Zika Virus Outbreak and NIAID Research Response

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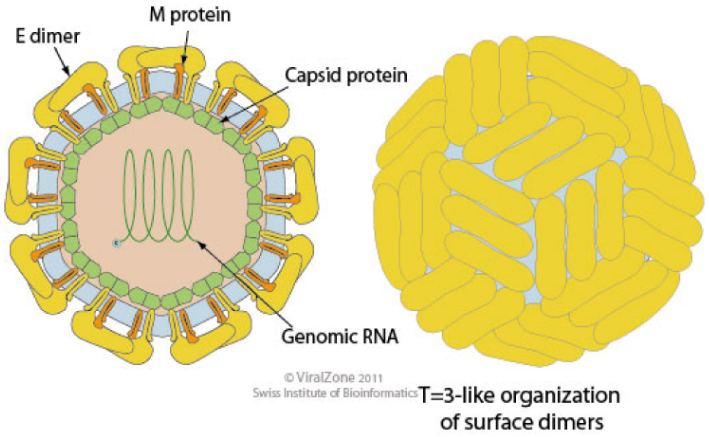
Zika Virus

- Single stranded, enveloped RNA Virus
- Family *Flaviviridae*, Genus *Flavivirus*
- Closely related to dengue, yellow fever, Japanese encephalitis and West Nile viruses
- Transmitted to humans primarily by A*edes* species mosquitoes



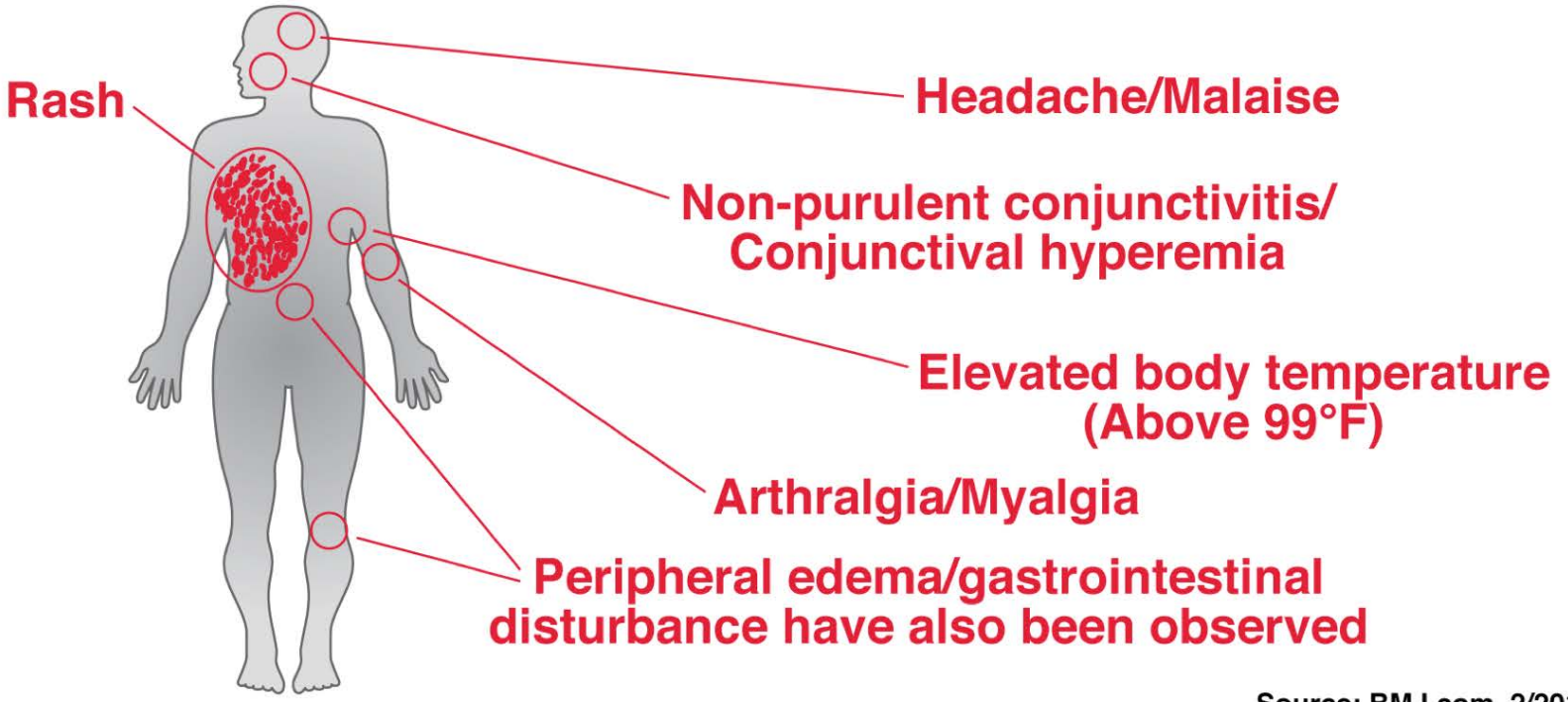
Source: CDC

Symptoms of Zika Virus Infection

- 4 in 5 individuals *asymptomatic*

Incubation
3-12 days

Mild symptoms
2-7 days



Source: BMJ.com, 2/2016

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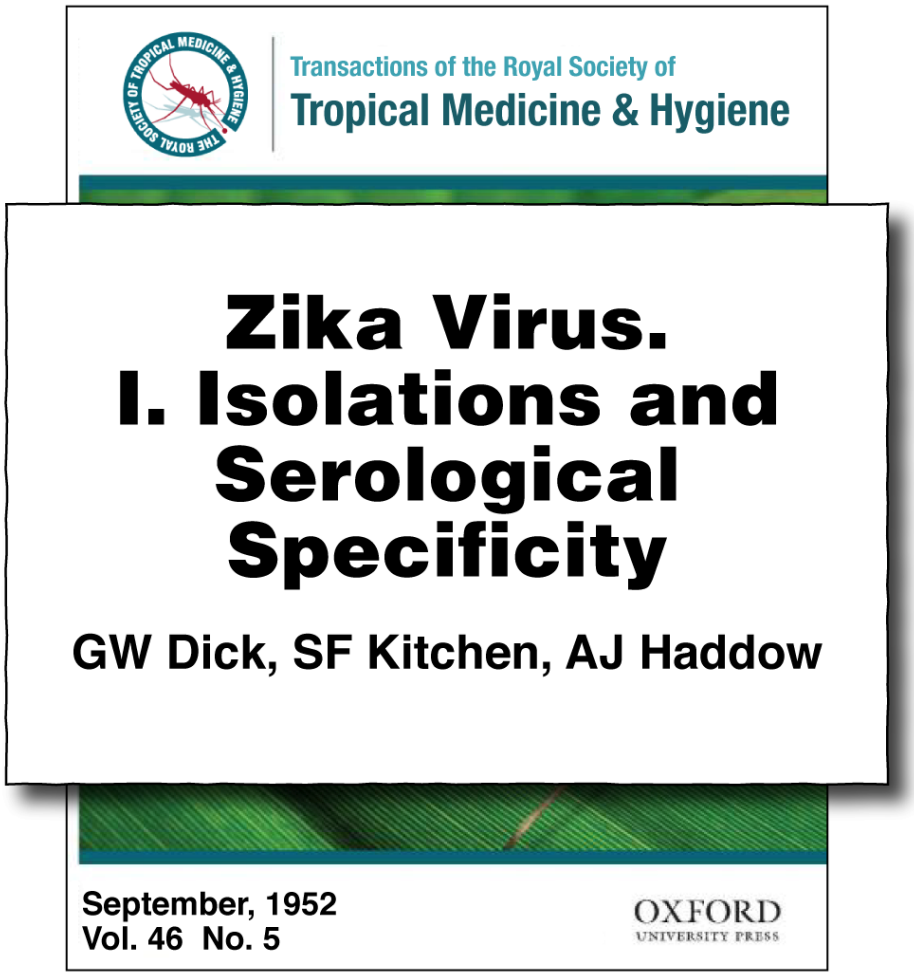

- Virus first isolated from a monkey in the Zika forest of Uganda in 1947

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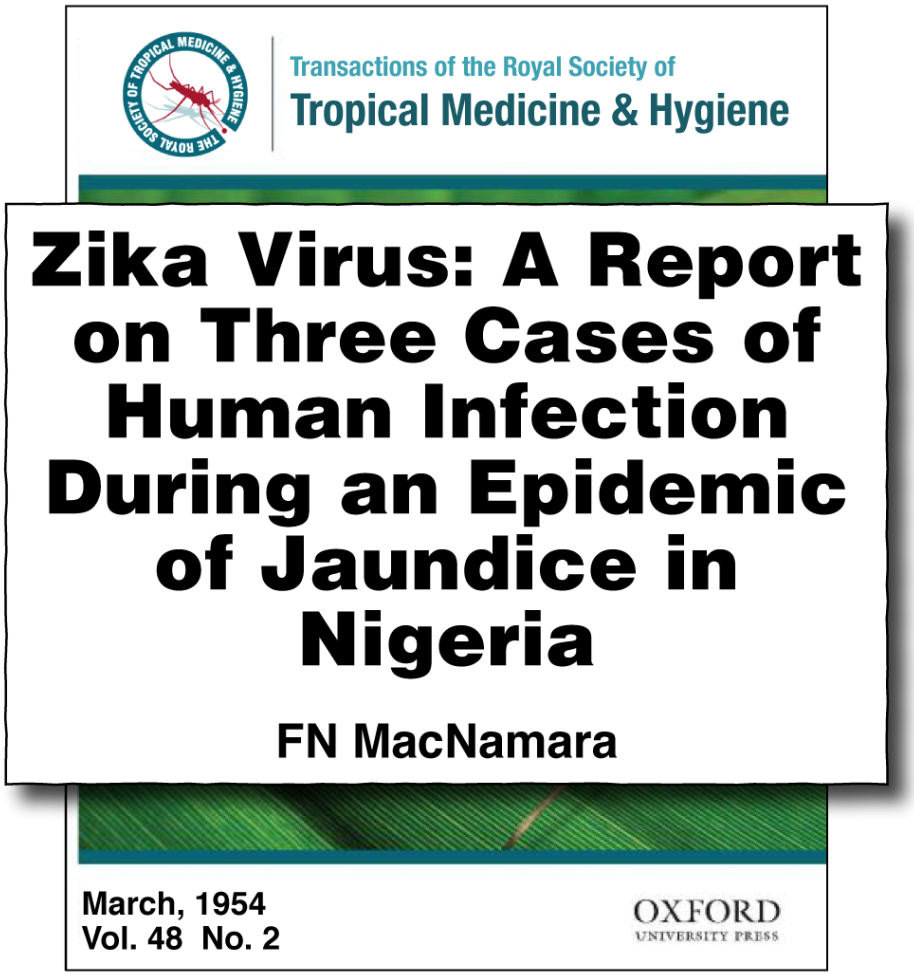

- First human cases reported in Nigeria in 1952

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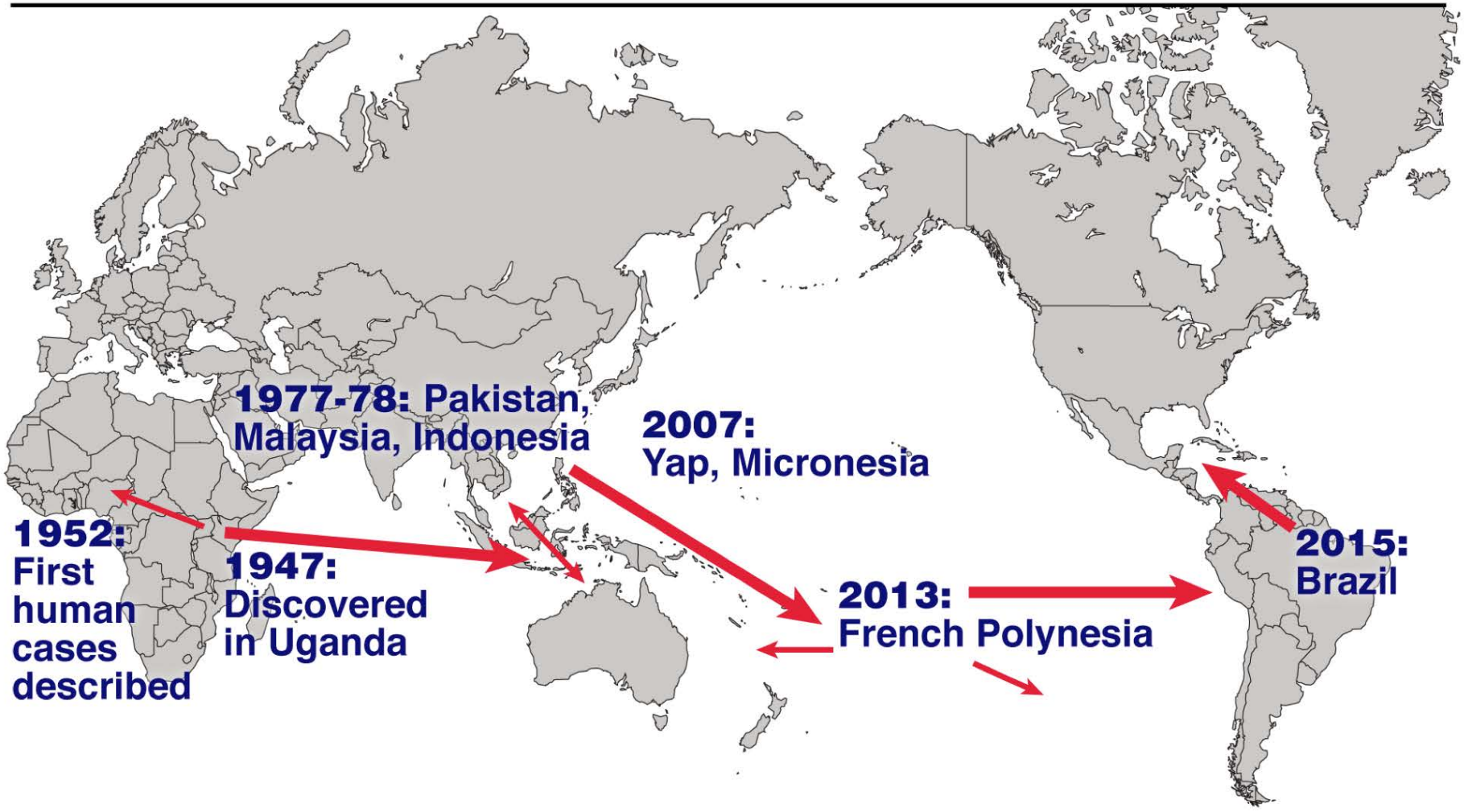
Zika Virus Spread, 1947-2016



Source: Lancaster University

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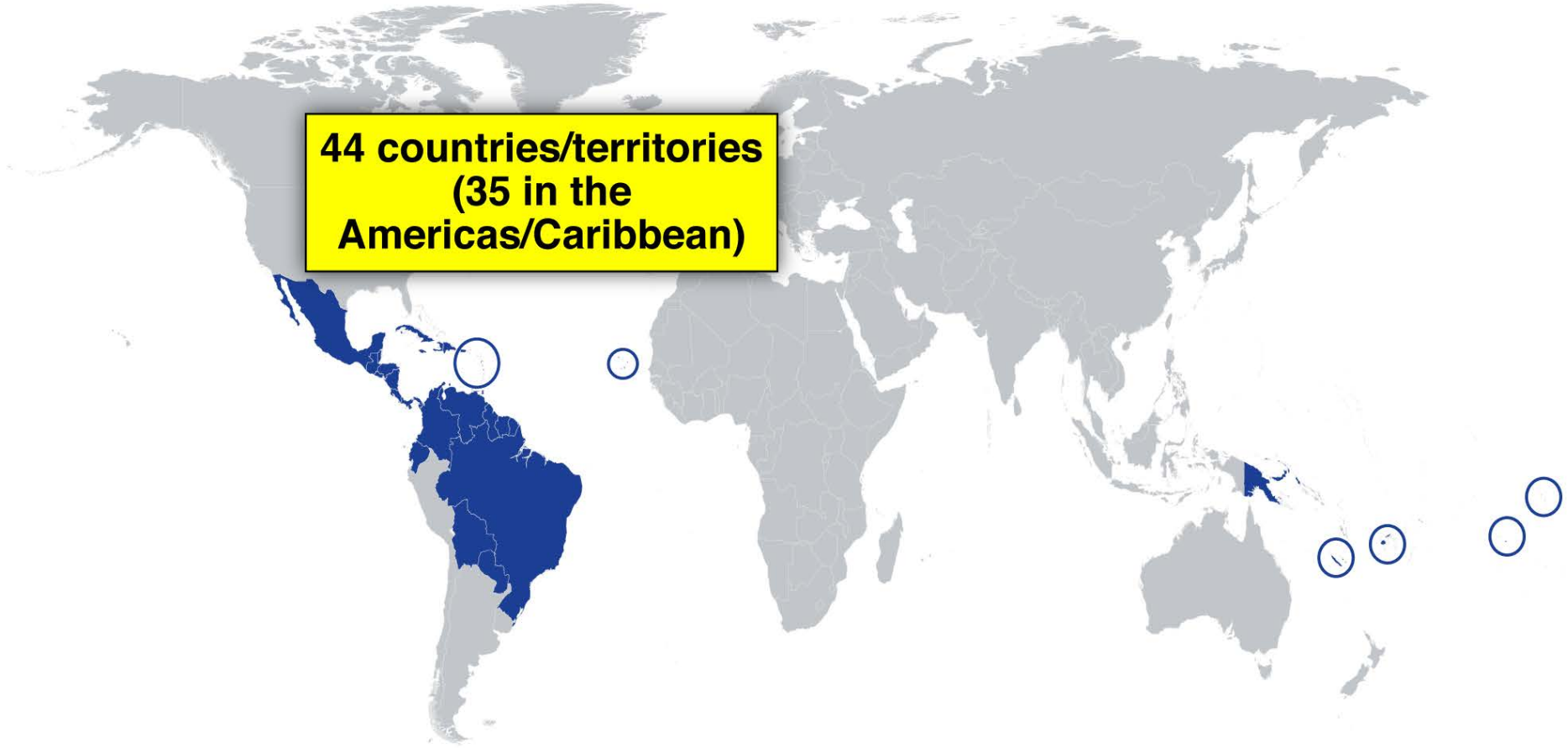
Countries and Territories with Active Zika Virus Transmission – April 2016



Source: CDC, April 29, 2016

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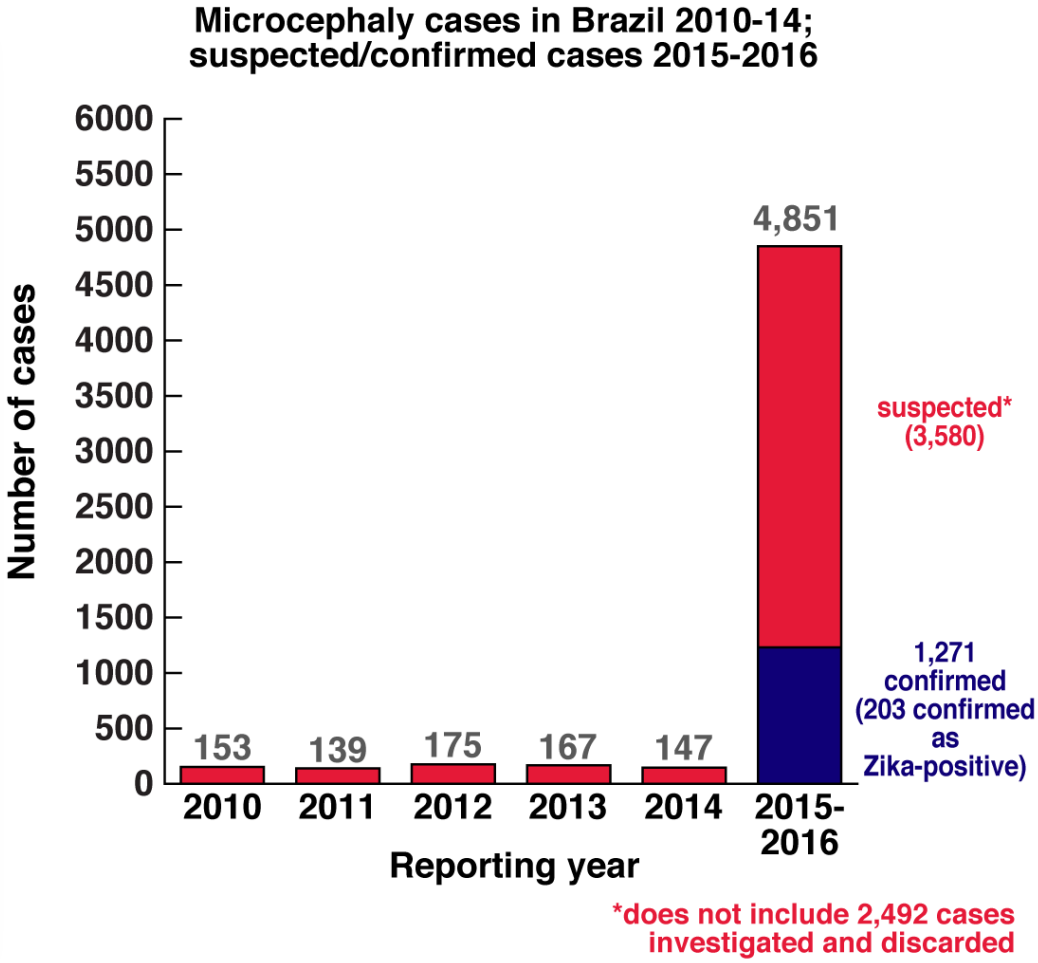
Marked Increase in Microcephaly Cases in Brazil

Associated Press

November 30, 2015

Brazil Links Mosquito-Borne Zika Virus to Microcephaly Birth Defect



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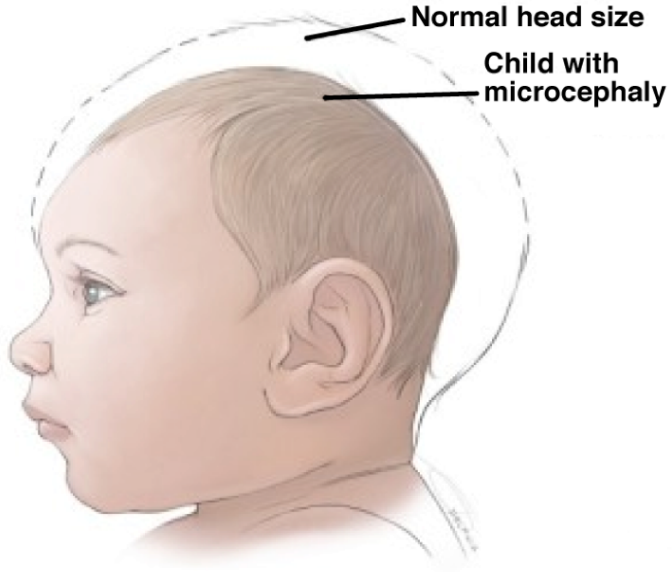
Source: Brazilian MOH; data as of 5/4/2016.

Microcephaly

- An occipitofrontal circumference at least 2 standard deviations below the mean (definitions differ)
- Associated with reduced life expectancy and abnormal neurocognitive development
- Major etiologies include:
  - Genetic anomalies
  - Fetal alcohol syndrome
  - Other maternal factors (malnutrition, endocrine disorders)
  - Maternal infections (including cytomegalovirus, toxoplasmosis, rubella)
  - Zika



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Microcephaly Attributed to Zika

Normal infant brain and head size

Microcephaly, Colombia 2015

Images: LatinAmericanScience.org

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Neonatal Manifestations of Congenital Zika Virus Infection

- Microcephaly
- Intracerebral calcifications (mostly periventricular)
- Hearing loss
- Vision abnormalities
- Lissencephaly
- Pachygyria
- Ventricular enlargement
- Arthrogryposis
- Muscular atrophy

Source: RW Steele: *Clin. Pediatr.*, 3/21/2016.

Neurological Disease Caused by Zika

- Guillain-Barré Syndrome
  - Acute, immune-mediated neuropathy

- Acute Myelitis
  - Spinal cord inflammation

- Meningoencephalitis

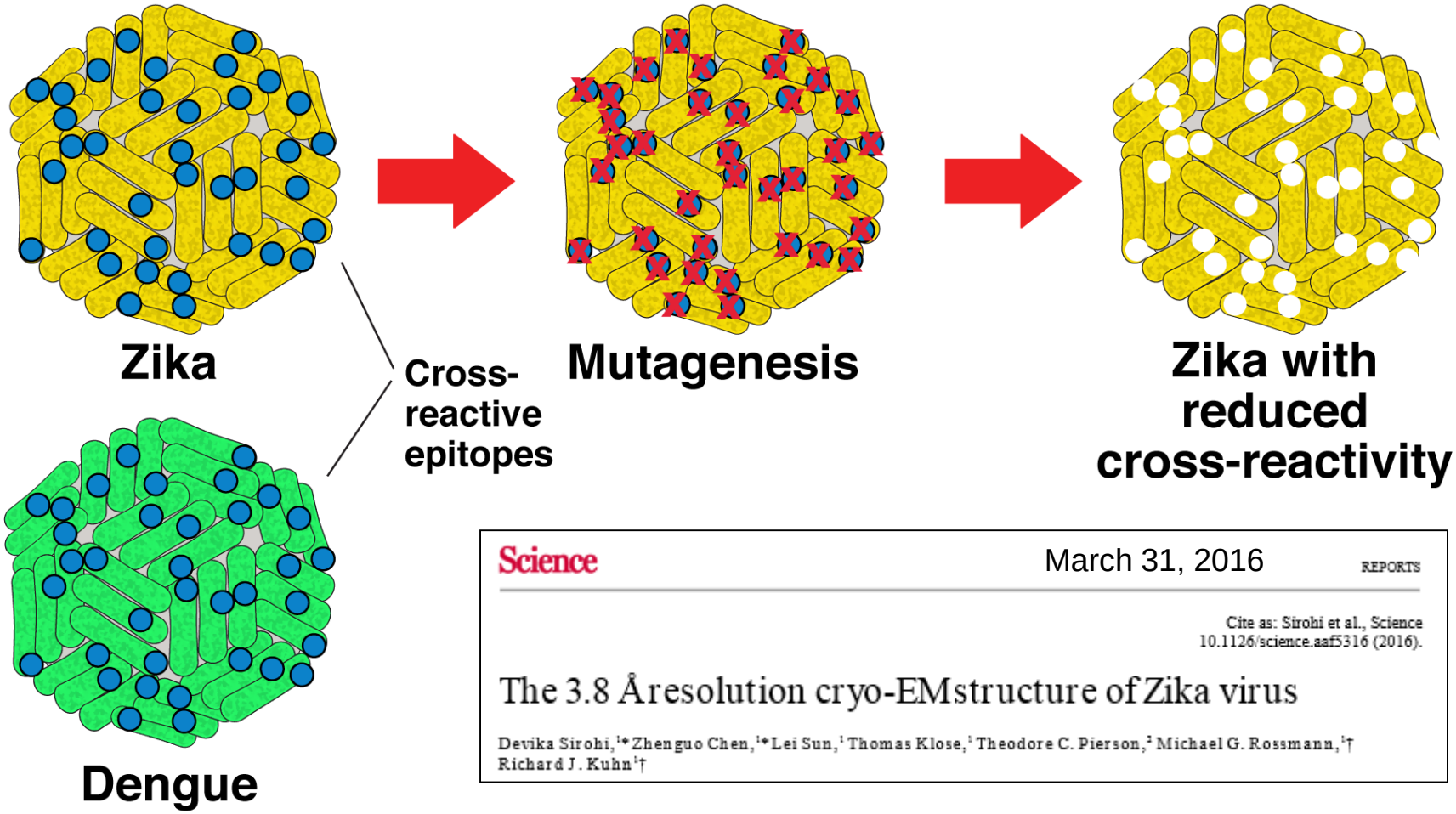
NIH National Institute of Allergy and Infectious Diseases

NIAID Research Response

- Leveraging existing Program on Flaviviruses to rapidly start research on Zika

- Since January 2016, over 40 projects initiated to:
  - Understand basic biology/structure/evolution of virus and competence of the mosquito vectors
  - Develop vaccines, diagnostics, therapeutics and vector control strategies
  - Elucidate the mechanism of pathogenesis and congenital infection

Developing Improved Diagnostics Through Mutagenesis



Science March 31, 2016 REPORTS

Cite as: Sirohi et al., Science 10.1126/science.aaf5316 (2016).

The 3.8 Å resolution cryo-EM structure of Zika virus

Devika Sirohi,[1]* Zhenguo Chen,[1]* Lei Sun,[1] Thomas Klose,[1] Theodore C. Pierson,[2] Michael G. Rossmann,[1]† Richard J. Kuhn[1]†

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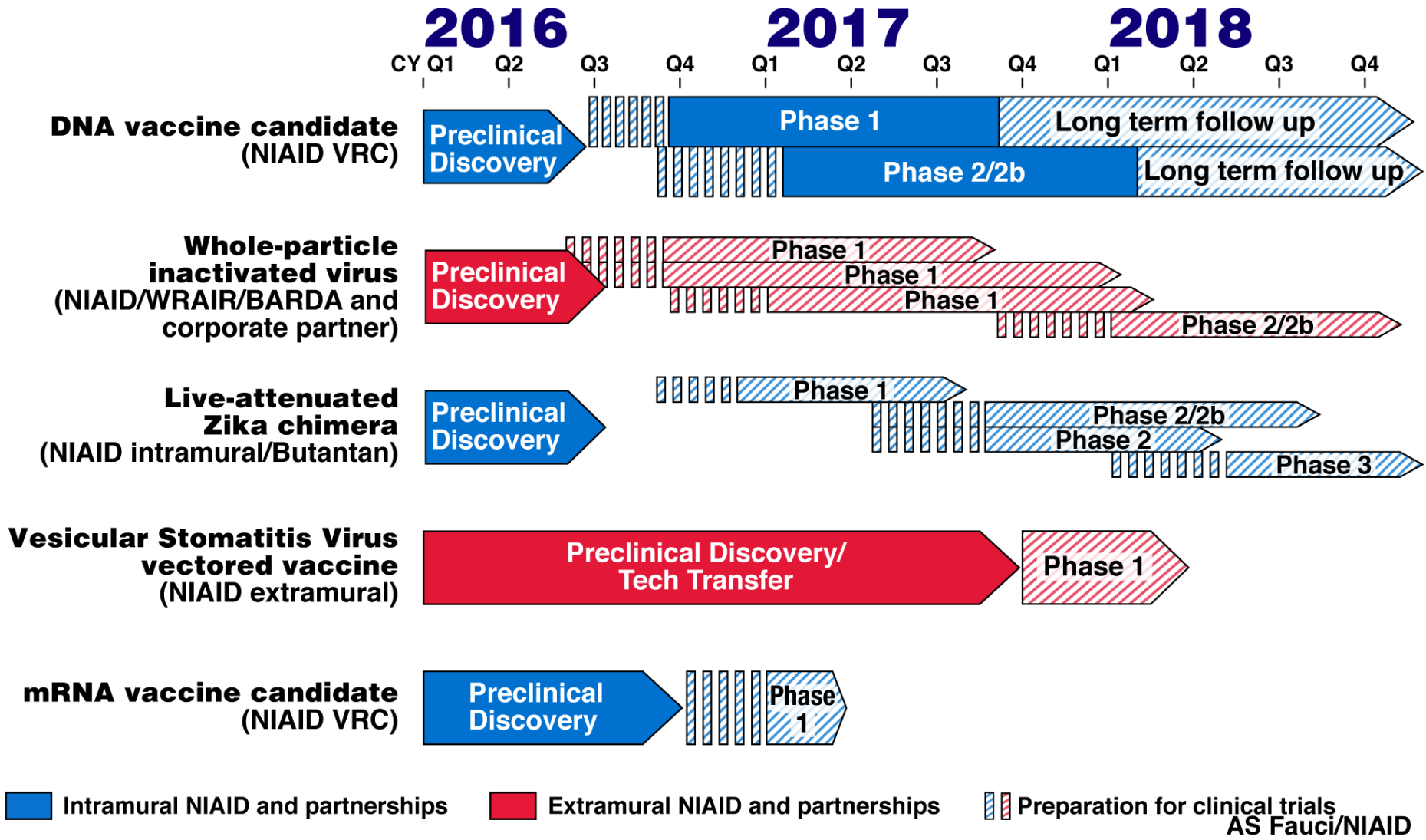
Antiviral Screening Program

- Developed Zika in vitro screening assay
- Tested 87 antiviral compounds with known activity against other flaviviruses
  - 14 have high to moderate activity against Zika virus
- Promising drug candidates are being further tested in Zika mouse model
  - BCX4430 found to protect immune-deficient mice infected with Zika virus
- Collaborating with NCATS and Gates Foundation to develop high throughput screening assay to screen existing libraries of approved drugs

Zika Vaccine Development Timeline



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Biomedical Research Response: Vector Control

- Vector competence: Ability of mosquitoes other than *Aedes aegypti* to carry and transmit Zika virus
- Novel insecticides
- Novel vector control methods – genetically modified mosquitoes; *Wolbachia*-infected mosquitoes

Pathogenesis Studies

- Natural history, cohort studies in pregnant and non-pregnant population
  - Role of existing flavivirus immunity
  - Role of asympthomatic infections in congenital disease
  - Viral loads/dynamics in different bodily fluids (transmission)
  - Long term observational studies in babies born from Zika-infected mothers

- Development of animal models
  - Mice
  - Hamsters
  - **NHPs (Dave O' Connor)**