

Emerging Viral Diseases

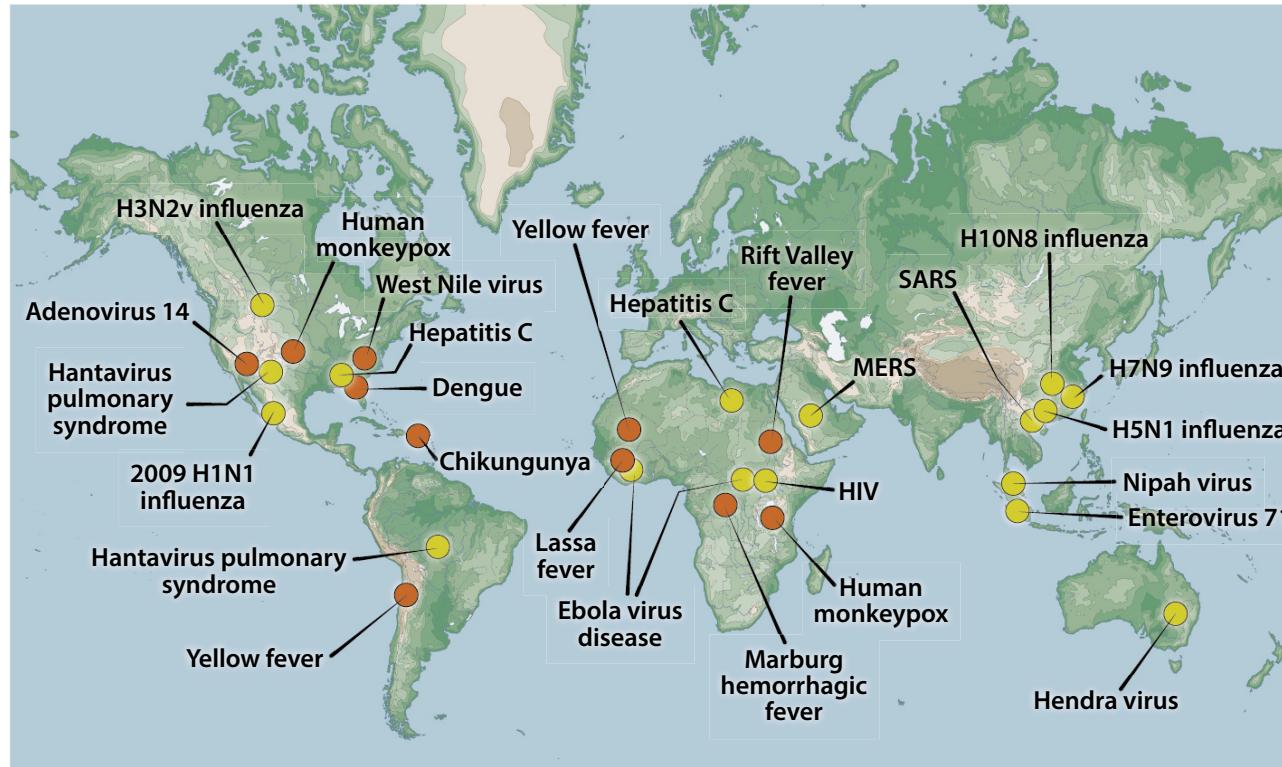
Dr. Timothy Sheahan
sheahan@email.unc.edu

Overview

- What are emerging viral diseases?
- Where do they come from?
- What can we do to protect ourselves?

“Newly emerging viruses are ‘**new**’ in a sense that they are not known to have previously infected or caused disease in humans”

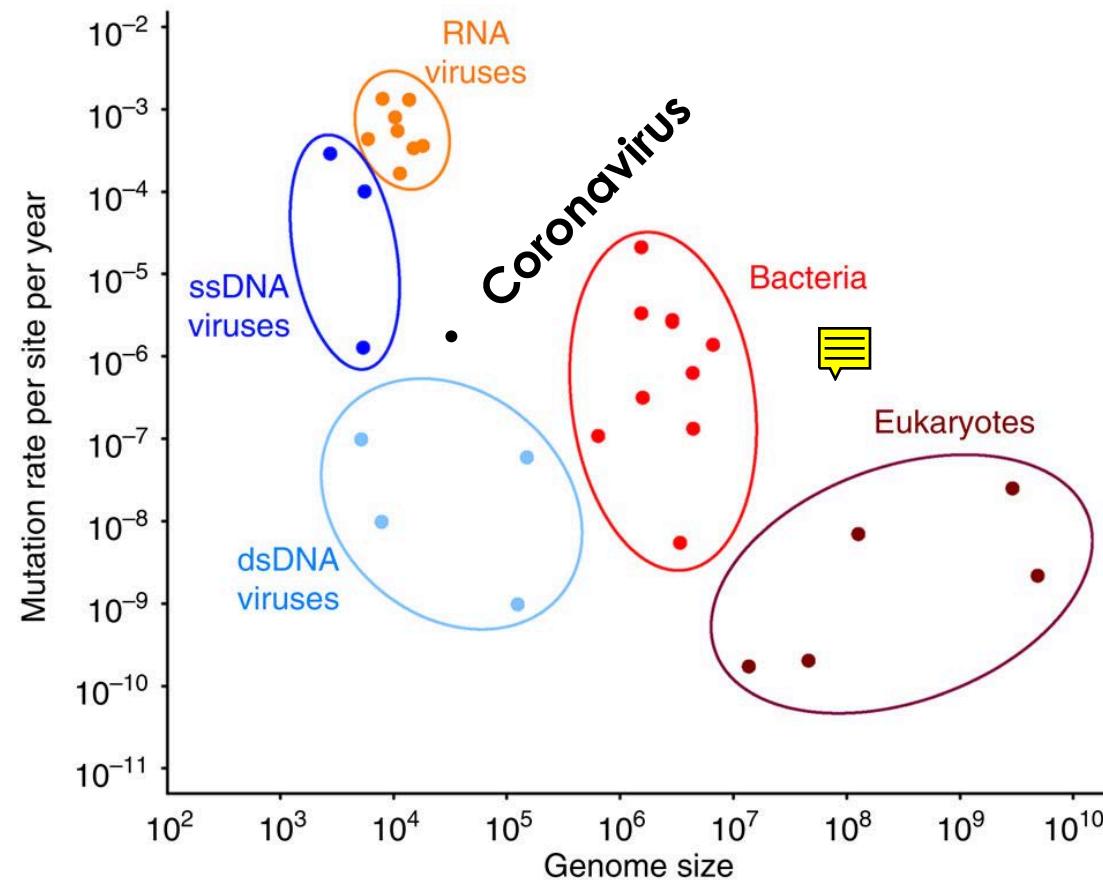
Emerging viral diseases



Viral and
human factors
promote
emergence

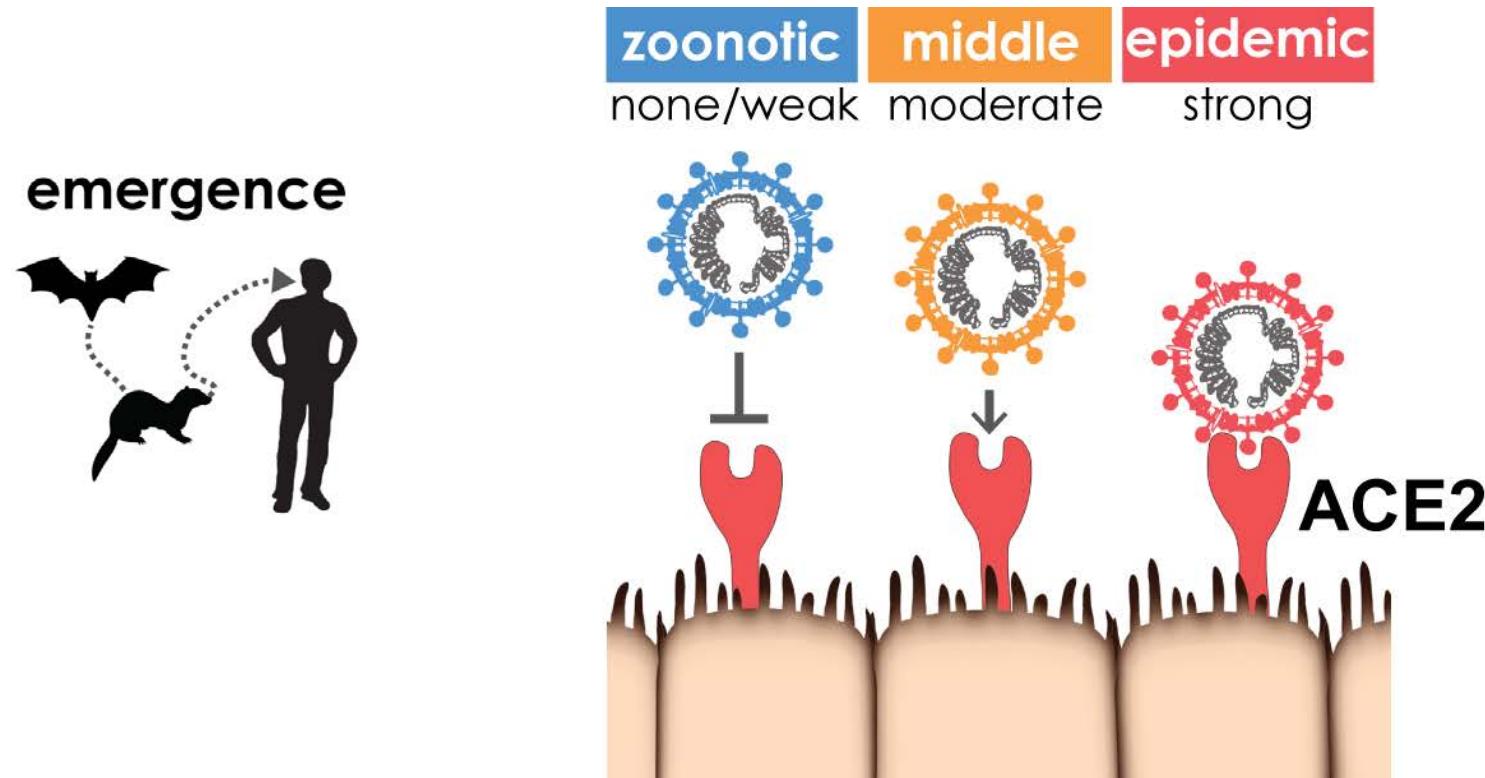
What kind of nucleic acid do almost all of these share?

Mutation rates can promote rapid emergence

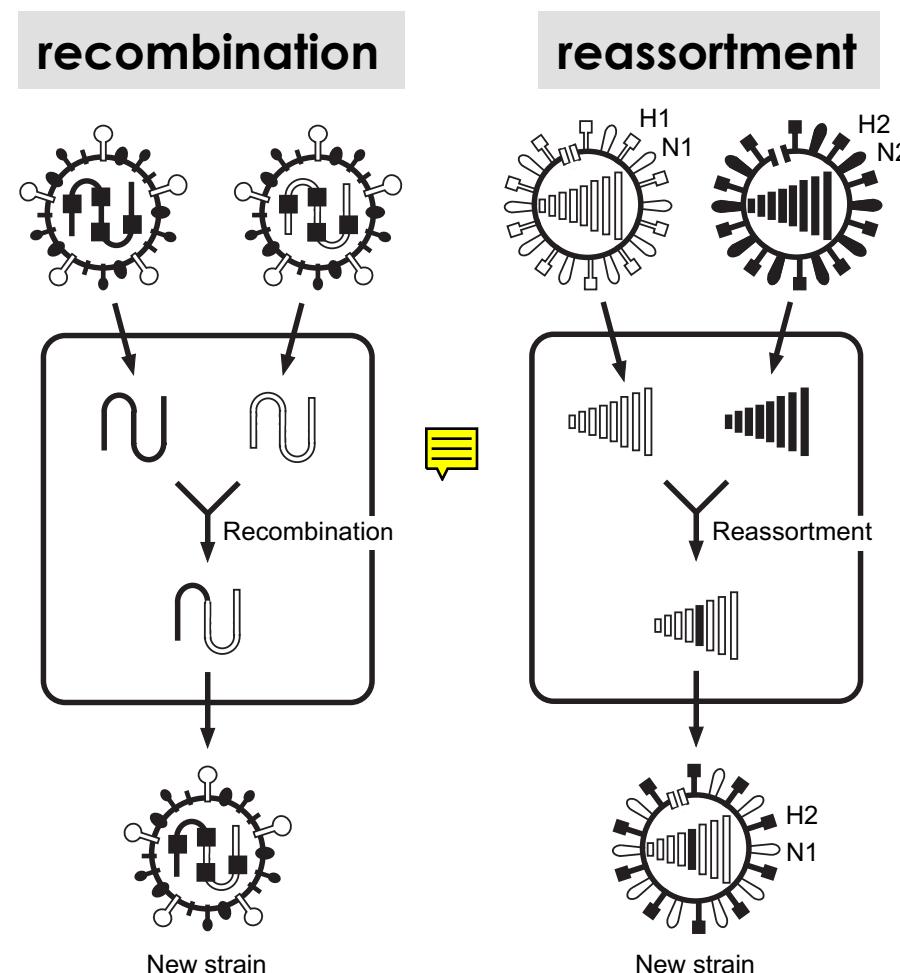


Mutation rates vary depending on genome size and composition

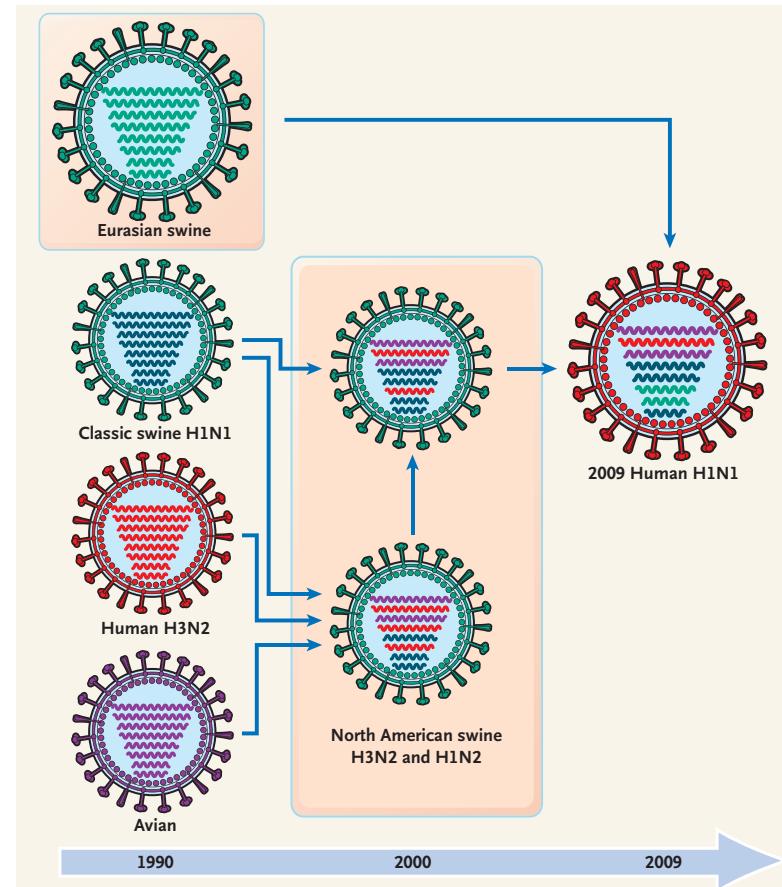
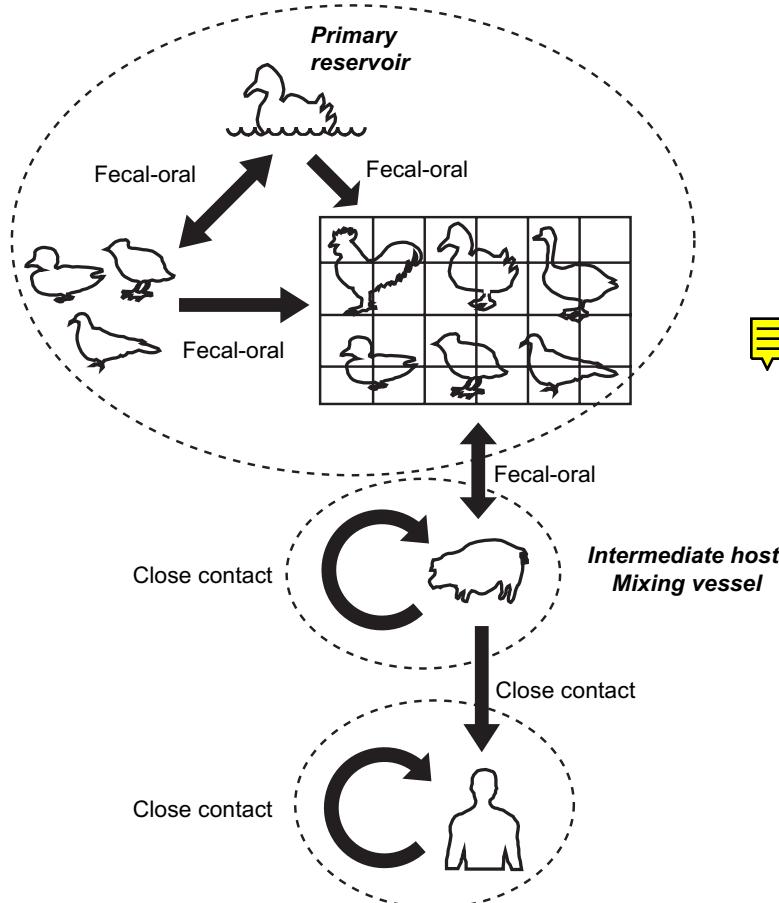
SARS Spike evolution during the epidemic



Viral Factors Guiding Emergence

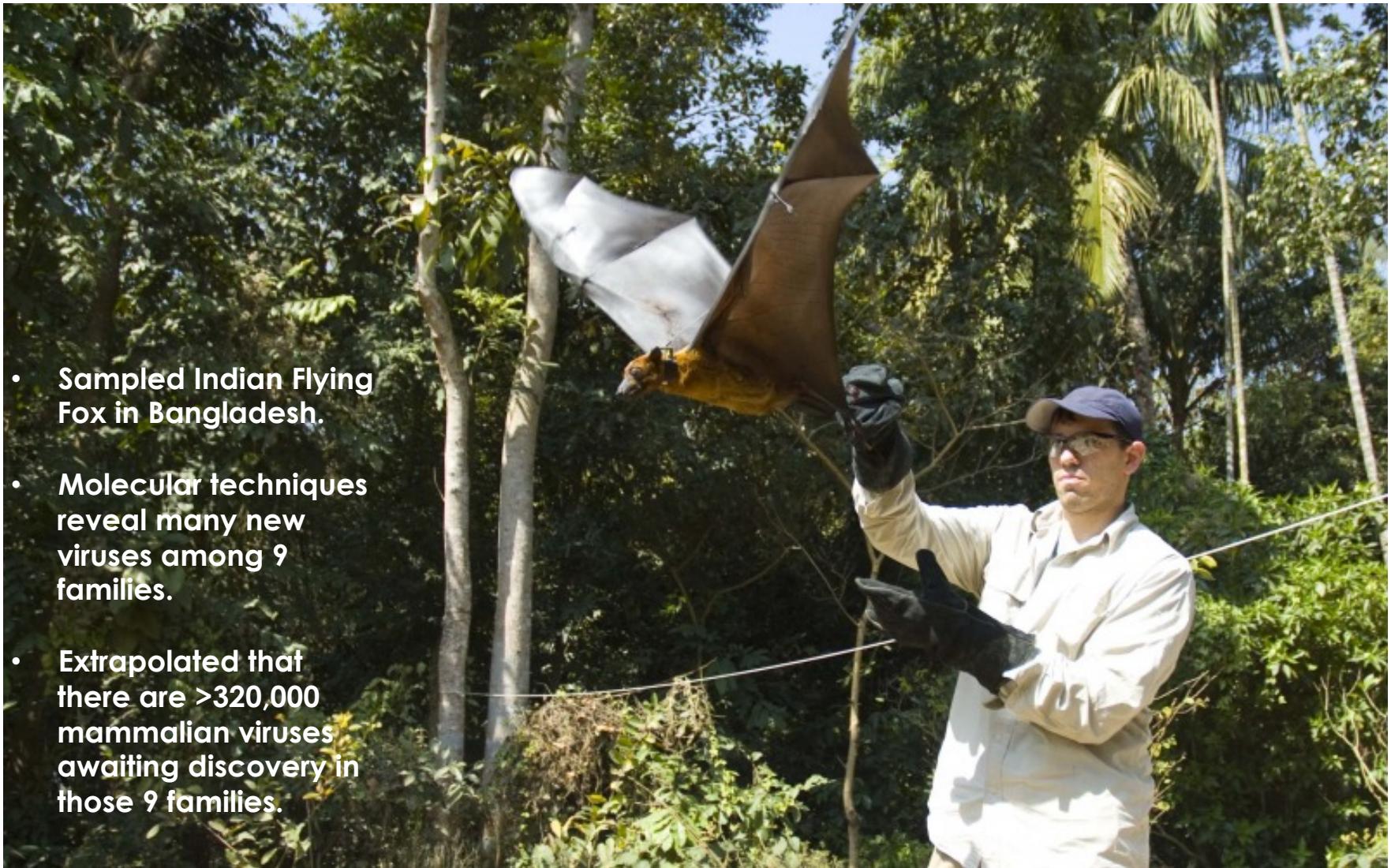


2009 Emergence of H1N1 Flu



- 6-18-2009, NEJM: Of 642 patients, 60% were 18 and under.
- Immunity from vaccine in 1976? 1918?

Virus diversity...the unknown



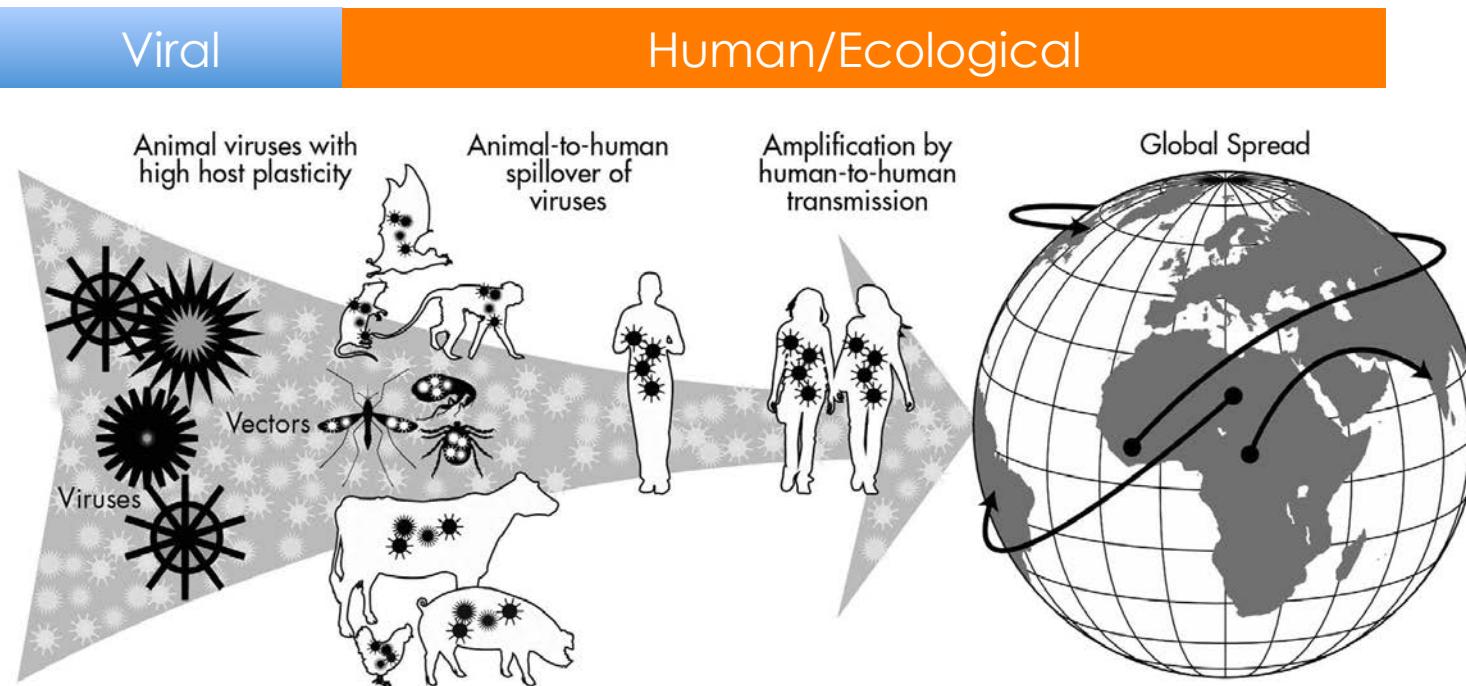
- Sampled Indian Flying Fox in Bangladesh.
- Molecular techniques reveal many new viruses among 9 families.
- Extrapolated that there are >320,000 mammalian viruses awaiting discovery in those 9 families.

Anthony et. al. A strategy to estimate unknown viral diversity in mammals. 2013 mBio. Photo: EcoHealth Alliance

Viral factors summary

- RNA viruses are predisposed for genetic change but are ultimately limited by fitness.
- Genetic drift and shift help guide viral genetic diversity.
- Global virus diversity is vast much of which remains unknown.
- How many zoonotic viruses exist with pathogenic potential in humans?

Factors driving novel virus emergence



Adapted from Johnson et. al. Sci Reports 2015

Human/Ecological Factors and Emergence

Factor	EBOV	YFV	WNV	MERS	SARS
Population growth and urbanization					
(Un)Planned human migration					
Human travel					
Vector travel					
Hunting/pasture practices					
Expanding agriculture/ deforestation					
Global commerce					
Human social behavior					
Unsafe medical practices					
Hospital practices					

Bats as vectors for emerging viral diseases



Nipah Virus (Paramyxovirus)

- 1st outbreak in 1998 in Malaysia. 105 human deaths. 1 million pigs culled.
- Farmers plant mango trees near pig pens. Bat to Pig transmission through urine. Pigs to humans.

Hendra virus (Paramyxovirus)

- 1st discovered in Hendra, Australia in 1994. Spread from flying foxes to horses to humans.

SARS Coronavirus. 1st outbreak in 2003.
Bat to civet to human?

MERS Coronavirus. Discovered in 2012.
Bat to camel to human.

Ebola virus (Filovirus). Discovered in 1976.
Bat to human or through an intermediate host.

Adapted from V. Racaniello Virology 2016

Ebola virus discovered in 1976

Preliminary Communications

ISOLATION AND PARTIAL CHARACTERISATION OF A NEW VIRUS CAUSING ACUTE HÆMORRHAGIC FEVER IN ZAIRE

K. M. JOHNSON
J. V. LANGE

P. A. WEBB
F. A. MURPHY

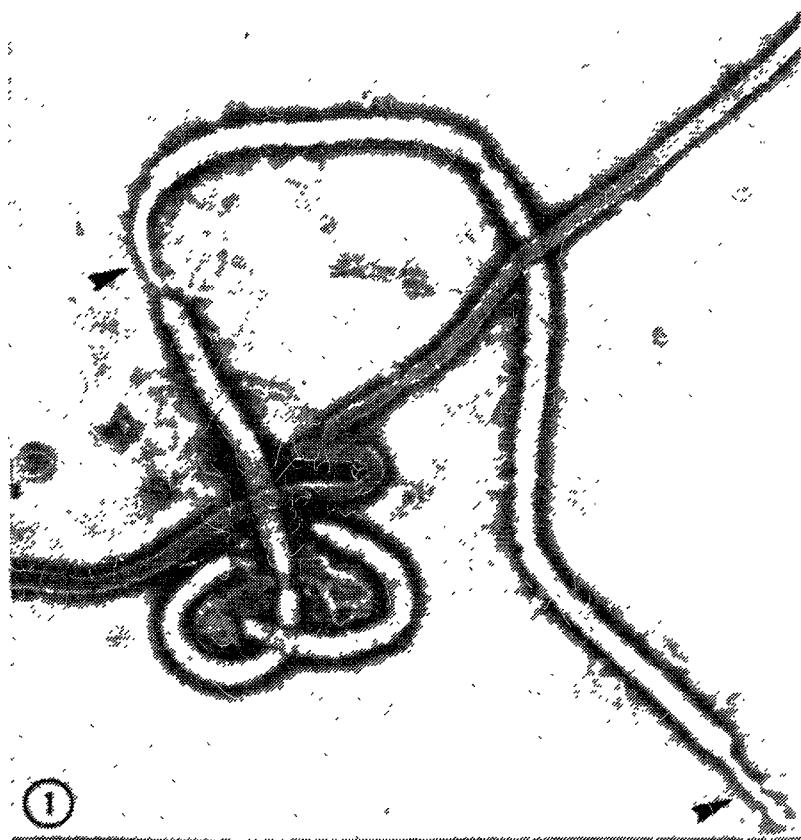
*Virology Division, Center for Disease Control,
Atlanta, Georgia 30333, U.S.A.*

AN outbreak of hæmorrhagic fever with an exceptionally high mortality-rate occurred in southern Sudan and northern Zaire with peak case-rates in September, 1976. A W.H.O. International Commission operated in Sudan and Zaire from October onward.^{1 2} Blood and tissue specimens from persons with hæmorrhagic disease were sent to laboratories in Belgium and England, and findings from these laboratories appear in the accompanying reports.^{3 4} While these specimens were being studied, Mr E. T. W. Bowen (Microbiological Research Establishment, Porton Down) sent an aliquot of an acute blood specimen from a patient in Zaire (no. 718, patient M.E.) to the Center for Disease Control, Atlanta, for additional study.

This specimen, and all subsequent acute specimens, were inoculated into Vero (African green monkey) cells. Three days later a distinct cytopathic change (focal rounding and refractivity) was evident, and an aliquot of supernatant fluid was removed for negative contrast electron microscopy.

ELECTRON MICROSCOPY OF CELL CULTURES

Carbon-coated grids were sequentially floated on droplets of



Johnson et. al. Lancet 1977

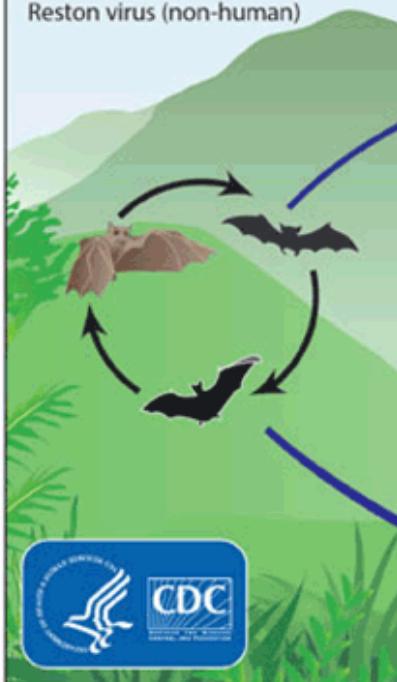
Ebola virus ecology

Enzootic Cycle

New evidence strongly implicates bats as the reservoir hosts for ebolaviruses, though the means of local enzootic maintenance and transmission of the virus within bat populations remain unknown.

Ebolaviruses:

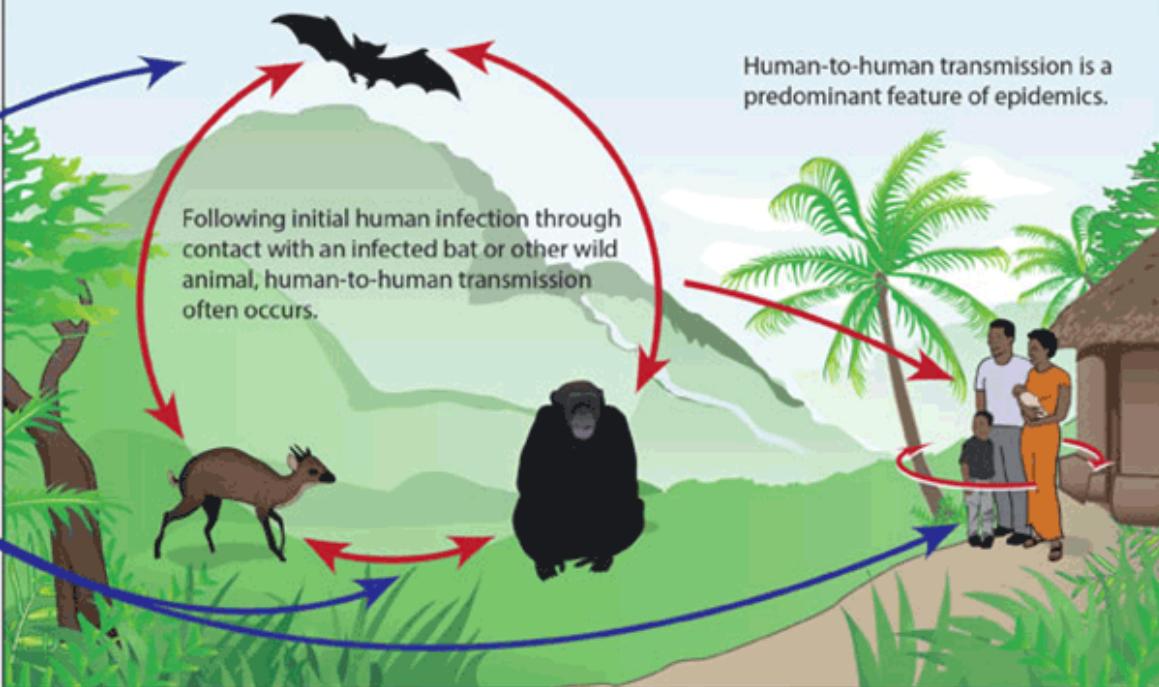
- Ebola virus (formerly Zaire virus)
- Sudan virus
- Tai Forest virus
- Bundibugyo virus
- Reston virus (non-human)



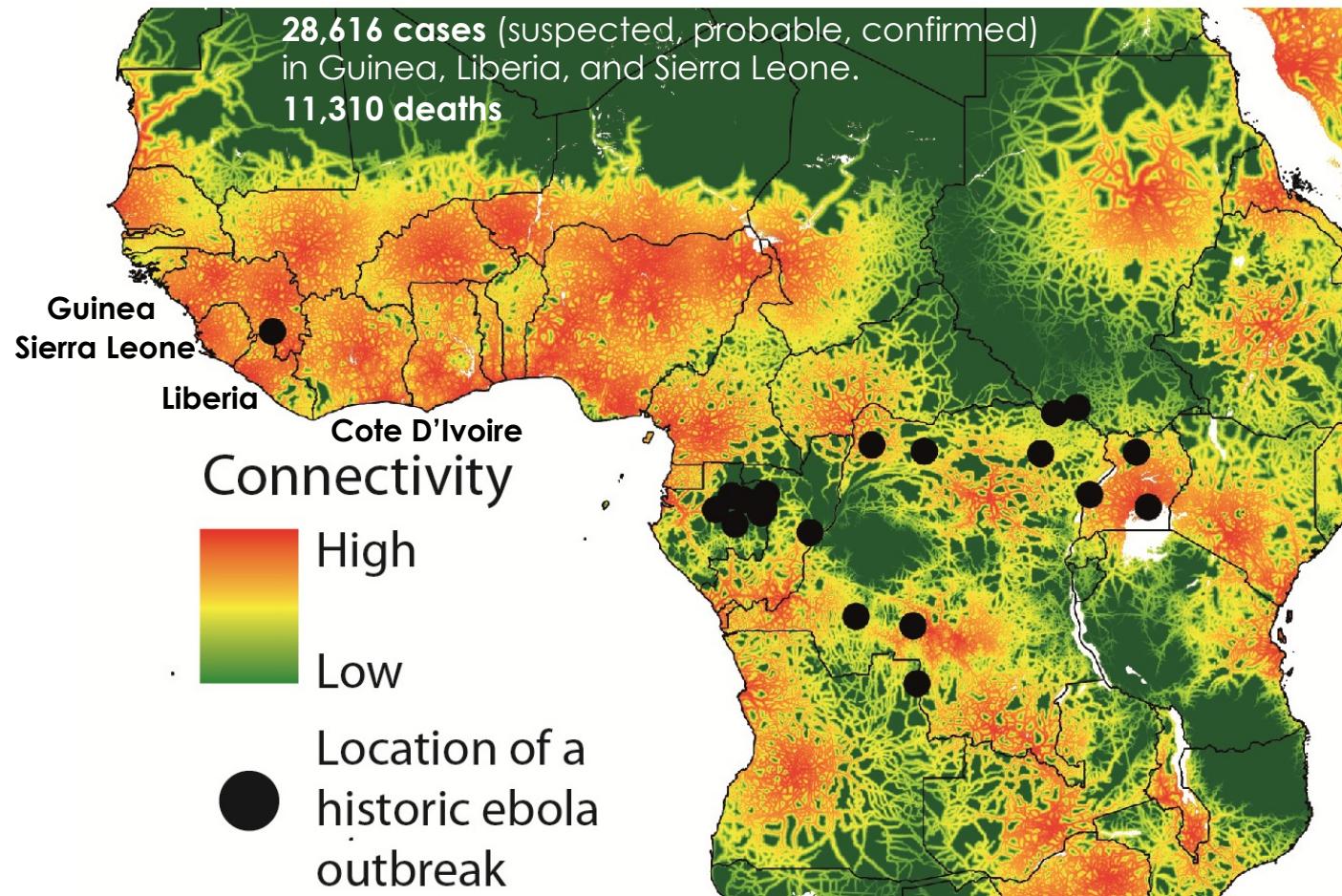
Epizootic Cycle

Epizootics caused by ebolaviruses appear sporadically, producing high mortality among non-human primates and duikers and may precede human outbreaks. Epidemics caused by ebolaviruses produce acute disease among

humans, with the exception of Reston virus which does not produce detectable disease in humans. Little is known about how the virus first passes to humans, triggering waves of human-to-human transmission, and an epidemic.



West African Ebola virus outbreak 2014



Wesolowski et. al. 2014 POLS Current Outbreaks. Map of strength of connectivity measured by travel time to the nearest settlement of population 500,000 or more, with dense areas of low travel time indicative of high connectivity. Case numbers from CDC.

Increasing overlap of wild animal/human ecologies

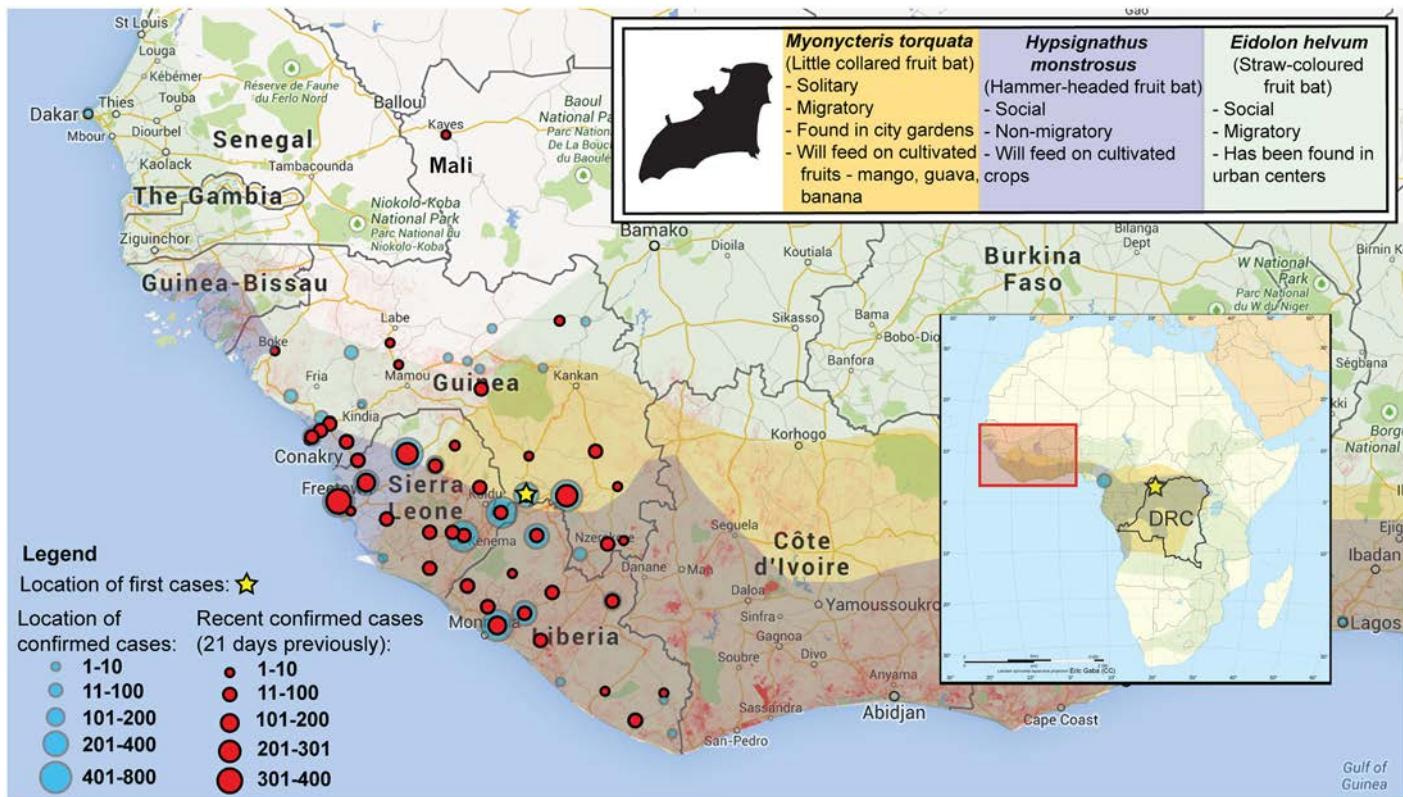
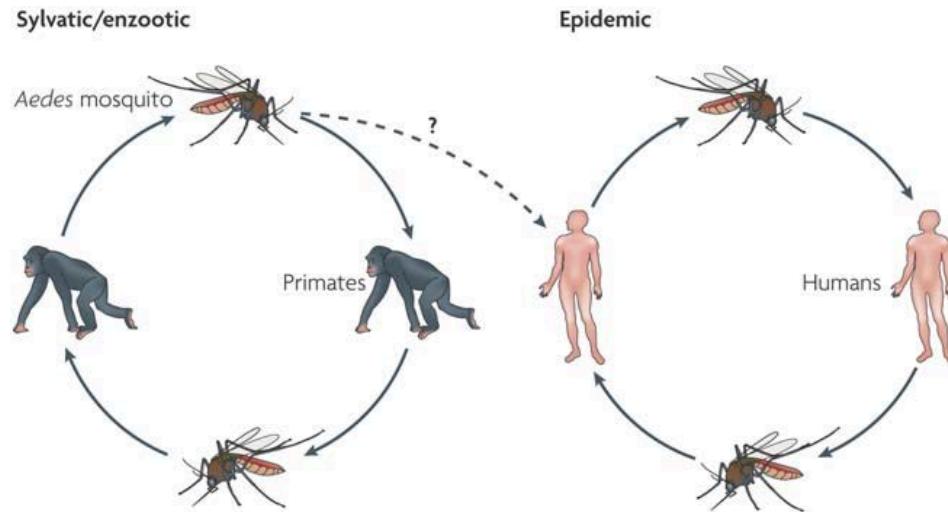


Fig 5. Range of bat species suspected of being reservoirs of Ebola, human population density, and Ebola case counts by location in West Africa.

Virus Spillover

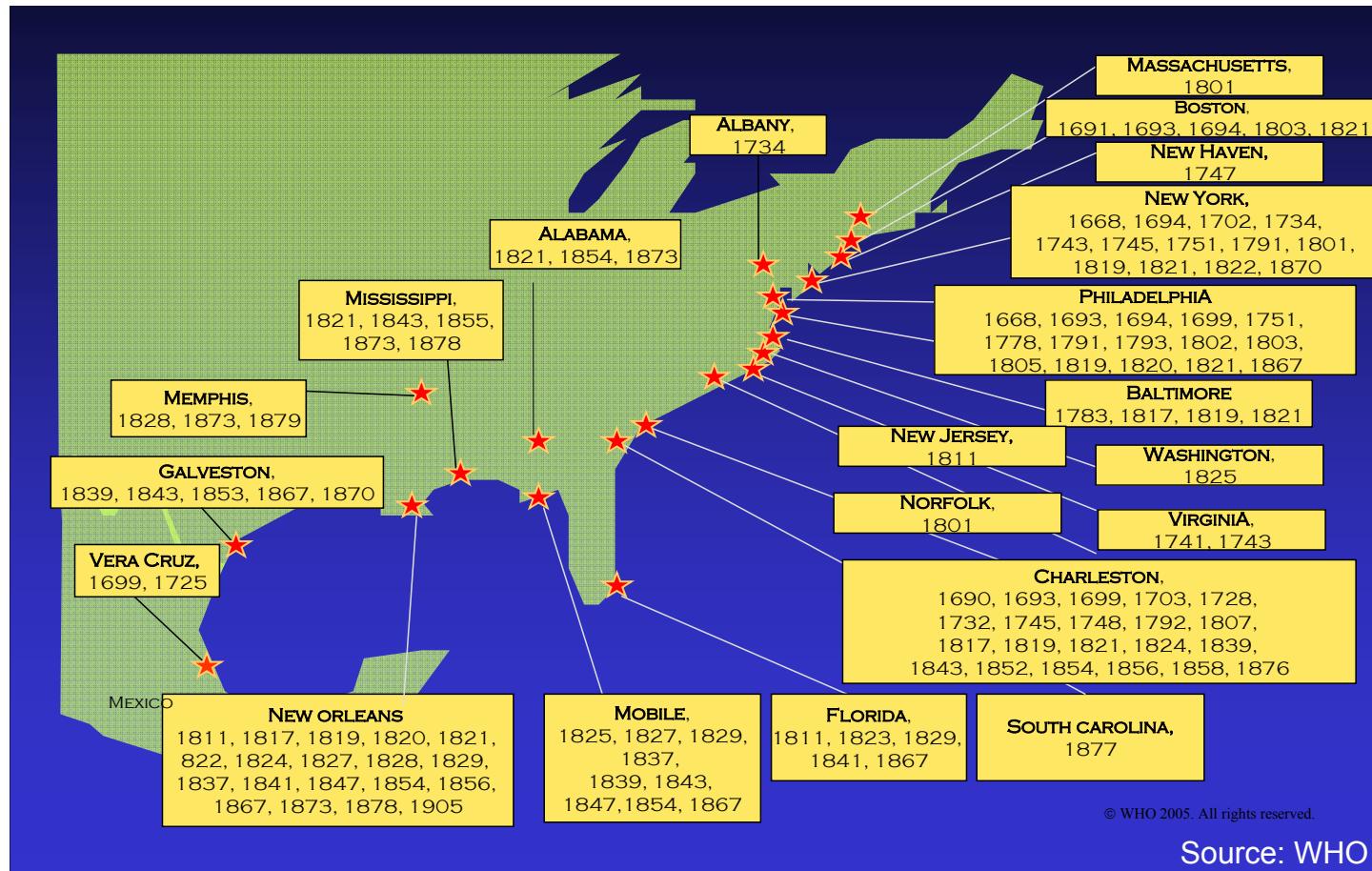
- Habitat loss.
- Forest/agricultural mosaics.
- Change in fruit bat feeding to urban areas.
- Bush meat consumption.

Yellow Fever Virus



- (+) sense RNA. **Flavivirus**.
- Arbovirus. Aedes egypti.
- Acute hemorrhagic fever.
- 200,000 cases/year.
- 30,000 deaths.
- 900 Million at risk.
- Vaccine.

Yellow Fever Virus in America



First epidemic in 1648. Fueled by slave trade, trade routes.

Yellow Fever Virus in America

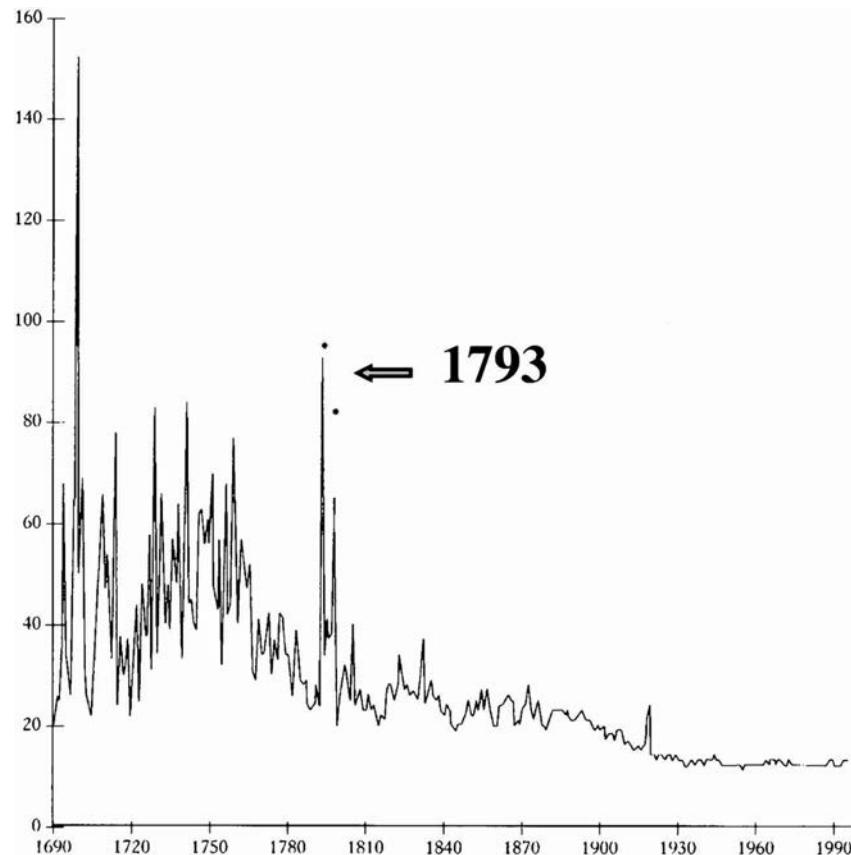


FIGURE 1. Crude death rates for Philadelphia, 1690–1990. Reprinted with permission.³⁰

- 1793. US Capital moves from Philly to D.C.
- 1807 outlawed Atlantic Slave. YFV retreats from North.
- 1878 Memphis Tennessee outbreak. 17,000 cases over 5000 deaths.

Motivation to understand YFV

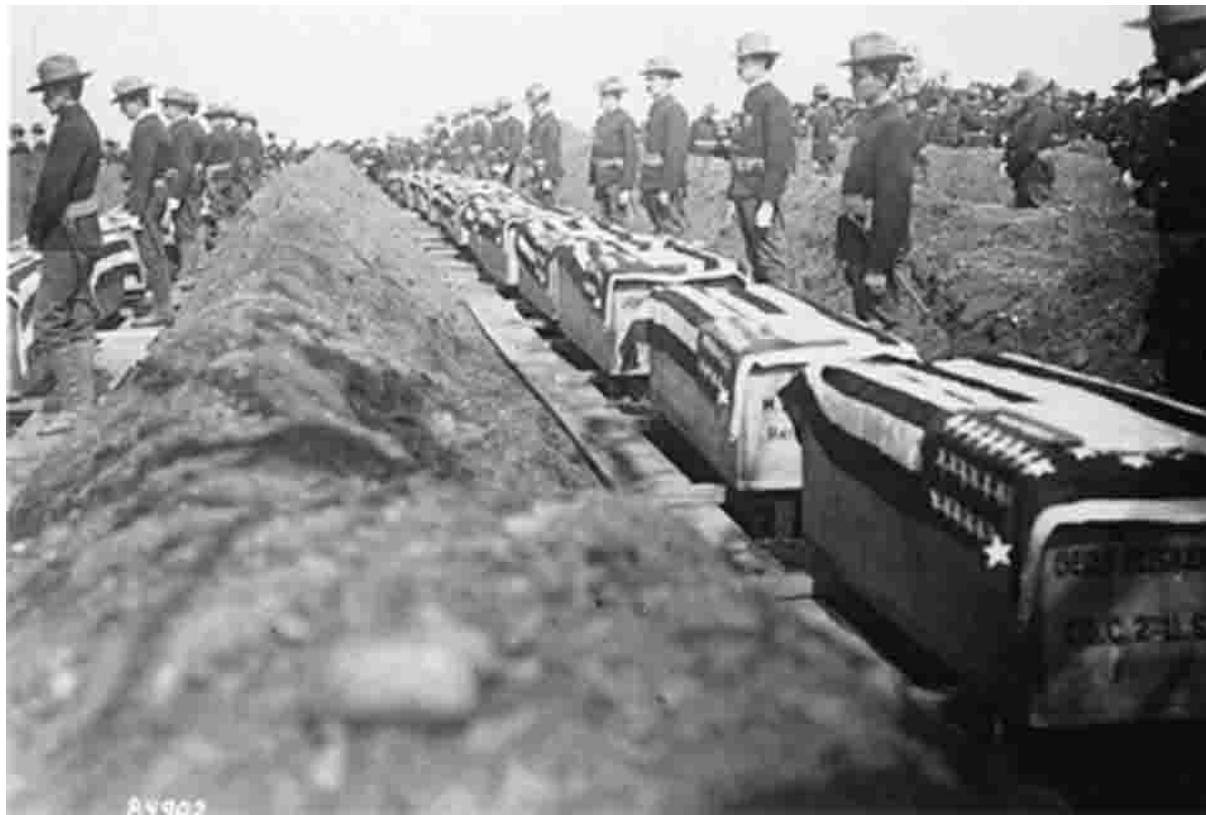


FIGURE 5. Burial of the dead, Cuba 1899. Hench Collection.

968 die in combat, 5000+ from YFV

Petri Am. J. Trop. Med. Hyg. 2004

YFV leads to many firsts...



FIGURE 4. Carlos Finlay (1833–1915).

- **1881** a Cuban physician, [Carlos Finlay](#), performs experiments to show YFV transmitted by mosquito but no one believes him.

Petri Am. J. Trop. Med. Hyg. 2004

Yellow Fever Commission 1900

Formed by the Surgeon General to identify the cause of YFV



James Carroll



Walter Reed

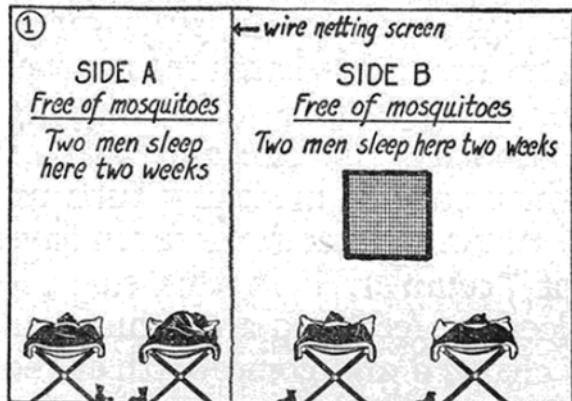


Jesse Lazear

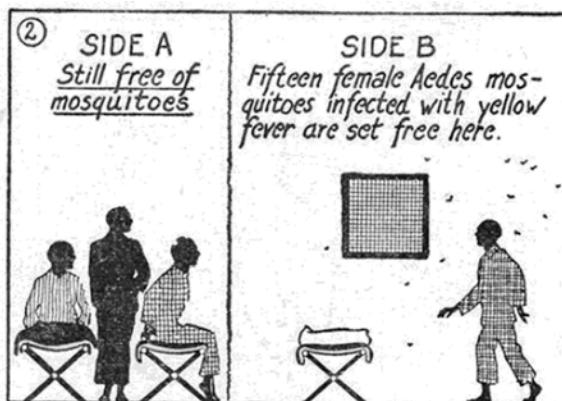


Aristide Agramonte

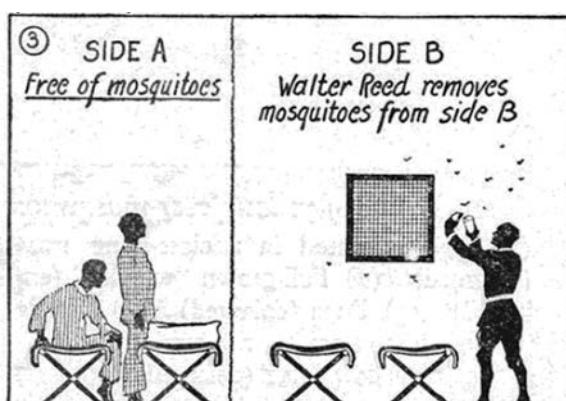
Yellow Fever Commission 1900



① All four men remain well. Therefore the building is not infected with yellow fever



② J. Moran enters side B, is bitten and has yellow fever in four days. The men in side A remain well. Therefore the presence of contaminated mosquitoes infected side B.



③ Men sleep on both sides of wire netting as before without taking yellow fever. Therefore side B has been disinfected by removing mosquitoes

Isolation of Yellow Fever Asibi



Asibi

Mahaffy

Hudson

Stokes

Bauer

Koch's postulates

THE TRANSMISSION OF YELLOW
FEVER TO MACACUS
RHESUS

PRELIMINARY NOTE *

ADRIAN STOKES, D.S.O., O.B.E., M.D. DUBL.,
F.R.C.S.I., M.R.C.P. LOND.

J. H. BAUER, M.D.

AND

N. PAUL HUDSON, M.D.

LAGOS, NIGERIA

The following is a preliminary report of studies on yellow fever carried out by the West African Yellow Fever Commission of the Rockefeller Foundation. A detailed report, covering the work presented here as well as other studies on this subject, will be published shortly.

Prevention of YFV

Etiology known, vector control efforts diminish YFV in Americas



THE USE OF YELLOW FEVER VIRUS MODIFIED BY IN VITRO CULTIVATION FOR HUMAN IMMUNIZATION

By MAX THEILER, M.R.C.S., L.R.C.P., AND HUGH H. SMITH, M.D.

(From the Laboratories of the International Health Division, The Rockefeller Foundation, New York)

(Received for publication, March 18, 1937)

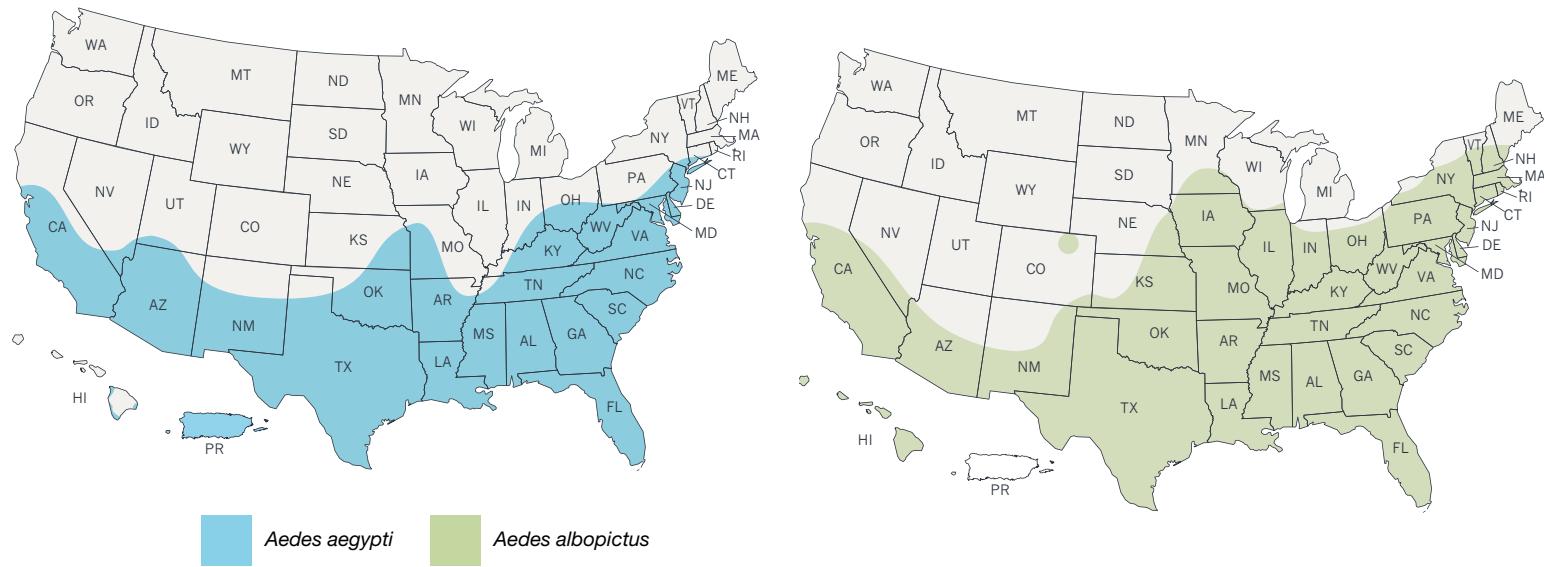
One of the most striking phenomena to the student of virus diseases is the occurrence of variants. This phenomenon is of particular importance in that several such variants are being used for the immunization of man. The two classical examples of the use of attenuated forms of virus for human vaccination are vaccinia and the fixed virus of rabies. The origin of vaccinia virus is a moot point, but it is almost universally considered to be a variant of smallpox obtained by passage through the cow. This virus was found as such in nature. The fixed virus of rabies was produced by serial propagation in rabbit brain. By this procedure a variant was produced which had lost to a considerable extent its pathogenicity for man and dog.

J. Ex. Med. 1937

YFV leads to many firsts...

- First isolation of human virus
- First demonstration that mosquitos transmit viral disease
- First and only Nobel prize awarded for a vaccine

YFV vector in the USA today



Some of the same factors that drove YFV emergence can now be applied to Zika, chikungunya and dengue.

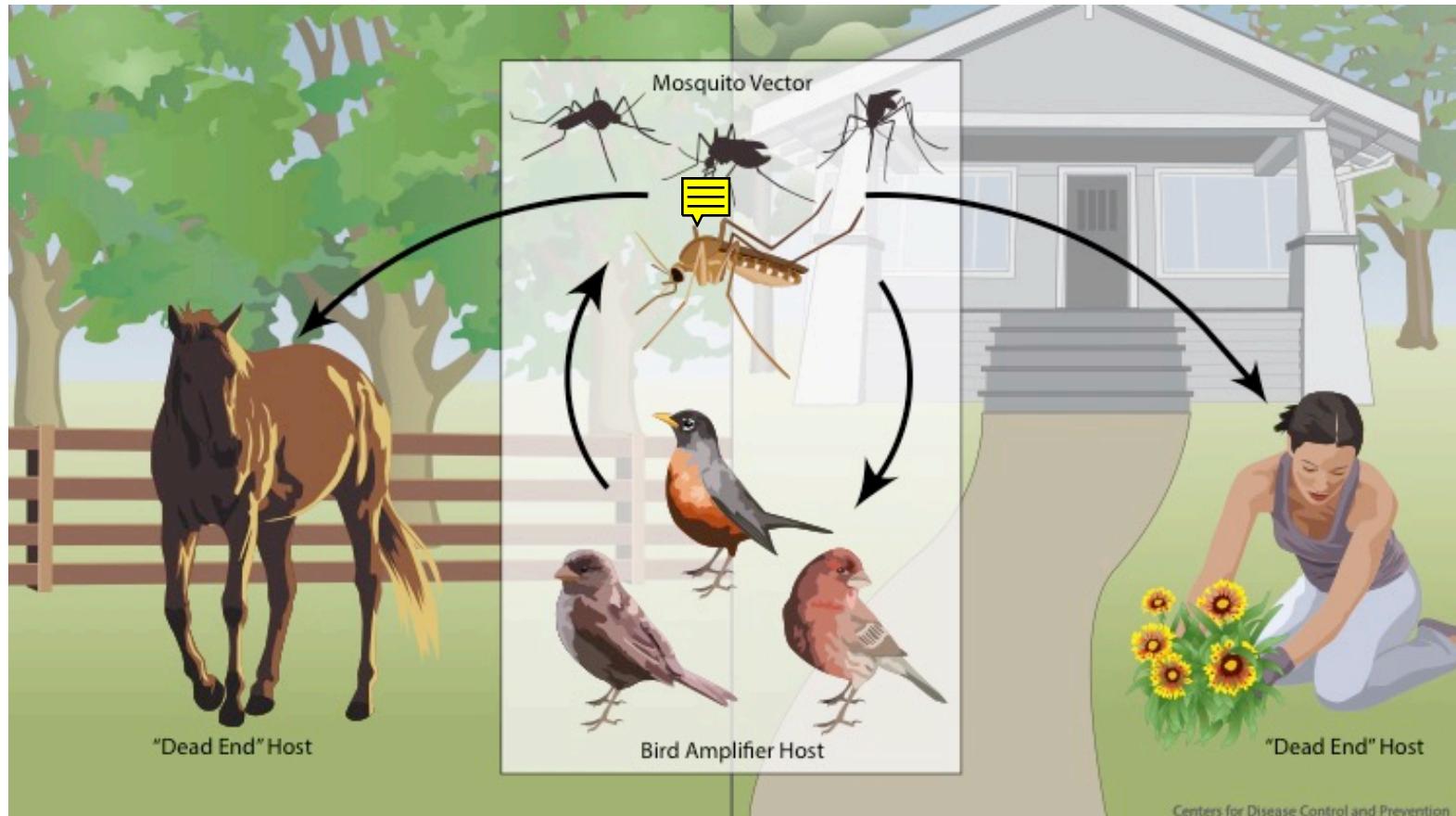
Maps from CDC

How did WNV arrive in America?



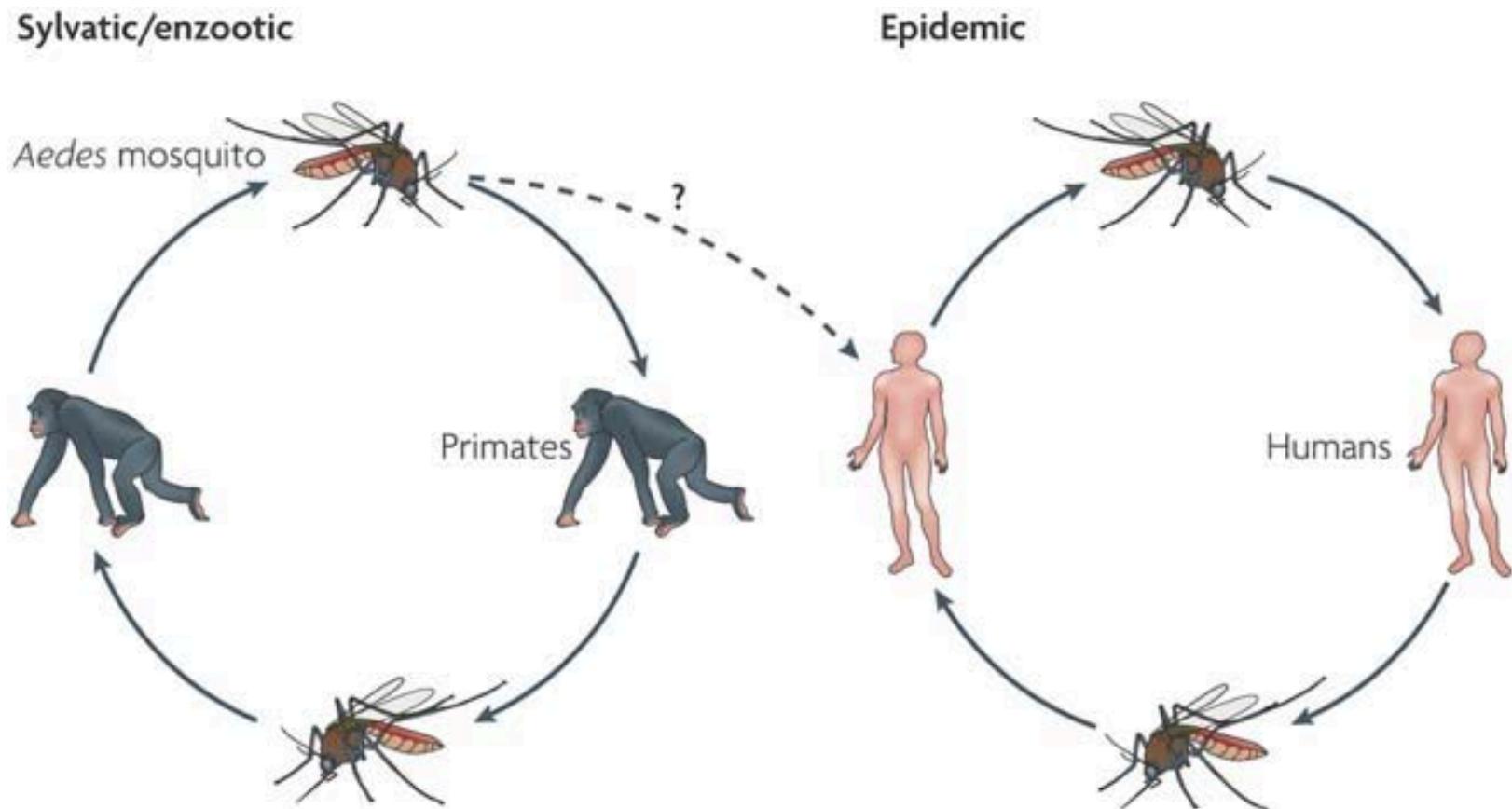
West Nile virus transmission

Human and equine infection is “accidental”

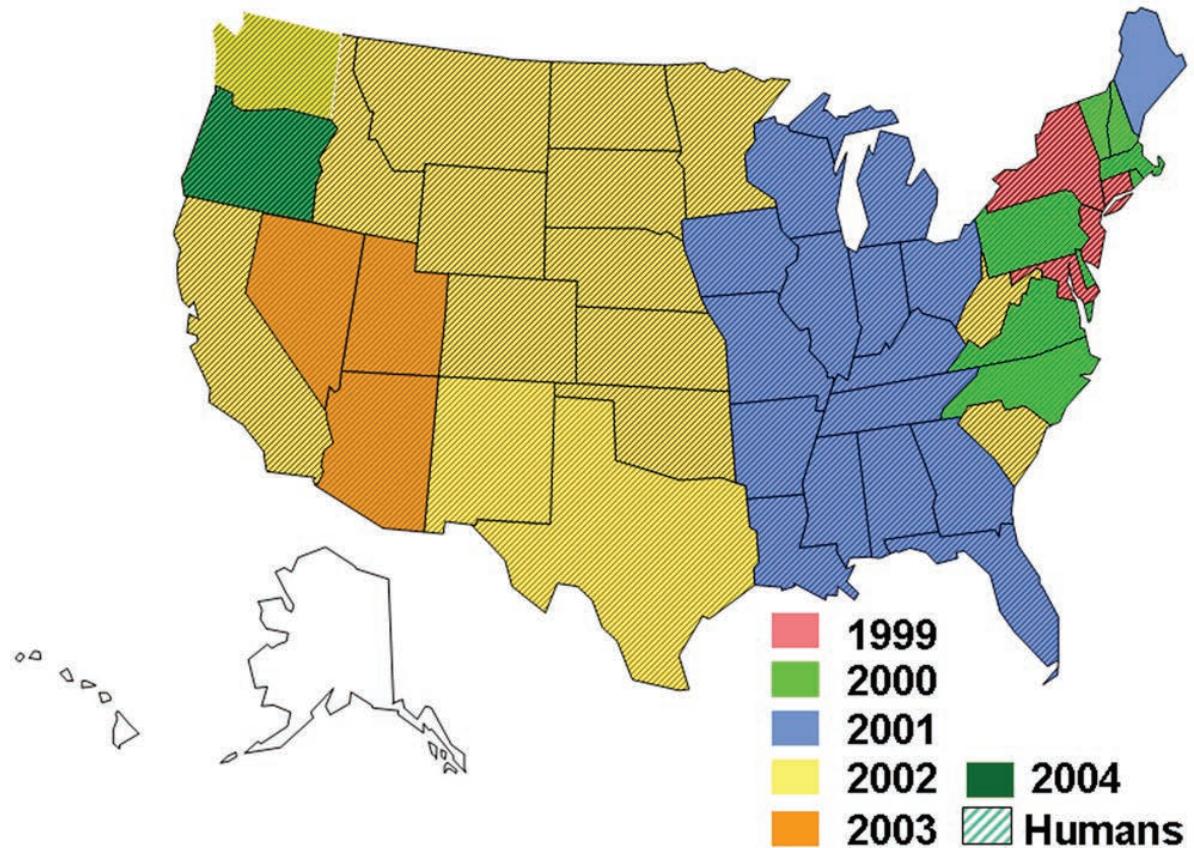


YFV/Zika/Dengue virus transmission

Like YFV, Human infection is “essential”

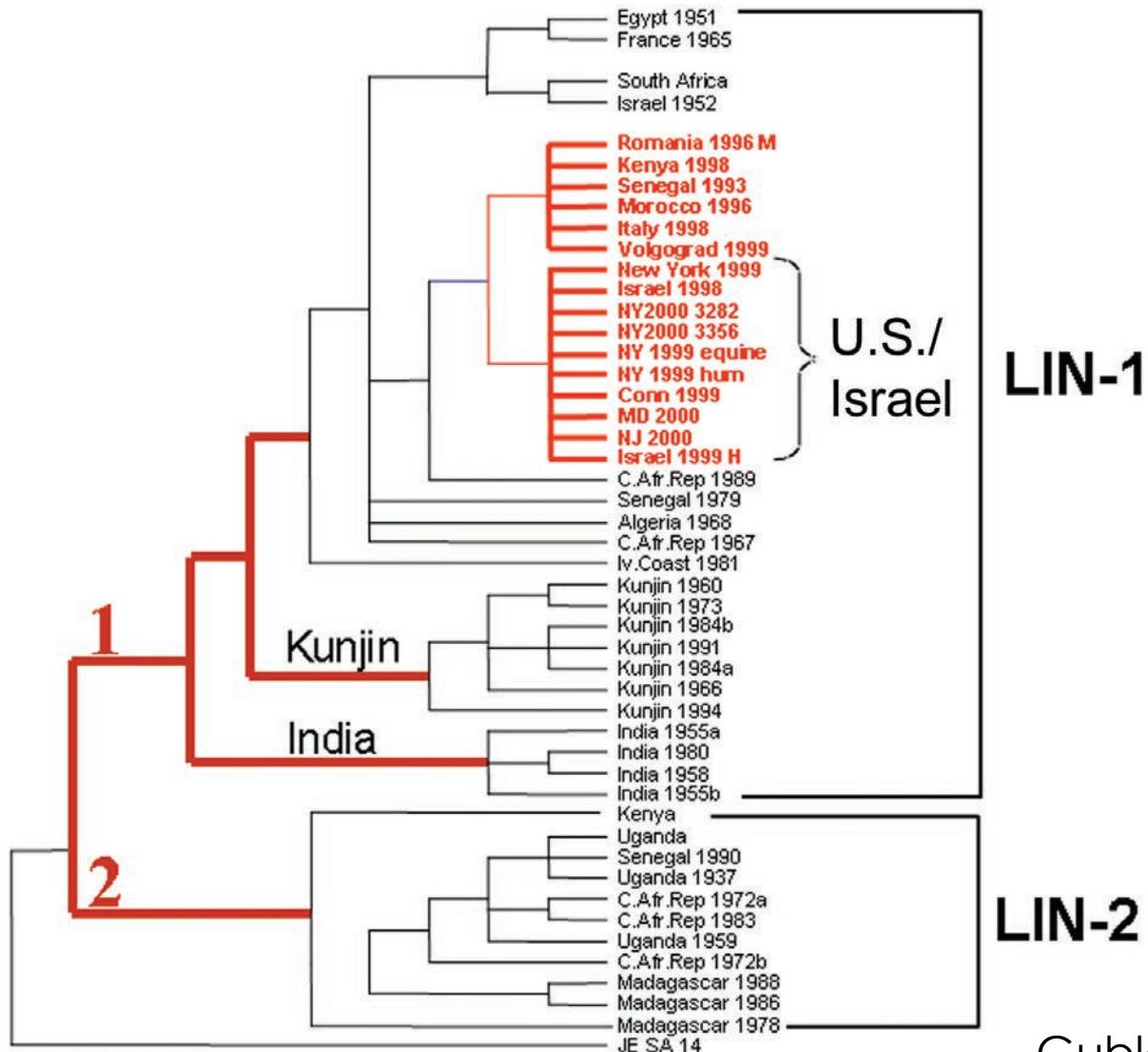


WNV Manifest Destiny



Gubler CID 2007

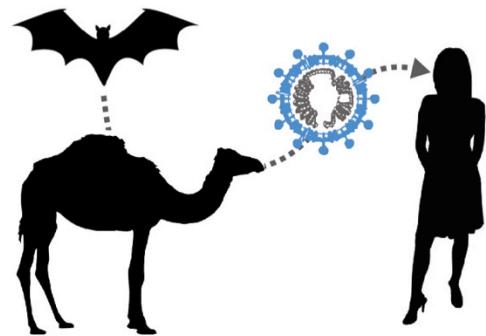
Origin of WNV in USA



Gubler CID 2007

MERS-CoV Emergence

2012
MERS

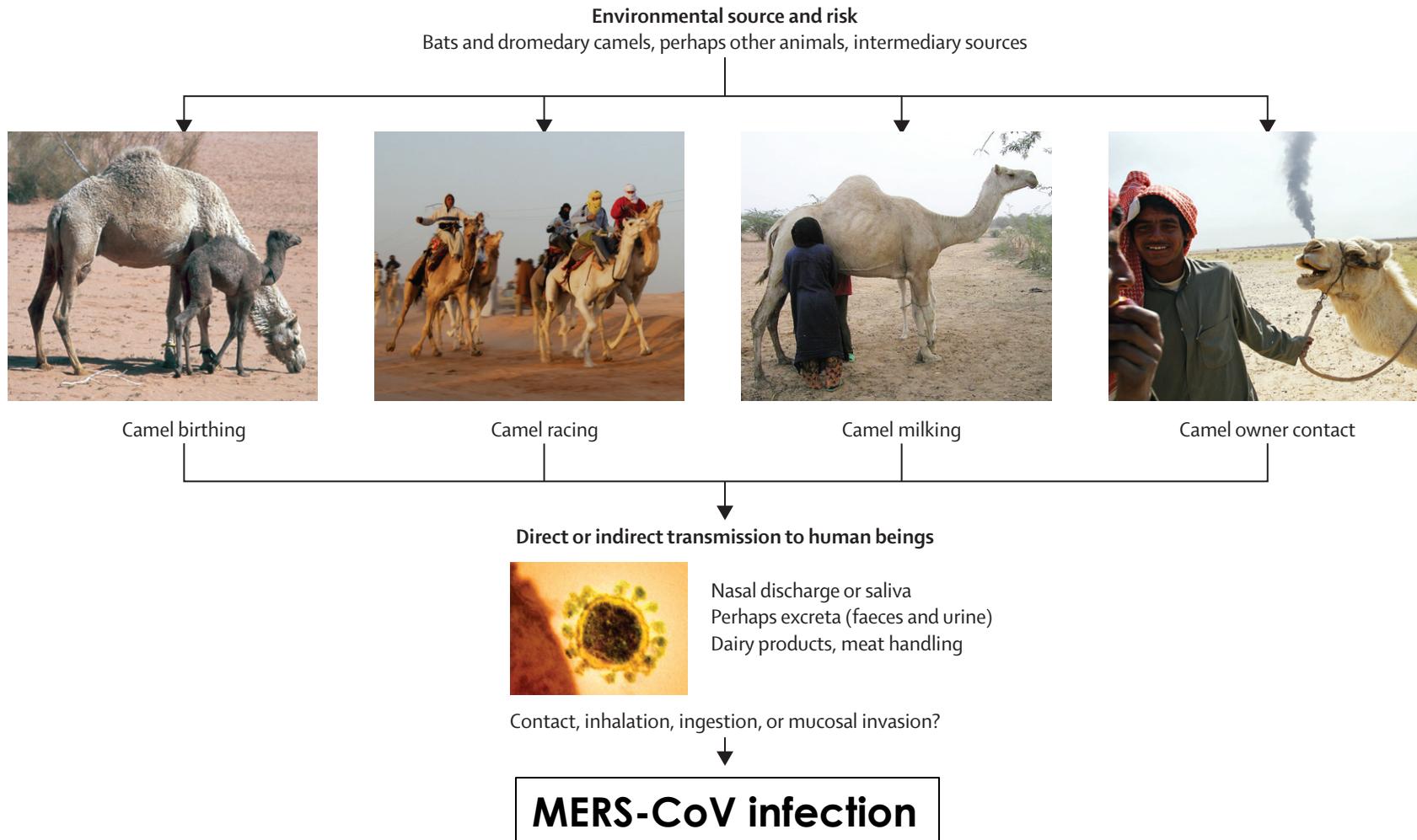


1728 cases
624 deaths
27 countries



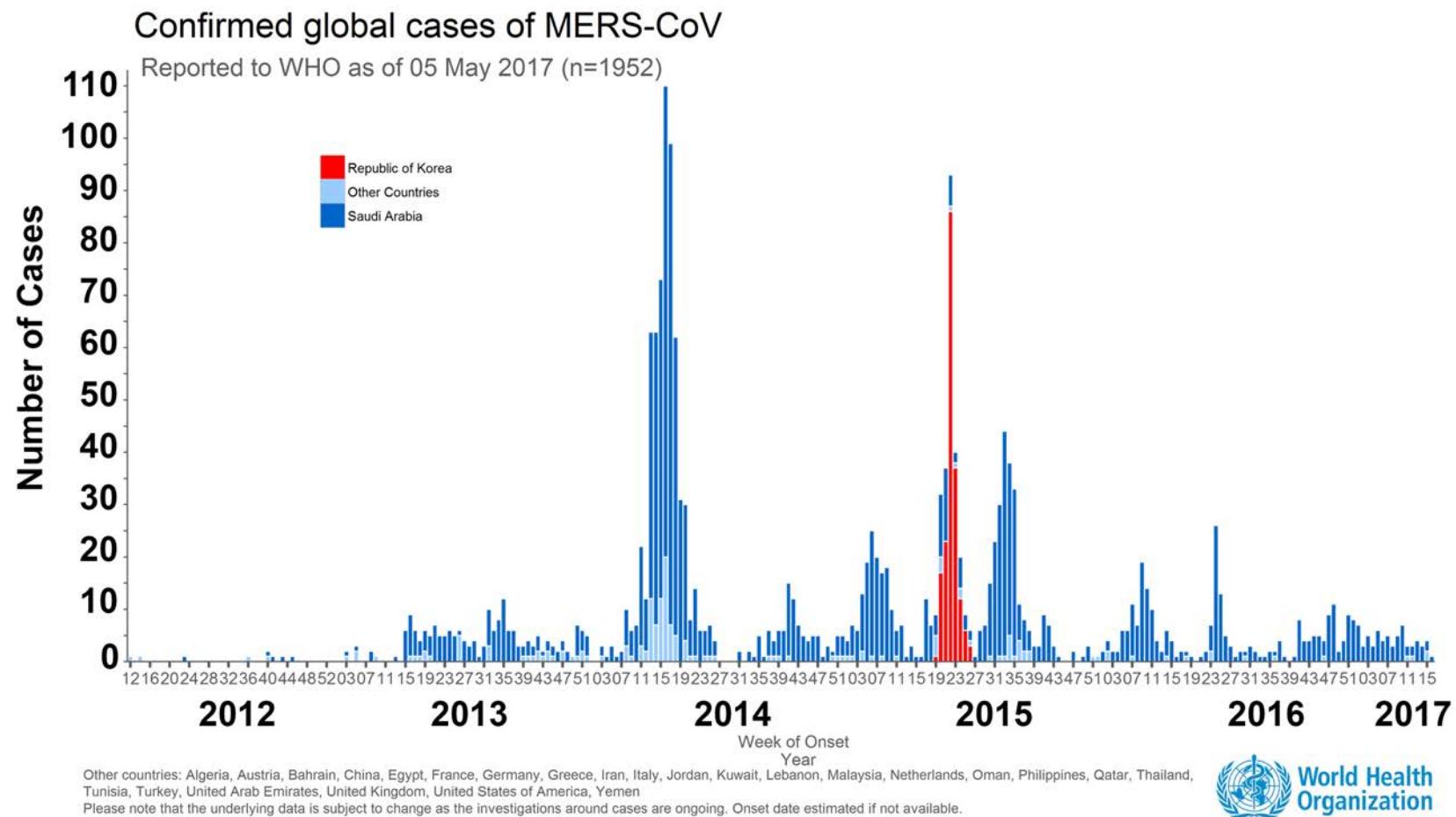
www.who.int

Factors Guiding MERS-CoV Emergence



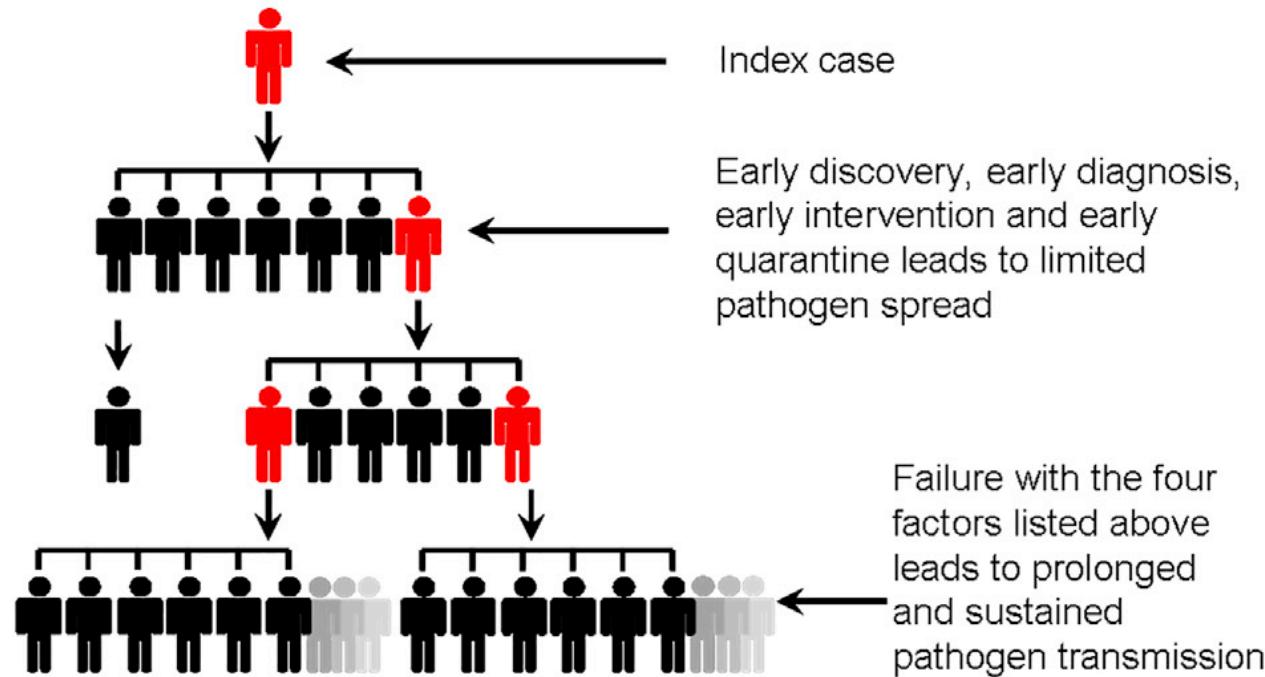
Zumla Lancet 2015

MERS-CoV Epicurve



Super-spreader Events

C Generic infection



Phase of disease is a major factor influencing super-spreading

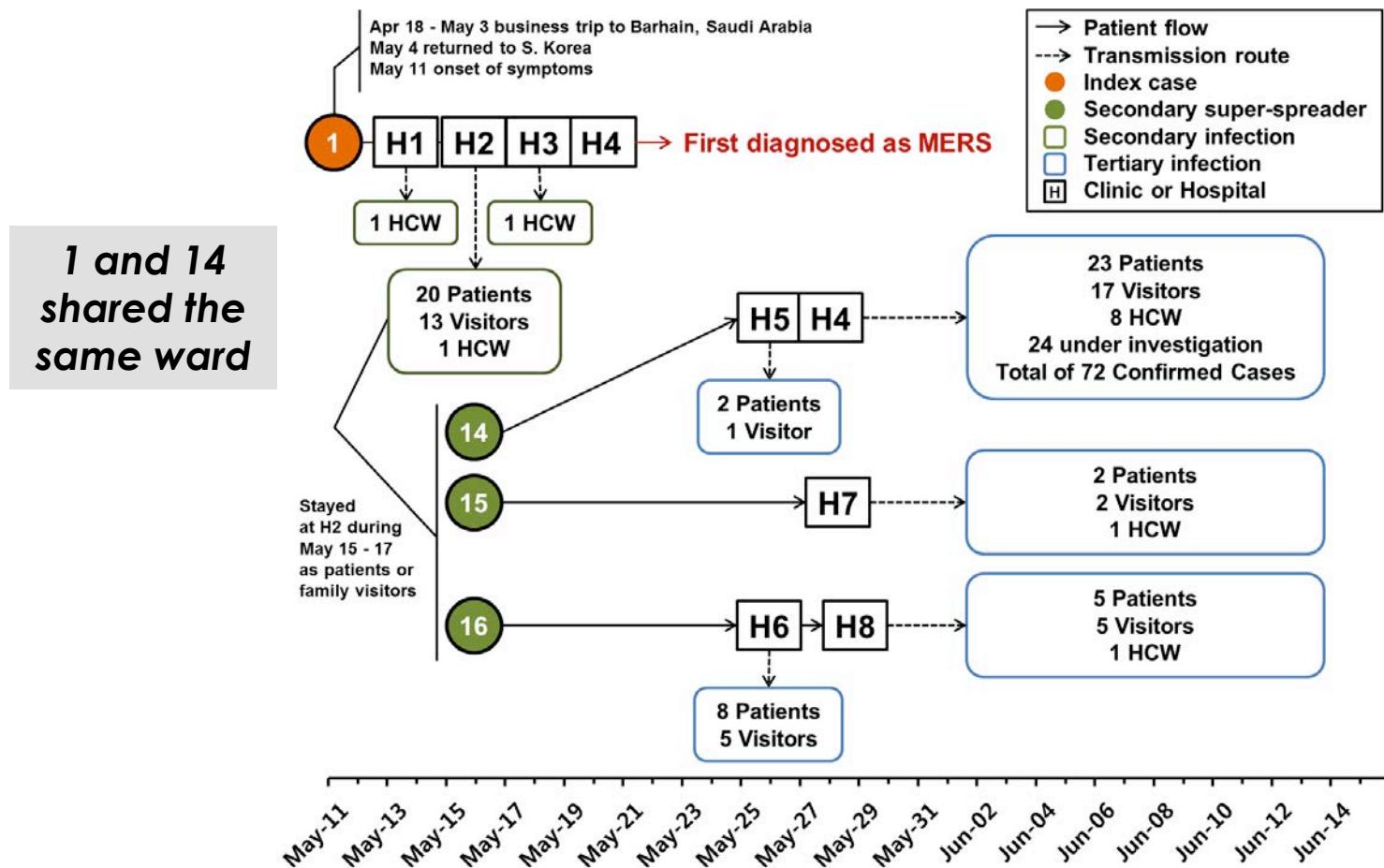
Wong Cell Host Microbe 2015

“During the 9 days before diagnosis, patient 1 visited 4 different healthcare facilities during 7 appointments.

This so-called ‘**doctor shopping**’-a well known South Korean tendency of hopping hospitals for second opinions-is suspected to have encouraged virus transmission.”

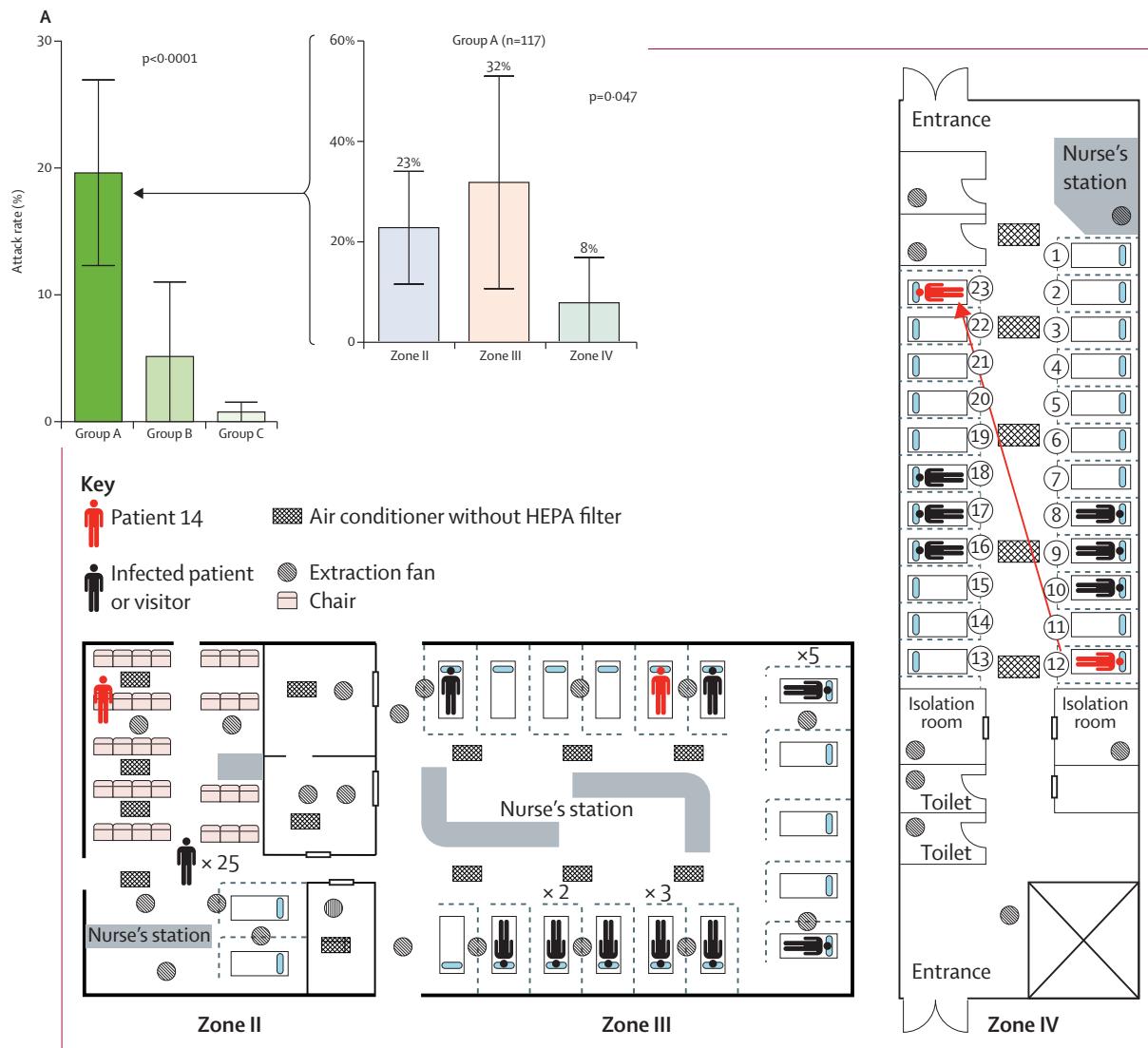
MERS-CoV in South Korea

186 confirmed cases from index patient recently back from KSA



BMJ 2015;350:h3403

MERS-CoV patient 14 super-spreader



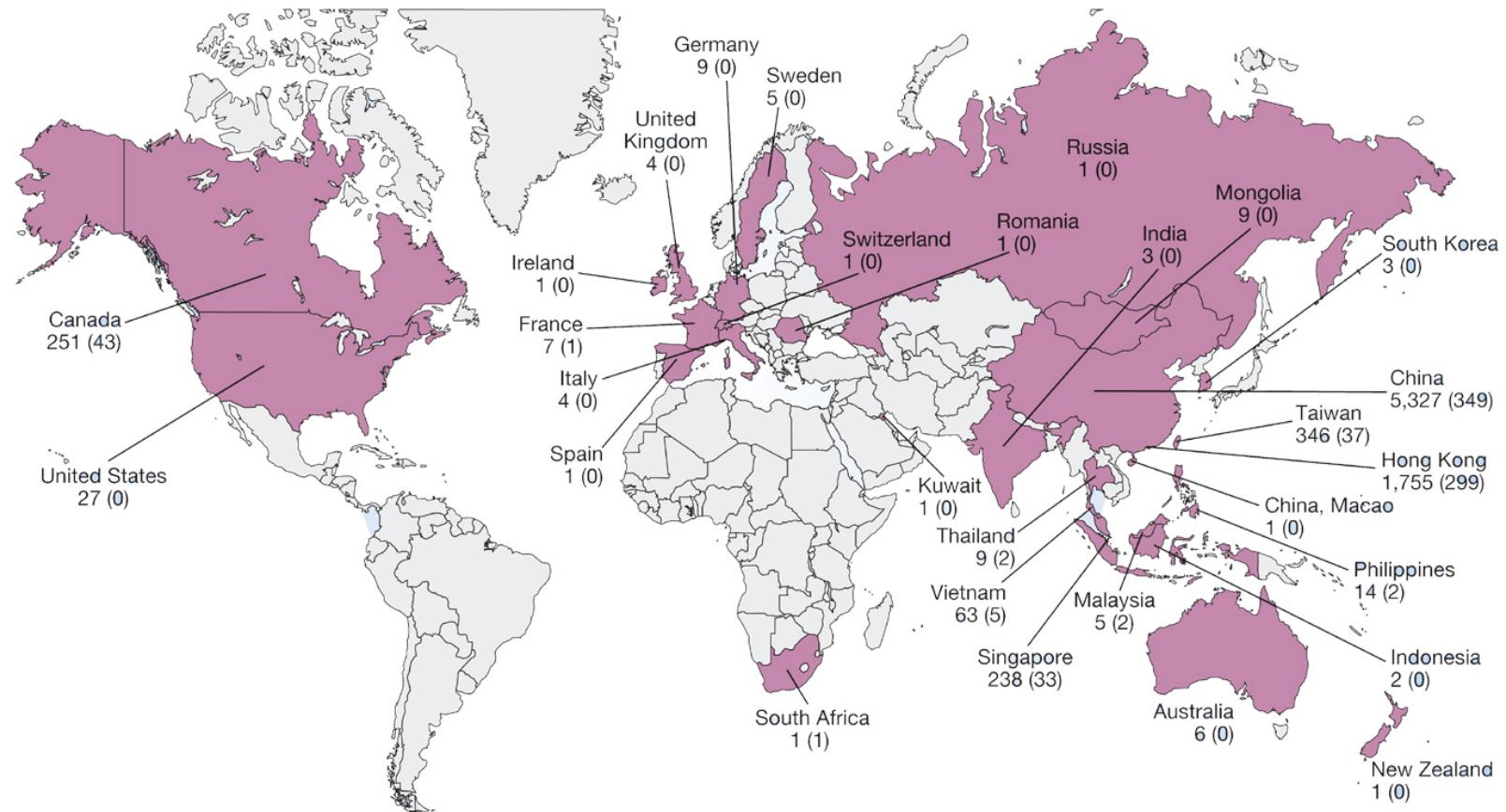
Patient 14 caused 82 cases!

Figure 4: Location of Patient 14 during his stay in the emergency room
HEPA=high-efficiency particulate arrestance.

Lancet 2016;388:994-1001

The global SARS epidemic

8,096 cases, 774 deaths, in 32 countries, Nov 1 2002 - July 31 2003



Lawsuit filed in effort to stop or delay planned

ZONING: Residents say city didn't follow proper procedure

By SUSAN ORR
Staff Writer

GREER — A group of Greenville County residents is suing the city of Greer, the Greer Planning Commission and an area developer in hopes of halting or delaying a planned shopping center.

The development, to be called North Hampton Market, is planned for Highway 29 at Fairview Road, on a 40-acre

tract that recently was annexed into Greer and zoned for highway commercial use.

The lawsuit, filed in Greenville County, alleges that Greer did not follow proper procedures when zoning the property, and it asks the court to either reverse Greer's zoning decision or demand that the zoning process be redone.

Attorney John Martin Foster of Rock Hill filed the suit on behalf of 16 individuals who live in unincorporated Greenville County, in a residential neighborhood very close to the planned development.

Foster said his clients fear the devel-

opment will bring them more traffic and a reduced quality of life.

"The allegation, quite simply, is that all of these people are going to be urbanized," Foster said.

"They're looking at the fact that it's now their neighborhood and it's now about to be changed out from under them."

Among other things, the lawsuit alleges that Greer's planning commission did not base its decision on a comprehensive study of the development's impact on the area; that it did not share its plans with Greenville County; that it did not allow the plaintiffs "a meaningful opportunity to accept, admit,

review, properly consider evidence contrary to the position of plaintiffs"; and that the city adequate notice before a hearing on the matter.

Greer Mayor Rick Danner said the city followed all proper procedure that Greer will file a response.

"We have walked this process 100 times. We feel confident that we've dotted every 'i' and crossed the 't's in this participation," Danner said.

Greer has been sued on various occasions before, Danner said, but is unusual because the plaintiff is not part of the annexation.

Confirmed case of SARS reported in North Carolina

By MARGARET LILLARD
Associated Press

RALEIGH, N.C. — A man who visited Toronto in mid-May contracted severe acute respiratory syndrome, or SARS, the state Department of Health and Human Services said Monday.

It is the eighth confirmed case of SARS in the United States.

The man was identified Friday as having a probable case of the illness. Test results from the Centers for Disease Control and Prevention confirmed the diagnosis, DHHS spokeswoman Carol Schriber said.

The man, a resident of Orange County whose name was withheld, developed a fever and respiratory problems after his trip. DHHS said in a

other acquaintances have been quarantined, she said.

State health officials are working with authorities in Canada to trace the source of his infection, she said. Officials here have gotten in touch with all the people they believe may have been exposed to the man while his condition was infectious, she said.

The state already had eight "suspected" cases of the disease as defined by criteria set by the Centers for Disease Control and Prevention.

The eight were reported in North Carolina between March 19 and April 28. All have fully recovered and their lab tests for SARS have turned out negative to date.

According to the World Health Organization, 8,421



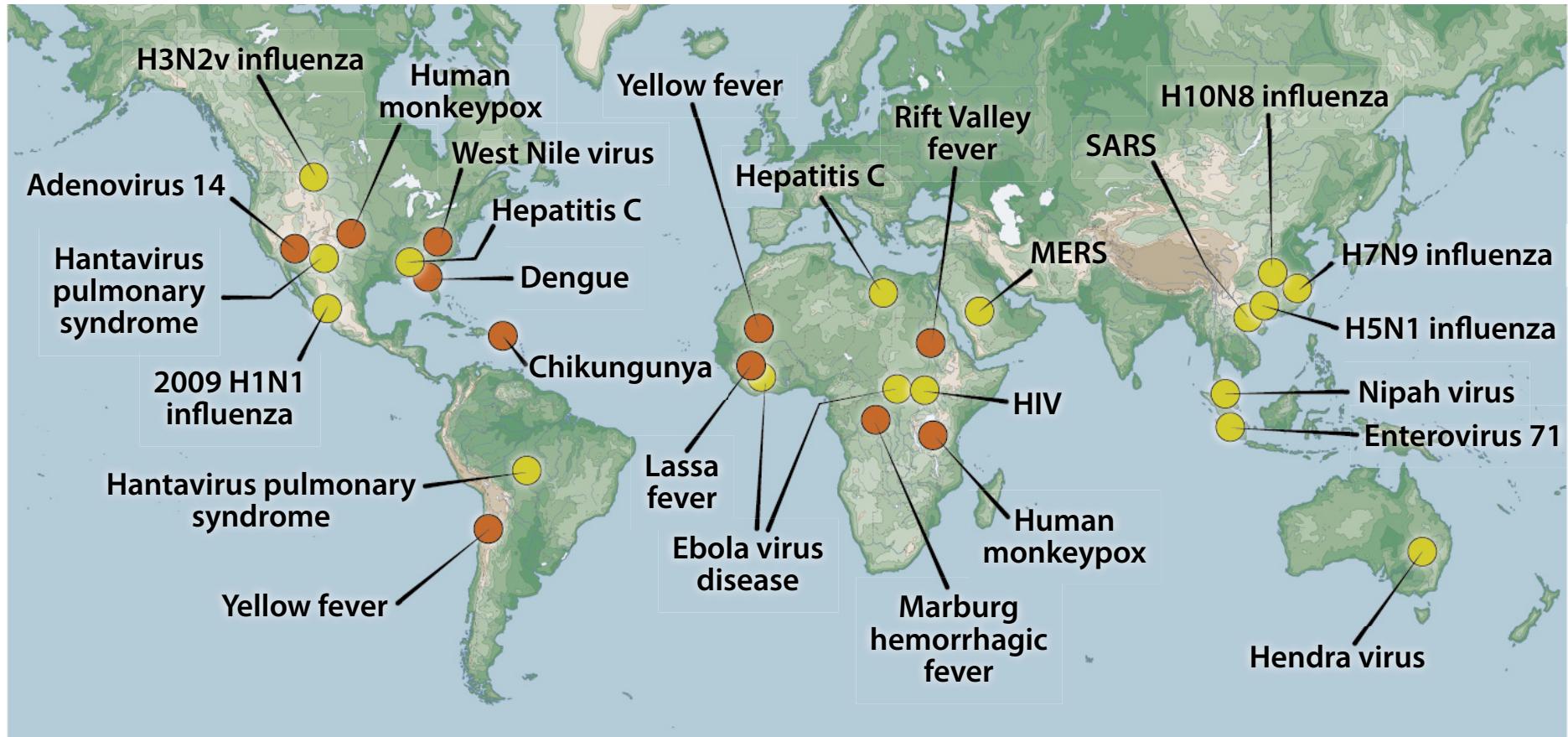
What to do about emerging viruses?

Table 1. Modern technologies that address the challenges of emerging viral infections.

Technology	Application to emerging viral infections
Genomic sequencing	Identification of new agents (such as SARS-CoV and MERS-CoV); evaluation of strain diversity (HIV, MERS-CoV)
Rapid diagnostics	Real-time reverse transcription-PCR for Ebola virus; distinguishing bacterial versus viral causes of certain acute respiratory illness
Structural biology	Vaccine design for influenza, HIV, respiratory syncytial virus; therapeutics design for HIV, HCV
New vaccine platforms	Viral vectors for Ebola virus, Marburg virus, HIV; virus-like particles for chikungunya virus; nanoparticle platforms for influenza virus immunogens

Broad-spectrum therapeutics!

Marston et. al 2014



- Virological factors
- Population growth and urbanization
- Planned human migration
- Human travel
- Vector travel
- Hunting/pasture practices
- Expanding agriculture/deforestation
- Global commerce
- Human social behavior
- Unsafe medical practice
- Hospital practices