COLLEGE OF MEDICINE
The UNIVERSITY of OKLAHOMA

Emerging Infectious Diseases in the Post-COVID-19 World

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Richard C. Staab, DO Memorial Symposium

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Relevant Disclosure and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Douglas A. Drevets MD, DTM&H, FIDSA

I have no relevant financial relationships or affiliations with commercial interests to disclose.

Emerging Infectious Diseases as defined by the NIAID

Infectious diseases that have newly appeared in a population or have existed but are rapidly increasing in incidence or geographic range, or that are caused by one of the NIAID Category A, B, or C priority pathogens

https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens
Content last reviewed on July 26, 2018

What Do EID Look Like?

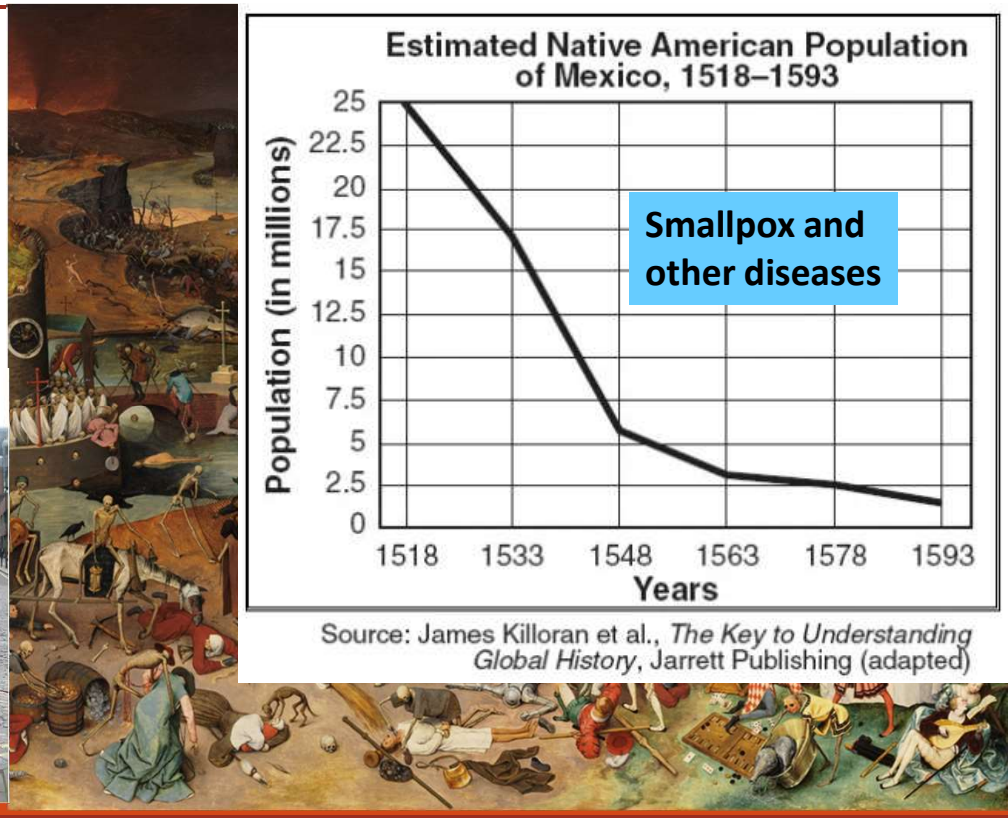
- **Local, small numbers**
  - Alaskapox
- **Regional impact, limited numbers**
  - Middle Eastern Respiratory Syndrome
- **Cross-continent, limited numbers**
  - SARS
- **Pandemic**
  - Limited numbers, e.g. MPOX
  - Unlimited numbers, e.g. SARS-2-CoV

Emerging Infectious Diseases

Historical EID That Went Pandemic

- **Bubonic Plague**
  - 1st pandemic: 541 to 750 AD
  - 2nd pandemic: 14th -16th century
  - 3rd pandemic: 1855 – early 20th century
- **Syphilis** (The Great pox) 15th-17th century
- **Smallpox** 16th-18th centuries
- **Tuberculosis** 18th century
- **Cholera** 19th century
- **Influenza** 20th century
- **HIV** 20th century

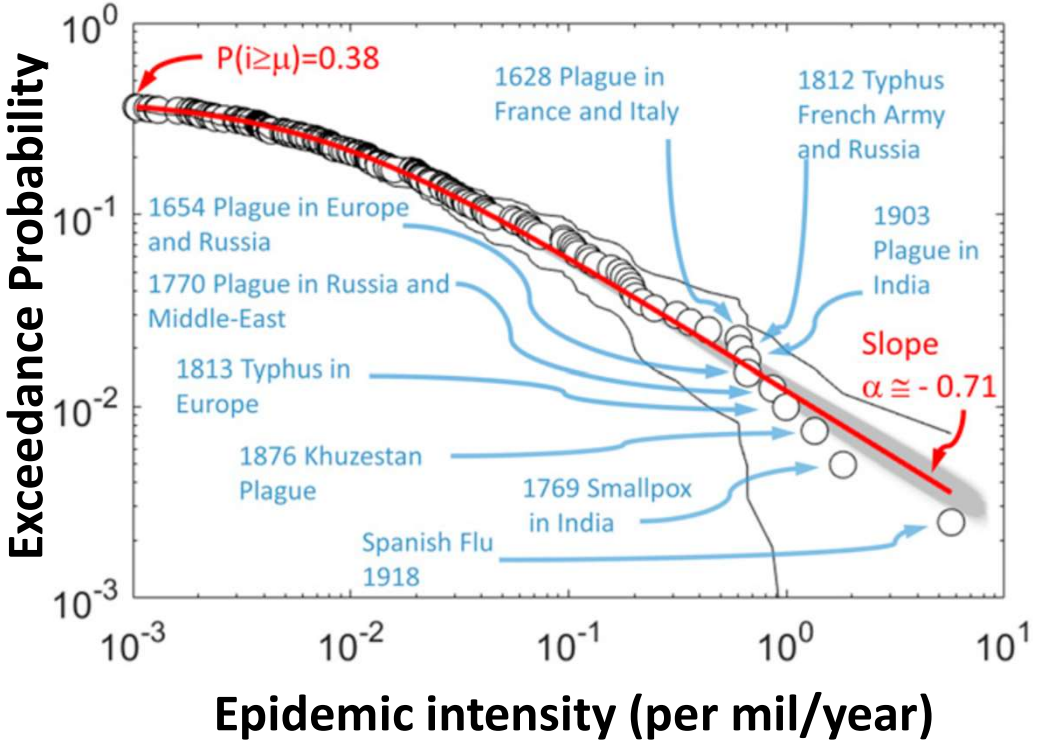
John Snow memorial
London,UK



The Triumph of Death Pieter Bruegel the Elder

Source: James Killoran et al., *The Key to Understanding Global History*, Jarrett Publishing (adapted)

Another pandemic! What are the chances?

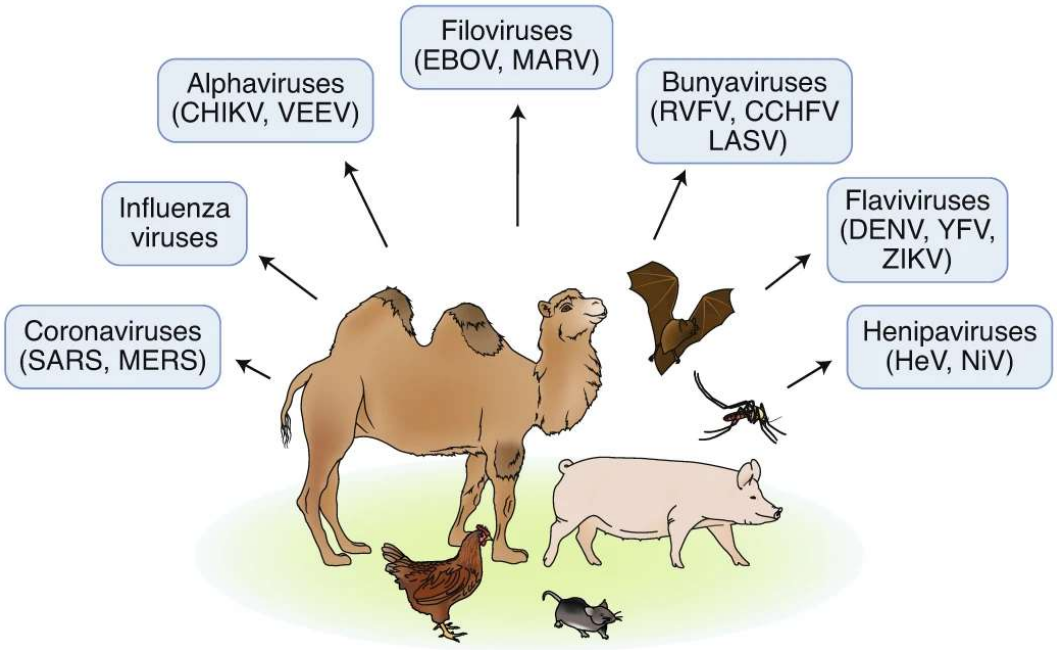


- A dataset of historical epidemics from 1600 to present was used to estimate the yearly probability of occurrence of extreme epidemics
- Yearly occurrence probabilities of extreme epidemics with the intensity of the "Spanish flu" varies between 0.27 and 1.9%
- The probability of experiencing pandemics similar to COVID-19 in one's lifetime is about 38% and may double in coming decades.

PNAS 2021 Vol. 118 No. 35 e2105482118
https://doi.org/10.1073/pnas.2105482118

How Does Emergence Happen?

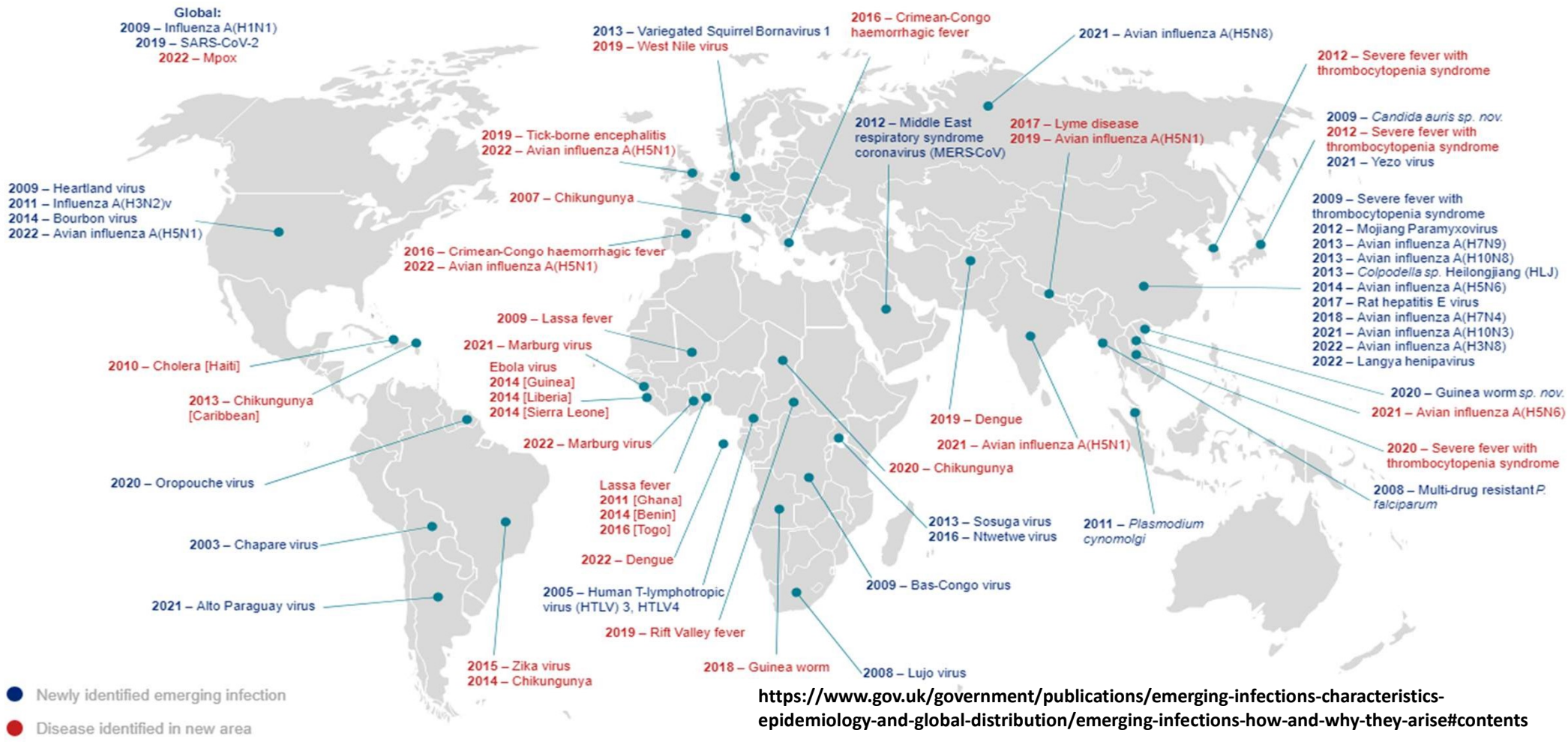
- Between 60% and 80% of EID are derived from animal sources.
- Emergence involves 2 main steps
  - Introduction of a microbe into a new host population.
  - The microbe becomes established an transmitted within the population



https://www.gov.uk/government/publications/emerging-infections-characteristics-epidemiology-and-global-distribution/emerging-infections-how-and-why-they-arise#contents

Nature Medicine volume 27, pages401–410 (2021)

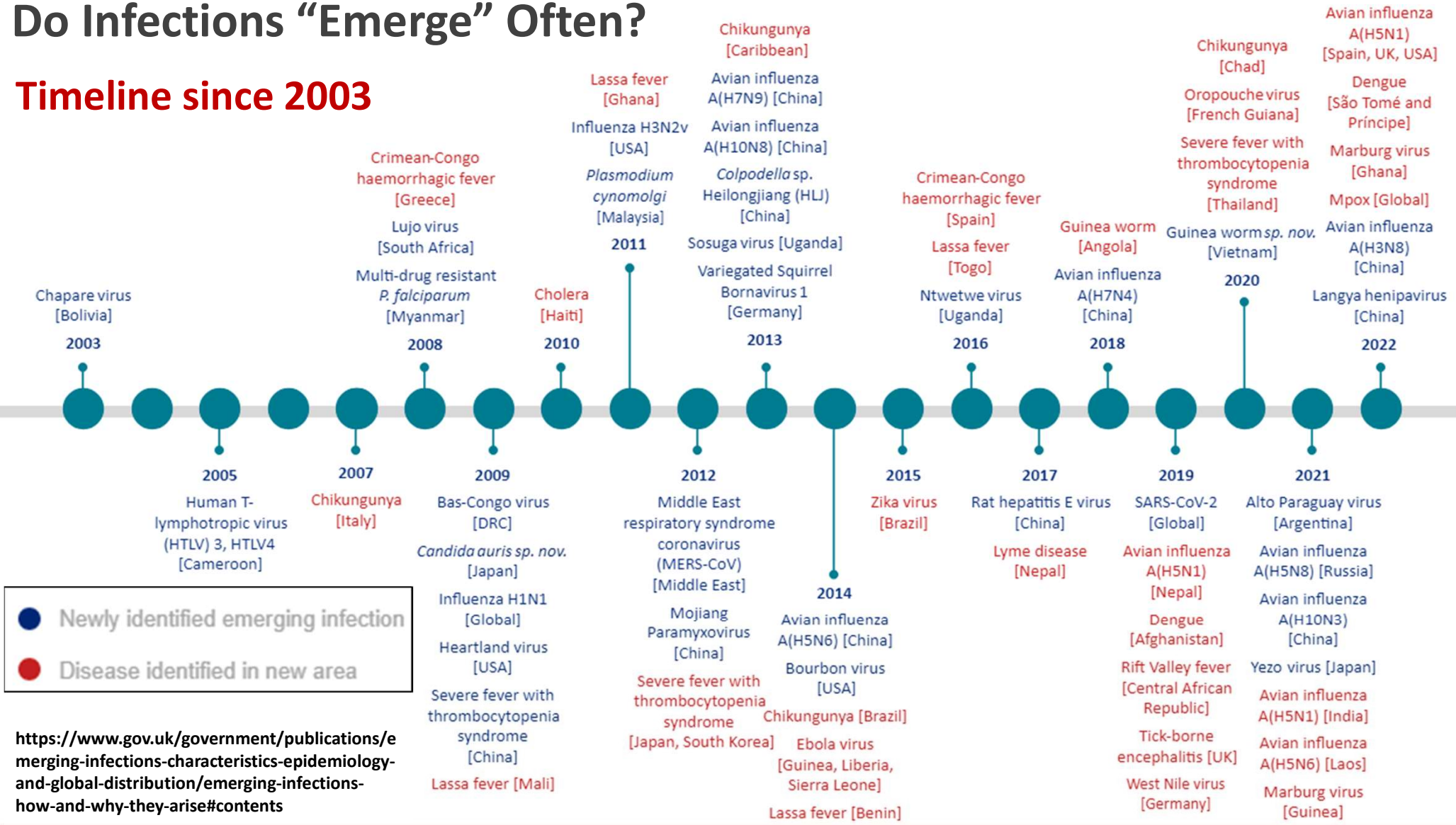
Geography of EID Since 2003



https://www.gov.uk/government/publications/emerging-infections-characteristics-epidemiology-and-global-distribution/emerging-infections-how-and-why-they-arise#contents

Do Infections "Emerge" Often?

Timeline since 2003



https://www.gov.uk/government/publications/emerging-infections-characteristics-epidemiology-and-global-distribution/emerging-infections-how-and-why-they-arise#contents

Factors That Trigger Emergence

- Multiple factors contribute to the emergence/re-emergence of infectious diseases
- The factors often differ between '**newly emerging**', '**re-emerging**' and '**deliberately emerging**' diseases

- Microbial adaptation and change
- Human susceptibility to infection
- Climate and weather
- Changing ecosystems
- Human demographics and behavior
- Economic development and land use

- International travel and commerce
- Technology and industry
- Breakdown of public health measures
- Poverty and social inequality
- War and famine
- Lack of political will
- Intent to harm

Nature volume 430, pages242–249 (2004)

Any Vector Borne Disease Can Emerge Outside Its Region Due to Change in Vector Range

Vector		Disease caused	Type of pathogen
Mosquito	***Aedes***	Chikungunya	Virus
		Dengue	Virus
		Lymphatic filariasis	Parasite
		Rift Valley fever	Virus
		Yellow Fever	Virus
		Zika	Virus
	Anopheles	Lymphatic filariasis	Parasite
		Malaria	Parasite
	Culex	Japanese encephalitis	Virus
		Lymphatic filariasis	Parasite
		West Nile fever	Virus
Aquatic snails		Schistosomiasis	Parasite
Blackflies		Onchocerciasis	Parasite

Vector	Disease caused	Type of pathogen
Fleas	Plague	Bacteria
	Tungiasis	Ectoparasite
Lice	Typhus	Bacteria
	Louse-borne relapsing fever	Bacteria
Sandflies	Leishmaniasis	Parasite
	Sandfly fever	Virus
Ticks	Crimean-Congo hemorrhagic fever	Virus
	Lyme disease	Bacteria
	Relapsing fever (borreliosis)	Bacteria
	Rickettsial diseases	Bacteria
	Tick-borne encephalitis	Virus
	Tularaemia	Bacteria
Triatome bugs	Chagas disease	Parasite
Tsetse flies	Sleeping sickness	Parasite

https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases

Ticks as Vectors of Emerging Infectious Diseases

- 1975 – **Lyme disease** identified in Connecticut, now in 70 countries/5 continents.
- 1994 – **HGA**, **HME**, and ***B. microti*** identified in humans.
- 2004 – ***Candidatus* Neoehrlichia mikurensis**, identified in Japan and now reported elsewhere in Asia, Europe and Africa.
- 2007- **Severe Fever with Thrombocytopenia Syndrome** (STFS) – discovered in China, also found in Japan & Korea.
- 2009 – **Heartland virus**, first identified in humans in Missouri, subsequently found in ticks is 13 states.
- 2014 – **Bourbon virus**?

American Dog Tick

Lone Star Tick

Black legged Tick

Baneth, Int. J. Parasitology. 44:591, 2014

www.cdc.gov/ticks/life_cycle_and_hosts

Mosquitos and Emerging Infectious Diseases (Mosquitos not actually life-sized)

Ades aegypti

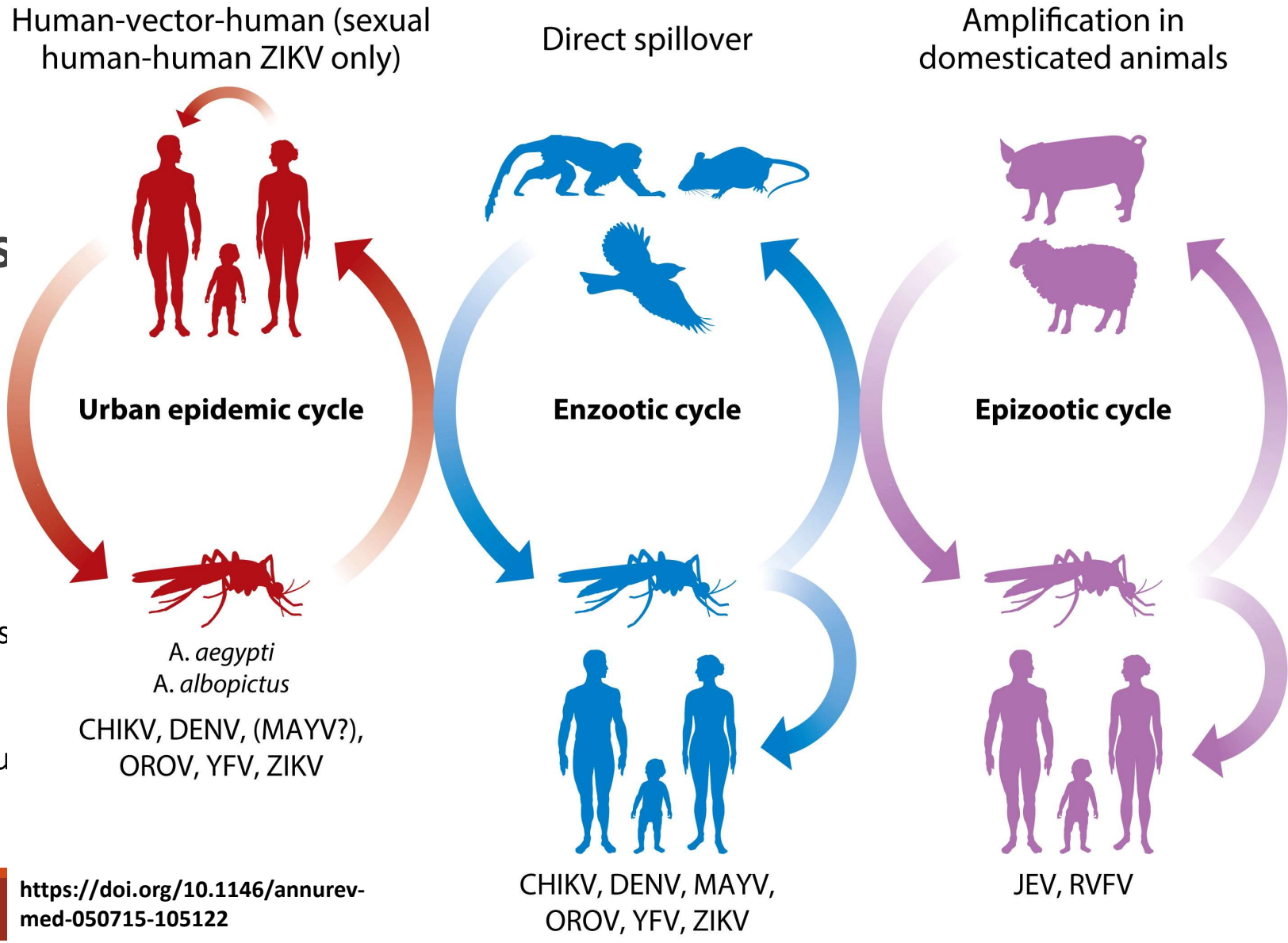
yellow fever virus, dengue virus, chikungunya virus, Zika virus

Ades albopictus

chikungunya virus, dengue virus and dirofilariasis

https://www.ecdc.europa.eu/en/disease-vectors/facts/mosquito-factsheets/aedes-albopictus

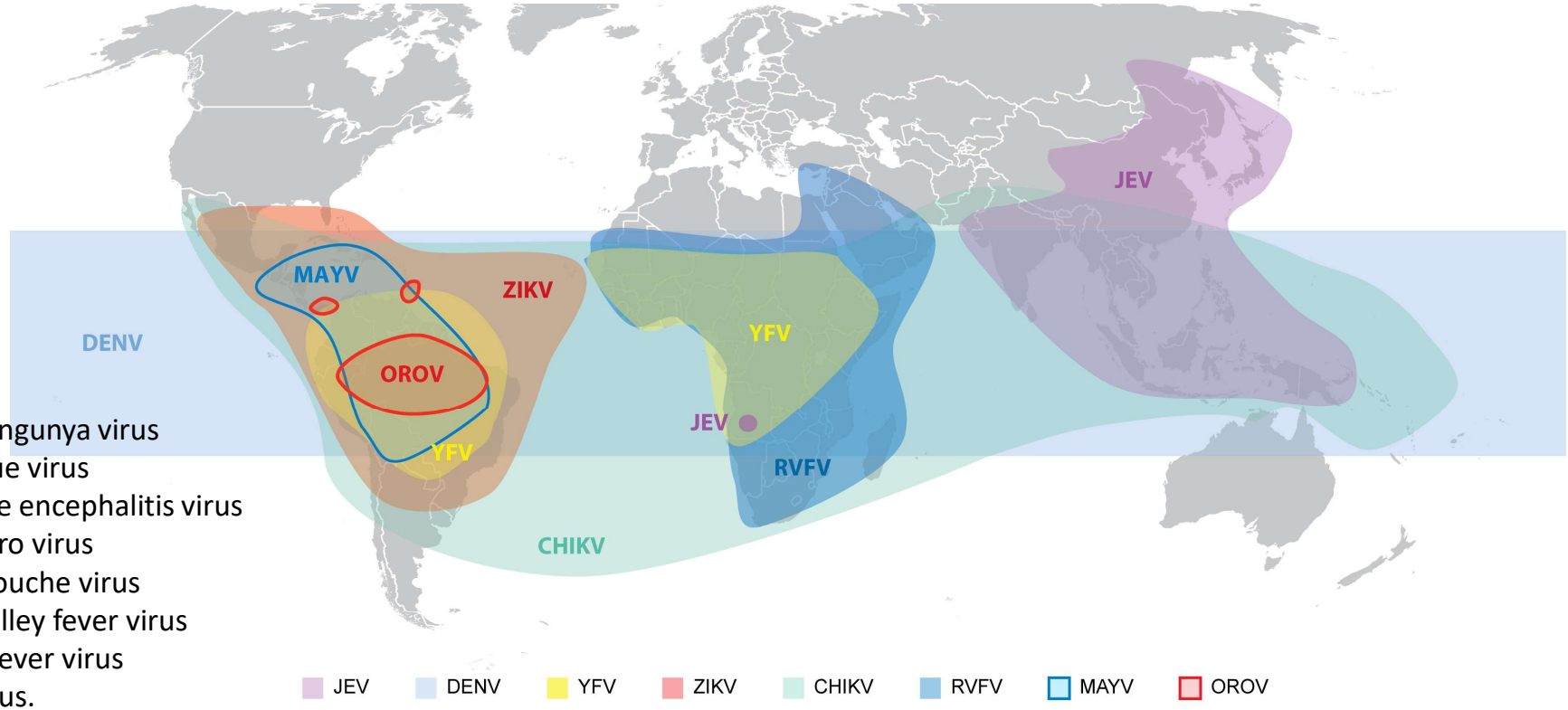
Emergence Mechanisms for Arboviruses



CHIKV, chikungunya virus
DENV, dengue virus
JEV, Japanese encephalitis
MAYV, Mayaro virus
OROV, Oropouche virus
RVFV, Rift Valley fever virus
YFV, yellow fever virus
ZIKV, Zika virus.

https://doi.org/10.1146/annurev-med-050715-105122

Reported Distributions of Emerging Arboviruses



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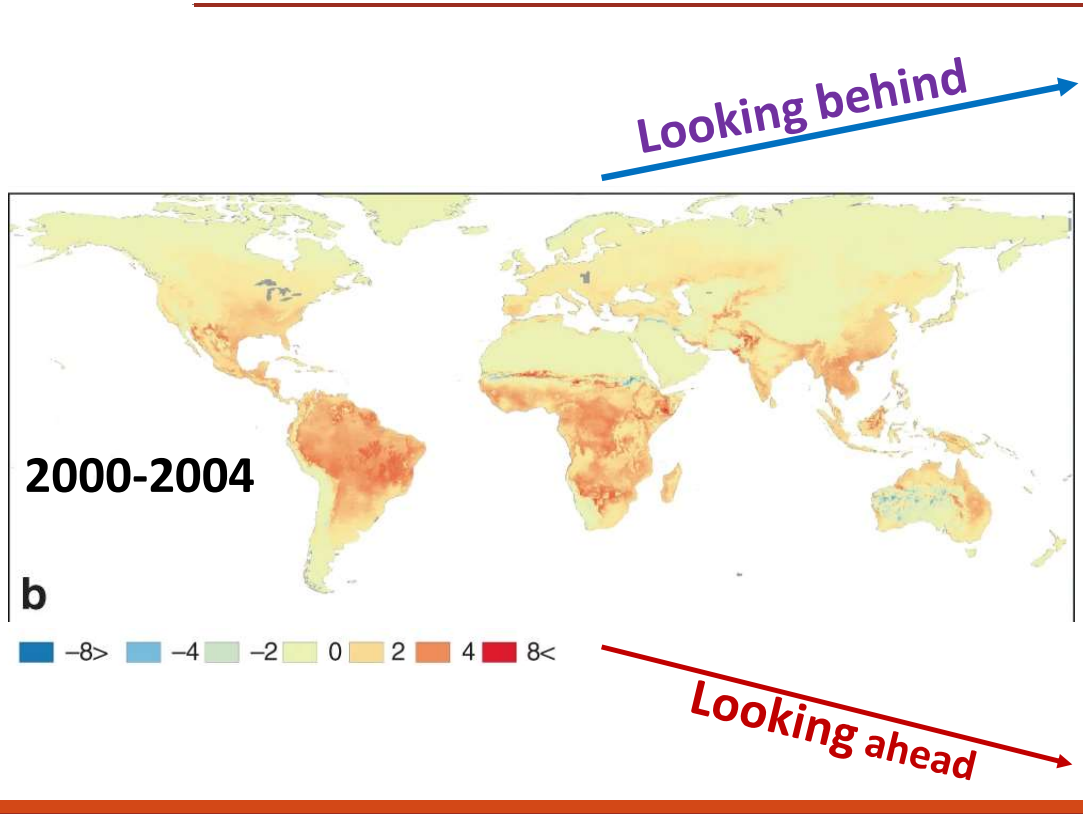
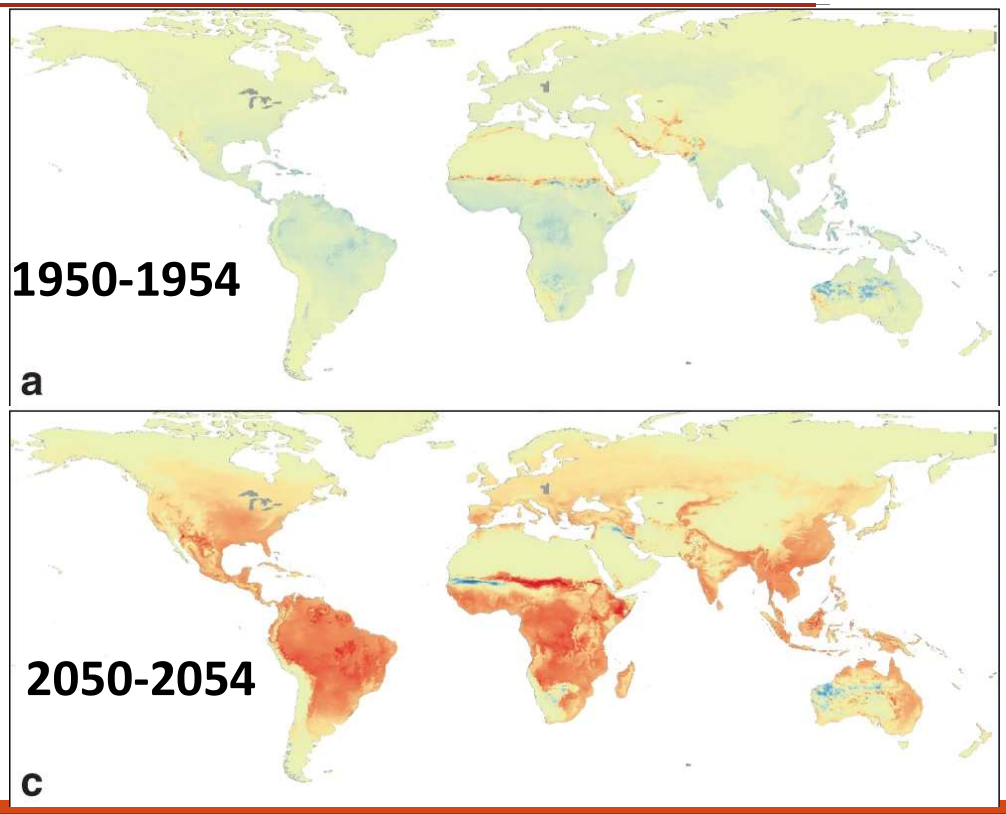
https://doi.org/10.1146/annurev-med-050715-105122

Differences in Life Cycle Completion of *Aedes aegypti* in 1950's and 2050's Relative to 2000's





https://www.nature.com/articles/s41467-020-16010-4

Key Lessons from History and Epidemiology

- EID most commonly are zoonoses that jump species to humans
  - Often involving a mammalian intermediate
  - Often vector borne – and vectors can move
  - Associated with mass movements of people
- Pandemic EID have shaped history, and will continue to do so
- Anytime, anywhere
- Frequent
- Another pandemic is inevitable, “WHEN not IF”

Emerging Infectious Diseases For Further Discussion

- MPOX
- Heartland virus
- Dengue

https://en.m.wikipedia.org/wiki/File:Chevalier_Roze_%C3%A0_la_Tourette_-_1720.PNG

Chevalier Roze à la Tourette – 1720
Michel Serre

MPOX (formerly known as Monkeypox virus) A brief history

- **1958** – identified in 2 colonies of laboratory monkeys with a pox-like illness
- **1970** - human MPOX infection identified in Dem. Rep. of Congo (formerly Zaire).
- **1970 - early 2000's** - sporadic disease/epidemics in Central and W. Africa.
  - Majority of cases were found in children, case fatality rates of 1-17%
  - Considered a zoonotic infection acquired from mammals (rodents, non-human primates)
  - 2 clades, Congo Basin and West African
  - 2003 – 47 cases in USA linked to infected rodents imported from Ghana
- **2017**- Nigeria, re-emergent outbreak in Nigeria with >100 suspected cases with epidemiological features that diverged from prior outbreaks.
- **2022** – rapid pandemic spread 93,497 global cases

Natural/Competent Hosts of MPOX virus

Host (species)	Location or Country
Gambian-pouched rat	Africa
Rhesus macaques	Copenhagen
Cynomolgus Macaque	Singapore/Copenhagen
Asian Monkeys	Copenhagen
Southern opossum	South America
Sun squirrel	Zaire
African hedgehogs	Africa
Jerboas	Illinois, USA
Sooty mangabey	Côte d'Ivoire

Host (species)	Location or Country
Woodchucks	USA
Short-tailed opossum	USA
Porcupines	Zaire
Giant anteaters	Rotterdam
Prairie dogs	USA
Elephant shrew	DR Congo
Domestic pig	DR Congo
Rope squirrel	Zaire
African dormice	USA

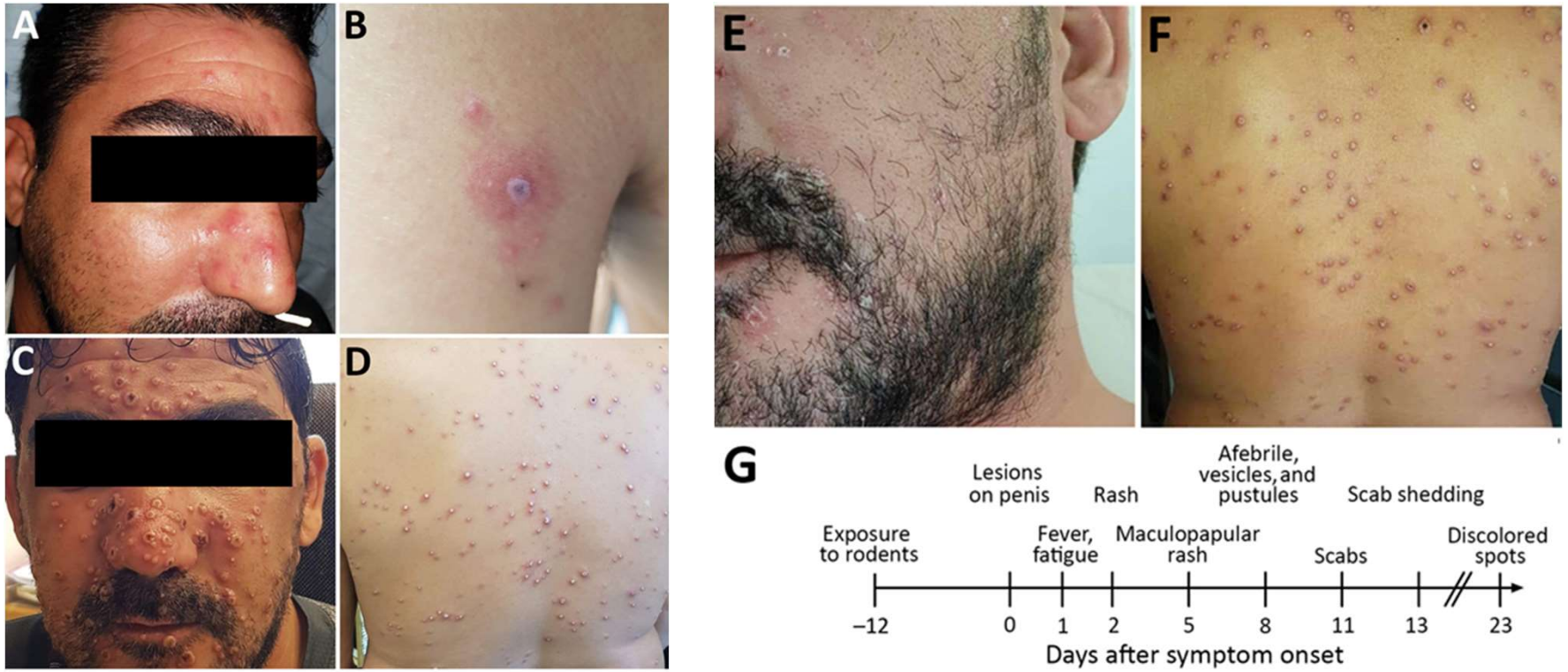
Viruses **2020, *12*(11), 1257; https://doi.org/10.3390/v12111257**

Exportation of MPOX from Nigeria 2018

Case	Age	Nationality	Sex	Reported Exposure & Risks	Other
UK1	32y	Nigerian	M	None	Lesions first appeared in groin
UK2	36y	Nigerian	M	Consumption of bushmeat and sick contact	Lesions first appeared in groin
UK3	40y	British	F	HCW who had contact with UK2	Sequencing confirmed same virus
ISR	38y	Israeli	M	Disposed of 2 rodent carcasses while traveling in Nigeria	Lesions first appear on penis
SING	38y	Nigerian	M	Reported potentially eating BBQ bushmeat at a wedding	Lesions on penis
BAY	30y	Nigerian	M	Occupational (HCW) from Bayelsa state	Bayelsa is adjacent to states (visited by export cases)

JID 2022, https://doi.org/10.1093/infdis/jiaa559
Eurosur 2018 https://doi.org/10.2807/1560-7917.ES.2018.23.38.1800509
EID 2020 10.3201/eid2608.191387
EID 2019 https://doi.org/10.3201/eid2505.190076

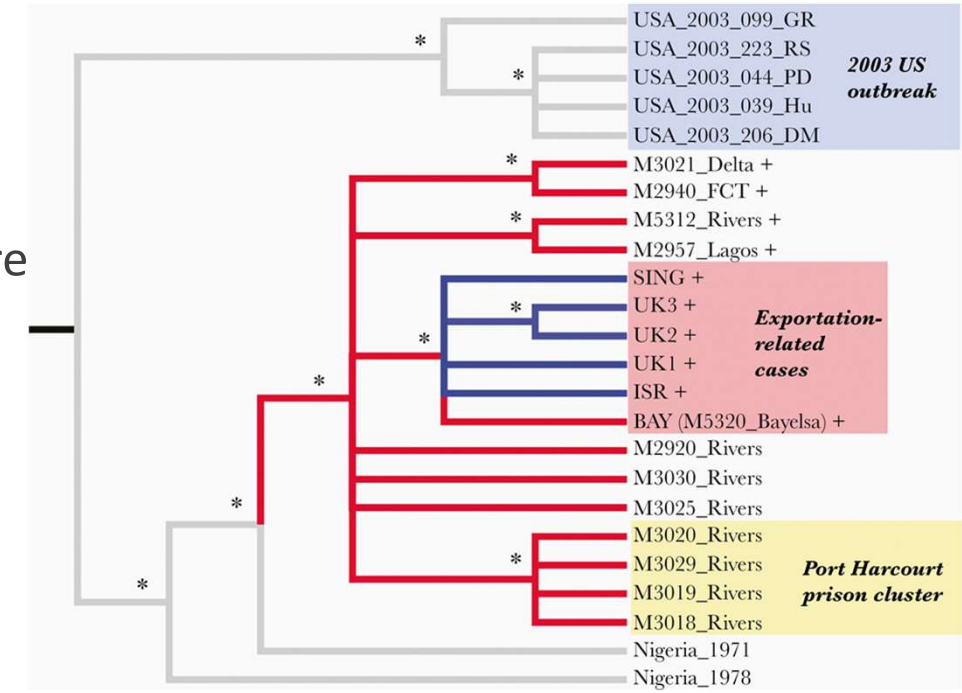
Human MPOX Infection: Israel 2018



EID 2019 https://doi.org/10.3201/eid2505.190076

Human MPOX: Just Before 2022

- **Key epidemiological points**
  - Animal contact diminished over time
  - Intra-household spread occurs
  - Contact with an active case became more relevant over time.
  - Data from 2017-2019 suggest new transmission networks – potentially via sexual spread – occurs in non-endemic counties
  - Genetic relatedness among cases

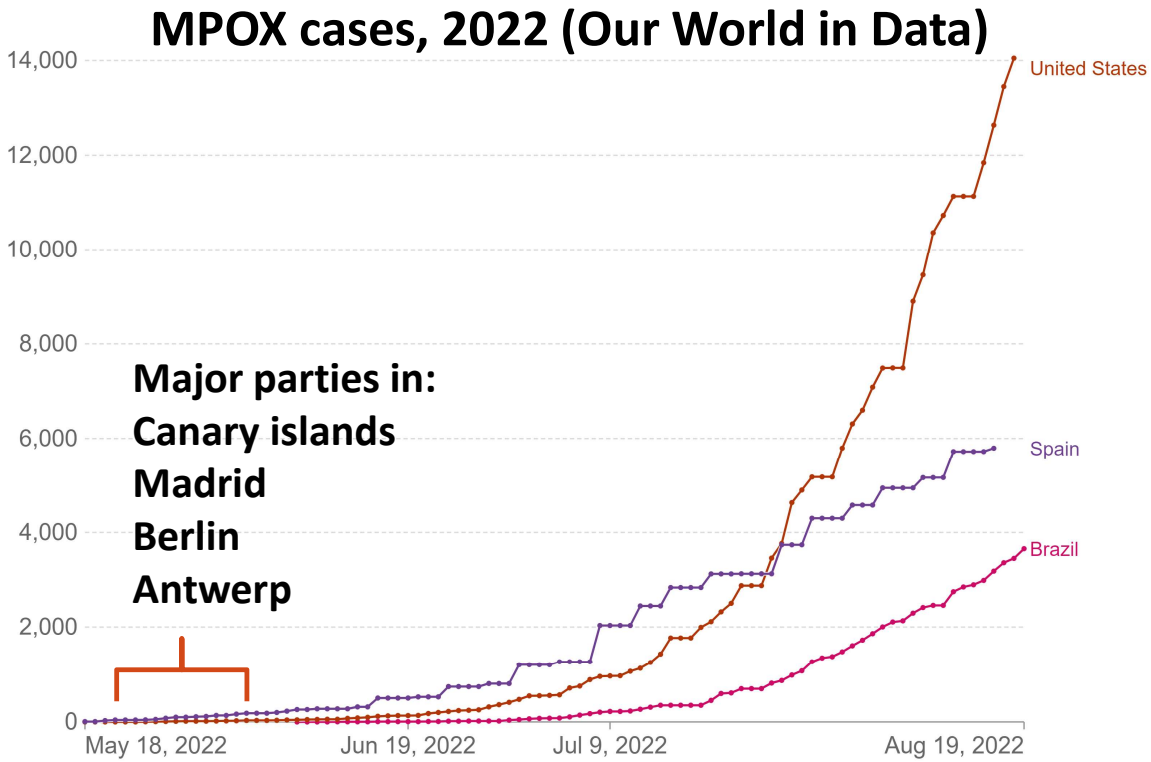


PLOS NTD 2019, https://doi.org/10.1371/journal.pntd.0007791
PNAS 2010 https://doi.org/10.1073/pnas.1005769107

JID 2022, https://doi.org/10.1093/infdis/jiaa559

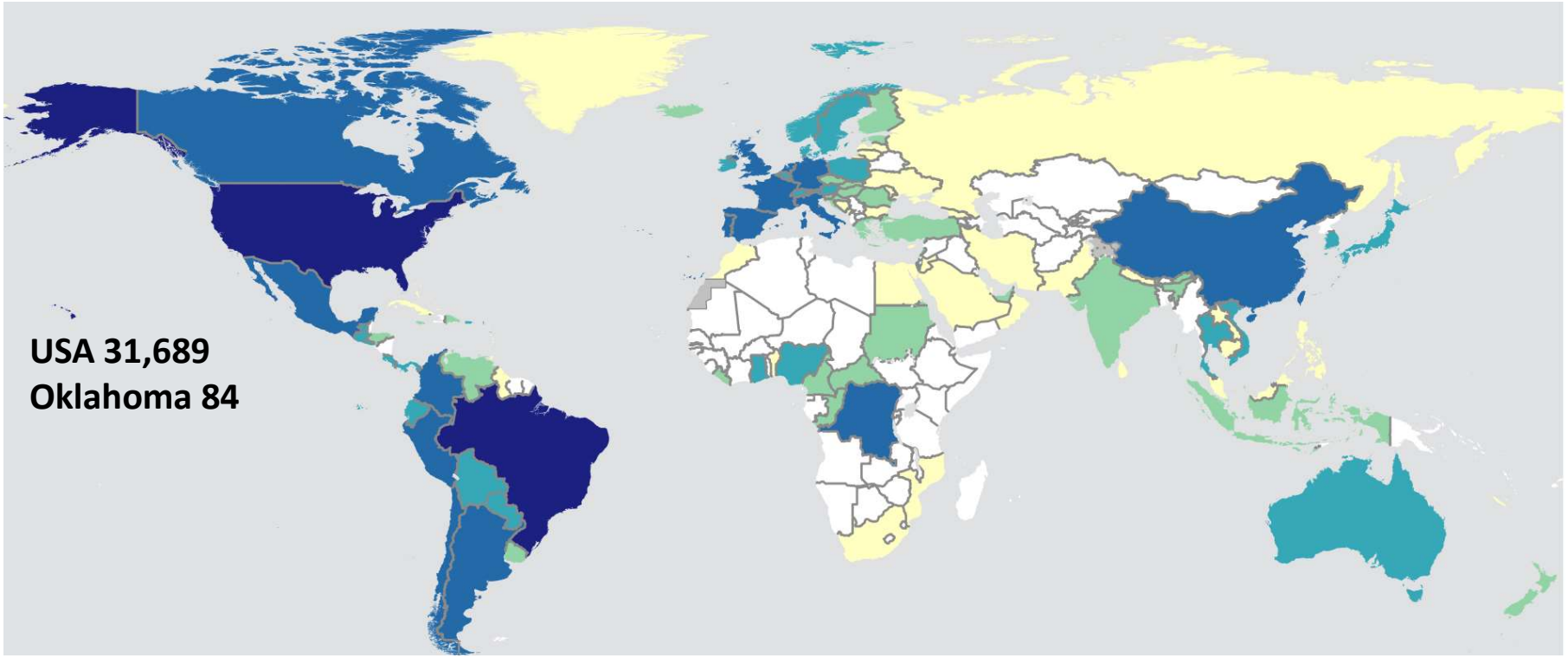
Human MPOX Infection 2022: The “Hockeystick”

- **7 May**: UK reported 1 case in a traveler from Nigeria
- **13–16 May**: London - 6 cases reported in gay/ bisexual men who have sex with men (MSM)
- **17 May**: Madrid - 7 suspected cases at a STD clinic
- **18 May**: Portugal- 14 cases of MPOX in men
- **23 July**: WHO declared Public Health Emergency of International Concern
- **5 August**: HHS (USA) declares Public Health Emergency



Eurosurveillance 2022 https://doi.org/10.2807/1560-7917.ES.2022.27.27.2200471

Human MPOX Infection:
Confirmed Cases Jan 1, 2022 – Jan 31, 2024



https://worldhealthorg.shinyapps.io/mpx_global/

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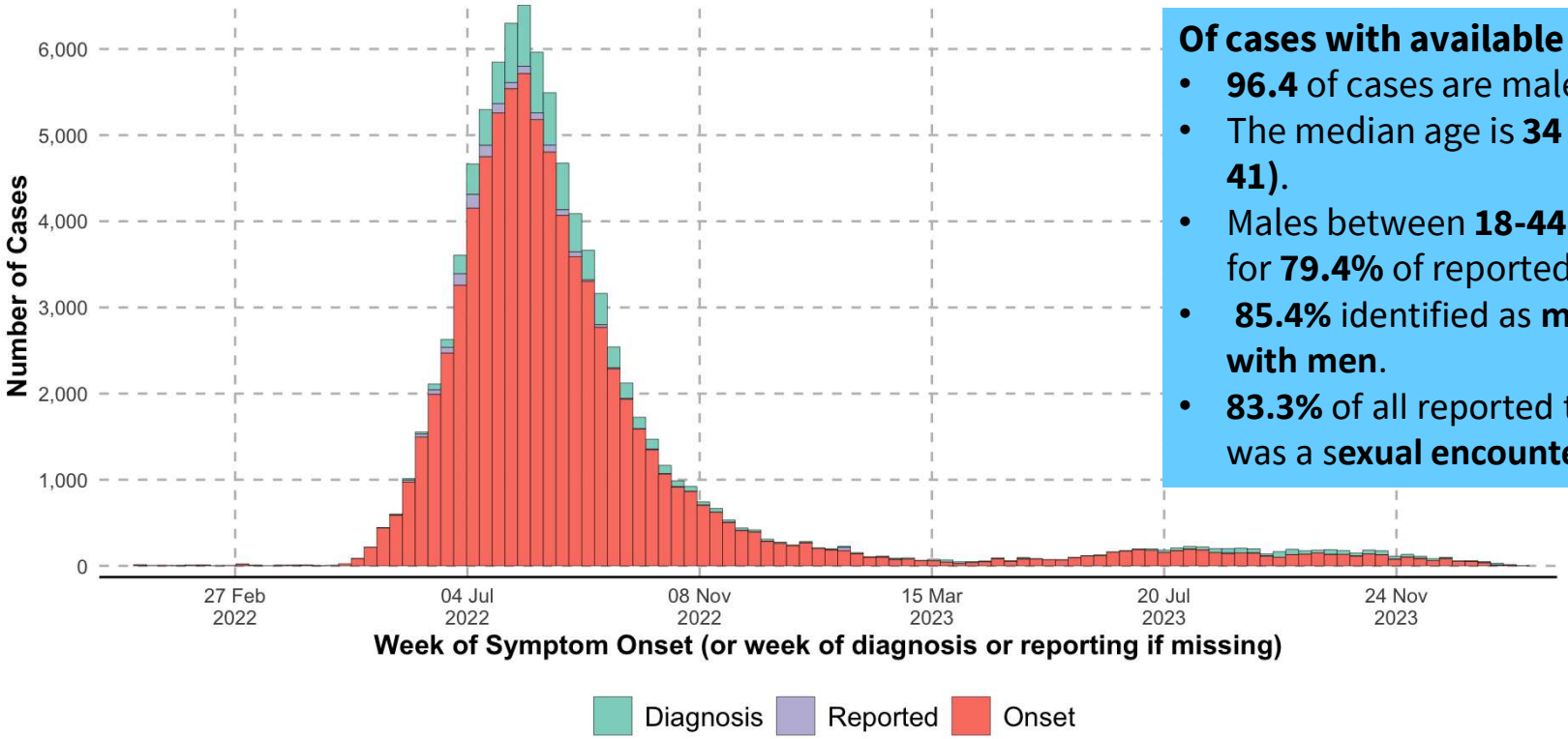


Of cases with available data:

- **96.4** of cases are male,
- The median age is **34 years (IQR: 29 - 41)**.
- Males between **18-44 years old** account for **79.4%** of reported cases.
- **85.4%** identified as **men who have sex with men**.
- **83.3%** of all reported transmission events was a s**exual encounter**

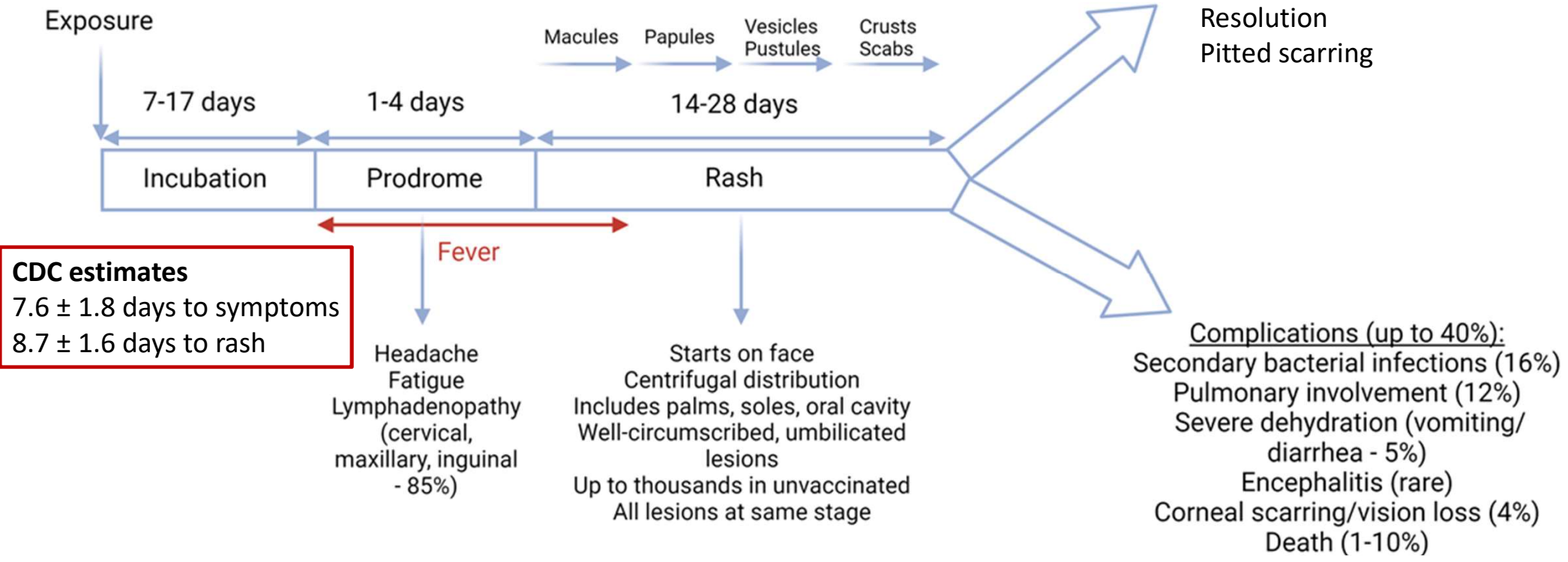
https://worldhealthorg.shinyapps.io/mpx_global/

Human MPOX Infection 2022: Clinical Features

- **Skin lesions**
  - Progress more or less uniformly from papules → vesicles → pustules → scabs → scars
  - Lesions are infectious!!!!!
  - 85% of individuals had ≤ 20 skin lesions
- **Well-controlled HIV infection does not change presentation/course**
- **4-13% of individuals admitted to hospital**
  - Pain control (anorectal)
  - Super-infection of skin lesions
  - Severe pharyngitis
  - Corneal lesions
  - Acute kidney injury
  - Myocarditis
- **12 deaths** out of 39,110 cases reported to WHO

Eurosurveillance 2022 https://doi.org/10.2807/1560-7917.ES.2022.27.27.2200471
NEJM 2022 DOI: 10.1056/NEJMoa2207323

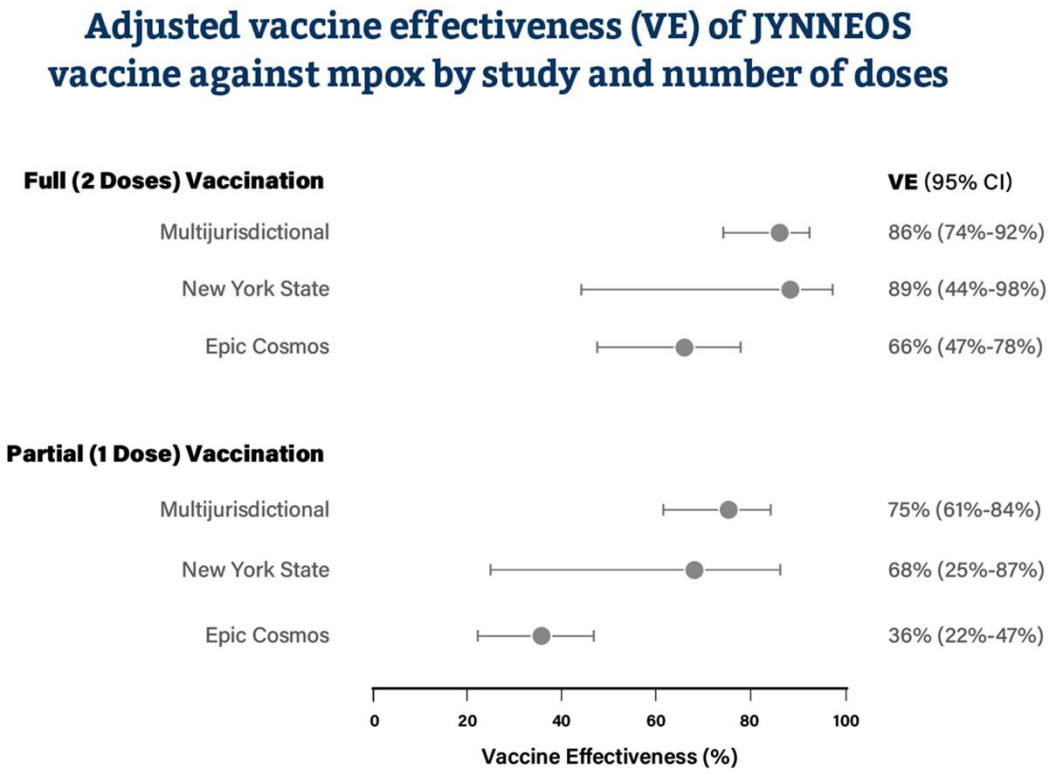
Human MPOX Infection 2022: Clinical Timeline



Siegrist and Sassine, CID 2022 https://doi.org/10.1093/cid/ciac622
https://www.cdc.gov/poxvirus/monkeypox/clinicians/technical-report.html#epi-parameters

Human MPOX Infection Treatment and Prevention

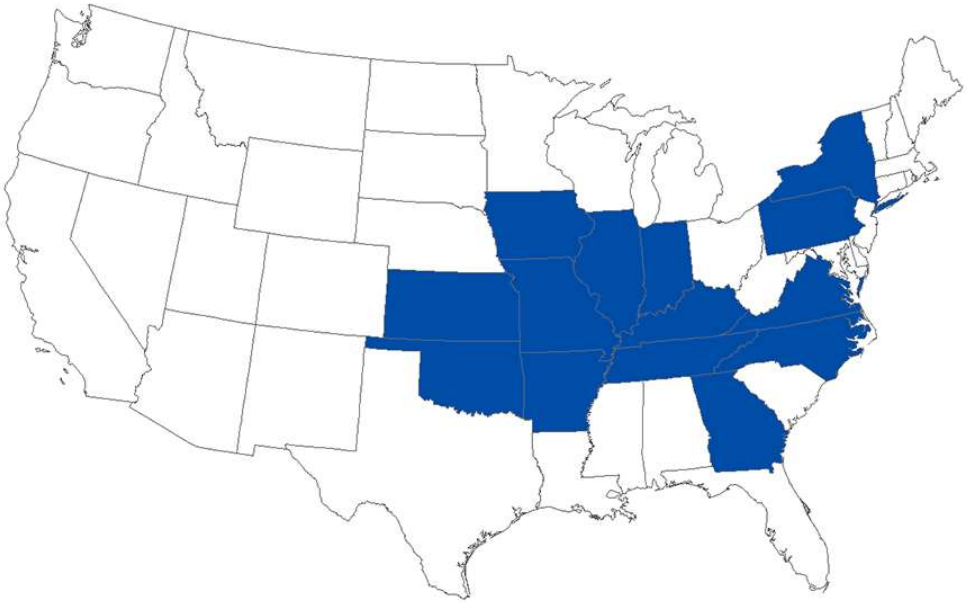
- **Treatment typically reserved for:**
  - Adults with severe disease or at risk of severe disease
  - Active exfoliate skin disease
  - Children (<8) and pregnant/breastfeeding women
- **Tecovirimat -** FDA approved for treatment of smallpox in adults and children
  - Available through strategic national stockpile, https://www.cdc.gov/poxvirus/monkeypox/clinicians/obtaining-tecovirimat.html
  - Treatment duration shorted than 14 days can lead to rebound infection
  - May need to be longer in immune suppressed individuals

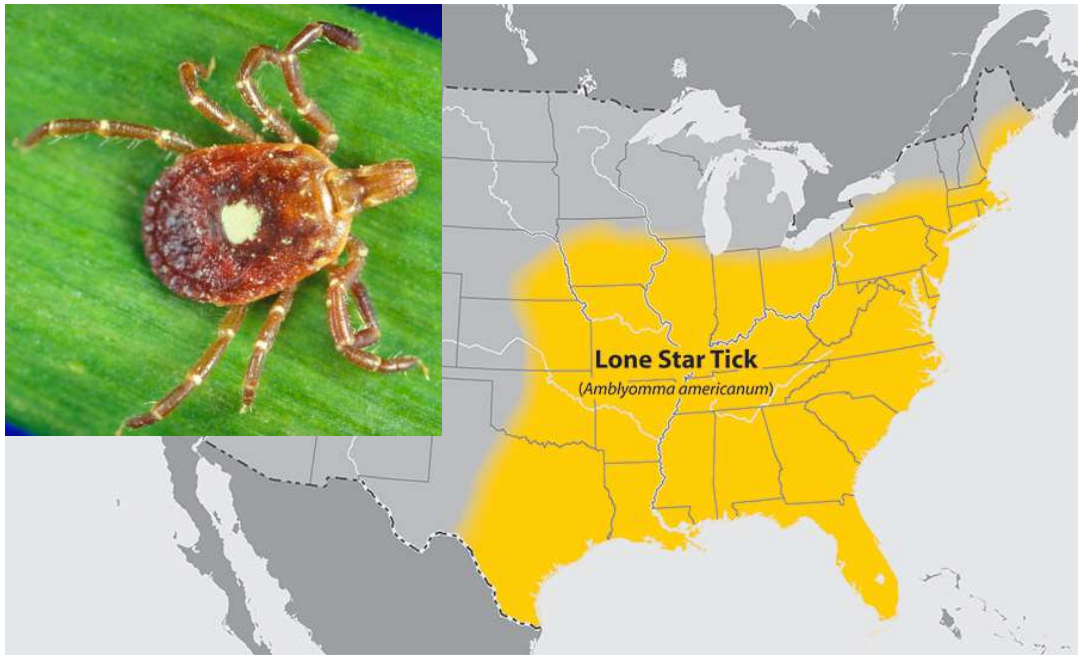


https://www.cdc.gov/poxvirus/mpox/clinicians/treatment.html#anchor_1655488284069

https://www.cdc.gov/poxvirus/mpox/cases-data/JYNNEOS-vaccine-effectiveness.html

Heartland Virus

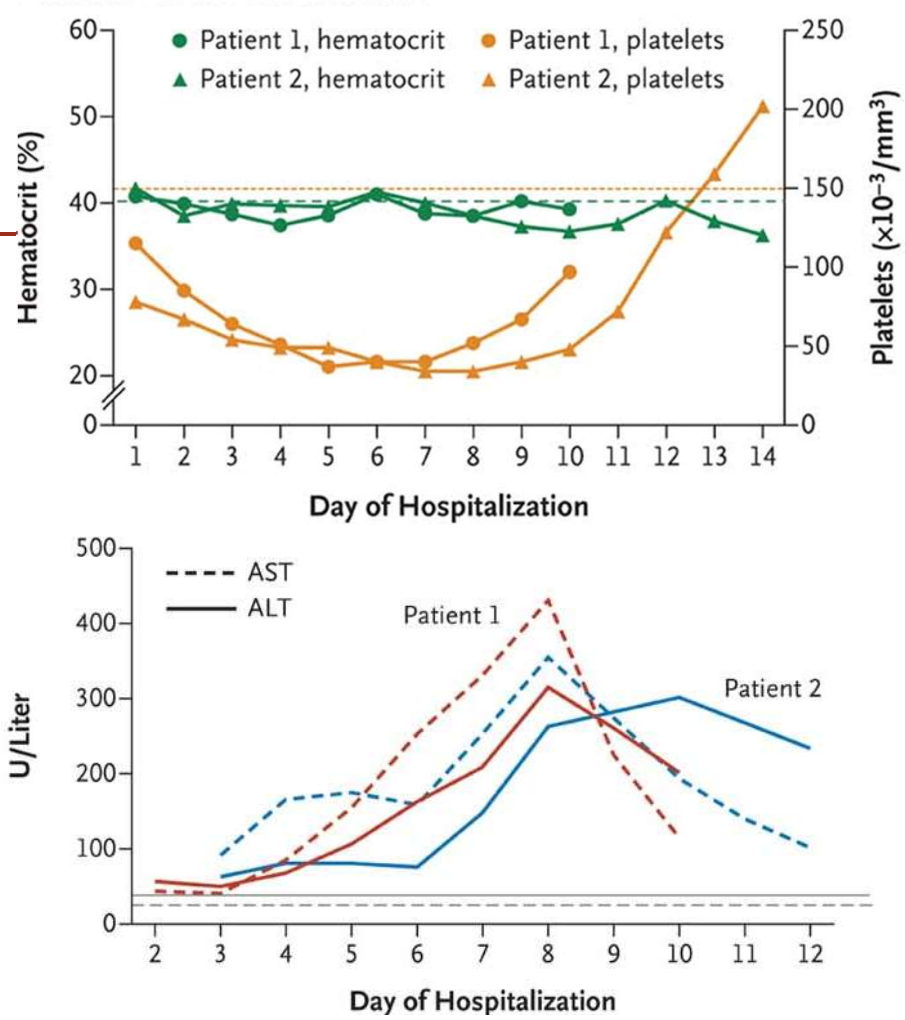




https://www.cdc.gov/heartland-virus/index.html

Heartland Virus Infection First 2 Cases in the US

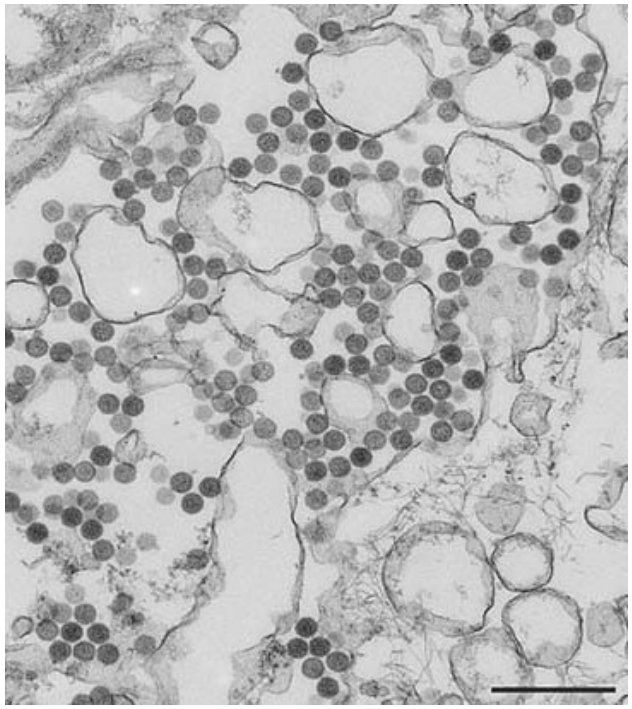
- 2 adult males from NW Missouri
- Sustained tick bites then illness within 1-7 days
- Fever, severe fatigue, headache, anorexia, nausea, non-bloody diarrhea, myalgia, dry cough.
- Leukopenia, thrombocytopenia
- AST/ALT elevation
- Discharged after 10-12 days



McMullan LK et al. N Engl J Med;367:841, 2012.

Identification of a Transmissible Virus in Patient Leukocytes

- EM revealed enveloped particles averaging 86 nm in diameter
- Full-length genome sequences were similar to phleboviruses in the Bunyaviridae family.
- **Phlebovirus -** A genus of RNA viruses, transmitted to people by the bite of infected insects.
  - Phleboviruses can cause hemorrhagic fevers, meningitis, and meningoencephalitis, among other illnesses
  - Genus includes Rift Valley fever virus and Toscana virus.
- Found in Lone Star tick nymphs at & around patient farms



Scale bar 500 nm

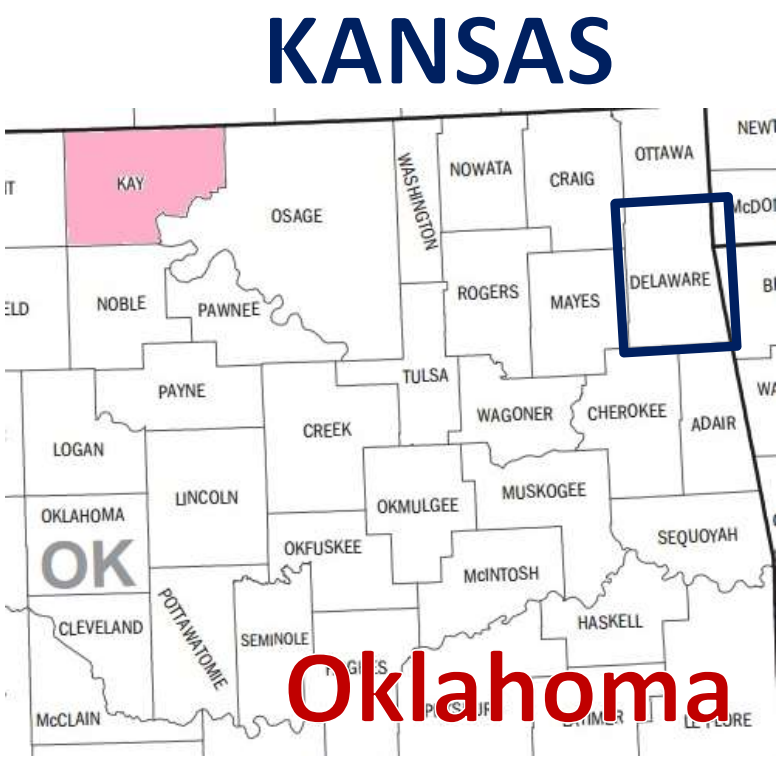
McMullan LK et al. N Engl J Med;367:841, 2012
Am J Trop Med Hyg 2013;89:445–52

Farlex Partner Medical Dictionary. (2012).

Fatal Heartland Virus Infection in Oklahoma May 27, 2014

Health officials say the Oklahoma case was the tenth known of the tick-borne virus and the second that proved to be fatal.

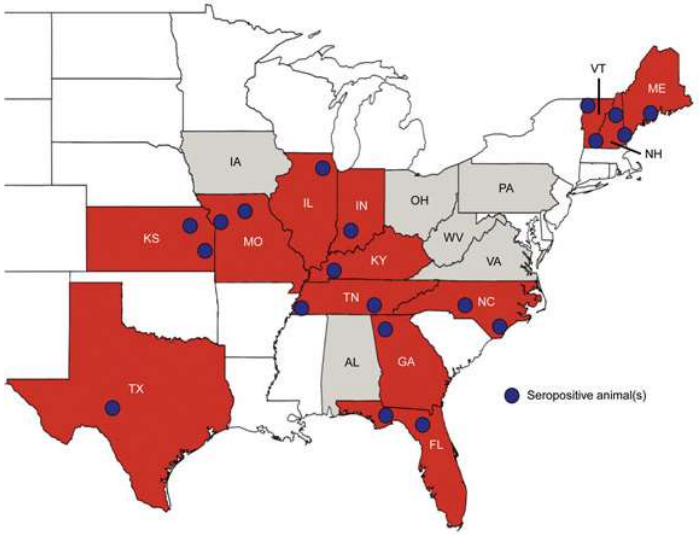
- An Oklahoma man has died after contracting the Heartland virus, marking the **10th known case** and **second known death** from the tick-borne illness.
- The OSDH confirmed the death of a Delaware County resident aged 65, due to complications from the virus.

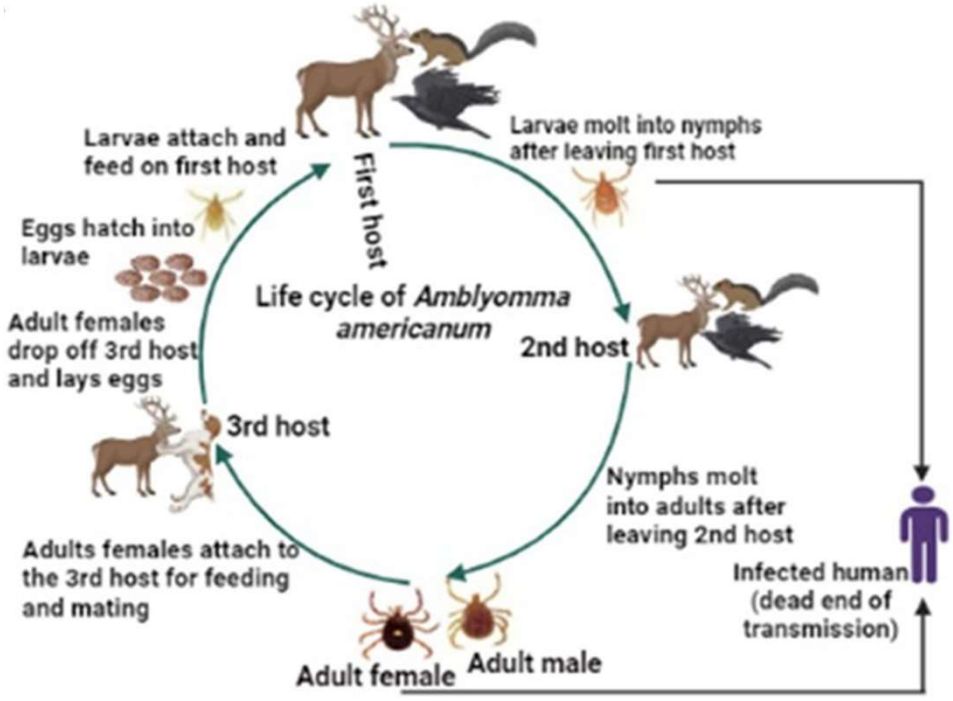


Dan Kedmey
http://time.com/123402/heartland-virus-oklahoma/

Heartland Virus: Widespread Presence in Animals

- 13 states had seropositive animals
- 103 of 1,428 animals tested were seropositive
  - 55 deer
  - 33 raccoon
  - 11 coyotes
  - 4 moose





Emerg Infect Dis. 2015 Oct . http://dx.doi.org/10.3201/eid2110.150380

https://doi.org/10.3389/fmicb.2023.1185829

Heartland Virus: Case counts and case definition

- 60 cases (as of Jan, 2023), 3 deaths
- Fever (≥100.4°F [≥38.0°C]),
- Leukopenia (white blood cell count <4,500 cells/mm^3),
- Thrombocytopenia (platelet count <150,000/mm^3
- No better /more likely clinical explanation.
- Diagnosis by
  - Positive PCR of blood or tissue
  - A ≥4-fold rise in virus-specific plaque reduction neutralization antibody titers between acute and convalescent serum specimens.

Heartland Virus & Severe Fever with Thrombocytopenia Syndrome (SFTS)

- An emerging hemorrhagic fever identified in China in 2007, now also reported in Japan and Korea.
- Caused by a **phlebovirus** in the **Bunyaviridae** family, now known as STFS virus.
- ~2500 reported cases
- Average case-fatality rate of 7.3%.
- Found in a variety of ticks and mites.
- Sero-prevalance in domestic animals
  - goats (57-95%), cattle (32-80%), dogs (6-55%), chickens (1-36%)
- Found in wild animals
  - deer, weasels, hedgehogs, etc.

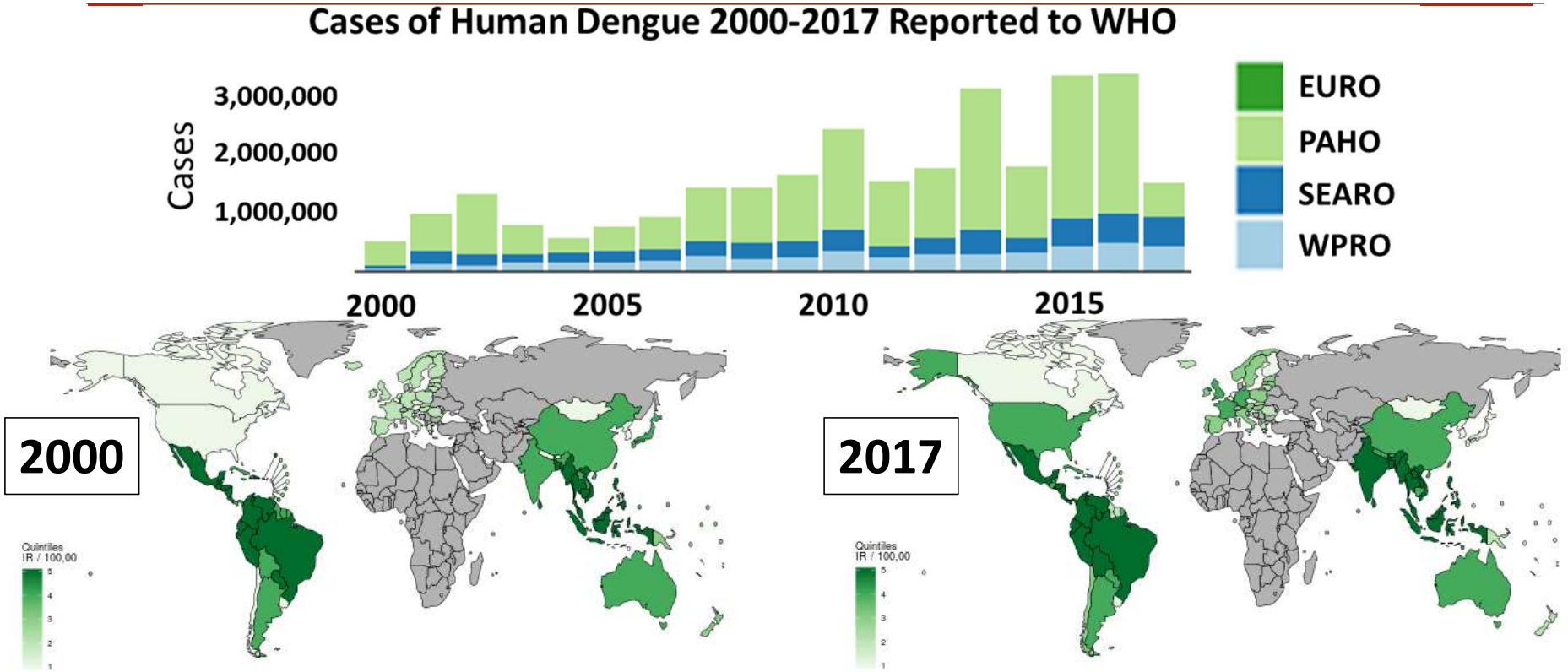
Liu, et al., Lancet Infectious Diseases, 14, 763, 2014

Dengue:
A Global Disease

- Before 1970, only 9 countries had experienced severe dengue epidemics, now endemic in more than 100 countries.
- Cases reported to WHO increased from 505 430 cases in 2000 to 5.2 million in 2019
- In 2013, 2.35 million cases of dengue were reported in the Americas
- The largest number of dengue cases ever reported globally was in 2019. The American Region reported 3.1 million cases, with more than 25 000 classified as severe.
- It also spawned a pop/rock band

https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

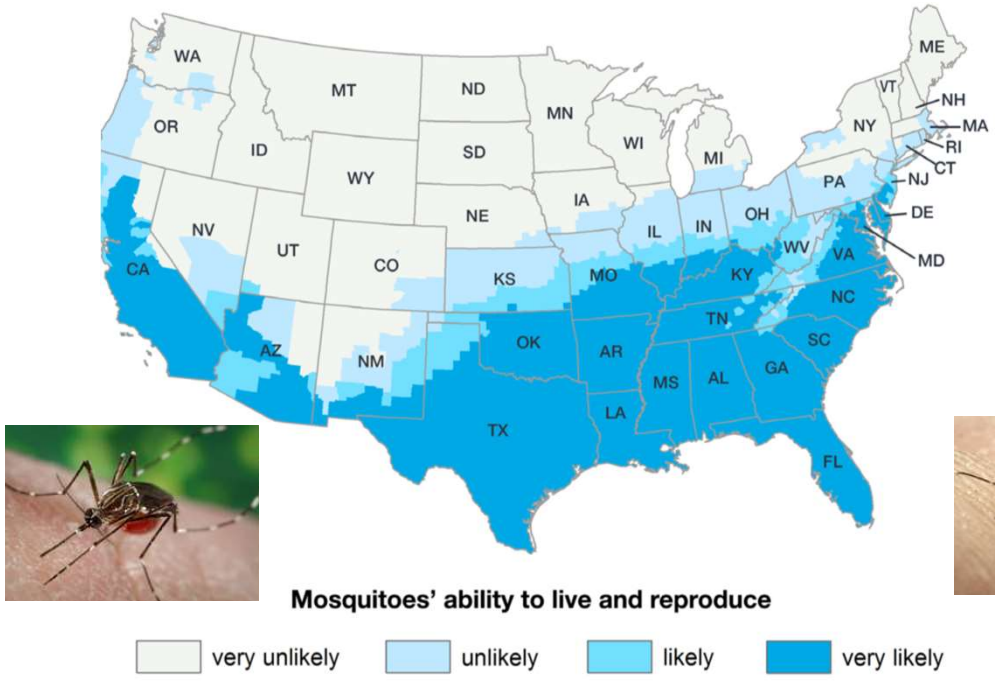
Dengue Infection Change Over Time



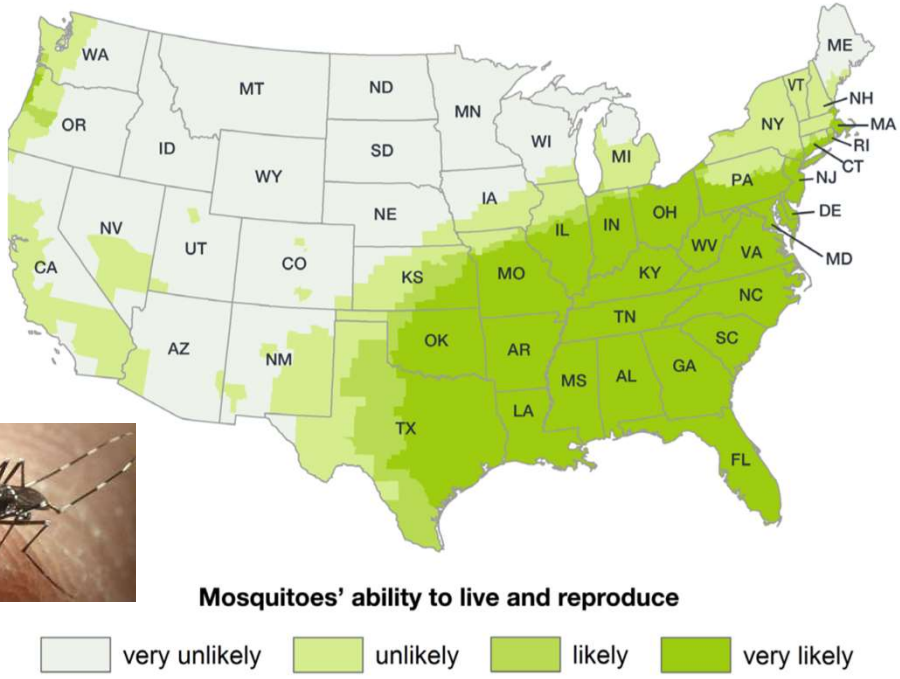
https://ntdhq.shinyapps.io/dengue5/

Ades Mosquitos in the United States

Est. Potential Range of *Ades aegypti*, 2017

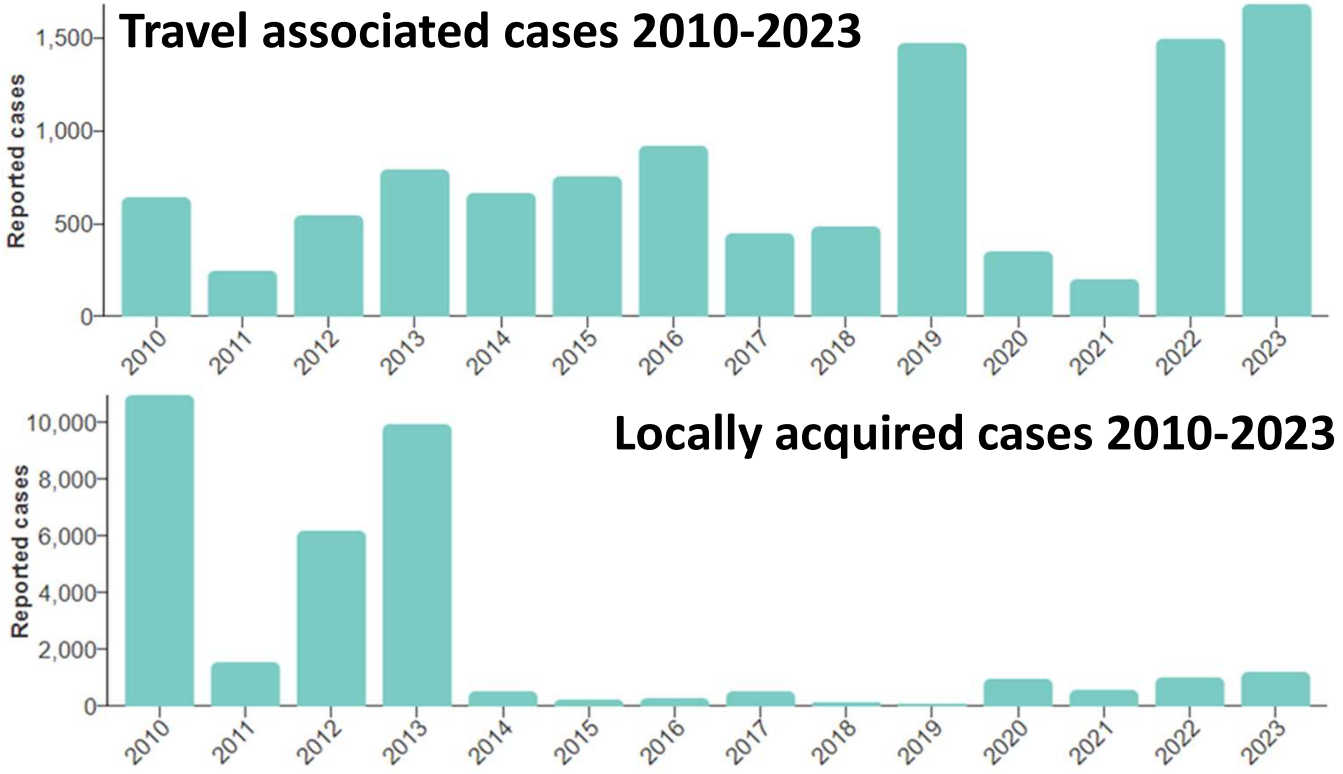


Est. Potential Range of *Ades albopictus*, 2017



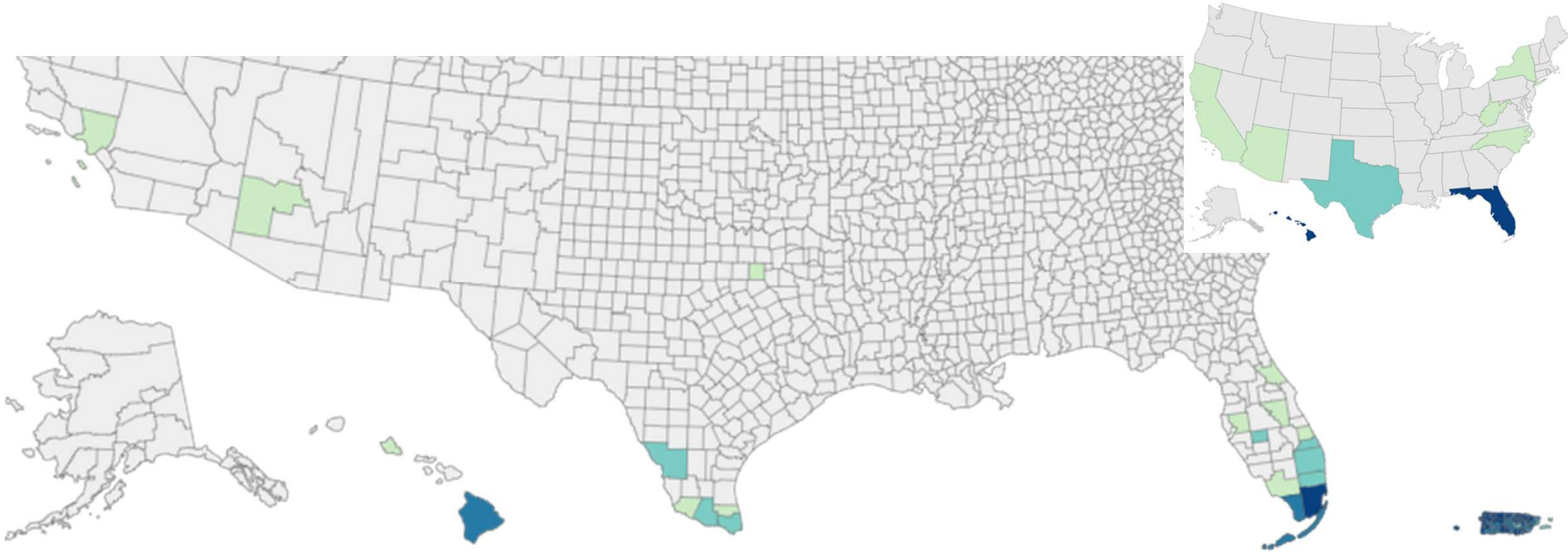
https://www.cdc.gov/mosquitoes/mosquito-control/professionals/range.html

Dengue in the United States



https://www.cdc.gov/dengue/statistics-maps/historic-data.html

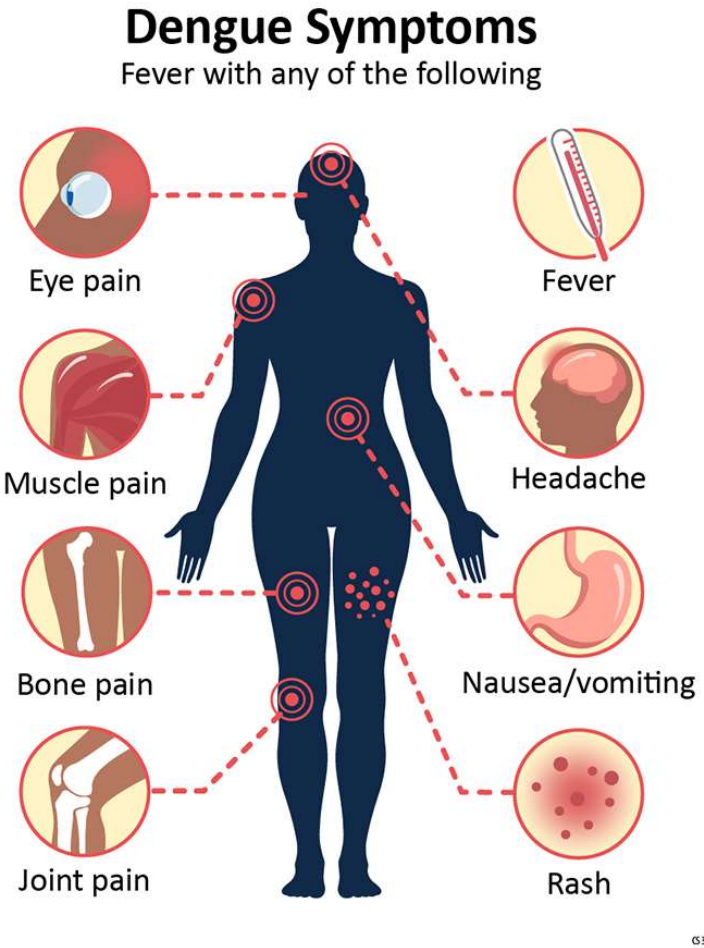
Locally Acquired Dengue in the United States



https://www.cdc.gov/dengue/statistics-maps/historic-data.html

Dengue: Clinical Features

- Dengue can be asymptomatic, mild, severe, or fatal
- Symptoms appear between 4 and 7 days after the patient has been bitten by the infected mosquito.
- Symptoms last 3-10 days
- Can develop hemorrhagic features
- Immunity to Dengue is serogroup specific and can worsen disease if infected by a different Dengue serogroup.



https://www.cdc.gov/dengue/symptoms/index.html

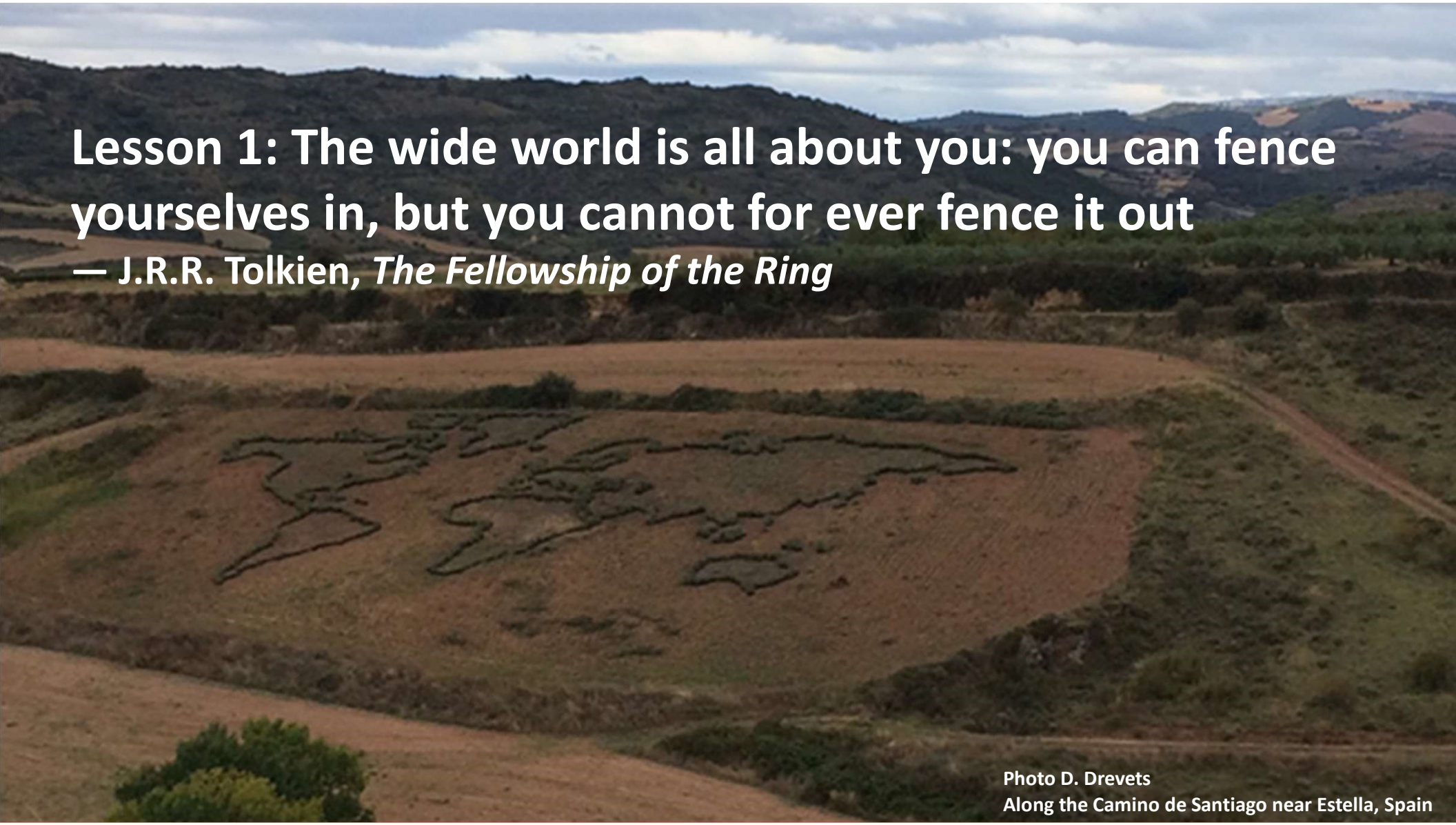
An FDA-Approved Vaccine for to Prevent Dengue Virus Infection and Disease

- Tetravalent, live-attenuated vaccine that replaces several genetic sequences in a yellow fever vaccine virus genome with the homologous sequences from the four dengue virus serotypes
- Approved for children and adolescents 9–16 years old with laboratory confirmed previous dengue virus infection and living in dengue-endemic areas.

Dengvaxia efficacy among children 9–16 yo with previous dengue virus infection	
Outcome	**Vaccine Efficacy (95% CI)**
Virologically confirmed disease	82% (67%–90%)
Hospitalization	79% (69%–86%)
Severe disease	84% (63%–93%)

NOT INDICATED for children <9, adults, travelers

https://www.cdc.gov/dengue/vaccine/hcp/safety-efficacy.html

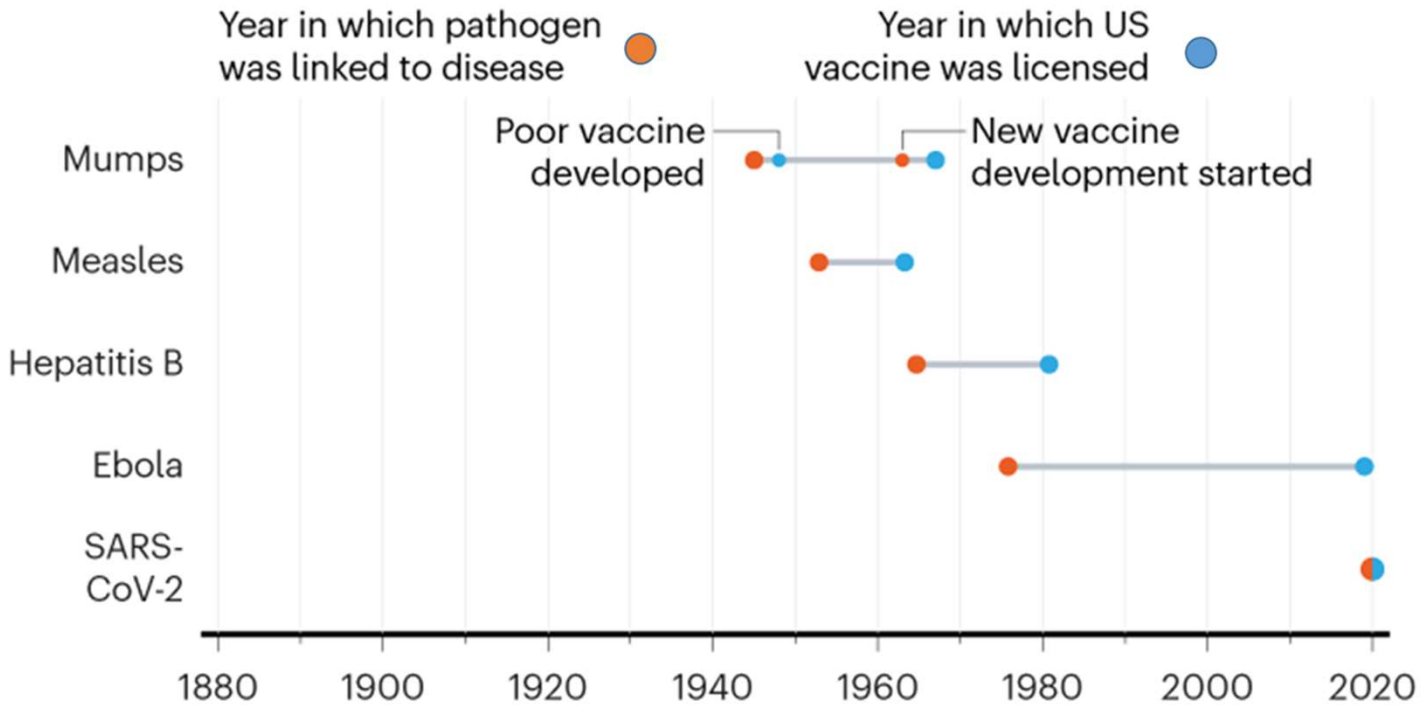

Lesson 1: The wide world is all about you: you can fence yourselves in, but you cannot for ever fence it out
— J.R.R. Tolkien, *The Fellowship of the Ring*
Photo D. Drevets
Along the Camino de Santiago near Estella, Spain

Critical Areas For The Next Emerging Infectious Disease That Goes Pandemic

- **Science & technology**
  - Resource allocation & support for low margin products, e.g. antimicrobials and vaccines
  - Rapid development of diagnostics/FDA
- **Health care**
  - Rapid trials network & stockpiles of PPE
- **Healthcare delivery**
  - Redundancy & reserve versus efficiency and margins
  - Public health infrastructure
  - State health depts. versus others, e.g. AMCs

Lesson 2:
Countermeasures, e.g. Vaccines, Also Emerge, But At A Slower Rate Than Infectious Diseases

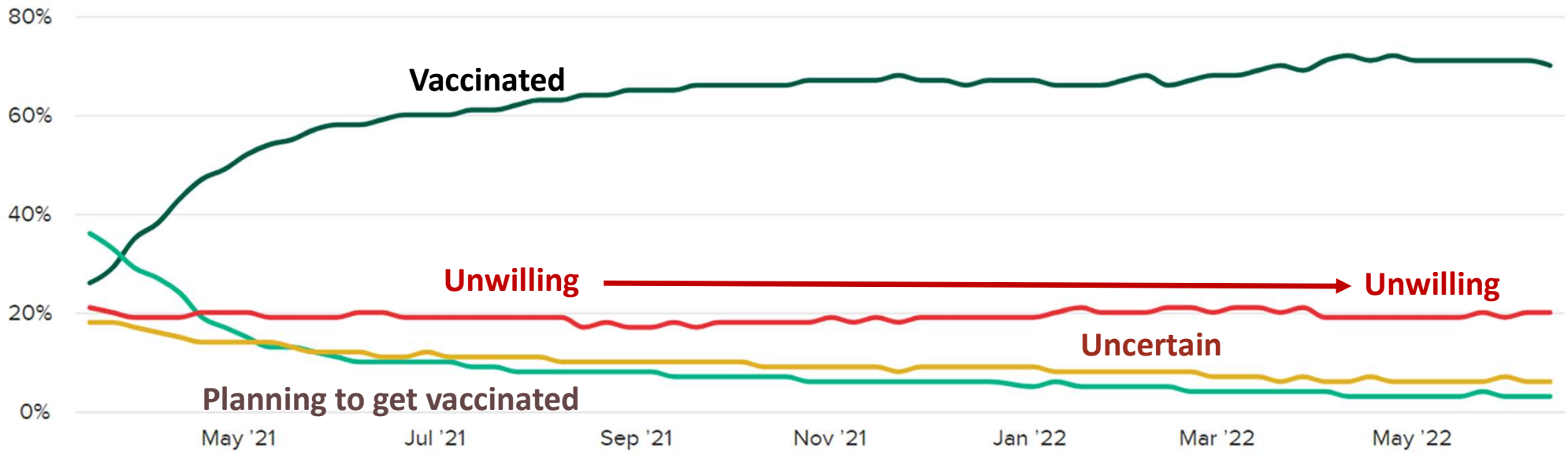
Timeline From Identification of Selected Pathogens to US Vaccine Licensing



Nature 600, 580-583 (2021)
doi: https://doi.org/10.1038/d41586-021-03686-x

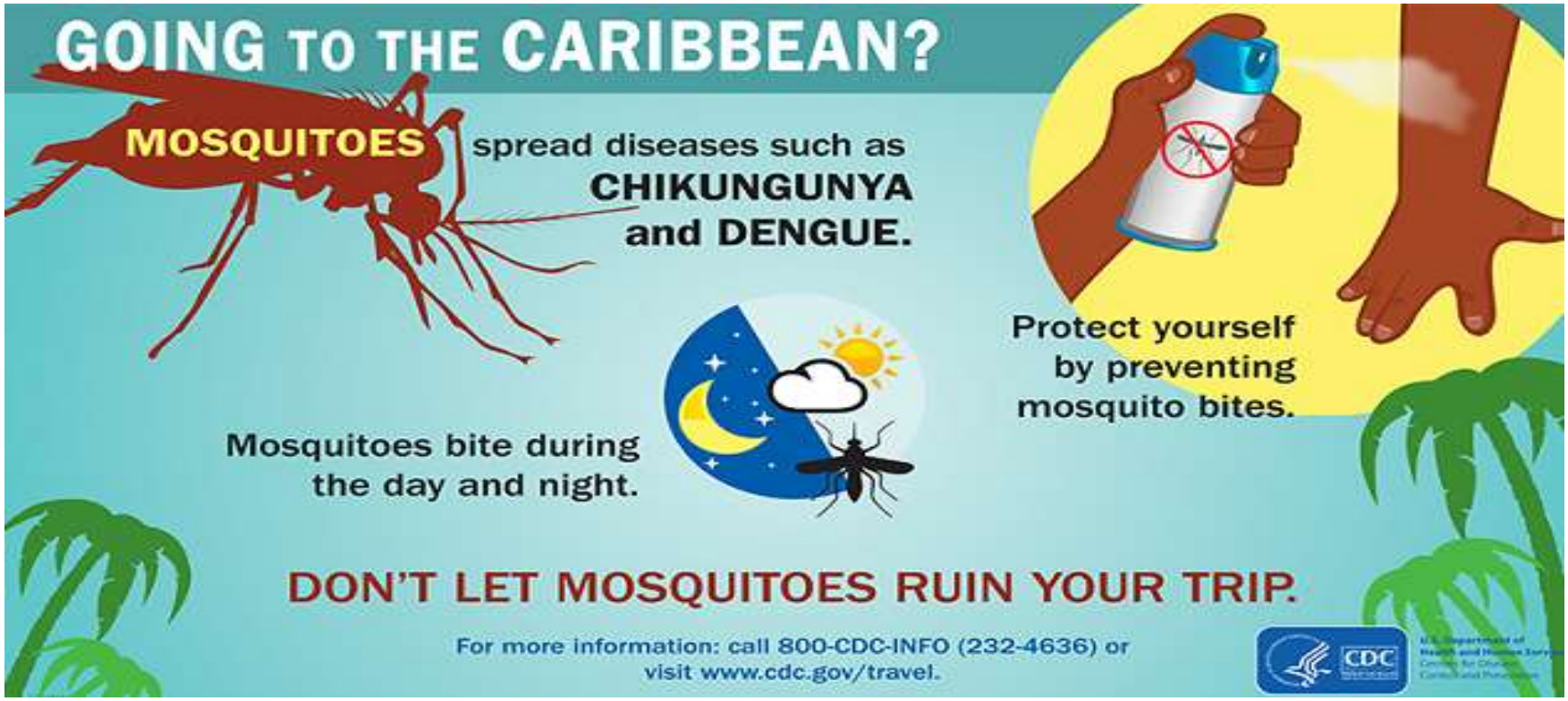
Lesson 3:
Public Acceptance of Countermeasures is a Wild Card and Not 100%

Responses to the question: “Have you gotten the vaccine, or not?”



https://morningconsult.com/covid19-vaccine-dashboard/

Lesson 4:
Protect Yourself



Thank you for listening