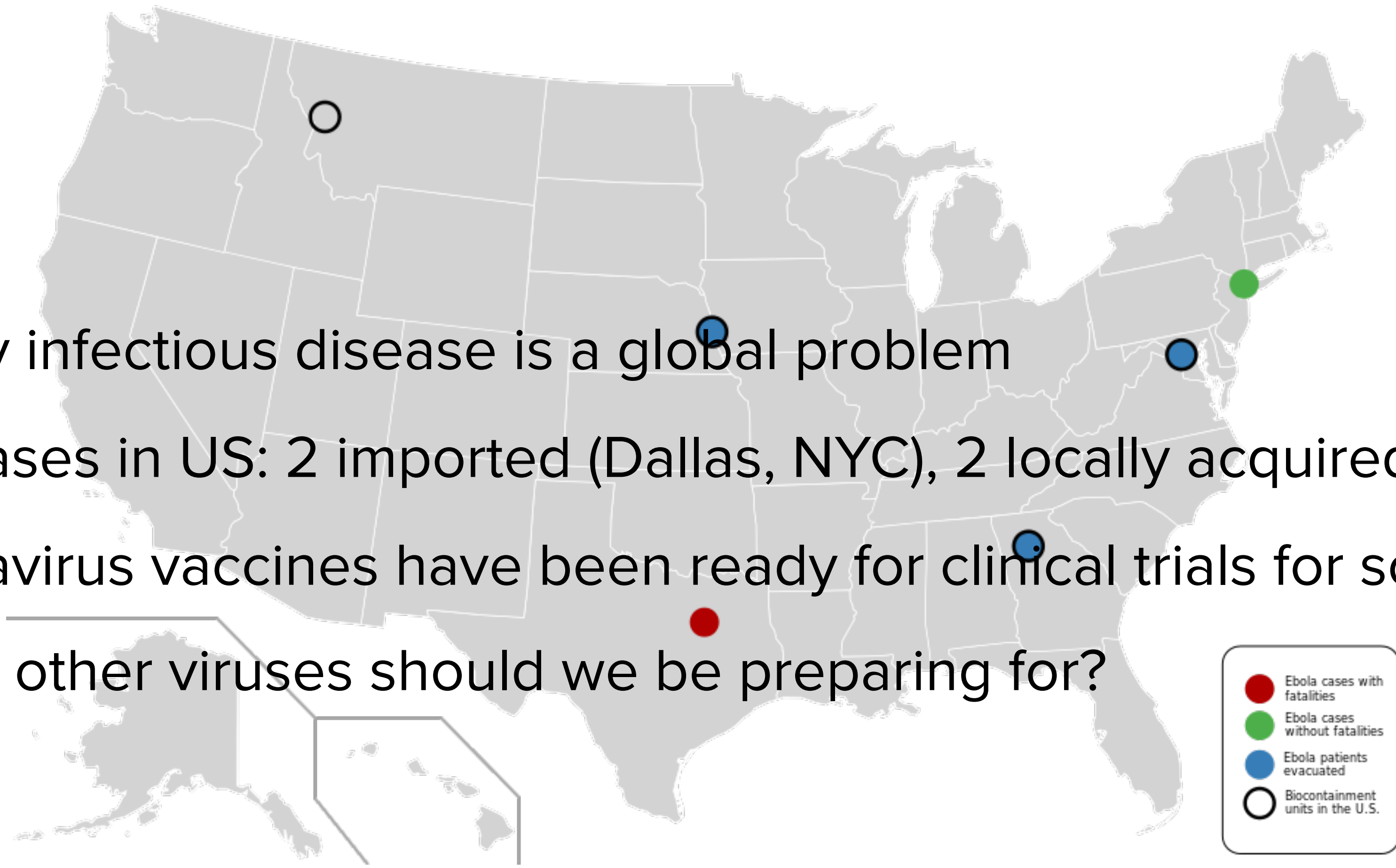


46/93 men (49%)

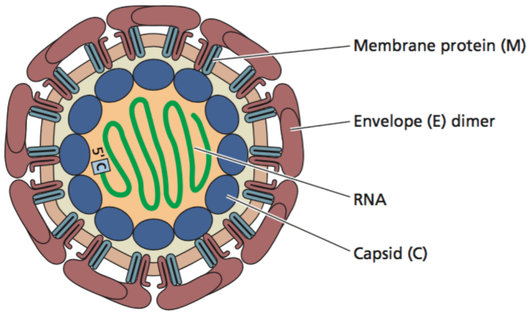
http://www.nejm.org/doi/pdf/10.1056/NEJMoa1511410

What have we learned?

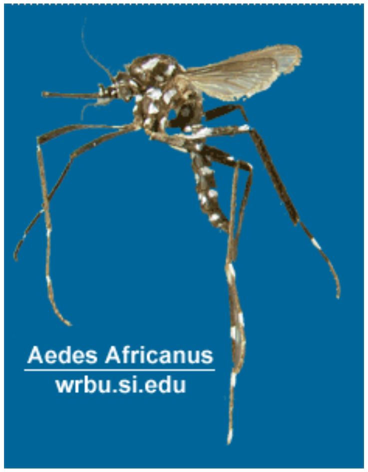
- Every infectious disease is a global problem
  - 4 cases in US: 2 imported (Dallas, NYC), 2 locally acquired
- Ebolavirus vaccines have been ready for clinical trials for some time
- What other viruses should we be preparing for?



https://en.wikipedia.org/wiki/Ebola_virus_cases_in_the_United_States#/media/File:USA-Ebola-outbreak-2014.svg

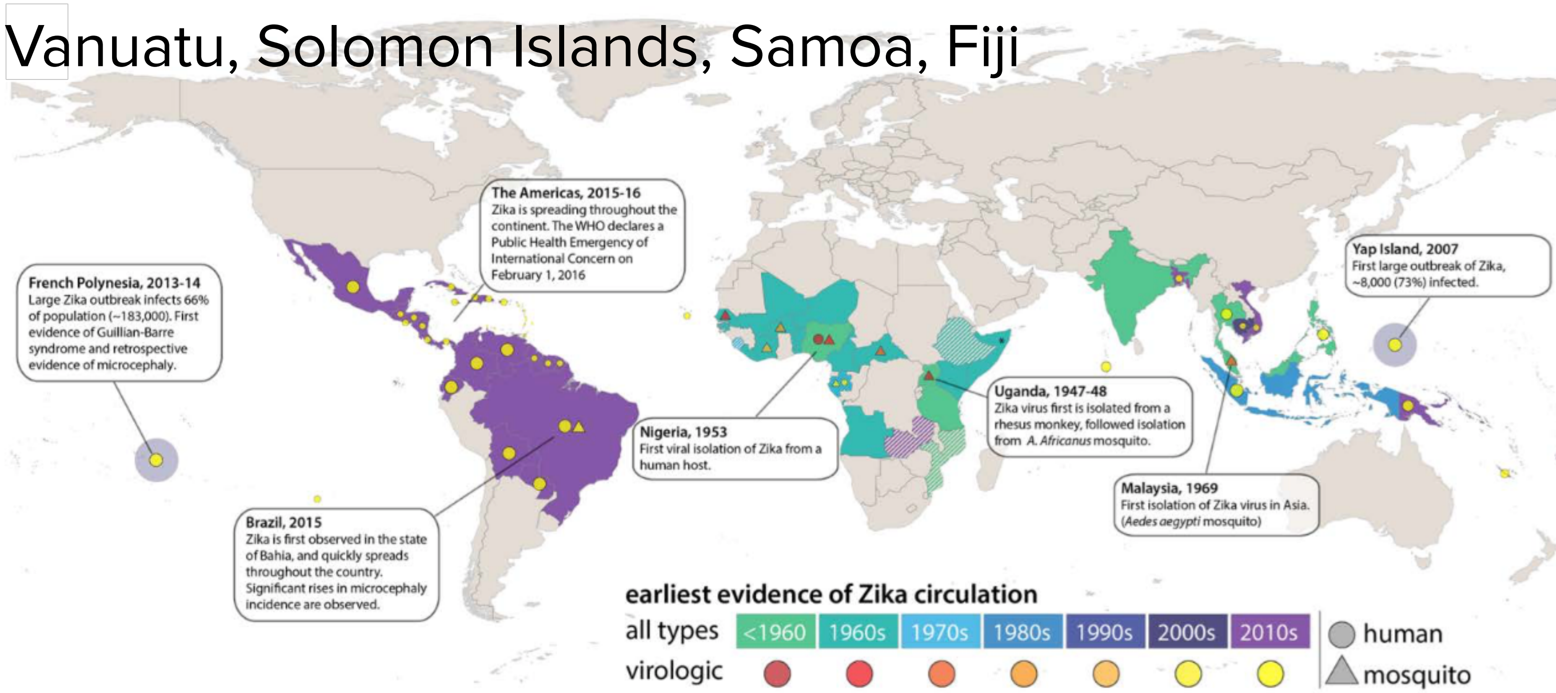


Zika virus

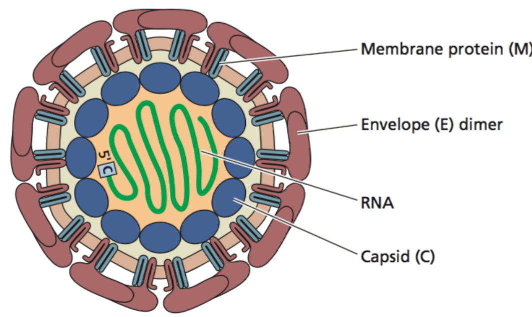


- 1947, Zika Forest, Uganda
- Isolated from *A. africanus*
- Virus isolated from humans, Nigeria, 1954
- Serological detection throughout Africa, Asia but no outbreaks
- Vector for human infections: *A. aegypti*
- <20 cases over next 50 years

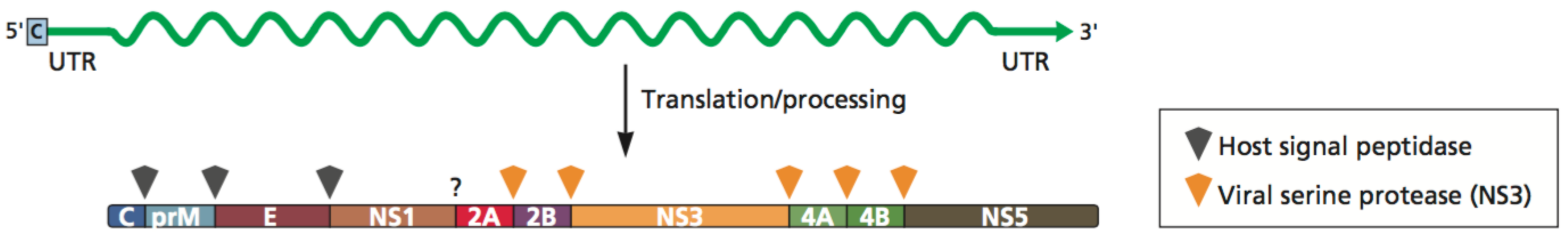
- 2007 outbreak on Yap Island (5,005/6,892 residents) first outside Africa, Asia
- 2013 outbreak French Polynesia (30,000, 11% of population)
- 2014 New Caledonia (1,400, 0.8%), Cook Islands (905), Easter Island (50)
- 2015 Vanuatu, Solomon Islands, Samoa, Fiji



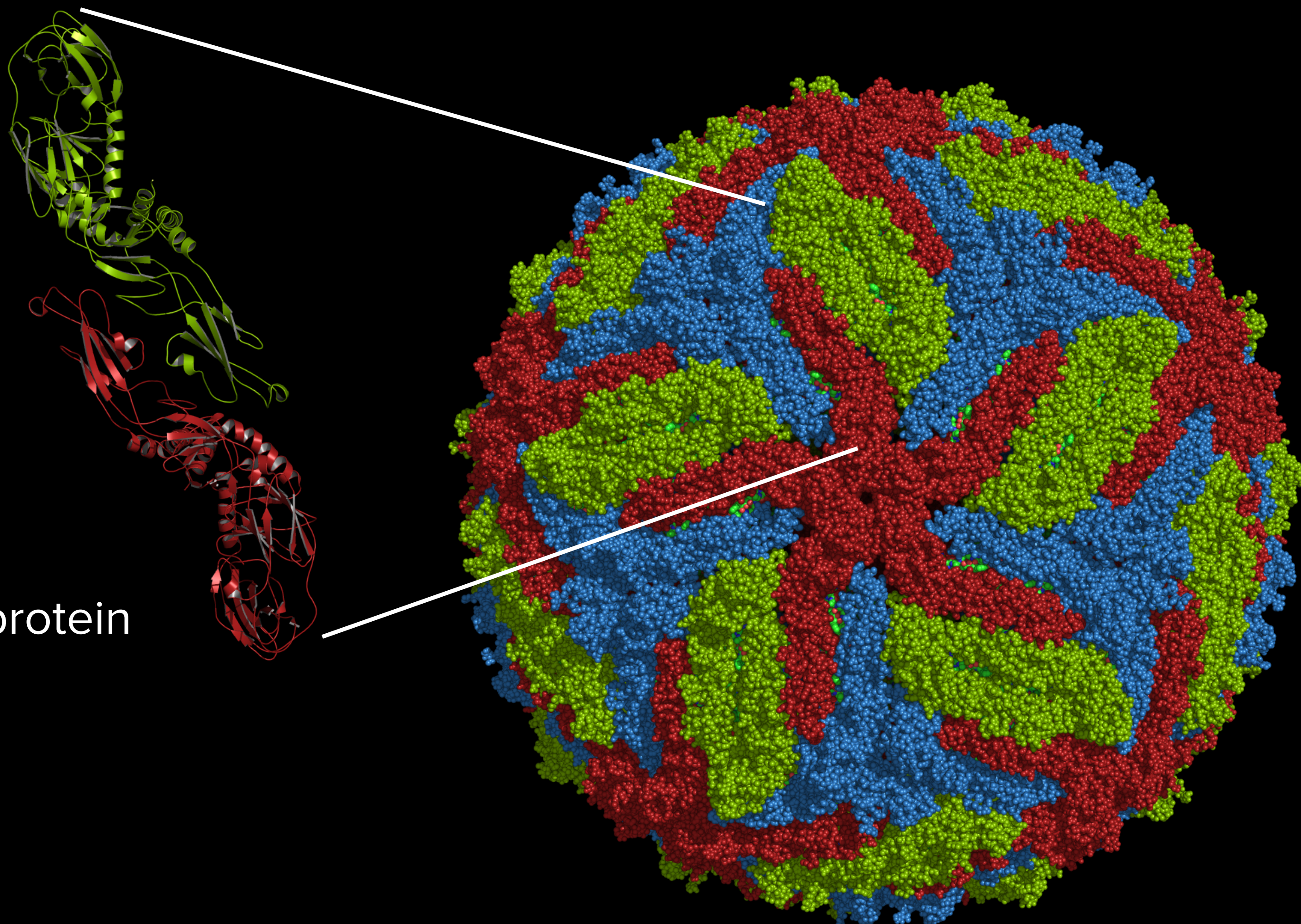
Zika virus



Membrane protein (M)
Envelope (E) dimer
5' C
RNA
Capsid (C)



5' C
UTR
3'
UTR
Translation/processing
?
C
prM
E
NS1
2A
2B
NS3
4A
4B
NS5
Host signal peptidase
Viral serine protease (NS3)

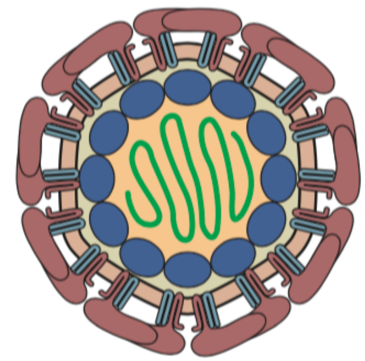


Type II fusion protein

Zika virus

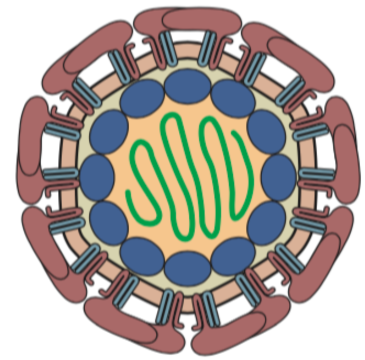
- Disease: rash, fever, joint pain, conjunctivitis, headache (similar to dengue, chikungunya)
- Incubation period 2-10 days
- 1 in 5 develop symptoms; 5 day course
- Fatalities rare

Zika virus shedding



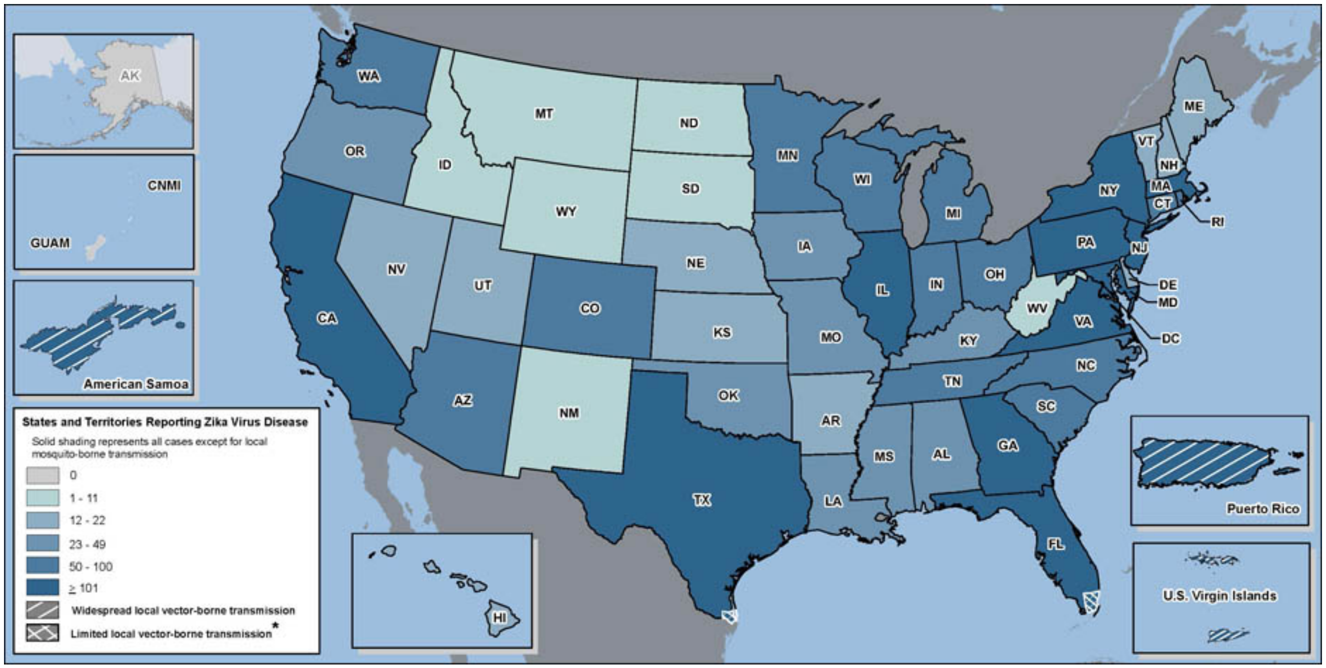
- Semen
- Urine (PCR) - up to 30 days after symptom onset
- Saliva (more frequently than in blood)
- Blood
- Breast milk
- Except for blood, unknown how virus reaches these sites

Zika sexual transmission



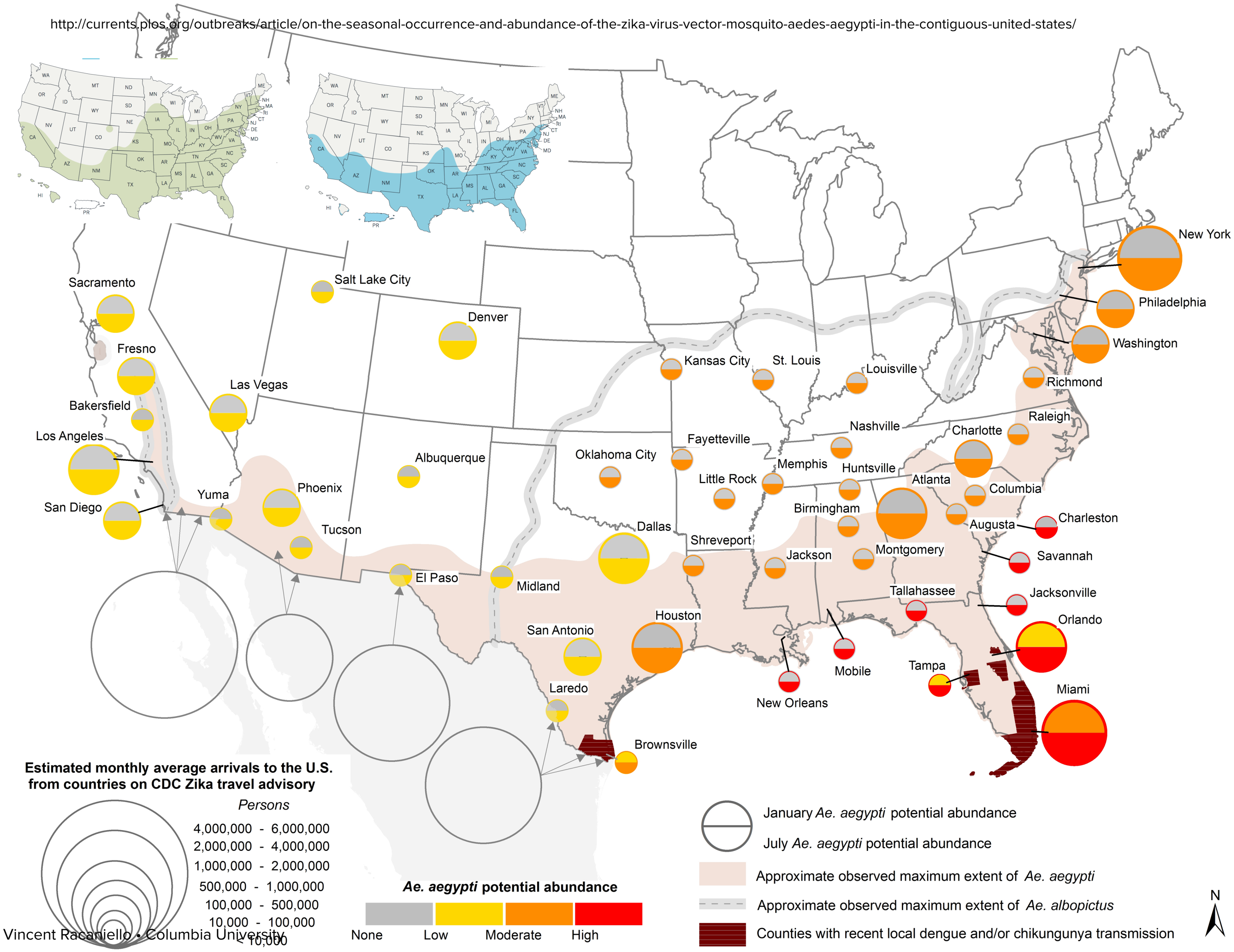
- CDC surveillance report shows 23 out of 2,382 (1%) reported cases resulted from sexual contact with a traveller to an affected area
- CDC advises against pregnant women traveling to endemic areas, or having unprotected sex with potentially infected partners
- RNA persists in semen 188 days, but is it infectious virus?
- Likely can't sustain transmission via sex alone: sexually transmissible, not sexually transmitted

Zika virus in the US

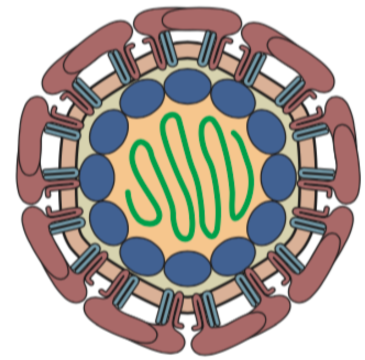


- 5011 travel-associated cases in states
- 223 locally vector-acquired cases (217 FL, 6 TX)
- US territories: 36,526 locally acquired cases (PR, US VI, American Samoa)

http://currents.plos.org/outbreaks/article/on-the-seasonal-occurrence-and-abundance-of-the-zika-virus-vector-mosquito-aedes-aegypti-in-the-contiguous-united-states/

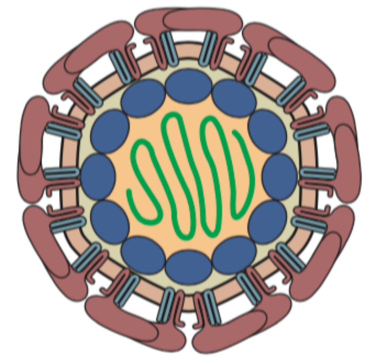


Zika in the US



- Minimal local US spread of dengue virus and chikungunya virus, vectored by *Aedes* (FL, TX)
- 1793 yellow fever epidemic, Philadelphia
- Screens, A/C, population density
- West Nile spread across US in 1999 - different mosquito (*Culex* sp), bird reservoir

Central nervous system complications associated with Zika virus infection

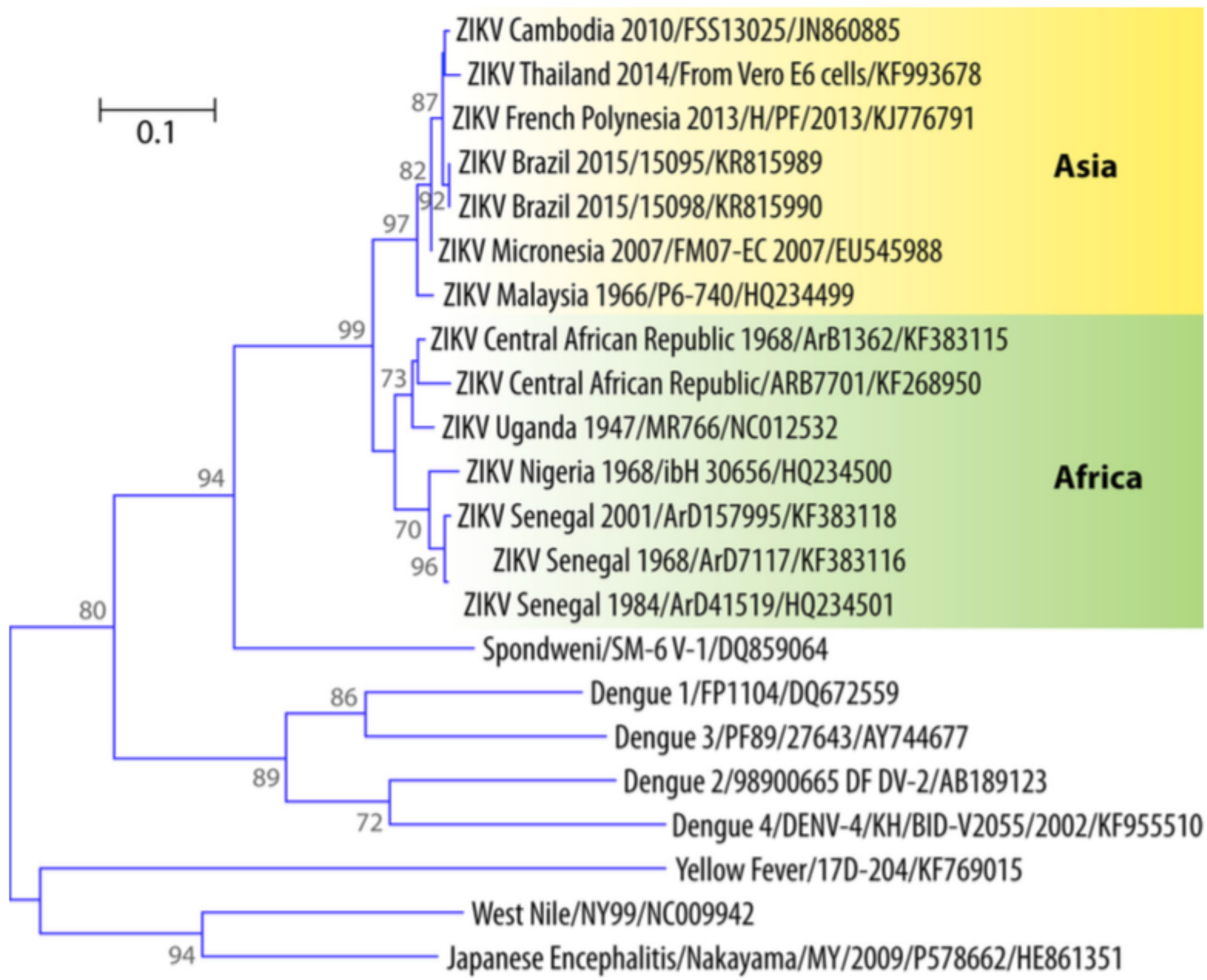


Adults

- Guillain-Barré Syndrome
  (post-infection autoimmune neuropathy; weakness, paralysis, death)
- Acute myelitis
- Encephalopathy
- Meningoencephalitis

Infants

- Microcephaly
- Lissencephaly
- Macular atrophy


0.1
ZIKV Cambodia 2010/FSS13025/JN860885
ZIKV Thailand 2014/From Vero E6 cells/KF993678
ZIKV French Polynesia 2013/H/PF/2013/KJ776791
ZIKV Brazil 2015/15095/KR815989
ZIKV Brazil 2015/15098/KR815990
ZIKV Micronesia 2007/FM07-EC 2007/EU545988
ZIKV Malaysia 1966/P6-740/HQ234499
ZIKV Central African Republic 1968/ArB1362/KF383115
ZIKV Central African Republic/ARB7701/KF268950
ZIKV Uganda 1947/MR766/NC012532
ZIKV Nigeria 1968/ibH 30656/HQ234500
ZIKV Senegal 2001/ArD157995/KF383118
ZIKV Senegal 1968/ArD7117/KF383116
ZIKV Senegal 1984/ArD41519/HQ234501
Spondweni/SM-6 V-1/DQ859064
Dengue 1/FP1104/DQ672559
Dengue 3/PF89/27643/AY744677
Dengue 2/98900665 DF DV-2/AB189123
Dengue 4/DENV-4/KH/BID-V2055/2002/KF955510
Yellow Fever/17D-204/KF769015
West Nile/NY99/NC009942
Japanese Encephalitis/Nakayama/MY/2009/P578662/HE861351
Asia
Africa
87
82
92
97
99
73
94
70
96
80
86
89
72
94

Emergence of Zika epidemics: Evolution or introduction into a new population?

Emergence of Epidemic Zika Virus Transmission and Congenital Zika Syndrome: Are Recently Evolved Traits to Blame?

http://mbio.asm.org/content/8/1/e02063-16

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- **Adaptive evolution:** Genetic changes in virus during spread to Pacific allowed higher replication in vectors, altered human tropism to include congenital infection
- **Stochastic introduction:** ZIKV was simply transported stochastically to locations with large-enough naive human populations, accompanied by large urban mosquito vector populations, for an explosive outbreak. Formerly rare conditions were suddenly recognized when large enough numbers of infections occurred.
- Peter Hotez, *NYT* Op-Ed 8 April 2016: “There are many theories for Zika’s rapid rise, but the most plausible is that the virus mutated from an African to a pandemic strain a decade or more ago and then spread east across the Pacific from Micronesia and French Polynesia, until it struck Brazil.”

How common are host range jumps?

- Dead end: Very common
- Those that produce sustaining transmission: Rare
- Can we predict them? No
- But we can know what is out there, and react (preparedness)