Bench to Bedside in Real Time: Rapid Progress Against Zika Virus

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Outline and Disclosures

- Biology of Zika Virus
- Current Zika Virus Disease Epidemic
  - Onset
  - Clinical features
  - Mortality events
- Surveillance, Diagnosis, Risk Assessment
- Future Disease Management

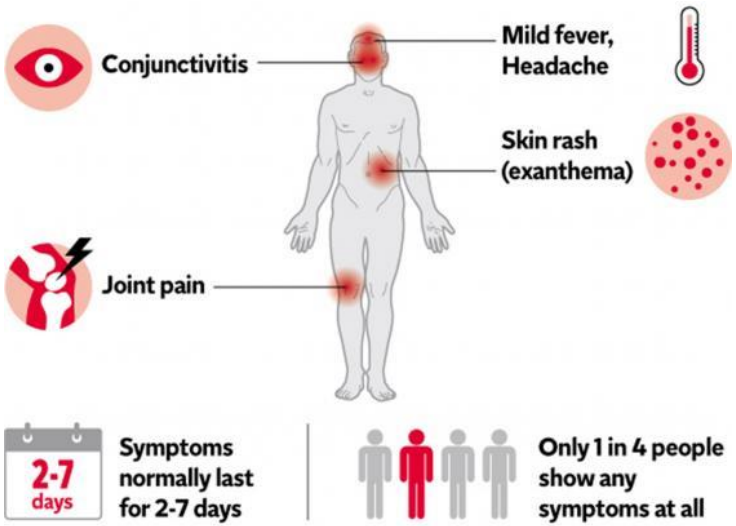
Nothing to disclose

Zika CME Learning Objectives

- Discuss the origins of the current outbreak
- Describe the clinical features of Zika virus disease in different patient populations
- Describe the current options for diagnosis and vaccination
- Advise patients on relative risk and best practices for prevention

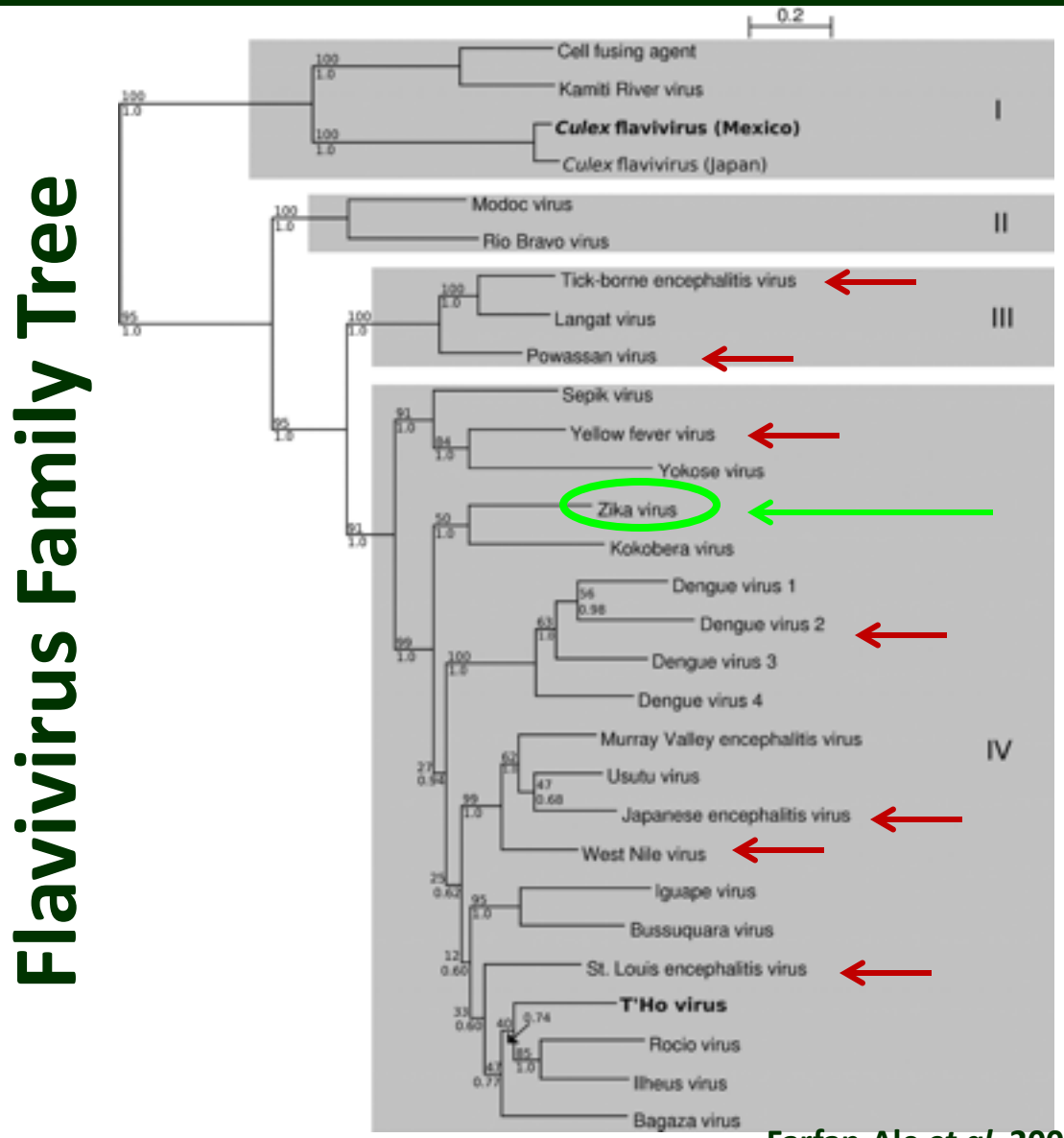
Zika Virus Disease

- Historical view of ZIKV disease



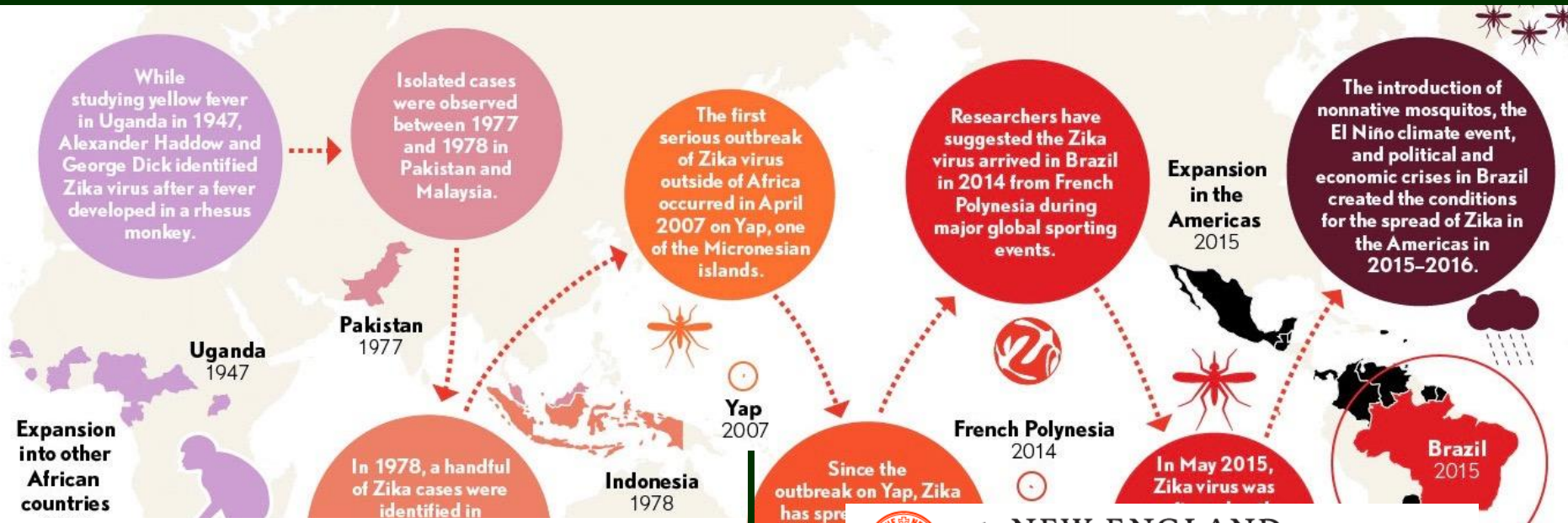
Zika Virus Biology

- Arbo Flavivirus
  - RNA
  - Latency?
  - Antivirals?
- Features of Flaviviruses
  - Transmission
  - Prevention
  - Diversity



Farfan-Ale *et al*, 2009

Zika Virus Disease in the Americas



Trans R Soc Trop Med Hyg. 1981;75(3):389-93.

Zika virus, a cause of fever in Central Java, Indonesia.

Olson JG, Ksiazek TG, Suhandiman, Triwibowo.

Abstract

In 1977 and 1978 selected in-patients at the Tegalyoso Hospital, Klaten, Indonesia who had recent onsets of acute fever were serologically studied for evidence for alphavirus and flavivirus infections. A brief clinical history was taken and a check list of signs and symptoms was completed on admission. Acute and convalescent phase sera from 30 patients who showed evidence that a flavivirus had caused their illnesses were tested for neutralizing antibodies to several flaviviruses which occur in South-east Asia. Paired sera from seven patients demonstrated a fourfold rise in antibody titre from acute to convalescent phase. The most common clinical manifestations observed in this series of patients included high fever, malaise, stomach ache, dizziness and anorexia. None of the seven patients had headache or rash despite the fact that headache and rash had been associated with two of the three previously studied. The onsets of illness clustered toward the end of the rainy season when populations of Aedes aegypti, a probable vector in Malaysia, were most abundant.

PMID: 6275577

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ORIGINAL ARTICLE

Zika Virus Outbreak on Yap Island, Federated States of Micronesia

Mark R. Duffy, D.V.M., M.P.H., Tai-Ho Chen, M.D., W. Thane Hancock, M.D., M.P.H., Ann M. Powers, Ph.D., Jacob L. Kool, M.D., Ph.D., Robert S. Lanciotti, Ph.D., Moses Pretrick, B.S., Maria Marfel, B.S., Stacey Holzbauer, D.V.M., M.P.H., Christine Dubray, M.D., M.P.H., Laurent Guillaumot, M.S., Anne Griggs, M.P.H., Martin Bel, M.D., Amy J. Lambert, M.S., Janeen Laven, B.S., Olga Kosoy, M.S., Amanda Panella, M.P.H., Brad J. Biggerstaff, Ph.D., Marc Fischer, M.D., M.P.H., and Edward B. Hayes, M.D.

N Engl J Med 2009; 360:2536-2543 | June 11, 2009 | DOI: 10.1056/NEJMoa0805715

Share:

Abstract | Article | References | Citing Articles (340)

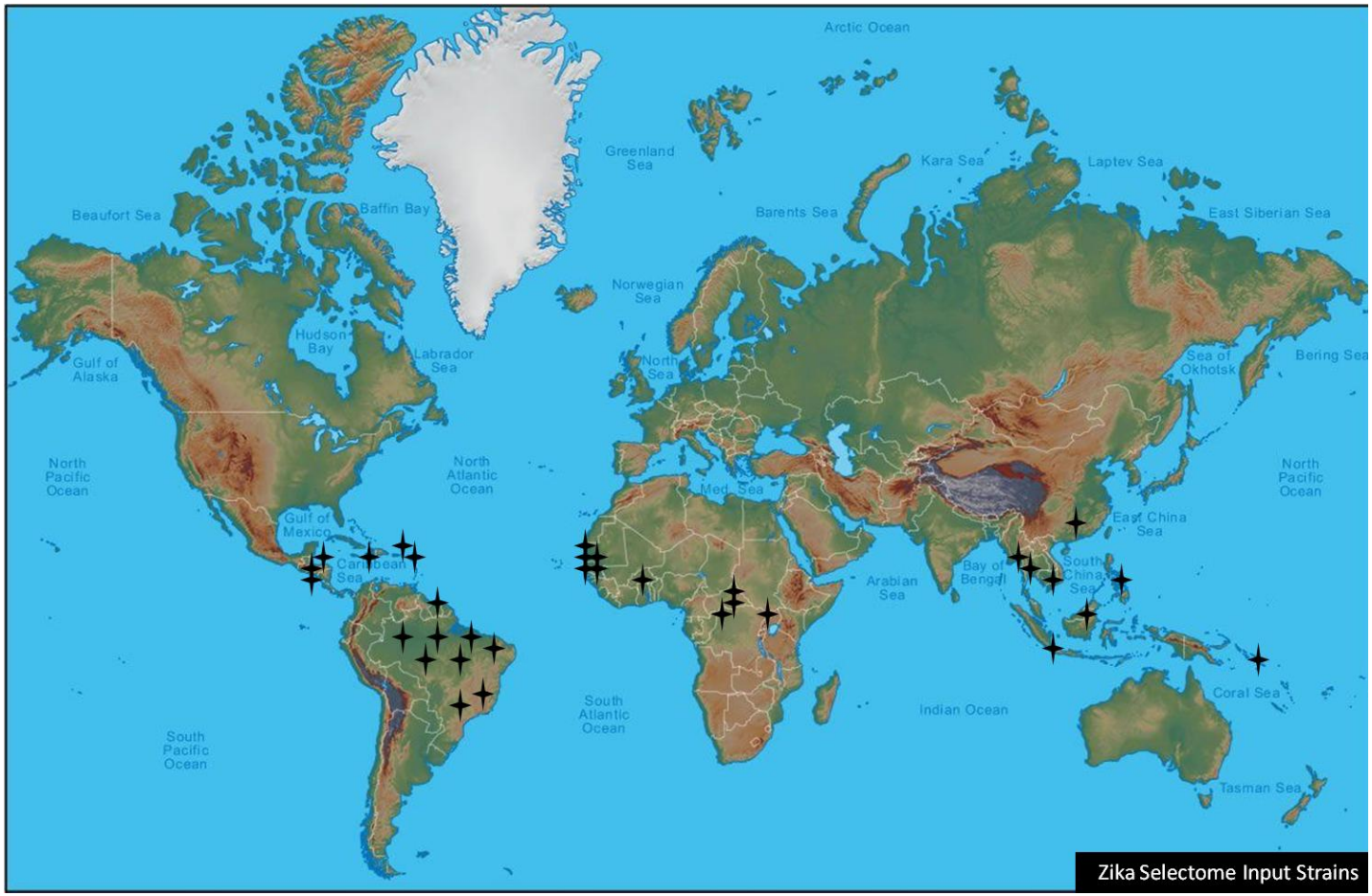
BACKGROUND

In 2007, physicians on Yap Island reported an outbreak of illness

MEDIA IN THIS ARTICLE

FIGURE 1

Diversity of Zika Virus

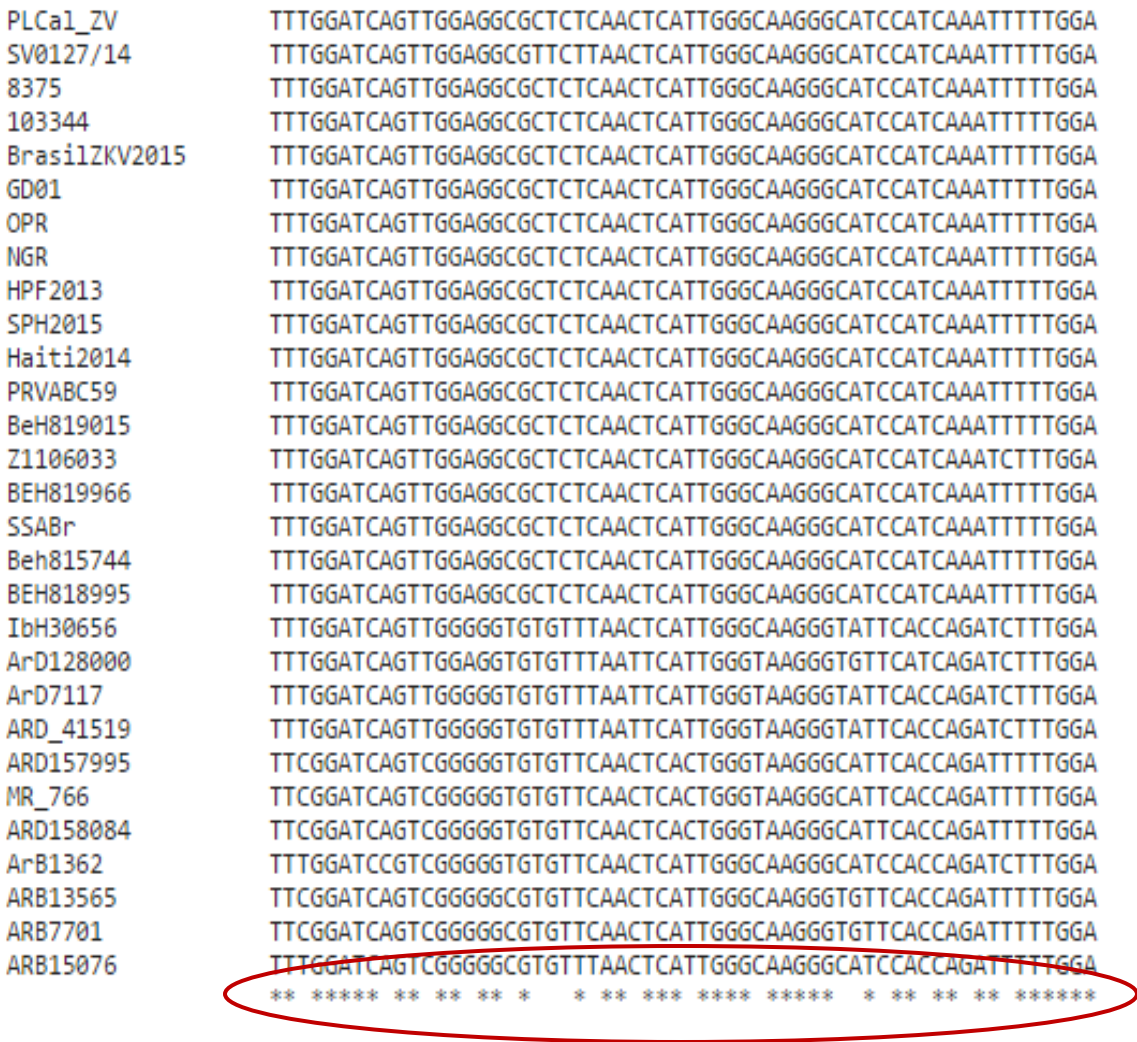


- 33 Assembled Genomes
  - Collection site, time, location varied substantially

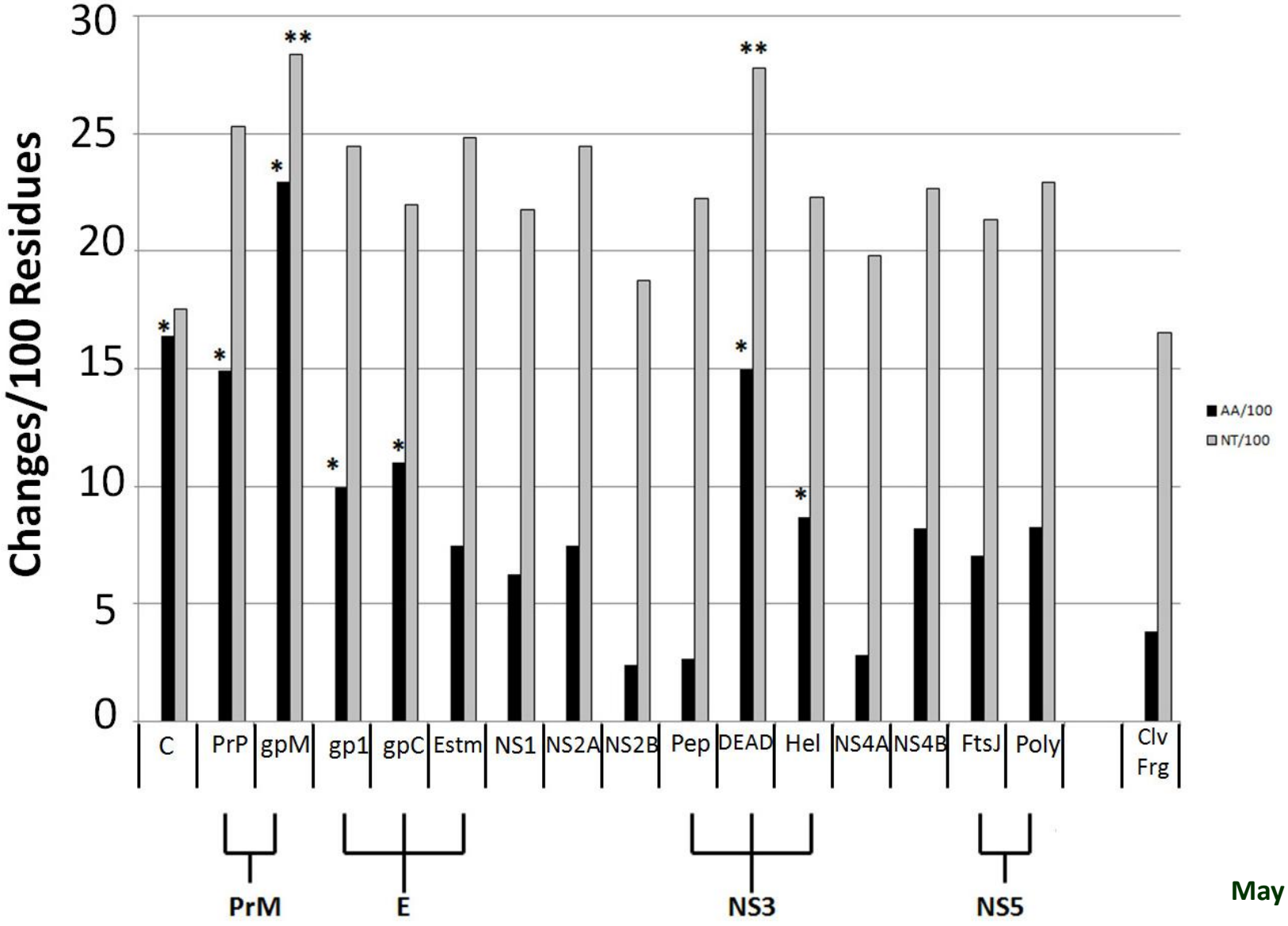
Zika Virus Sequence Alignment

- Aligned all 33 genomes
  - ClustalΩ
- SNP-level diversity

70 OF 10,000+ BASES



Zika Diversity by Gene

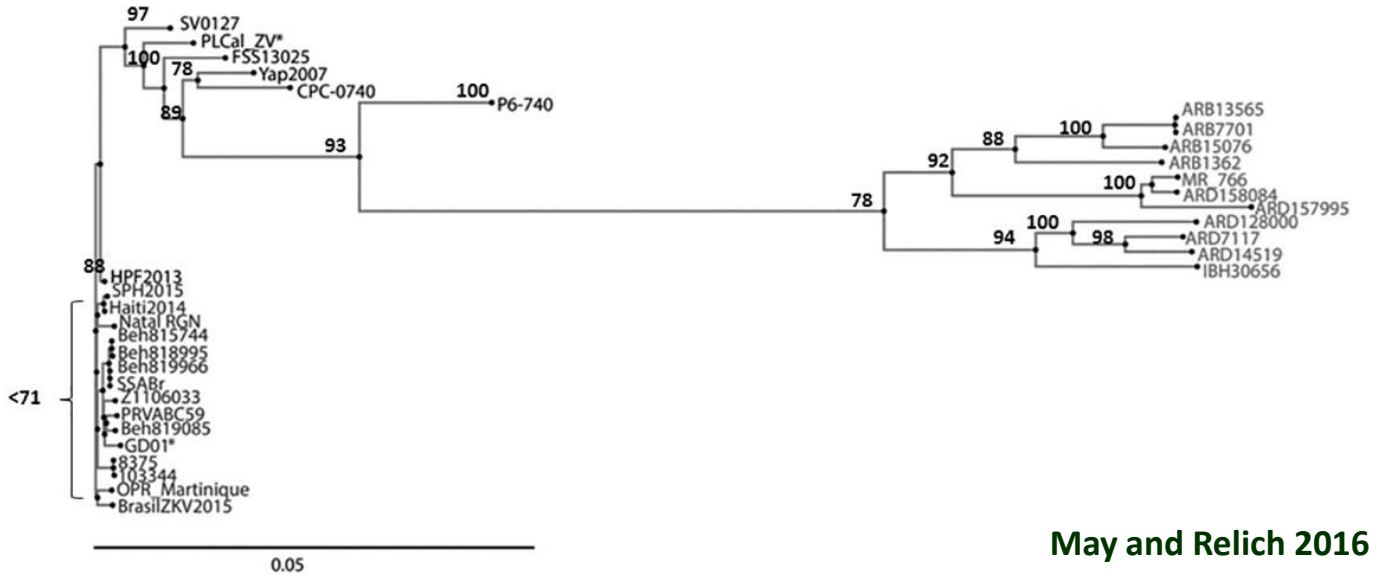


May and Relich 2016

Clinical Relevance?

- Diagnostics, vaccines (more on this later!)

- Outbreak history
  - How did Zika arrive in the Western hemisphere?



May and Relich 2016

Clinical Relevance?

- Diagnostics, v
- Outbreak hist
  - How did Zika

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Volume 21, Number 10—October 2015

Letter

Zika Virus Transmission from French Polynesia to Brazil

Suggested citation for this article

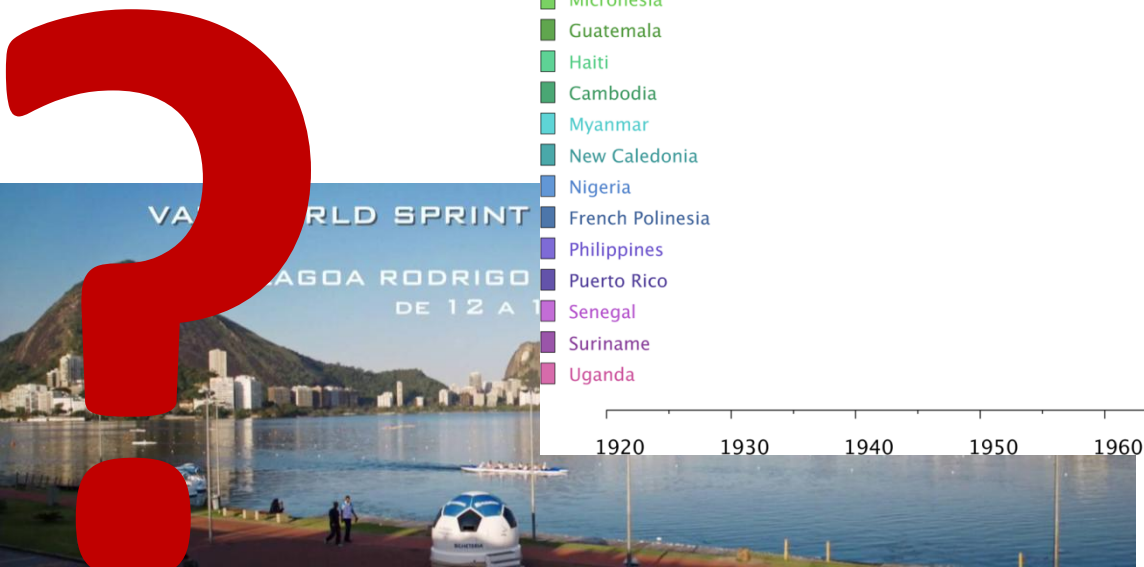
To the Editor: Campos et al. (*1*) reported a Zika virus (ZIKV) outbreak in Brazil in 2015. This response adds complementary data related to the propagation of this mosquitoborne disease.

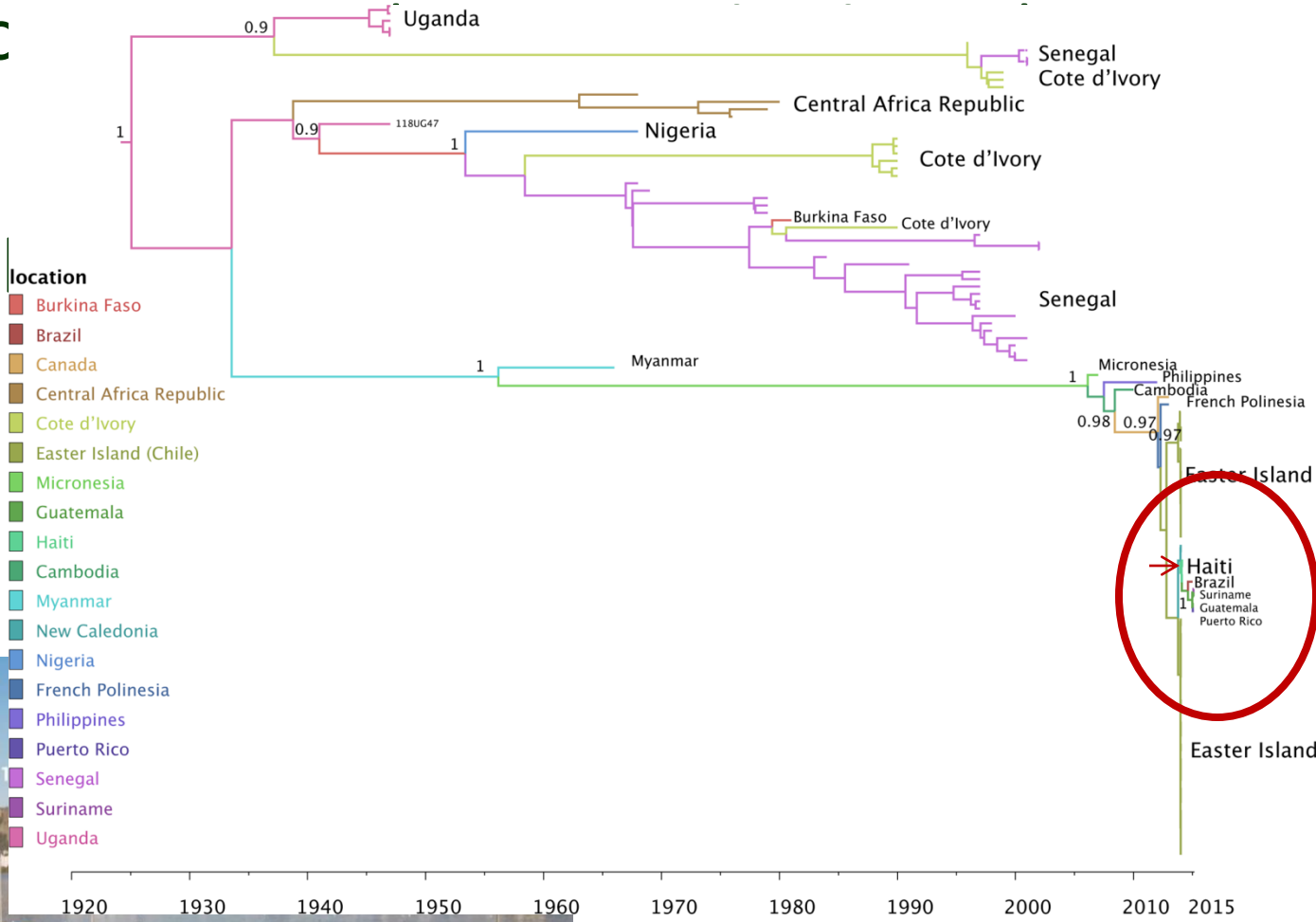
To date, the largest ZIKV outbreak occurred in French Polynesia during 2013–2014. The outbreak spread to other Pacific Islands: New Caledonia, Cook Islands, Easter Island, Vanuatu, and Solomon Islands (*2*). The origin of introduction of ZIKV to French Polynesia remains unknown; introduction of ZIKV in New Caledonia was after imported cases from French Polynesia (*3*); introduction to Easter Island was suspected to have occurred among attendees of the annual Tapati festival, including those from French Polynesia (*4*). The virus was likely transmitted to New Caledonia, Cook Islands, and Easter Island when infected travelers from French Polynesia were bitten by vectors while on the islands. Frequent travel between New Caledonia and Vanuatu is likely related to the introduction of ZIKV in the latter country.

dies showed that the closest strain to the one that emerged in Brazil was isolated from samples ts in French Polynesia and spread among the Pacific Islands (*1*); both strains belong to the Asian en assumed that ZIKV was introduced to Brazil during a World Cup soccer competition in 2014 IKV-endemic Pacific countries competed. However, in August 2014, the Va'a World Sprint noe race was held in Rio de Janeiro, Brazil. Four Pacific countries (French Polynesia, New

Clinical Relevance?

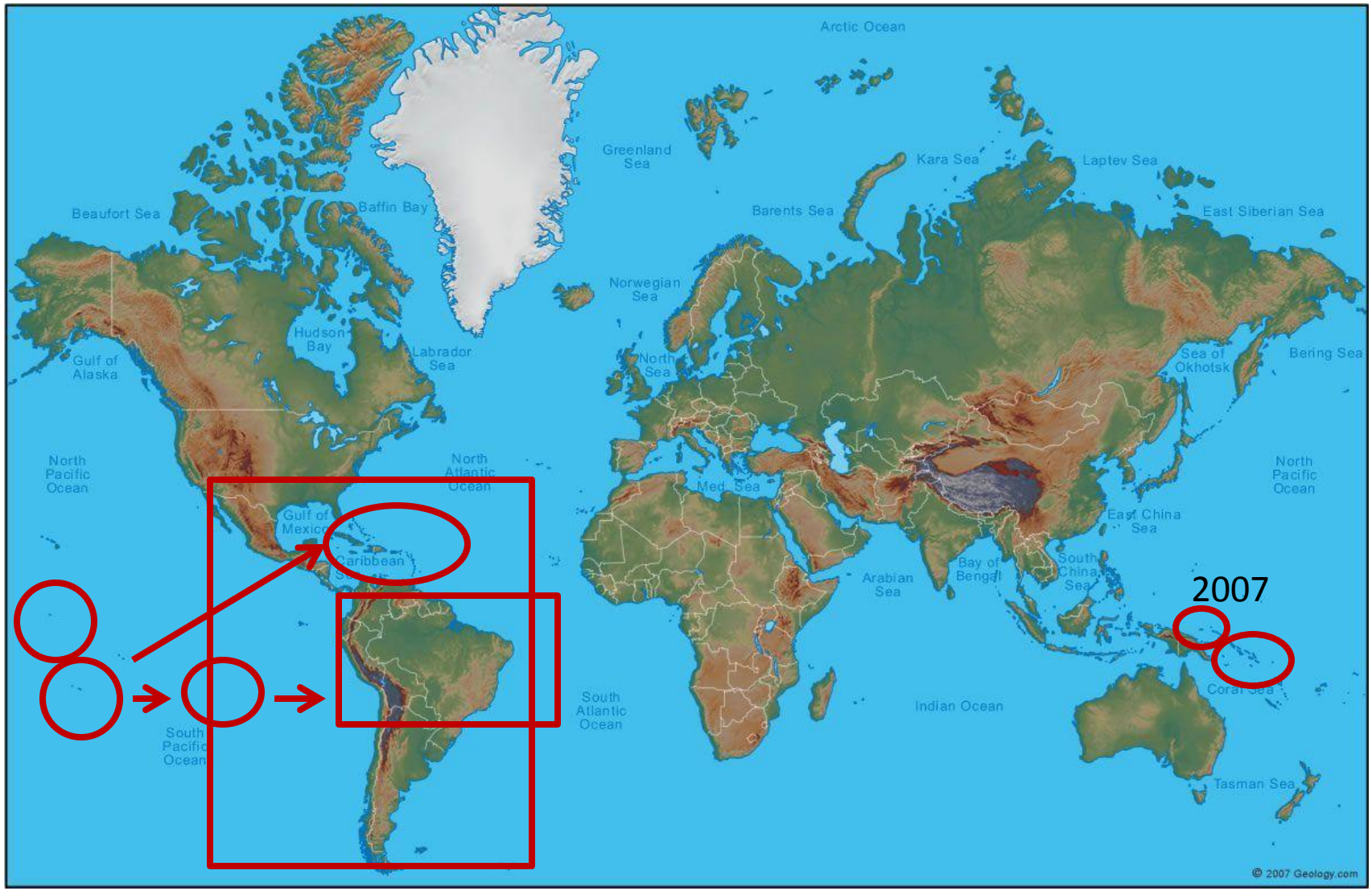
- Diagnostic
- Outbreak
  - How did





Lednicky *et* al., 2016

Zika Introduction into the Western Hemisphere in Summation



Clinical Presentation* of Zika Virus Disease

- Classic
  - Mild, febrile illness with malaise
  - Conjunctivitis
  - *Itchy* rash

Maculopapular rash

Zika Emergence and Microcephaly Spike

- Zika confirmed May 2015
- Microcephaly spike October 2015
  - Contemporary, but causal?

Congenital Zika Syndrome

- Microcephaly
  - Diagnosing [<2 SD vs. <3 SD vs. 3%ile]

- Brain Abnormalities
  - Cerebral calcification
  - Atrophy, abnormalities

Broxmeyer *et al.* 2016

Congenital Zika Syndrome

- Non-microcephalic infants?

Research

JAMA Neurology | Original Investigation

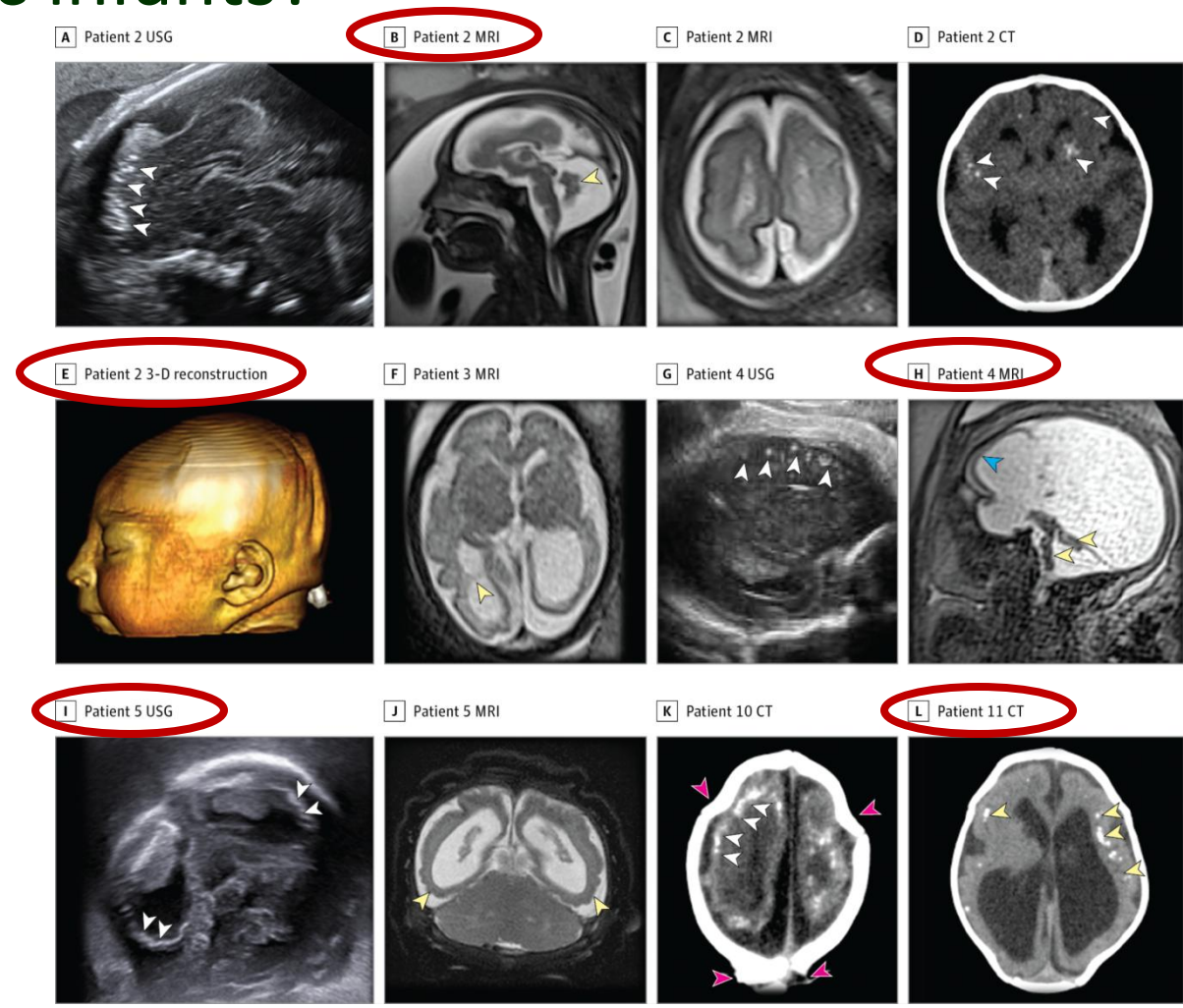
Congenital Zika Virus Infection
Beyond Neonatal Microcephaly

Adriana Suely de Oliveira Melo, MD, PhD; Renato Santana Aguiar, PhD; Melania Maria Ramos Amorim, MD, PhD; Monica B. Arruda, PhD; Fabiana de Oliveira Melo, MD; Suelem Taís Clementino Ribeiro, MD; Alba Gean Medeiros Batista, MD; Thales Ferreira, MD; Mayra Pereira dos Santos, MD; Virgínia Vilar Sampaio, MD; Sarah Rogéria Martins Moura, MD; Luciana Portela Rabello, MD; Clarissa Emanuelle Gonzaga, MD; Gustavo Malinger, MD; Renato Ximenes, MD; Patricia Soares de Oliveira-Szejnfeld, MD; Fernanda Tovar-Moll, MD, PhD; Leila Chimelli, MD, PhD; Paola Paz Silveira, MSc; Rodrigo Delvechio, MSc; Luiza Higa, PhD; Loraine Campanati, PhD; Rita M. R. Nogueira, PhD; Ana Maria Bispo Filippis, PhD; Jacob Szejnfeld, MD, PhD; Carolina Moreira Voloch, PhD; Orlando C. Ferreira Jr, MD, PhD; Rodrigo M. Brindeiro, PhD; Amilcar Tanuri, MD, PhD

IMPORTANCE Recent studies have reported an increase in the number of fetuses and neonates with microcephaly whose mothers were infected with the Zika virus (ZIKV) during pregnancy. To our knowledge, most reports to date have focused on select aspects of the maternal or fetal infection and fetal effects.

OBJECTIVE To describe the prenatal evolution and perinatal outcomes of 11 neonates who had developmental abnormalities and neurological damage associated with ZIKV infection in Brazil.

DESIGN, SETTING, AND PARTICIPANTS We observed 11 infants with congenital ZIKV infection from gestation to 6 months in the state of Paraíba, Brazil. Ten of 11 women included in this study presented with symptoms of ZIKV infection during the first half of pregnancy, and all 11 had laboratory evidence of the infection in several tissues by serology or polymerase chain reaction. Brain damage was confirmed through intrauterine ultrasonography and was complemented by magnetic resonance imaging. Histopathological analysis was performed on the placenta and brain tissue from infants who died. The ZIKV genome was investigated in several tissues and sequenced for further phylogenetic analysis.

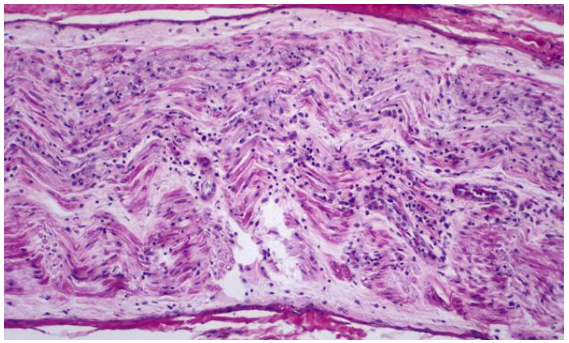


Blindness, deafness, ataxia, swallowing difficulties, seizures, hyperirritability…. in infants. Children/adults?

Melo *et al.*, JAMA Neurol. October 03, 2016

Neuropathies in Children and Adults

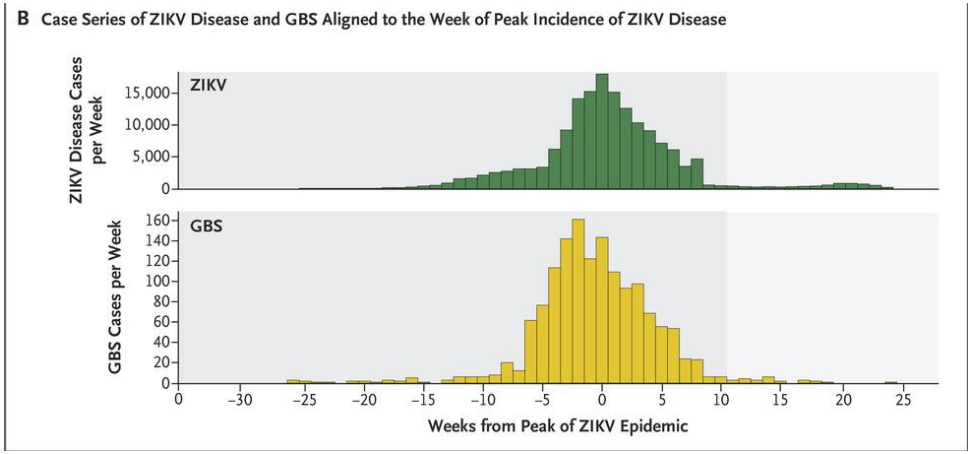
- Guillain-Barré syndrome
  - Zika confirmed in May 2015
  - Spike June 2015



H&E in peripheral nerve during GBS

- Presentation
  - Ascending paresis, tetraparesis

- Treatment
  - IV IgG, plasmaphoresis



dos Santos *et al*. N Engl J Med 2016

Emerging Neurotropism?

- Was this always part of Zika's clinical picture?

Mortality

- 10 total case reports
- Encephalitis
  - 47 yo female, hx unremarkable
- Zika fever w/ thrombocytopenic pupura
  - 70 yo male, hx unremarkable
- Zika fever
  - 15 yo female, hx includes sickle cell disease
- Zika “shock syndrome”
  - 73 yo male, hx includes sero+ Dengue

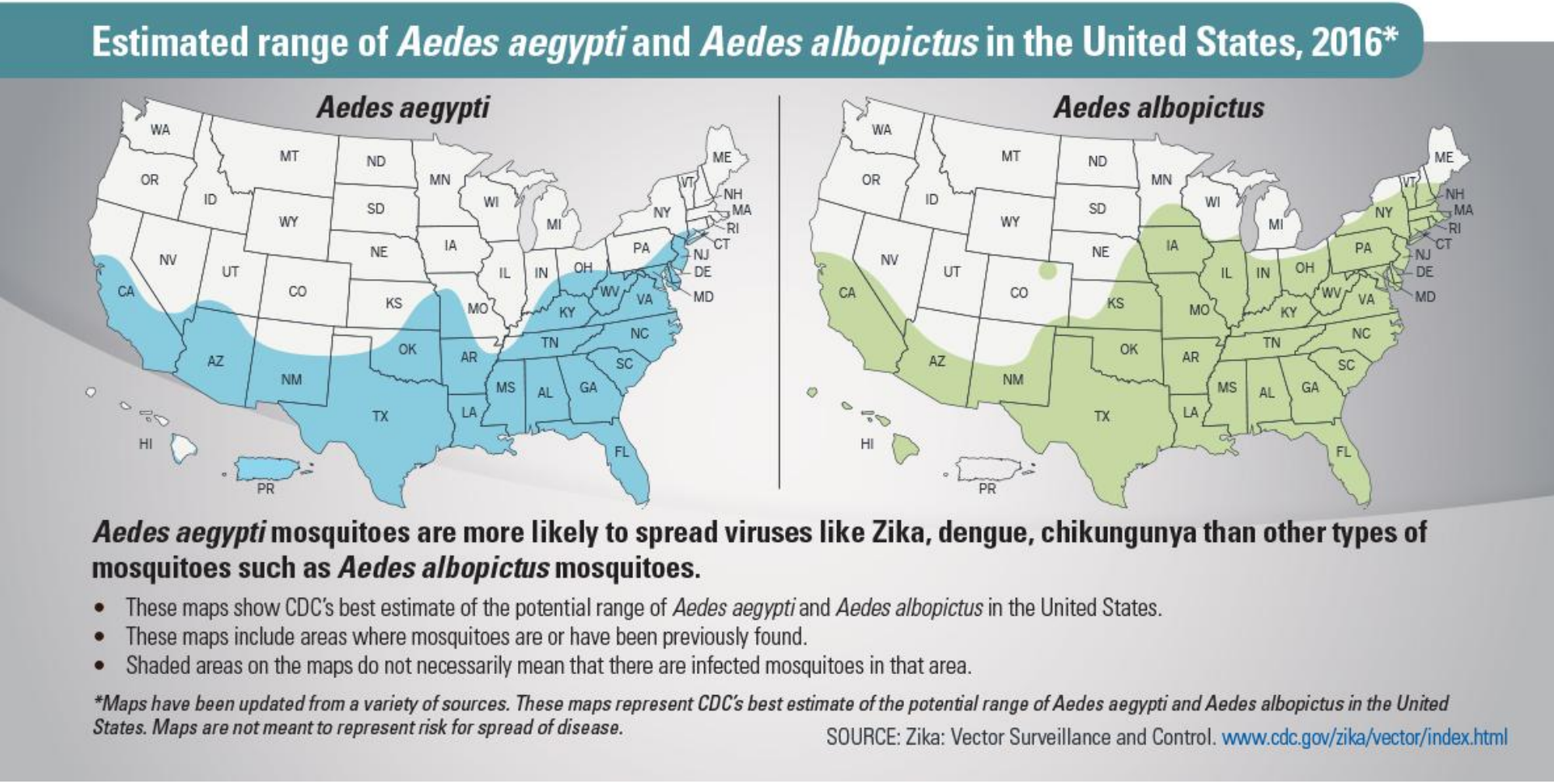
Outline and Disclosures

- Biology of Zika Virus
- Current Zika Virus Disease Epidemic
  - Onset
  - Clinical features
  - Mortality events
- Surveillance, Diagnosis, Risk Assessment
- Future Disease Management

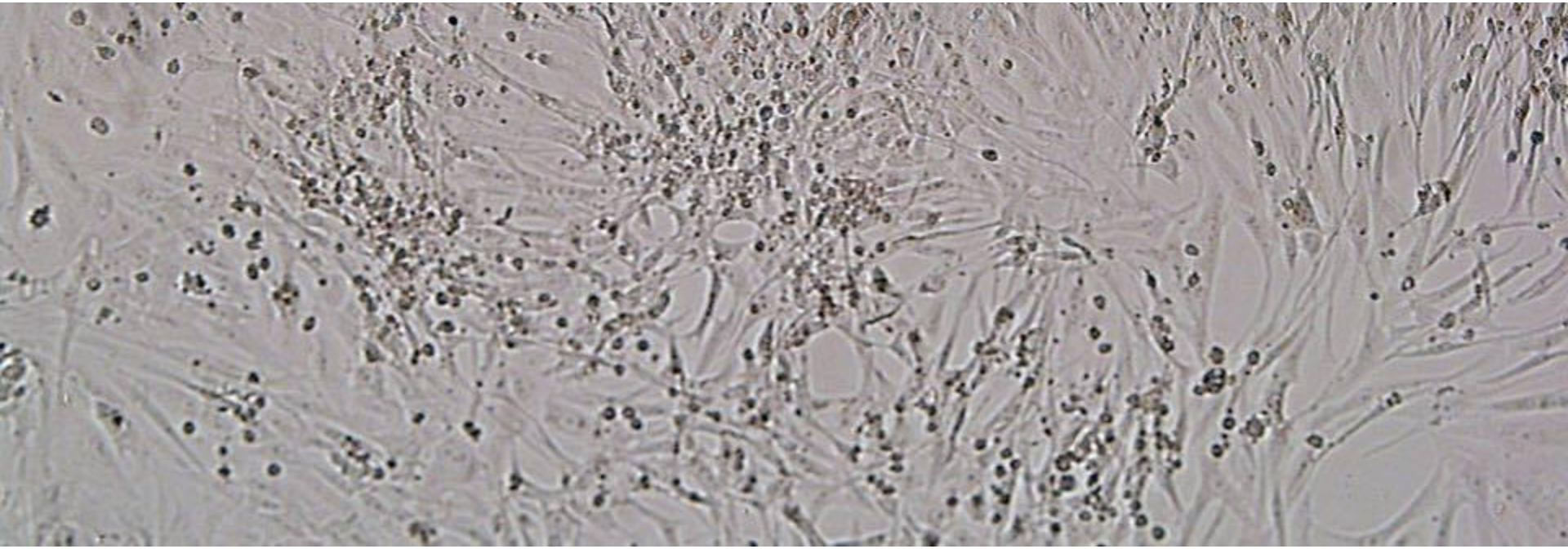
Nothing to disclose

Transmission and Risk in the U.S.

- Vectorborne



Clinical Laboratory Features



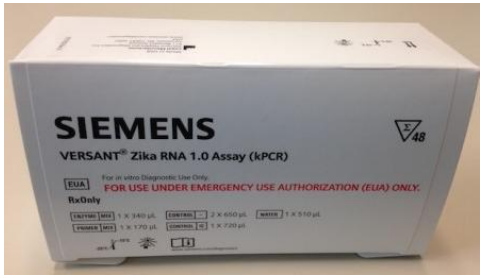
ZIKV-infected Vero cells
Image: R. Relich IU Med

- Biosafety level [2?3? Complicated…]
- Virus isolation [Vero cells]
  - DPH vs. contract labs
- NAATs
  - DPH vs. contract labs

Shameless Plug for Infectious Agent Isolation

NAATs

- Specimens
  - Blood, urine*, CSF, amniotic fluid
- Numerous have received FDA EUA
  - CDC uses Trioplex (Zika/Chikungunya/Dengue)
  - xMAP (Luminex)
    - 6 different RNA targets (minimize false negs)



Positive Zika Diagnosis…Now What?

- Report to the state

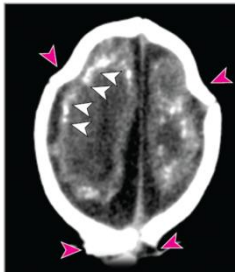
- Most Patients
  - Fever control, supportive care
  - Advise on sexual transmission
  - Advise on mosquito repellant
  - Monitor for GBS 2-3 weeks

Management of Obstetric Patients

- General
  - Travel advisories!!!!!!!!!!!!!!!!
  - Insect repellant; sexual transmission
- Suspect
  - Time to confirmed diagnosis
  - Imaging
- Confirmed
  - CVS for virus detection, path in patients >12wks

Management of Infants with Prenatal Zika Exposure

- Aggressive monitoring
  - Cognitive, behavior, sensory,etc.
  - Not just microcephalic



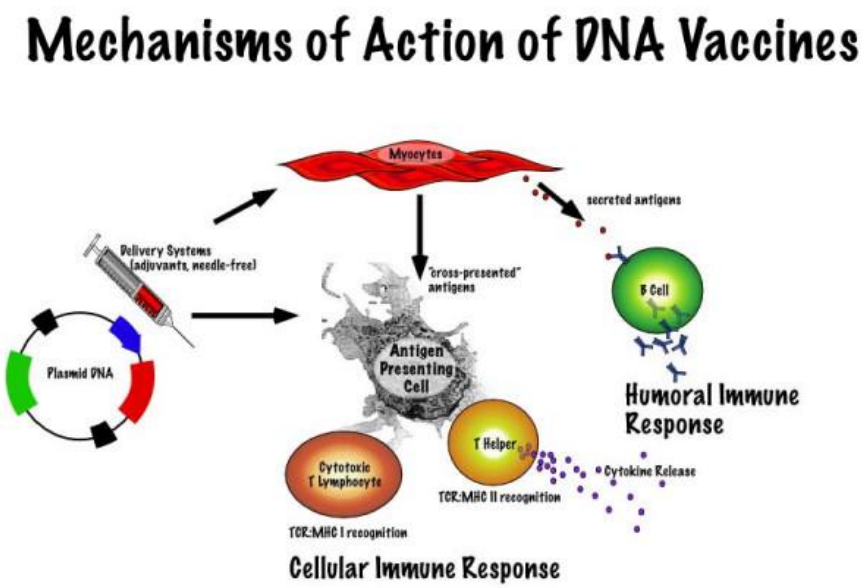
Calcifications and deformities in an infant [HC was WNL]

- Early intervention
  - Demonstrated benefit

- Refer to social work colleagues for support services

Zika Vaccine Trials

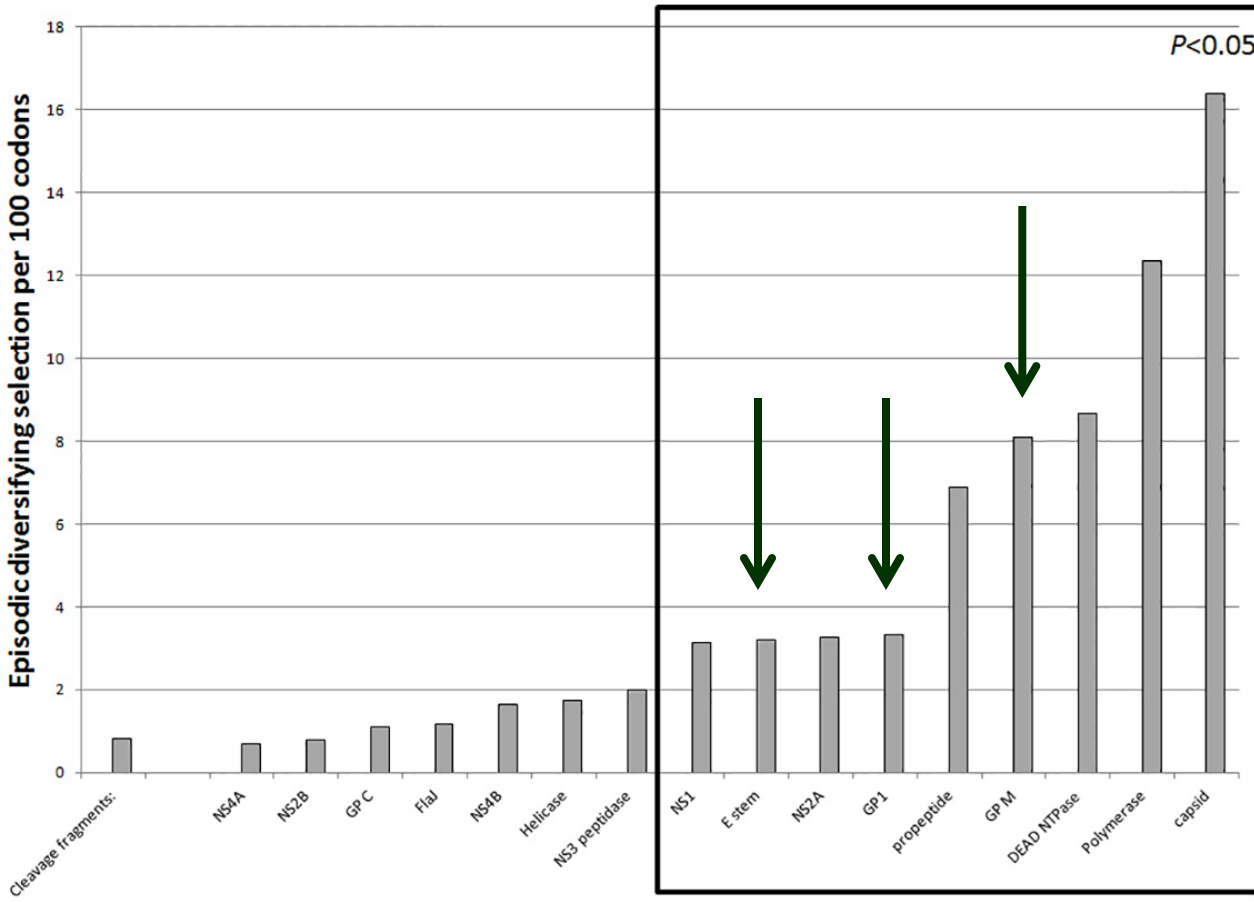
- Target population
  - Greatest risk (XX, CBA)
  - Rubella vax model



- NIH/NIAID trial
  - safety stage
  - DNA vaccine; E protein
    - Previous Flavivirus vaccines

Zika Vaccine Trials…Complications?

- Envelope Protein as a vaccine antigen
  - E is under sig (*P*<0.05) diversifying selection in Zika
  - NOT SO for WNV, DENV
- Vaccine escape?



May and Relich PLoS One 2016

Summary

- Zika virus is a rapidly developing situation
- Majority of patients are subclinical or recover fully
- Congenital syndrome is concerning
- EUA has been issued for diagnostics, vaccines

Additional Resources

- CDC Clinical Guidance for Zika
  - http://www.cdc.gov/zika/hc-providers/index.html
- WHO Guidelines for Infants and Neonates with Zika Exposure
  - http://apps.who.int/iris/bitstream/10665/204475/1/WHO_ZIKV_MOC_16.3_eng.pdf?ua=1
- CDC Guidance for Infants with possible congenital Zika
  - http://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm
- Zika and insect repellants during pregnancy
  - https://www.ncbi.nlm.nih.gov/pubmed/27548647
- Zika Diagnostic tests: FDA EUA list
  - http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika
- NIH Considerations for Zika Vaccine Design
  - https://respond.niaid.nih.gov/conferences/Zika/Presentations/Julie%20E.%20Ledgerwood.pdf