



Zika V.2.0

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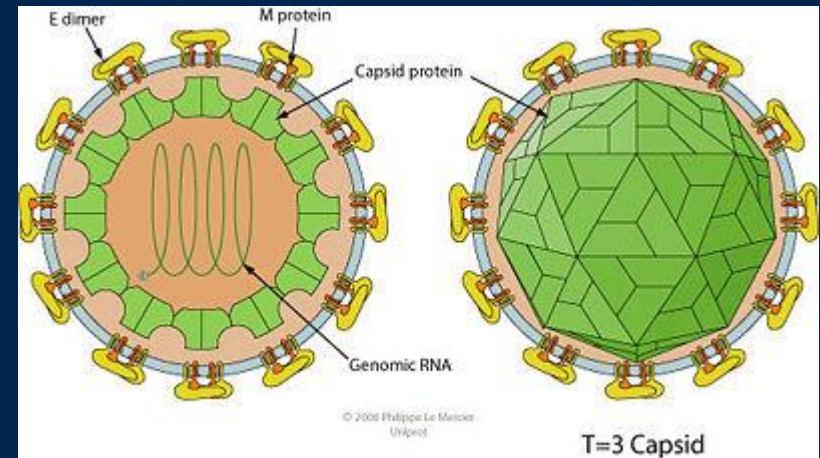
@PeterHotez



Zika is an arbovirus and a flavivirus

FLAVIVIRUSES (ss +RNA)

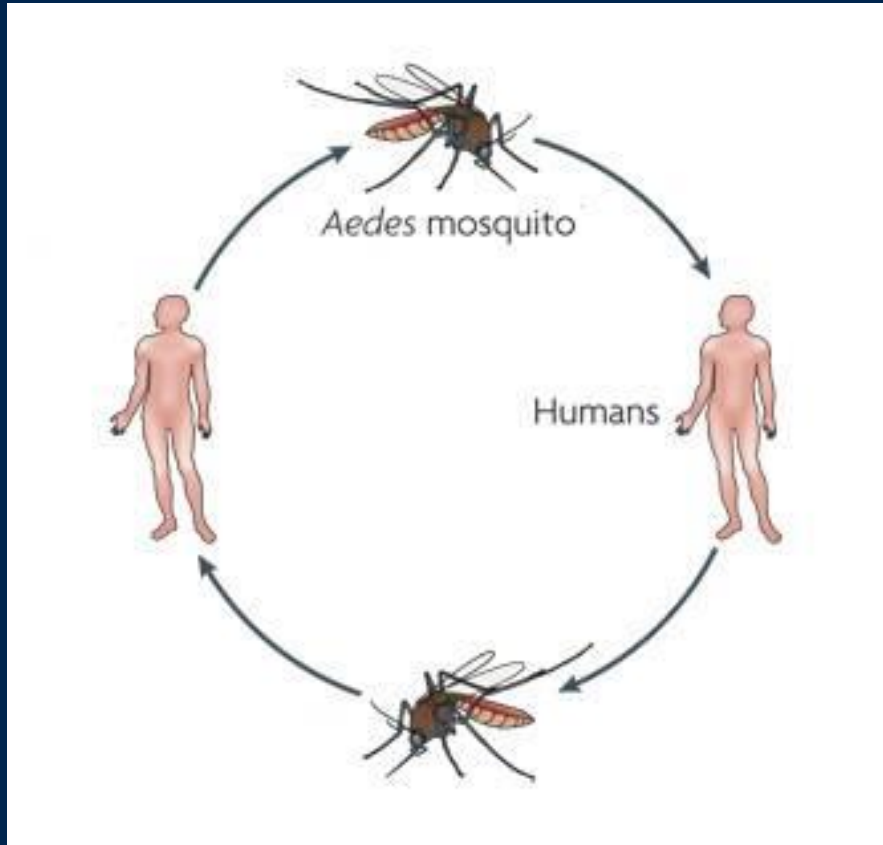
- Dengue Virus
- Yellow Fever Virus
- Japanese Encephalitis Virus
- West Nile Virus
- St. Louis Encephalitis Virus
- Zika Virus



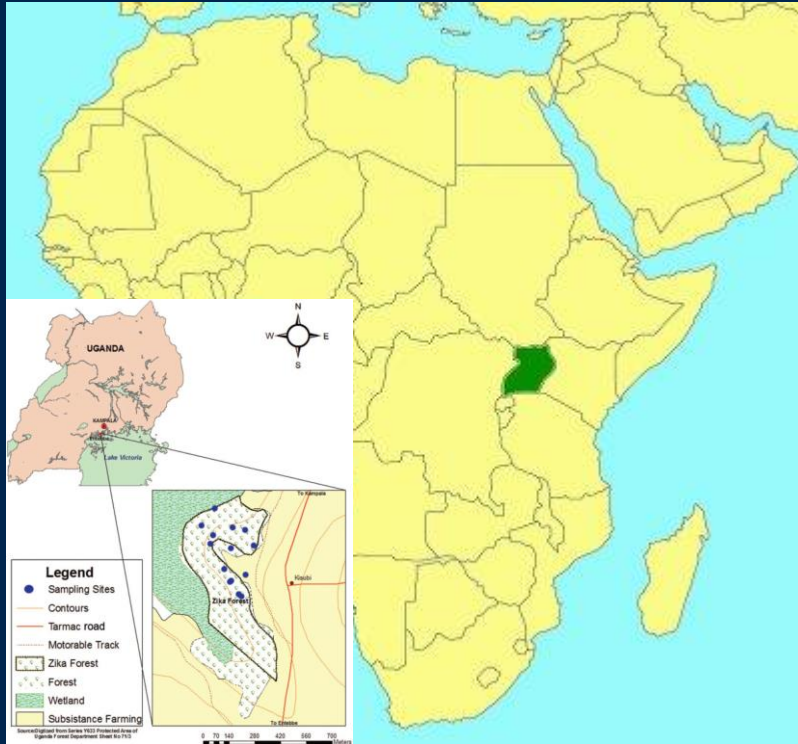
TRANSMITTED BY AEDES MOSQUITOES

- Dengue, YF but NOT WNV

Aedes mosquitoes including *Aedes aegypti* (humans) and *Ae. albopictus* (mammals, birds) in New World



Origins in the Zika Forest of Uganda

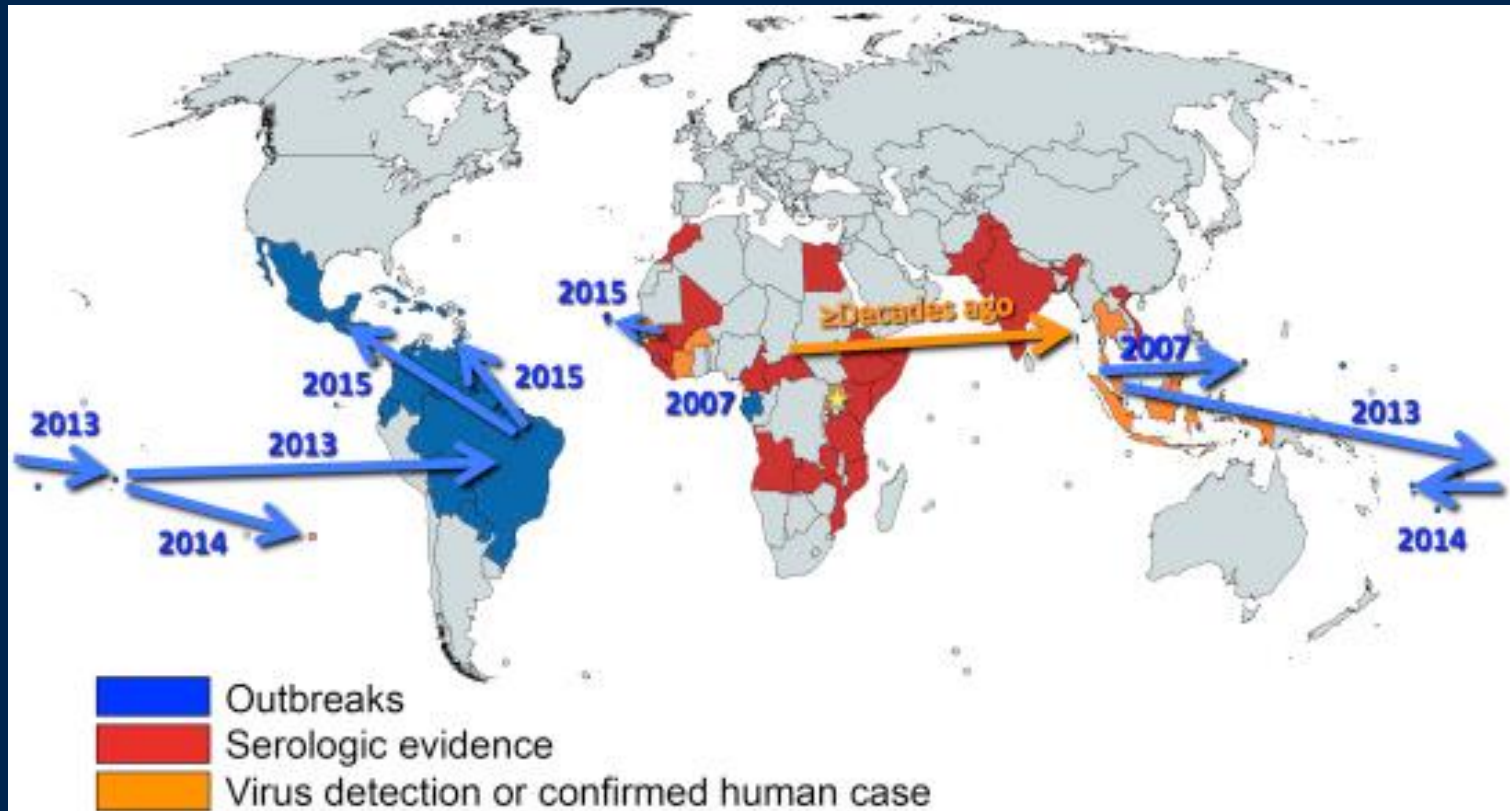


Zika means “Overgrowth”
Aedes africanus vector

Found in 1947
Virus Isolation published in 1952
First human case in Nigeria in 1954

14 cases in Africa

Zika Path: Explosive Pacific Outbreaks



Where will Zika head next?

- Asian-lineage strain now moving into Cape Verde Islands
- Mix with African strain
- Is Asian strain more virulent?
- New loop-mediated amplification (LAMP) differentiates Chotiwan et al Sci Trans Med 2017

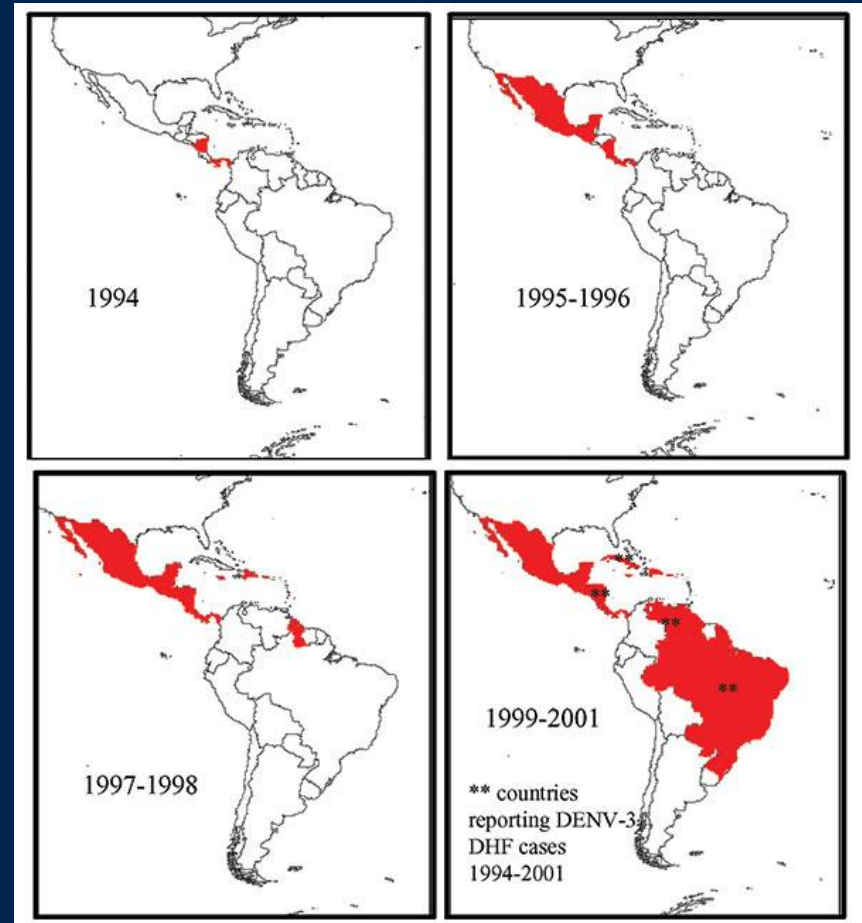
What made Zika spread so quickly?

- Hypothesis 1:
- Zika is going by the same playbook used by dengue and chikungunya
- Part of a general expansion of insect and snail-transmitted diseases into the Americas and Europe

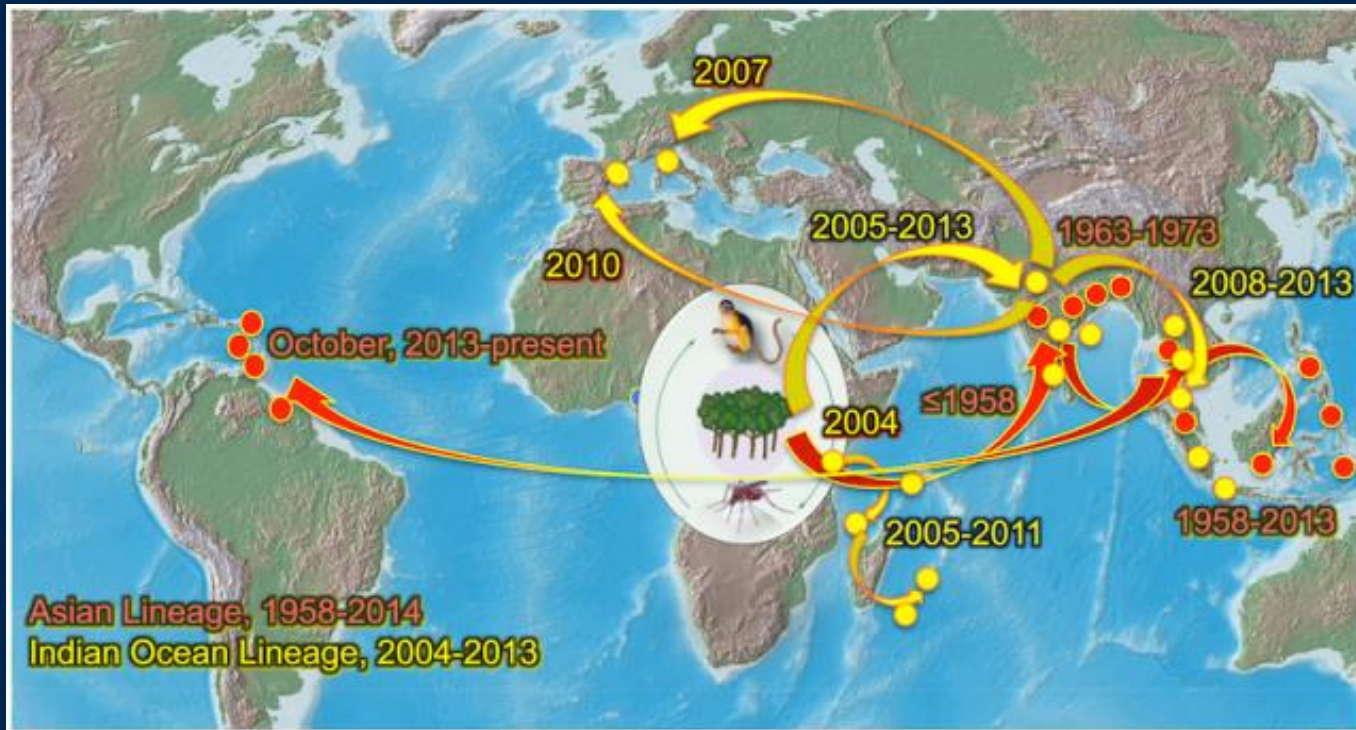
Global spread similar to Dengue and Chikungunya



Emergence of Dengue in the New World in 1980s, 1990s

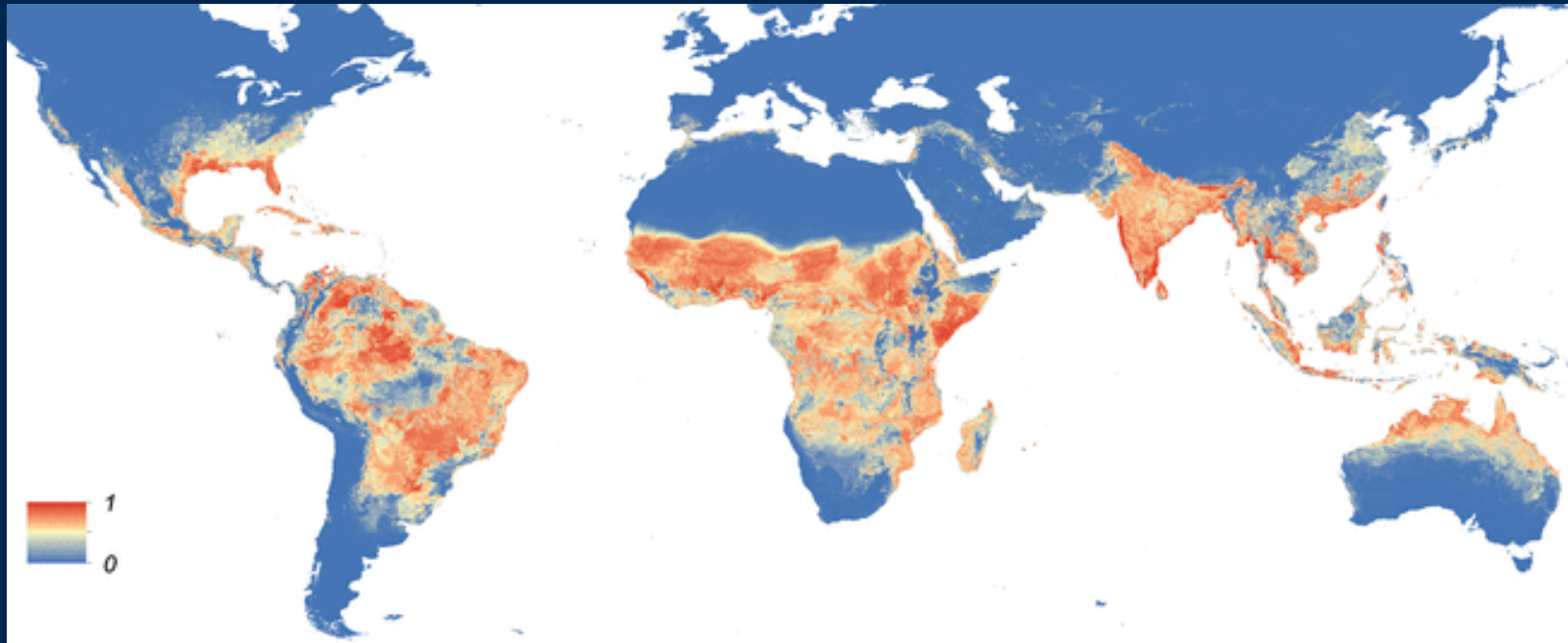


Emergence of Chikungunya in New World in 2013 (Saint Martin)



Current Range of *Aedes aegypti*

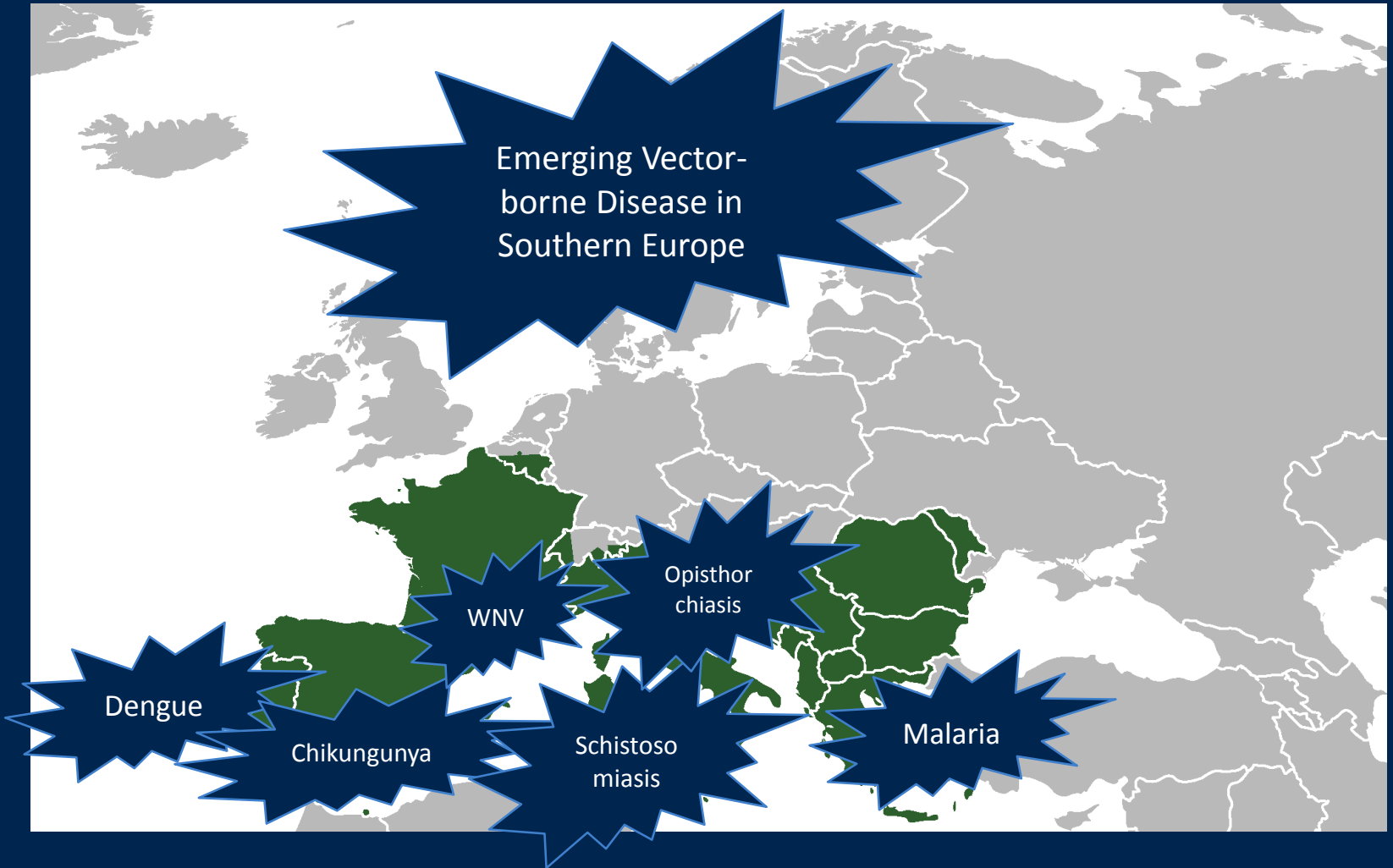
THE MOST EFFICIENT VECTOR FOR HUMAN ARBOVIRUSES



Ae. aegypti is anthroponotic - humans

[The global distribution of the arbovirus vectors *Aedes aegypti* and *Ae. albopictus*.](#)

Kraemer MU, Sinka ME, Duda KA, Mylne AQ, Shearer FM, Barker CM, Moore CG, Carvalho RG, Coelho GE, Van Bortel W, Hendrickx G, Schaffner F, Elyazar IR, Teng HJ, Brady OJ, Messina JP, Pigott DM, Scott TW, Smith DL, Wint GR, Golding N, Hay SI. Elife. 2015 Jun 30;4:e08347. doi: 10.7554/elife.08347.



Disease in MENA spilling over to Southern Europe??

Global now forces now promoting the spread of vector-borne disease

Poverty

Human Migrations

Conflict

Urbanization

Deforestation

Climate Change



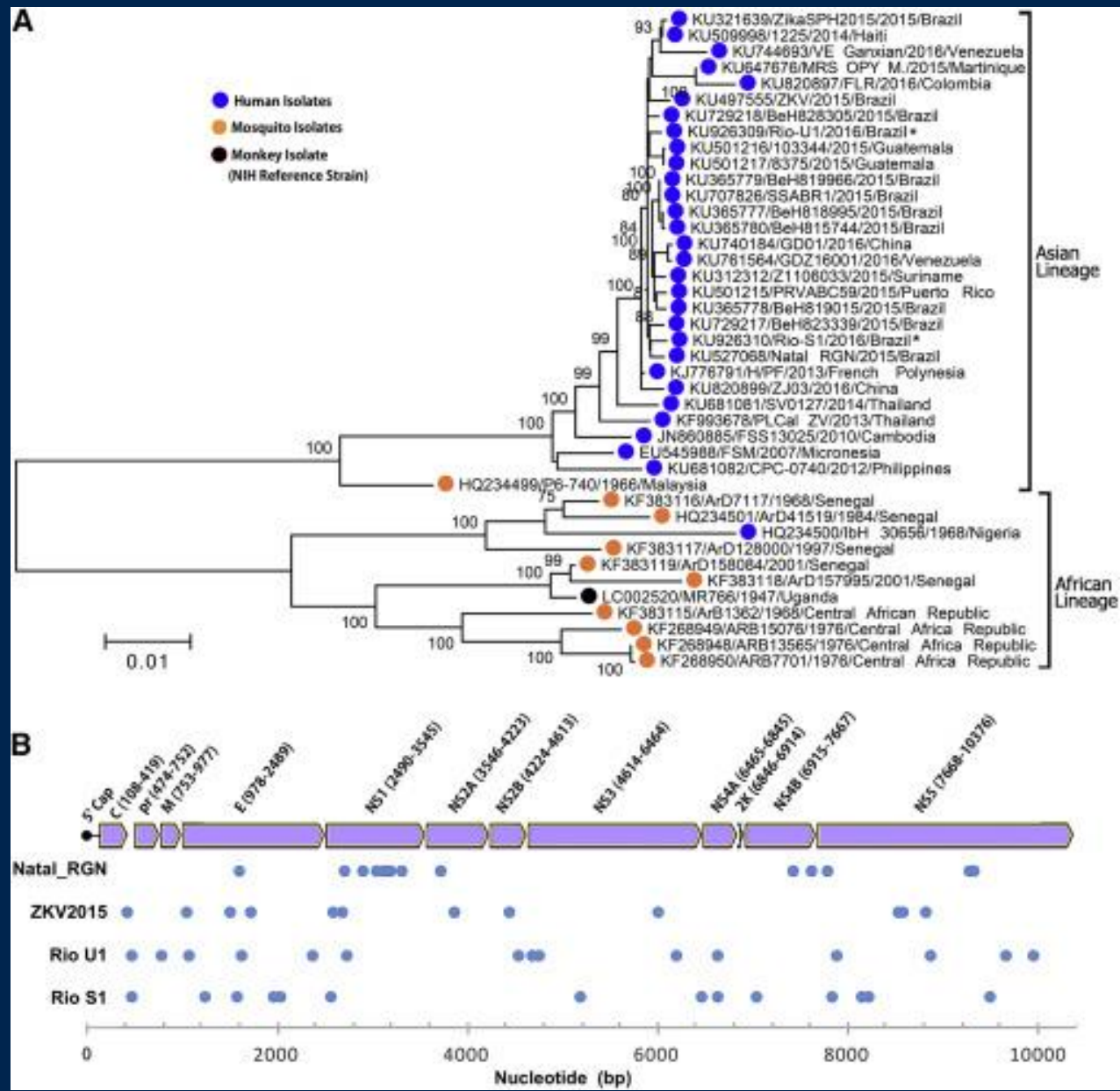
What made Zika spread so quickly?

- Hypothesis 2: Something uniquely Zika*
 - “Pandemic strain” of Zika vs. African strain
 - Codon usage of NS1 gene
 - Increases fitness for replication in human host without changes in protein sequence
 - Codon usage by pandemic strains is optimized for replication in human cells
 - Higher viremias and increased infectivity for mosquitoes
 - Evolutionary strain

*Maj Gen Philip K Russell MD

Asian vs African Lineage

Nucleotide sequences from 41 strains were included in the analysis: 30 human isolates (including two newly reported here), ten mosquito isolates, and one monkey isolate.



[From Mosquitos to Humans: Genetic Evolution of Zika Virus.](#)

Wang L, Valderramos SG, Wu A, Ouyang S, Li C, Brasil P, Bonaldo M, Coates T, Nielsen-Saines K, Jiang T, Aliyari R, Cheng G.

Cell Host Microbe. 2016 Apr 14. pii: S1931-3128(16)30142-1. doi: 10.1016/j.chom.2016.04.006. [Epub ahead of print]

NS1 Gene

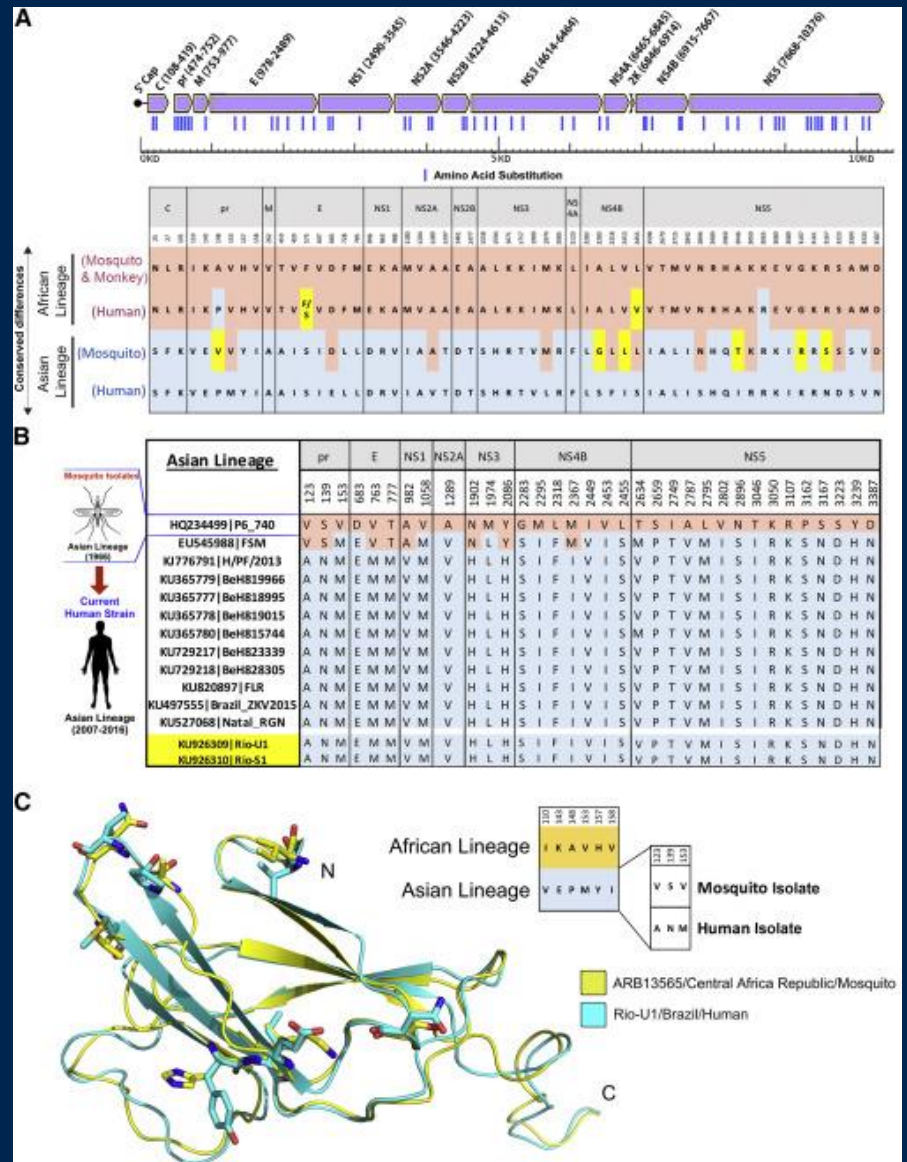
- Strains from the recent epidemic in Brazil showed 14–18 nucleotide mutations compared to the other strains of the Asian lineage isolated from humans. 50% of the mutations in Natal_RGN, which was isolated from the brain, are located in the NS1 gene (Wang et al Cell Host Microbe 2016).
- The flavivirus nonstructural protein 1 (NS1) is a 50 kDa intracellular homodimeric glycoprotein that plays a pivotal role in DENV replication, and there is evidence that it also plays an important role in dengue severity and pathogenesis. The NS1 protein associates with organelle membranes and in particular with lipid-rafts, suggesting that it is involved in signal transduction pathways (Silva EM, PLOS One 2013)

Pre-M Protein

PrM protein of ZIKV shows significant structural alterations

PrM forms a heterodimer with the main viral surface protein, E, in the neutral pH of the lumen of the endoplasmic reticulum (ER)

The role of prM in viral pathogenesis has been under extensive investigation over the past few years. It has been shown that prM plays a critical role in viral assembly, maturation, heterodimer formation with the E protein, particle secretion, and virulence



From Mosquitos to Humans: Genetic Evolution of Zika Virus.

Wang L, Valderramos SG, Wu A, Ouyang S, Li C, Brasil P, Bonaldo M, Coates T, Nielsen-Saines K, Jiang T, Aliyari R, Cheng G. *Cell Host Microbe*. 2016 Apr 14. pii: S1931-3128(16)30142-1. doi: 10.1016/j.chom.2016.04.006. [Epub ahead of print]

What made Zika spread so quickly?

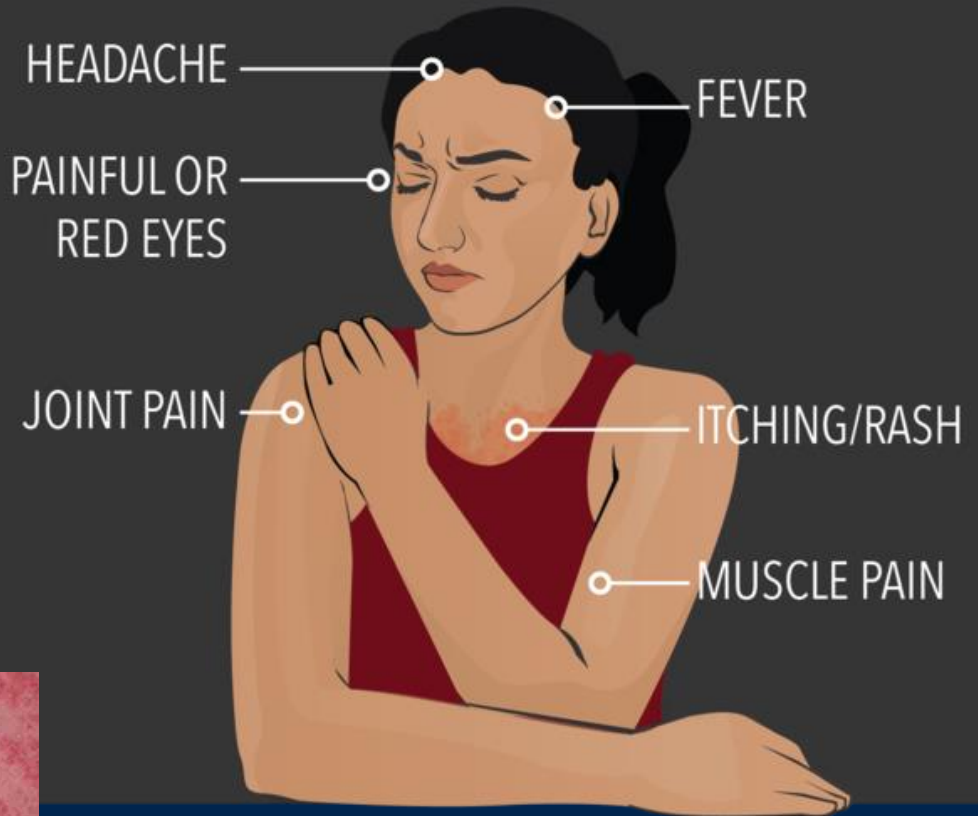
- **Hypothesis 3: Immune enhancement***
 - Previous flavivirus epidemics – dengue or chikungunya
 - Non-neutralizing cross reactive antibodies
 - Penetration of cells through Fc receptor
 - Increased virus replication
 - Zika virus enhanced in culture by heterologous flaviviruses
 - Dengue overlap

*Maj Gen Philip K Russell MD

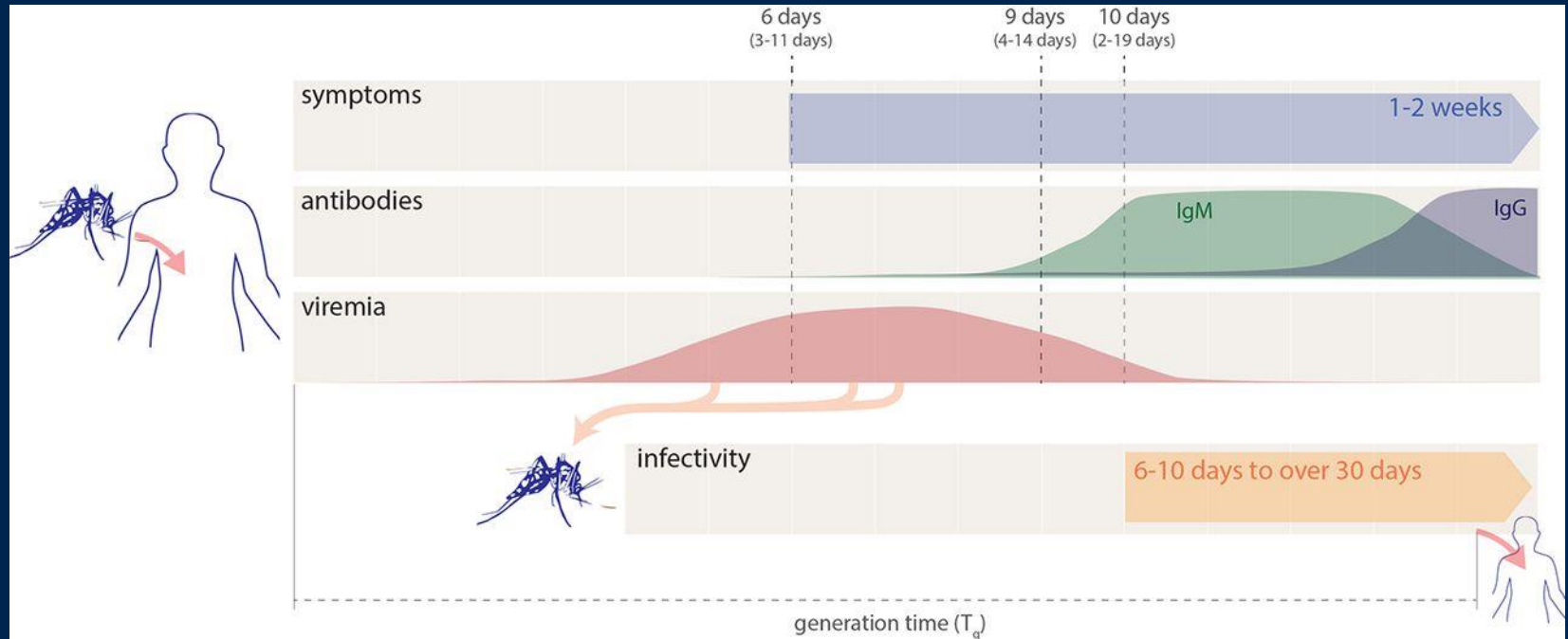
Clinical Zika

Fever
Maculopapular
Rash (pruritic)
Headache
Conjunctivitis
Retroorbital pain

SYMPTOMS OF ZIKA VIRUS



Schematic of the course of human and mosquito infection.



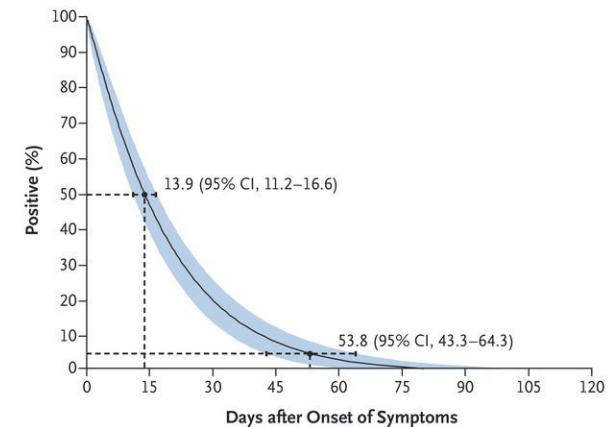
Justin Lessler et al. Science 2016;science.aaf8160

Persistence of Zika
Virus in Body Fluids —
Preliminary Report
Gabriela Paz-Bailey,
M.D., Ph.D., et al

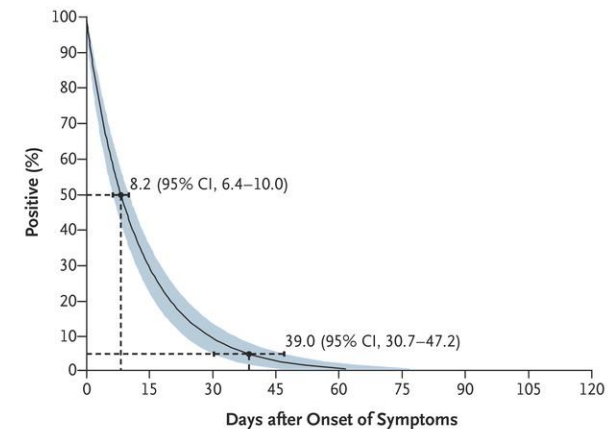


The prolonged time until ZIKV RNA clearance in serum in this study may have implications for the diagnosis and prevention of ZIKV infection. Current sexual-prevention guidelines recommend that men use condoms or abstain from sex for 6 months after ZIKV exposure; in 95% of the men in this study, ZIKV RNA was cleared from semen after about 3 months.

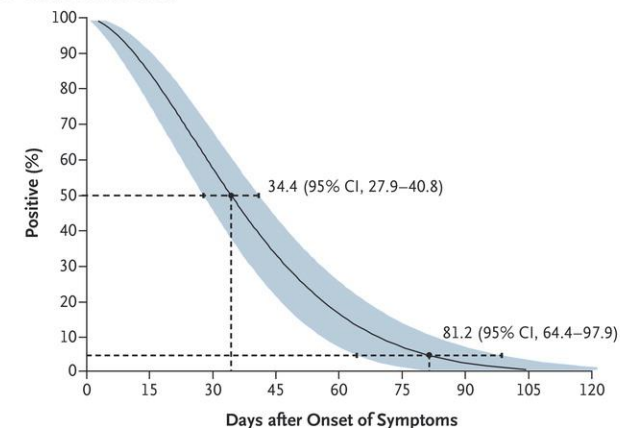
A ZIKV RNA in Serum



B ZIKV RNA in Urine

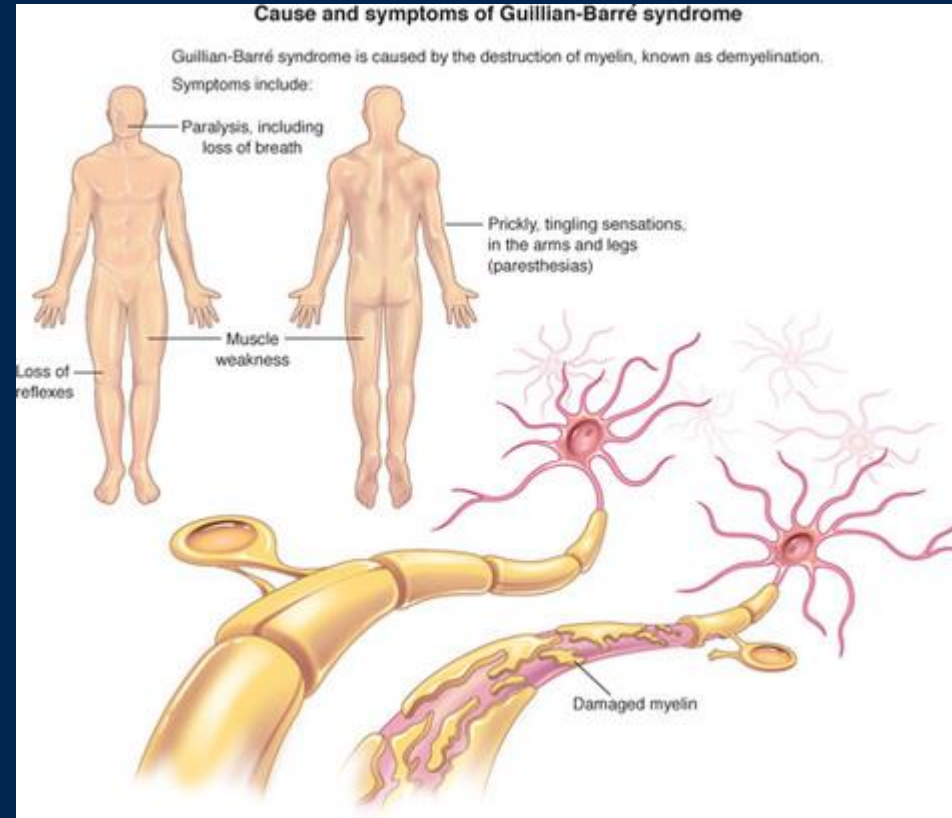


C ZIKV RNA in Semen

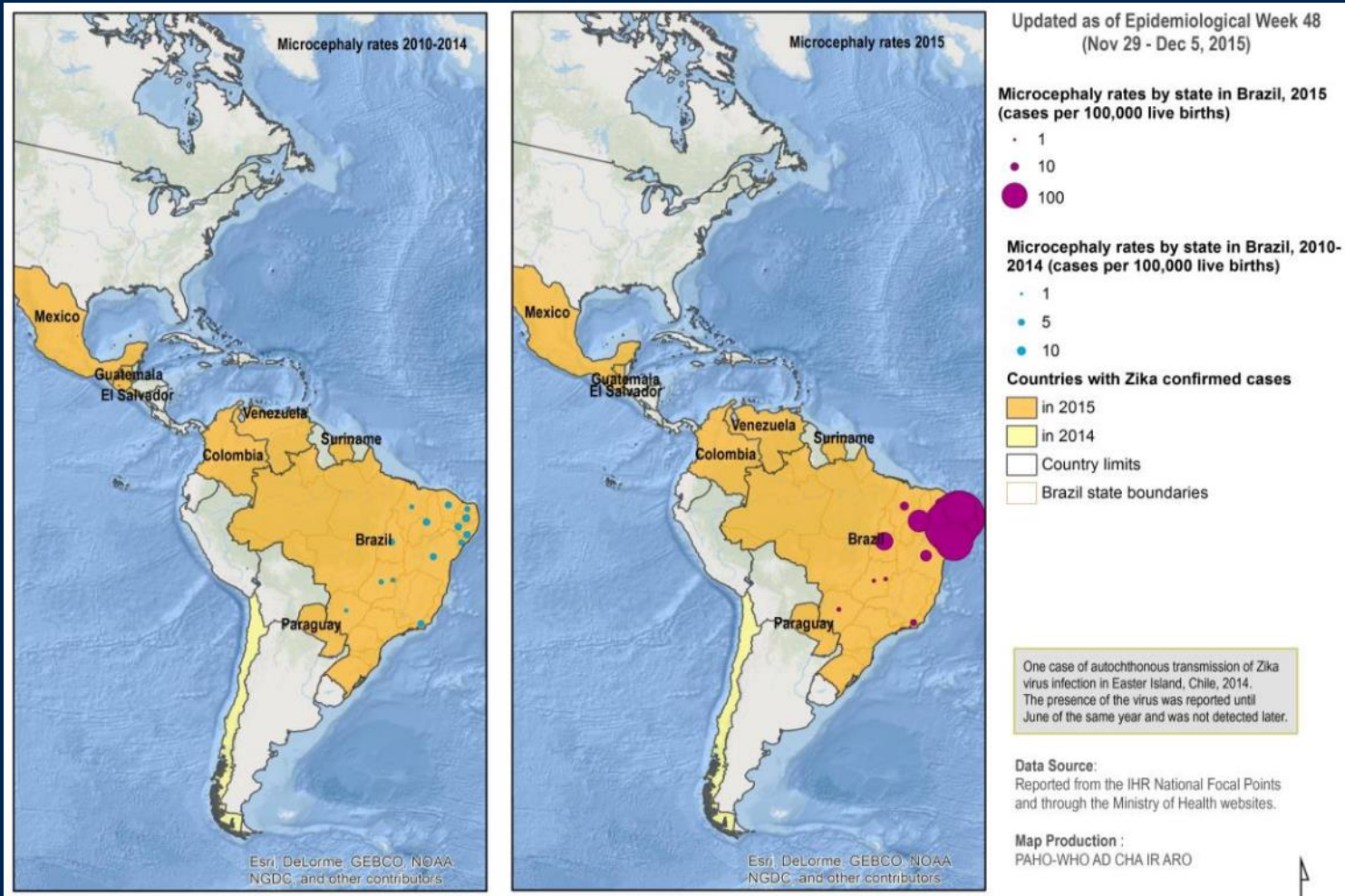


Guillain-Barre syndrome

- Recent history of zika (within 6 days)
- Zika IgM/IgG
- 1/3 respiratory assistance
- Anti-glycolipid antibody (GA1)
- Guillain Barre
 - 1/1,000 French Polynesia
 - 554 cases in Brazil
 - Increase in El Salvador

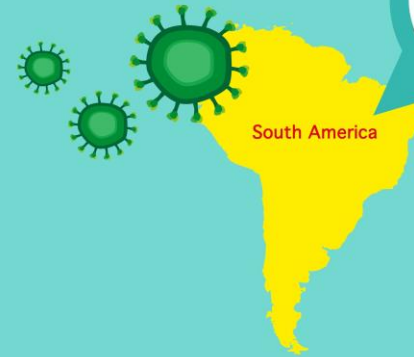
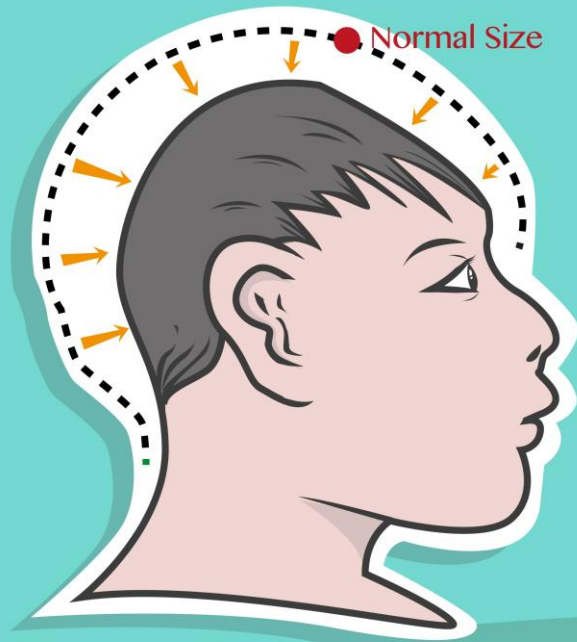


Microcephaly cases in NE Brazil



MICROCEPHALY

Abnormal smallness of the head, a congenital condition associated with incomplete brain development.



Zika Fever Virus from *Aedes aegypti* mosquito is linked to microcephaly birth defect cases mostly in South America



Microcephaly



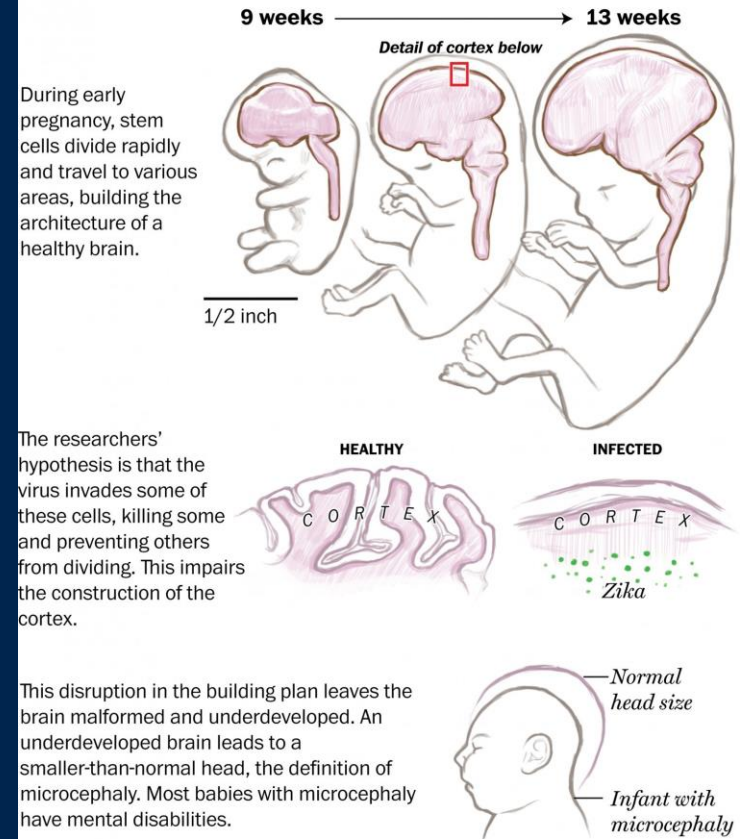
Occipitofrontal circumference (OFC) more than 3 standard deviations (SD) below the mean for a given age, sex, and gestation. Other times, it is defined as an OFC more than 2 SD below the appropriate mean (ie, less than the 3rd percentile).

Recovery of zika virus

- Zika genome in amniotic fluid (Brazil)
- Zika genome in placentas of two women who miscarried (CDC)
- Zika genome in blood and other tissues of newborns (Brazil)

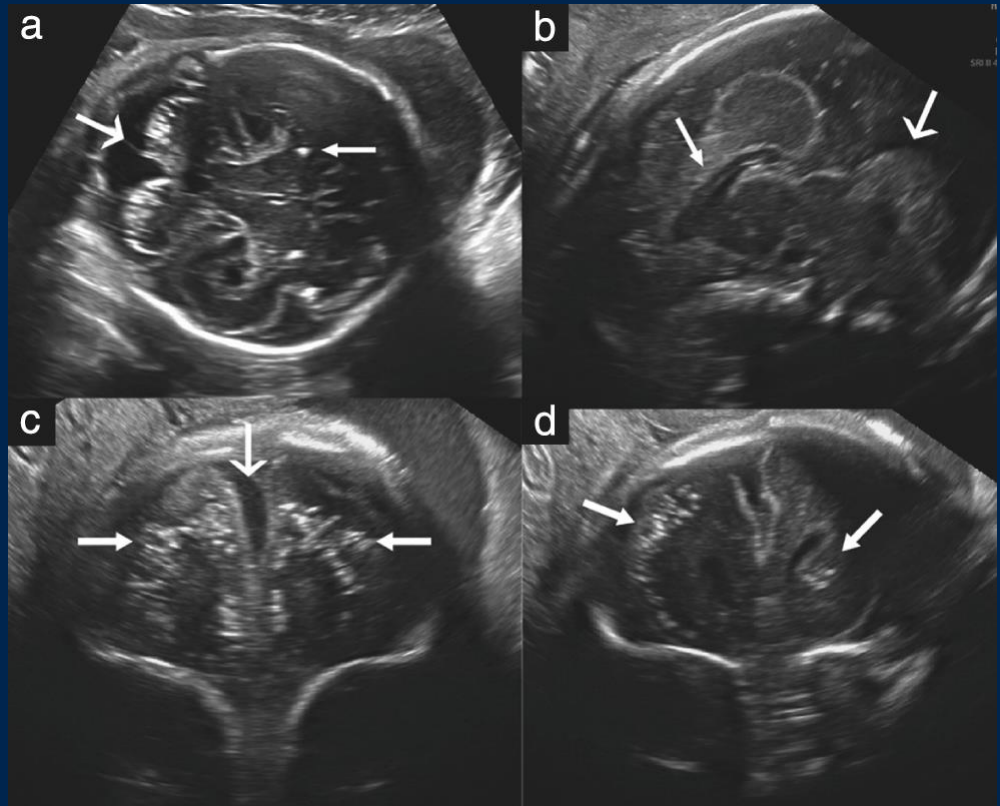
A possible link between Zika and microcephaly

A group of scientists working with lab-grown cells may have found a clue to how the Zika virus could cause abnormally small heads in the children of women who contract the virus early in pregnancy.

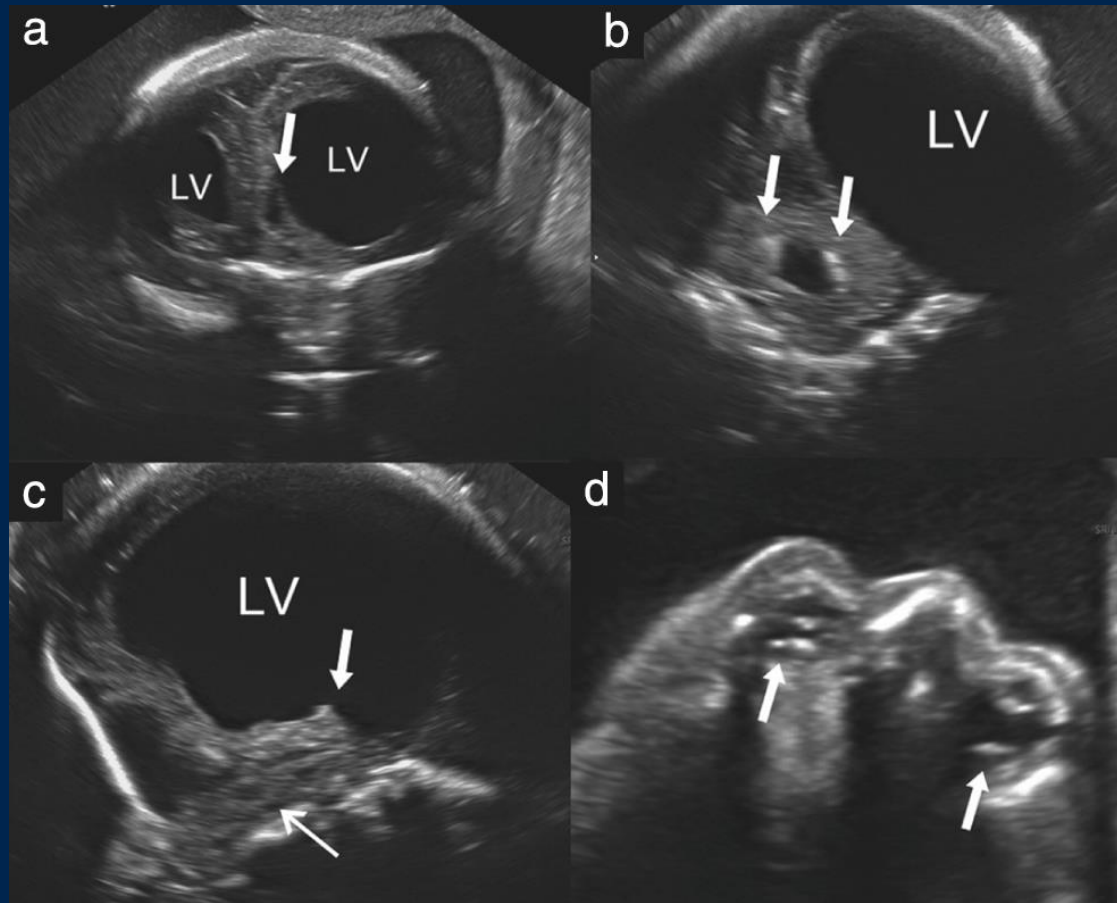


Sources: Zhexing Wen, researcher at the Johns Hopkins Medical Institute; the Dana Foundation; BrainFacts.org, American Journal of Neuroradiology
BONNIE BERKOWITZ AND LAZARO GAMIO/THE WASHINGTON POST

Cerebral calcifications



Ventriculomegaly, absent thalamus, thin pons, eye calcifications



Fetal Brain Disruption Sequence

- The fetal brain disruption sequence is a recognizable pattern of defects that includes moderate to profound microcephaly, overlapping sutures, occipital bone prominence, and scalp rugae. The condition is postulated to arise from partial brain disruption....with subsequent fetal skull collapse resulting from decreased intracranial hydrostatic pressure. Proposed causes include prenatal viral or parasitic infections and vascular disruptions. We report seven infants with the fetal brain disruption sequence. Two of these patients died. A changing phenotype with time was seen in three. Recognition of this phenotype is critical because the condition has a uniformly poor prognosis for infants but the recurrence risk in future pregnancies is low.
- Moore, Weaver, Bull et al (1990) J Pediatrics

Brasil P et al (Dec 2016) NEJM

- Zika virus infection in pregnant women in Rio de Janeiro
 - Overall adverse outcomes 46% among offspring of Zika + pregnant women
 - Among 117 live infants born to 116 Zika + women
 - 42% grossly abnormal clinical or brain imaging findings or both
 - 4 infants with microcephaly
 - Adverse outcomes noted regardless of the trimester women were infected with Zika virus



MMWR Findings in US



- 1,297 pregnant women in 44 states were reported to USZPR.
- Zika virus-associated birth defects were reported for 51 (5%) of the 972 fetuses/infants from completed pregnancies with laboratory evidence of possible recent Zika virus infection
- Birth defects were reported in 15% of fetuses/infants of completed pregnancies with confirmed Zika virus infection in the first trimester.
- All infants born to women with laboratory evidence of possible recent Zika virus infection during pregnancy should receive postnatal neuroimaging and Zika virus testing in addition to a comprehensive newborn physical exam and hearing screen.

Hotez PJ JAMA Pediatrics

Unknown long-term impact

- On infants born to Zika positive mothers without structural abnormalities
- On children who acquire Zika in first year of life or afterwards



Spread of Zika in the Americas



Poverty in Northeastern Brazil



Recife



Salvador de Bahia

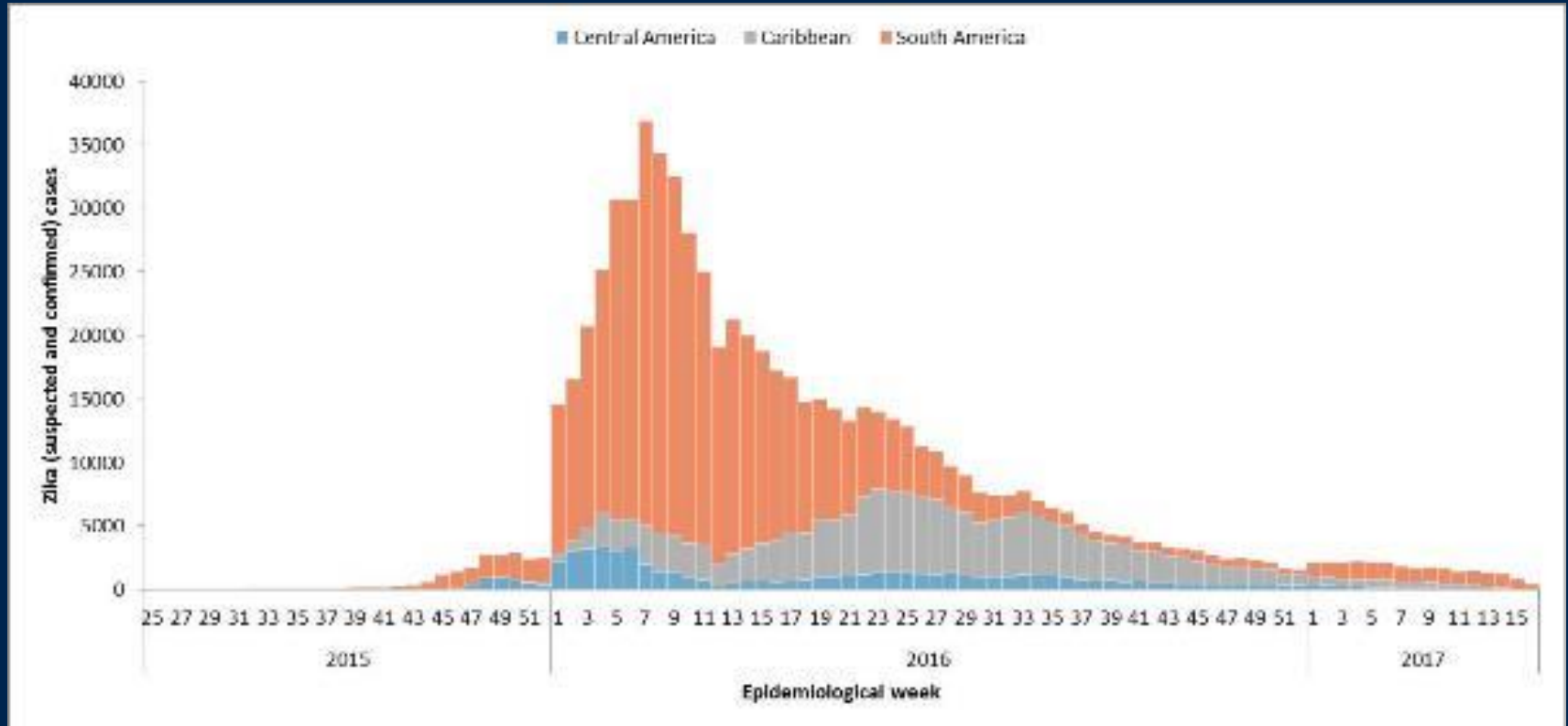
WHERE

ZIKA VIRUS

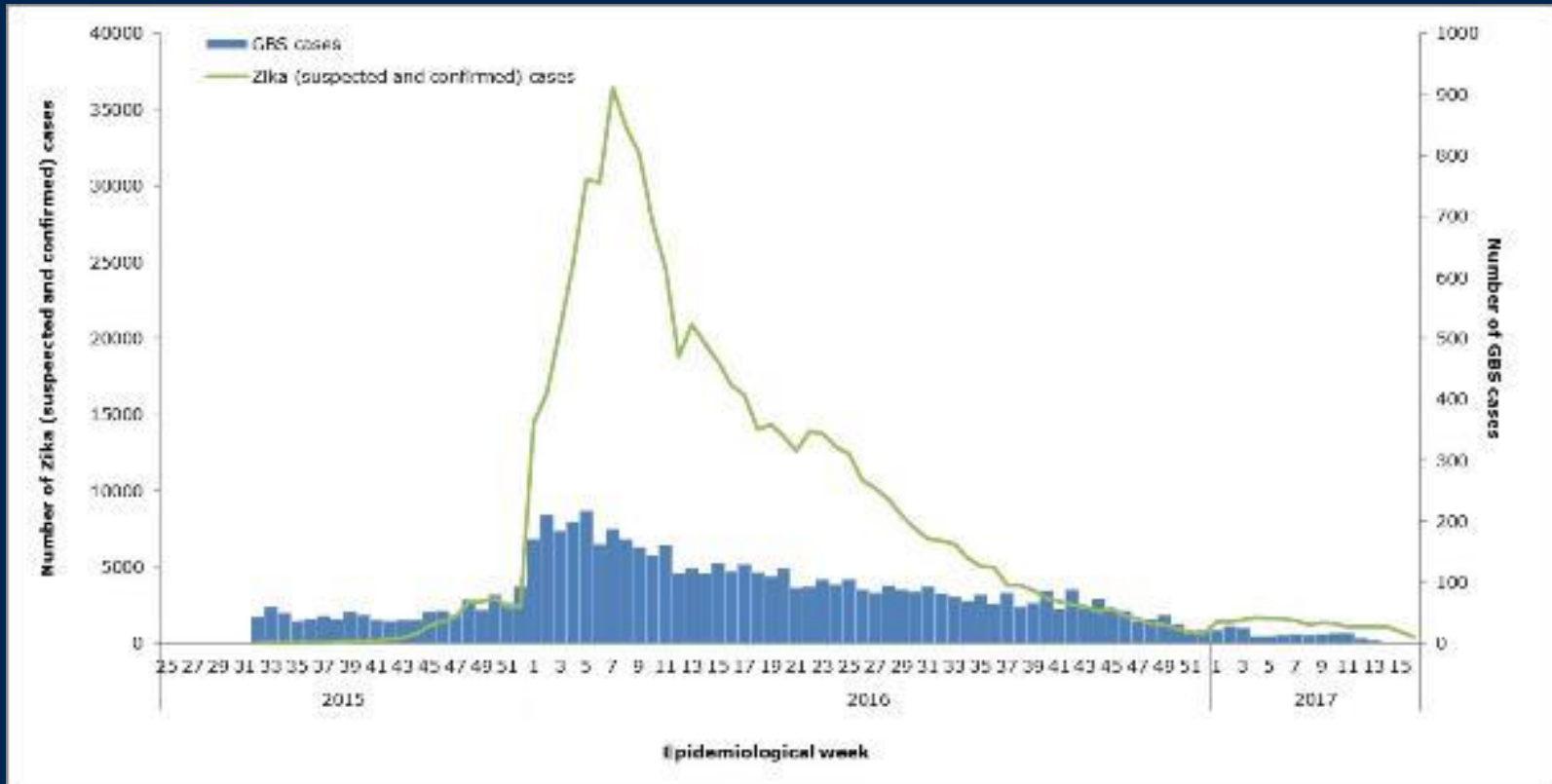
IS SPREADING



PAHO: Zika Virus Transmission

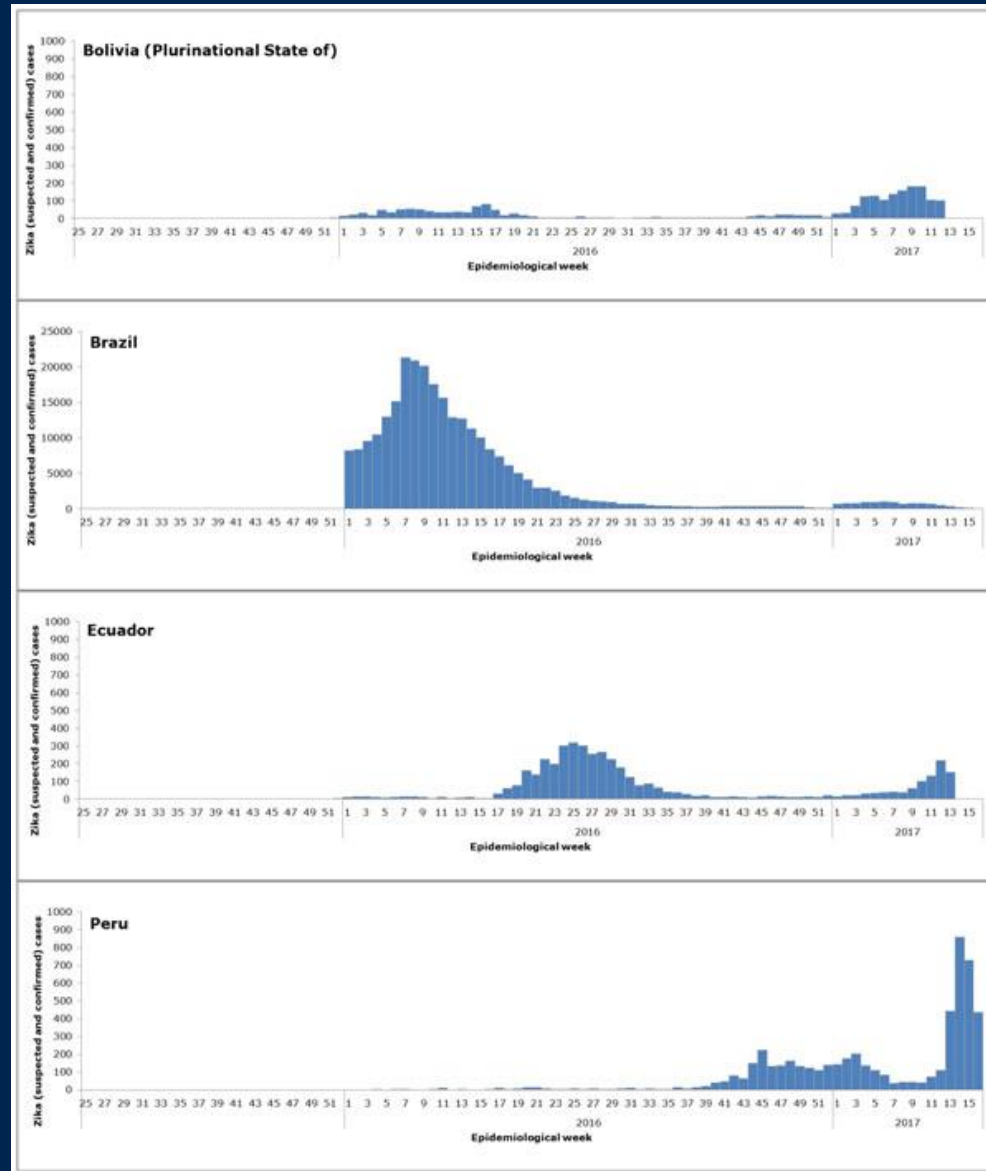


GBS Cases



Zika in Americas

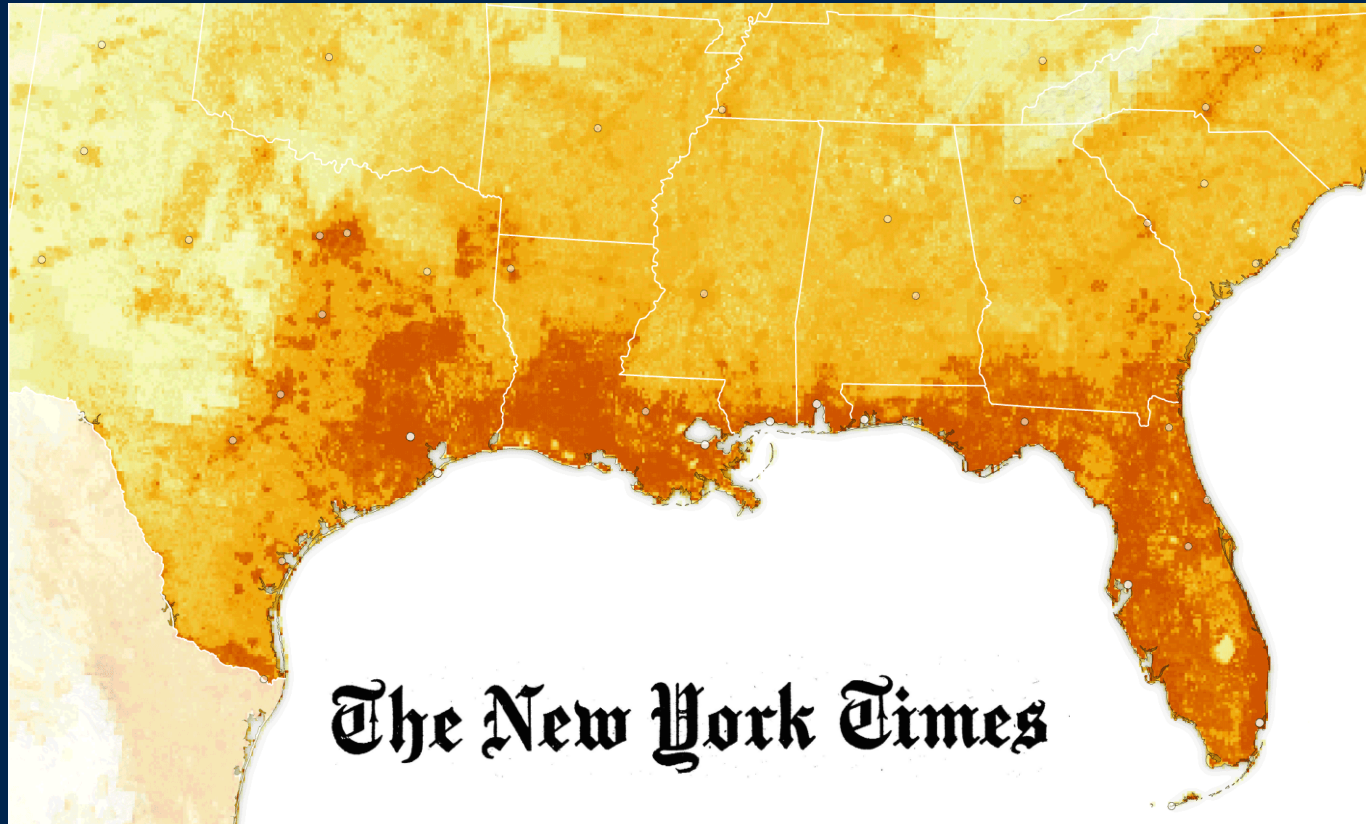
- Mexico and Central America continue to decline (except Guatemala)
- Caribbean decreasing trend everywhere except Aruba
- Increasing trend of reported cases in South America mainly due to increases in the number of cases in Bolivia (Plurinational State of), Brazil, Ecuador, and Peru



Ranking of Zika cases

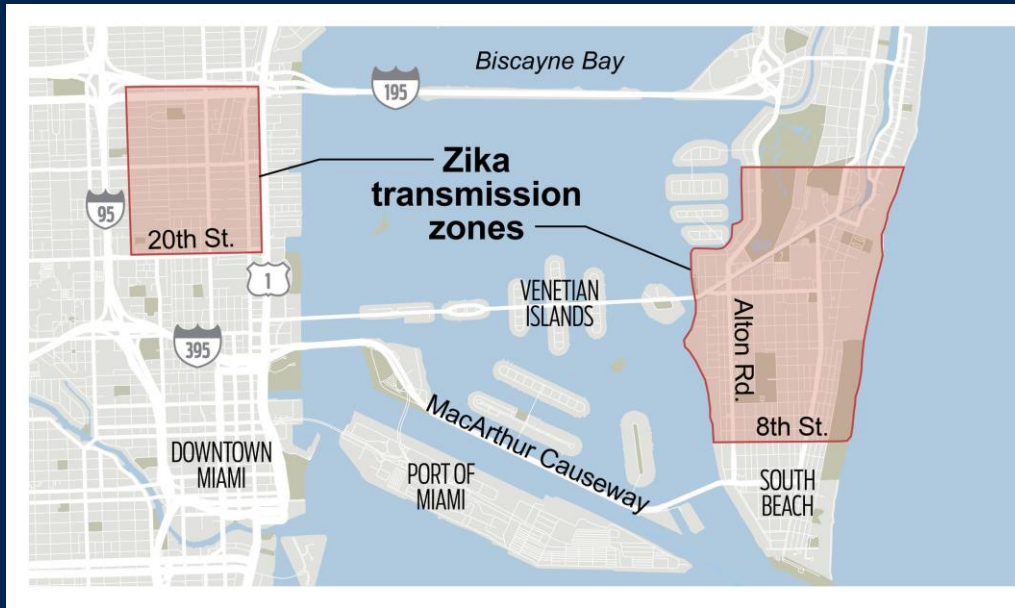
-Country	Suspected or Confirmed Cases	
-Brazil	220,213	• 559,750 in the Americas
-Colombia	97,884	• May 4 2017
-Venezuela	59,965	• 3,125 congenital Zika cases
-Puerto Rico	40,134*	(2,653 in Brazil, 148
-Martinique	36,680	Colombia)
-Honduras	32,130	• U.S.:
-Guadeloupe	30,845	• 225 autothonous cases
-El Salvador	11,490	• 4,973 imported cases,
-French Guiana	10,385	• 66 congenital cases
-Mexico	8,721 *	

Hotez PJ “Zika is Coming” *The New York Times* April 9, 2016



217
Autochthonous
Cases as of
Jan 2017

Zika in South Florida



- 210 locally acquired cases
- Dec 9, 2016 CDC removed red area designations after 3 mosquito incubation periods passed without any new ;ocally transmitted cases.



Zika in South Texas



6 known local cases of Zika transmission including 1 Zika pregnancy case

Cameron County, Texas

Map



Where will the next shoe fall?



Houston's Fifth Ward

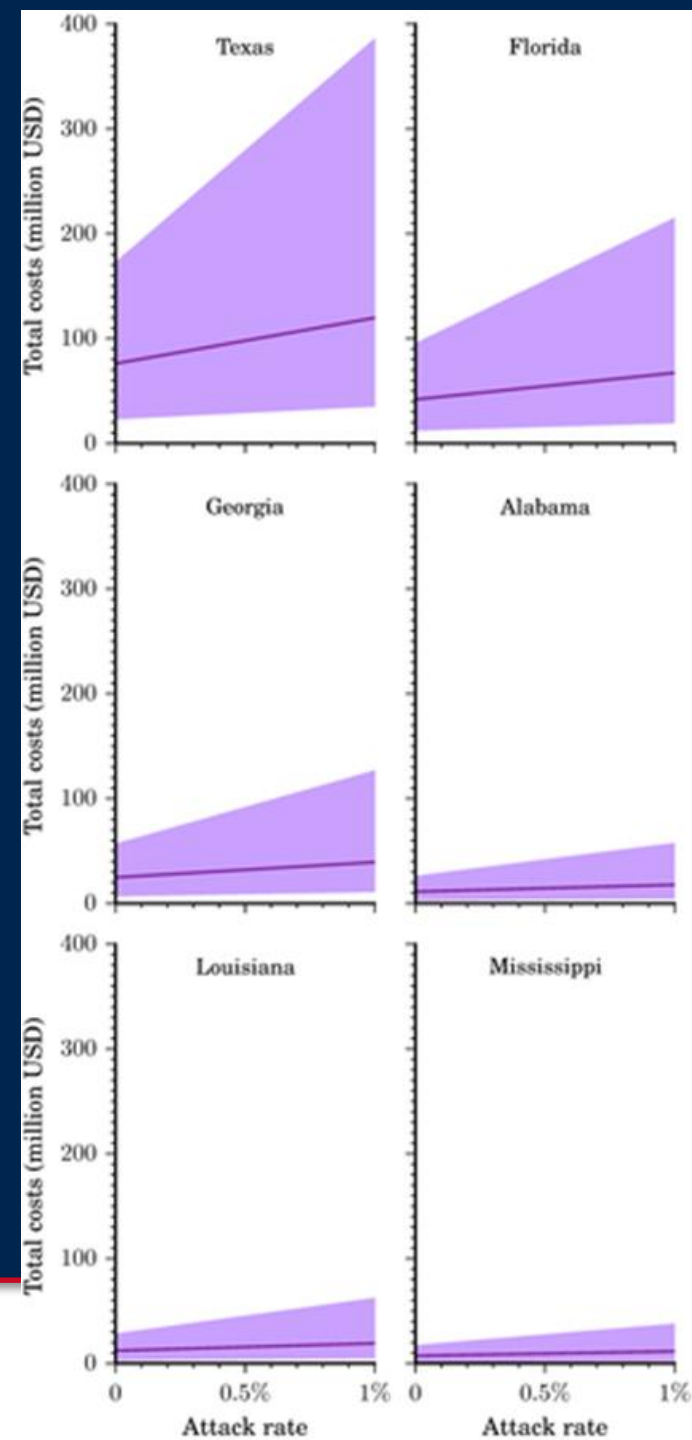
Anna Grove Photographer

Potential economic burden of Zika to Gulf Coast States

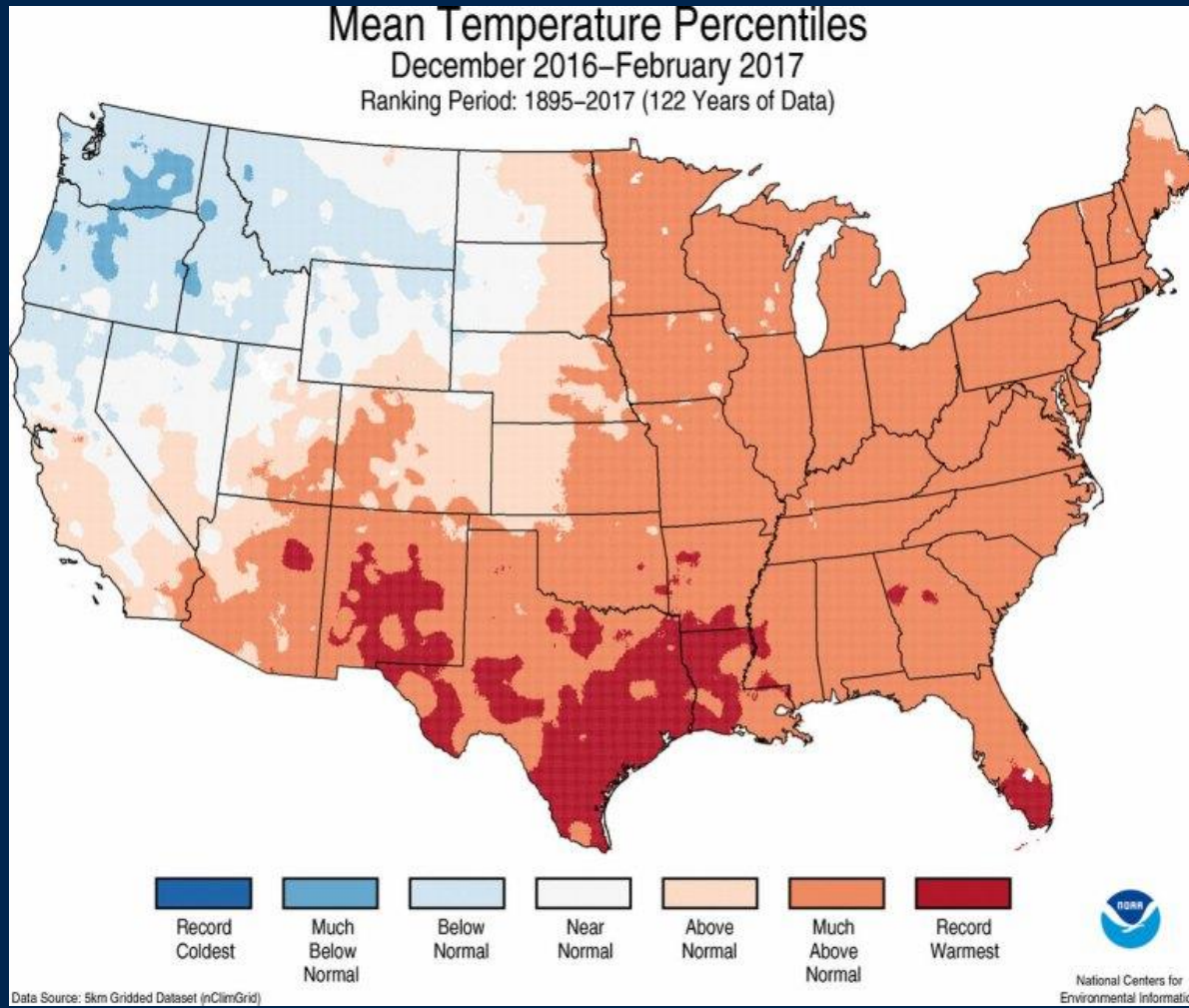
- Total Costs

- Productivity losses
- Medicaid costs
- Direct medical costs
- Direct medical resource utilization

- Across the six states, an attack rate of 0.01% is estimated to cost \$183.4 million to society (\$117.1 million in direct medical costs and \$66.3 million in productivity losses), 0.025% would result in \$198.6 million (\$119.4 million and \$79.2 million), 0.10% would result in \$274.6 million (\$130.8 million and \$143.8 million) and 1% would result in \$1.2 billion (\$268.0 million and \$919.2 million).



Bad News for Spring/Summer 2017

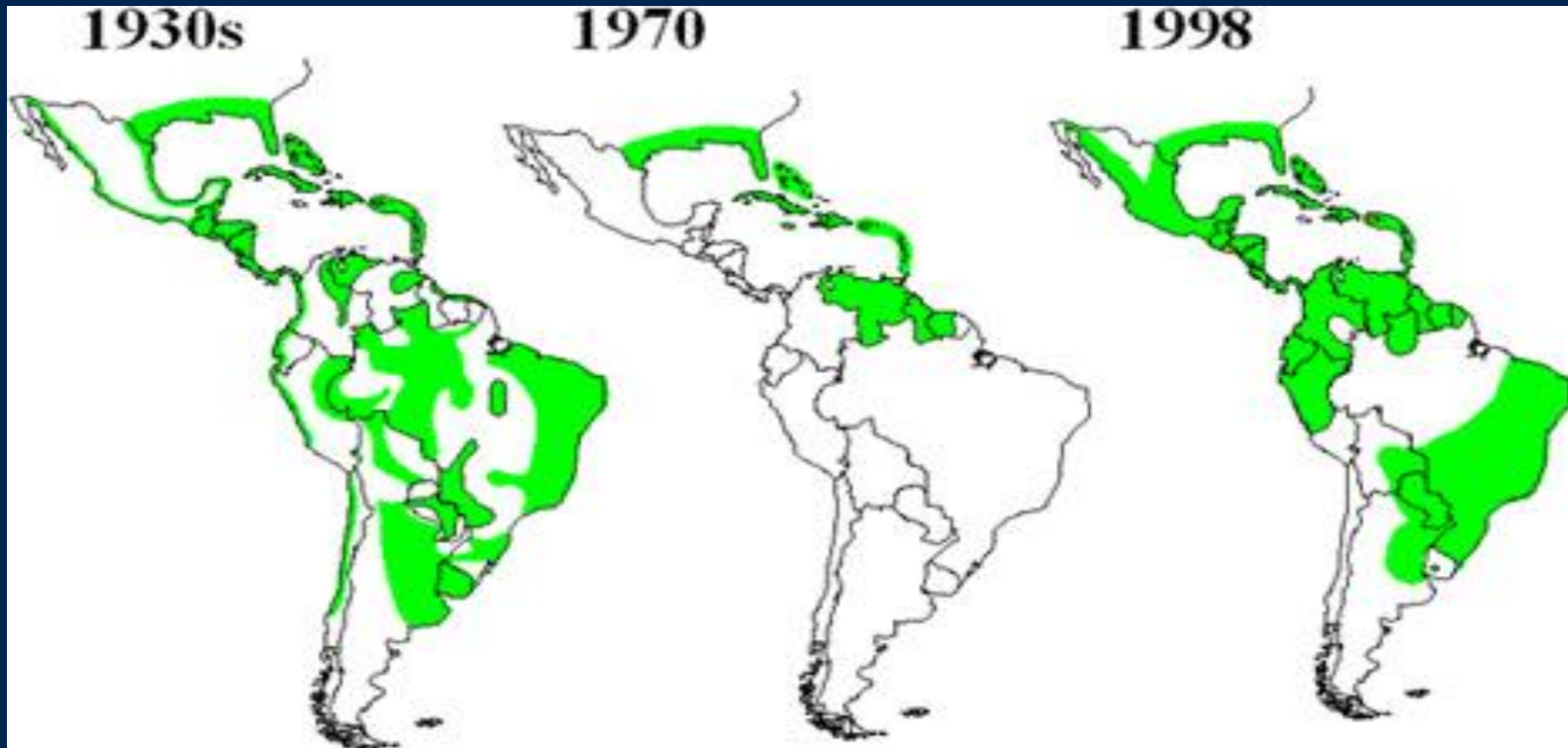


PAHO/WHO Mosquito Eradication Campaign 1947-1962



US has no track record in *Aedes aegypti* control

- US did not participate in PAHO Eradication Program
- Began in 1965 halted in 1969

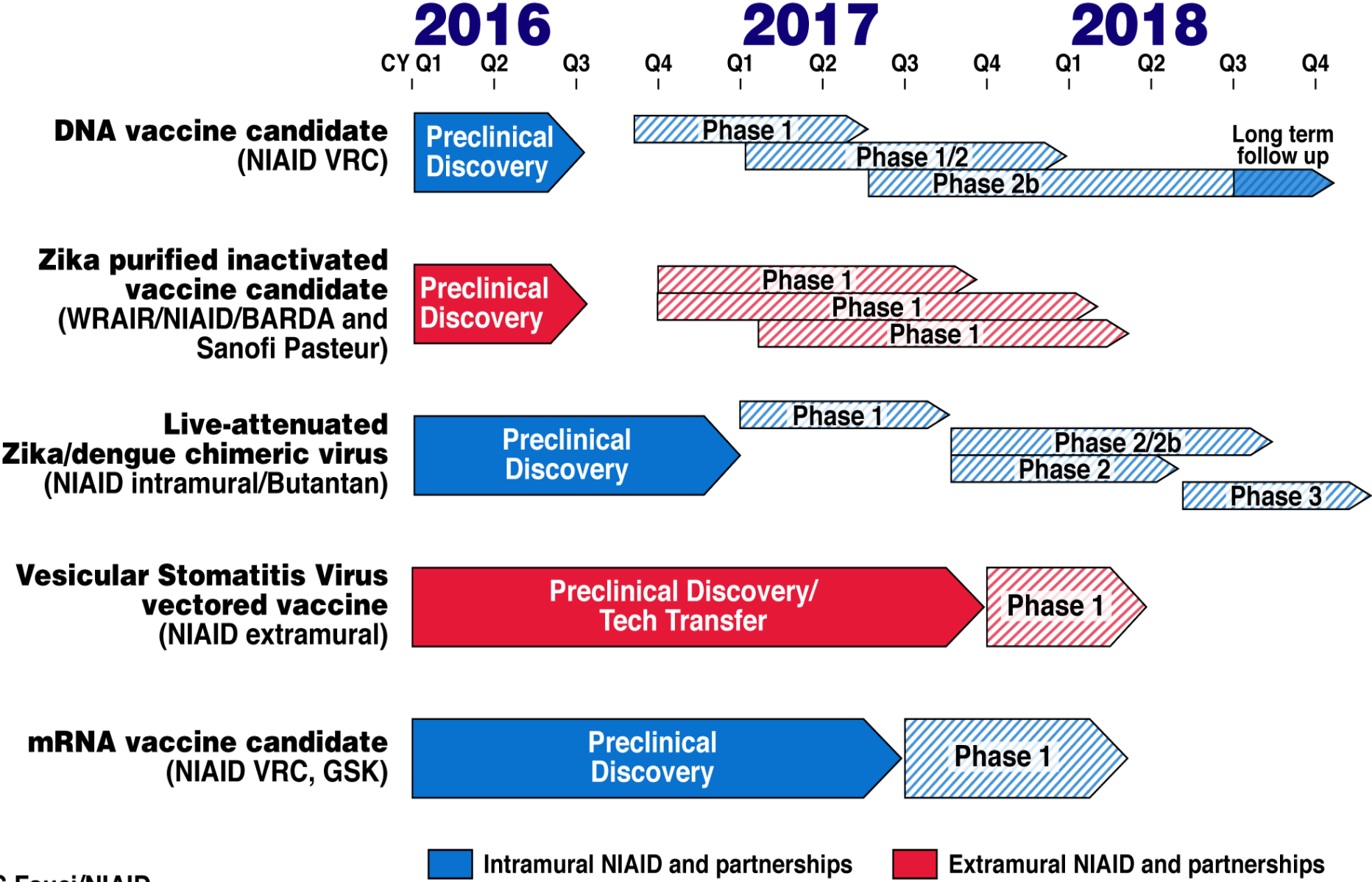


Oxitec



GMO Aedes Mosquitoes “The company's scientists genetically alter the male mosquitoes so that any offspring they father don't develop properly. These genetically modified males mate with the females, which lay dud eggs.”

Zika Vaccine Development Timeline



National School of Tropical Medicine

Baylor
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TROPICAL
MEDICINE

