

# **Zika Virus: An Introduction**

Robert T. Schooley, M.D.  
University of KwaZulu Natal  
MEPI Symposium  
March 9, 2016

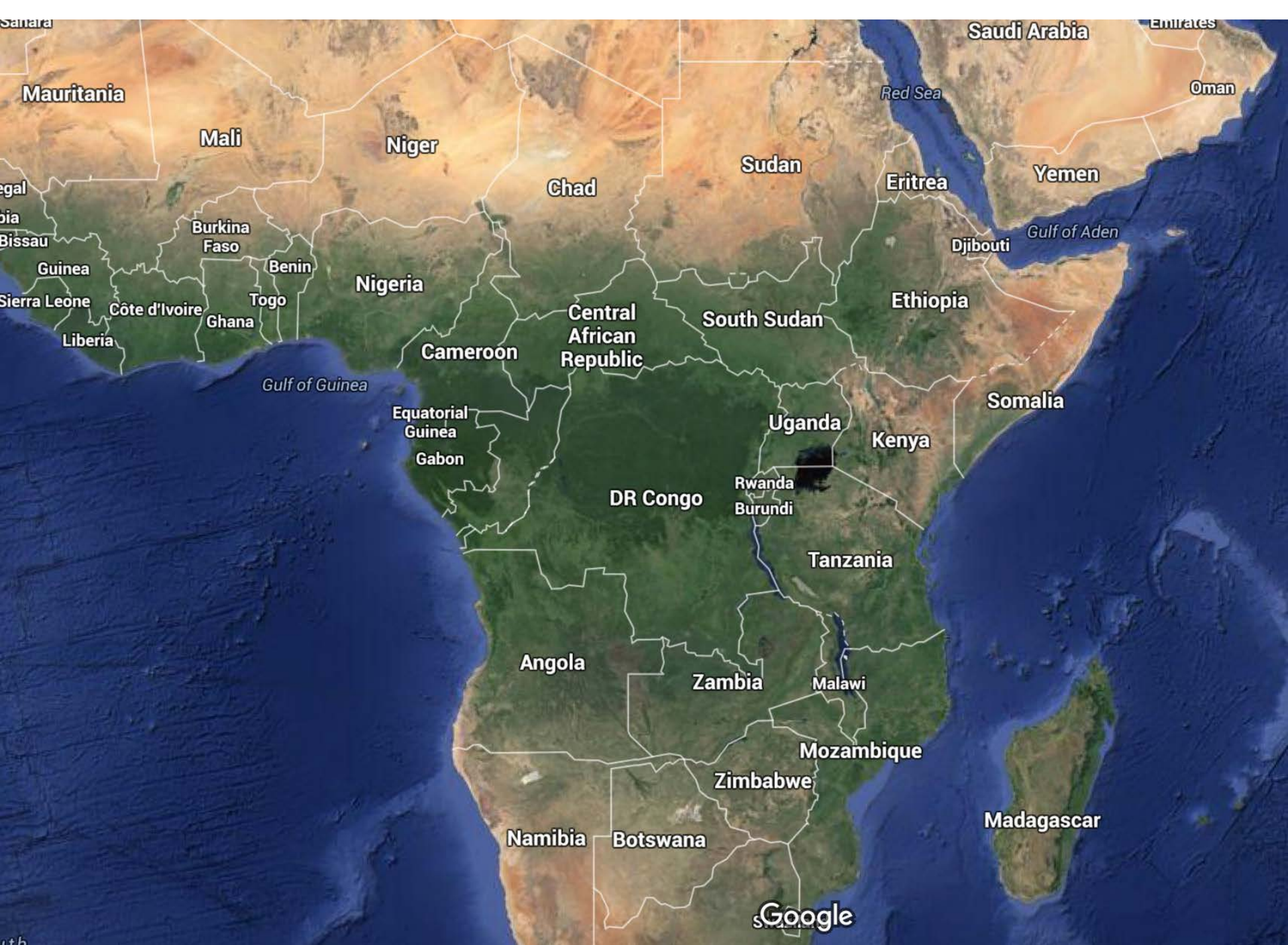
# **Zika Virus: An Introduction**

- Historical origin
- Virology
- Clinical manifestations and complications
- Prevention strategies
- Research questions

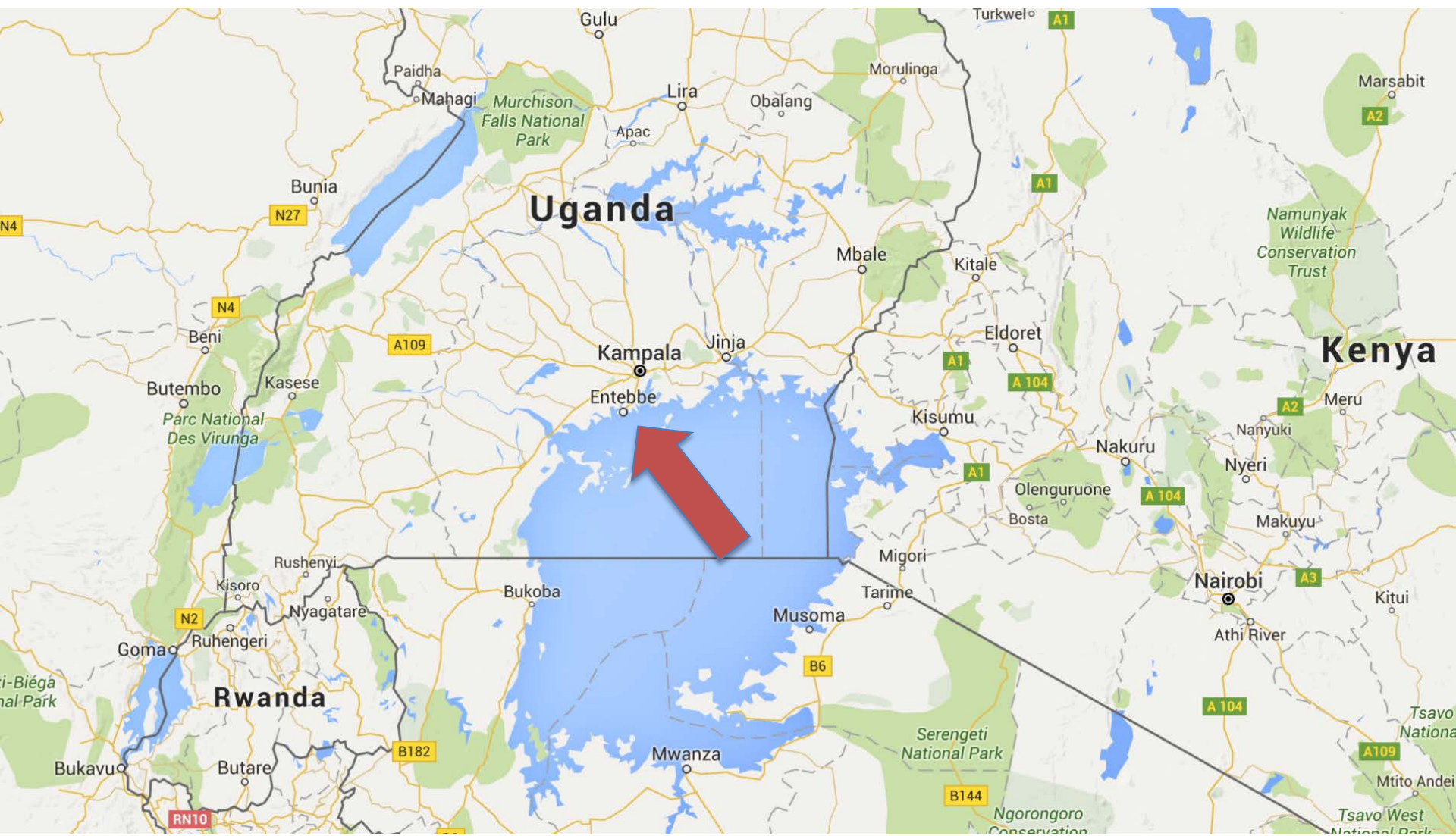
**ZIIKA FOREST.  
PROPERTY  
OF**

**UGANDA VIRUS RESEARCH  
INSTITUTE (UVRI)  
P.O. BOX 49 ENTEBBE  
TEL: 0414-32063**









Sign in

**Waiya Bay**

**Uganda Virus  
Research Institute**



Lulongo

Nakiwogo Rd

Kasanje Rd

Lyamutundwe

Ssesse Gateway  
Beach

Kasenye Road

Nakiwogo Rd  
Kiwafu Rd

Nsamizi Rd

Portal Rd

Beach

**Entebbe**

Entebbe  
International Airport

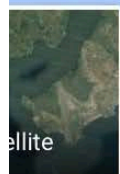
Buku Rd

Tunnel Rd

Sports Beach

Entebbe Bay

Kasenye Road



Google





# Uganda Virus Research Institute



**Chikungunya, West Nile Virus, Semliki Forest Virus,  
O'nyong'nyong virus, Burkitt's Lymphoma**

TRANSACTIONS OF THE ROYAL SOCIETY OF  
TROPICAL MEDICINE AND HYGIENE.  
Vol. 46. No. 5. September, 1952.

## COMMUNICATIONS

### ZIKA VIRUS

#### (I). ISOLATIONS AND SEROLOGICAL SPECIFICITY

BY

G. W. A. DICK,

*The National Institute for Medical Research, London*

S. F. KITCHEN,

*Formerly staff member of the Division of Medicine and Public Health, The Rockefeller Foundation, New York, U.S.A.*

AND

A. J. HADDOW,

*Formerly staff member of International Health Division, The Rockefeller Foundation, New York, U.S.A.*

*(From the Virus Research Institute, Entebbe, Uganda.)*



# Zika: The First Case

**RHESUS 766**

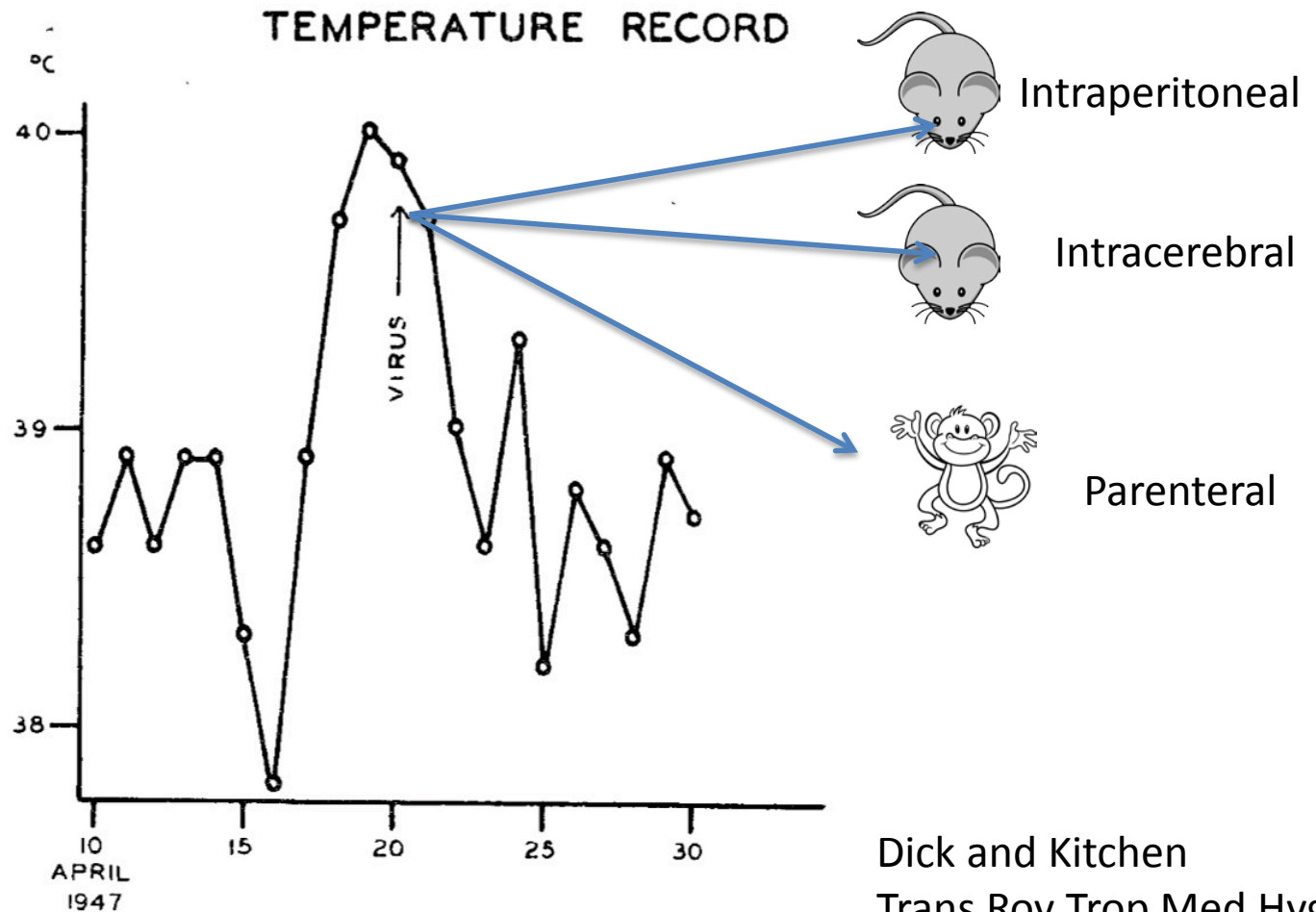


FIG. 1

Dick and Kitchen  
Trans Roy Trop Med Hyg  
46: 1952

# Additional Findings

- Wild caught *A. africanus* mosquito homogenates caused lethargy and death in intracranially inoculated mice
- There was no serologic cross reactivity with yellow fever, Chikungunya, Lymphocytic choriomeningitis virus, dengue virus, Saint Louis Encephalitis, Venezuelan Equine Encephalitis or multiple other viruses
- 6.1% of healthy adults living in the Entebbe area had antibodies to the virus

# First Human Cases

TRANSACTIONS OF THE ROYAL SOCIETY OF  
TROPICAL MEDICINE AND HYGIENE.  
Vol. 48. No. 2. March, 1954.

ZIKA VIRUS : A REPORT ON THREE CASES OF HUMAN INFECTION  
DURING AN EPIDEMIC OF JAUNDICE IN NIGERIA

BY

F. N. MACNAMARA\*

*Acting Director, Virus Research Institute, Yaba, Nigeria*





A map of Nigeria showing its state boundaries. The country is colored in a light yellowish-beige, while the surrounding regions are in a light grey. Blue lines represent rivers and water bodies. The word "Nigeria" is written in large, bold, black letters in the center of the country. A red star is located in the southeastern part of the country, near the border with the Gulf of Guinea, and is labeled "Afikpo" in red text.

# Nigeria

 Afikpo

TRANSACTIONS OF THE ROYAL SOCIETY OF  
TROPICAL MEDICINE AND HYGIENE.  
Vol. 50. No. 5. September, 1956.

ZIKA VIRUS INFECTION EXPERIMENTALLY INDUCED IN A HUMAN  
VOLUNTEER

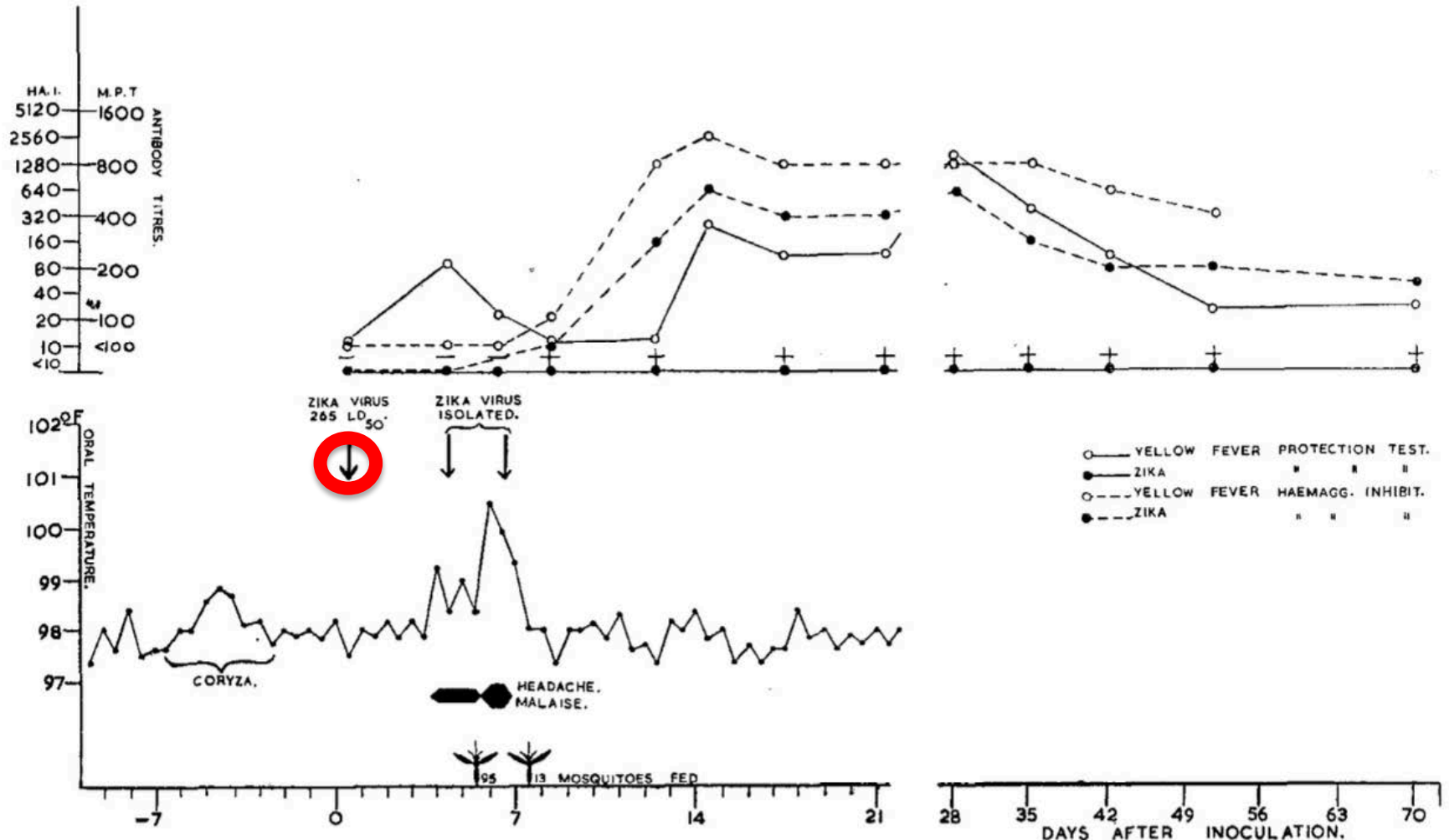
BY

W. G. C. BEARCROFT\*

*West African Council for Medical Research Laboratories, Lagos, Nigeria.*

# Human Challenge

Course of infection and antibody response to Zika virus.



+ or - denote a positive or negative mouse protection test to Zika virus.

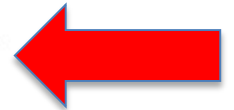


# Zika in Malaysia

THE AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE  
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Vol. 18, No. 3  
Printed in U.S.A.

## ISOLATION OF ZIKA VIRUS FROM *Aedes Aegypti* MOSQUITOES IN MALAYSIA\*

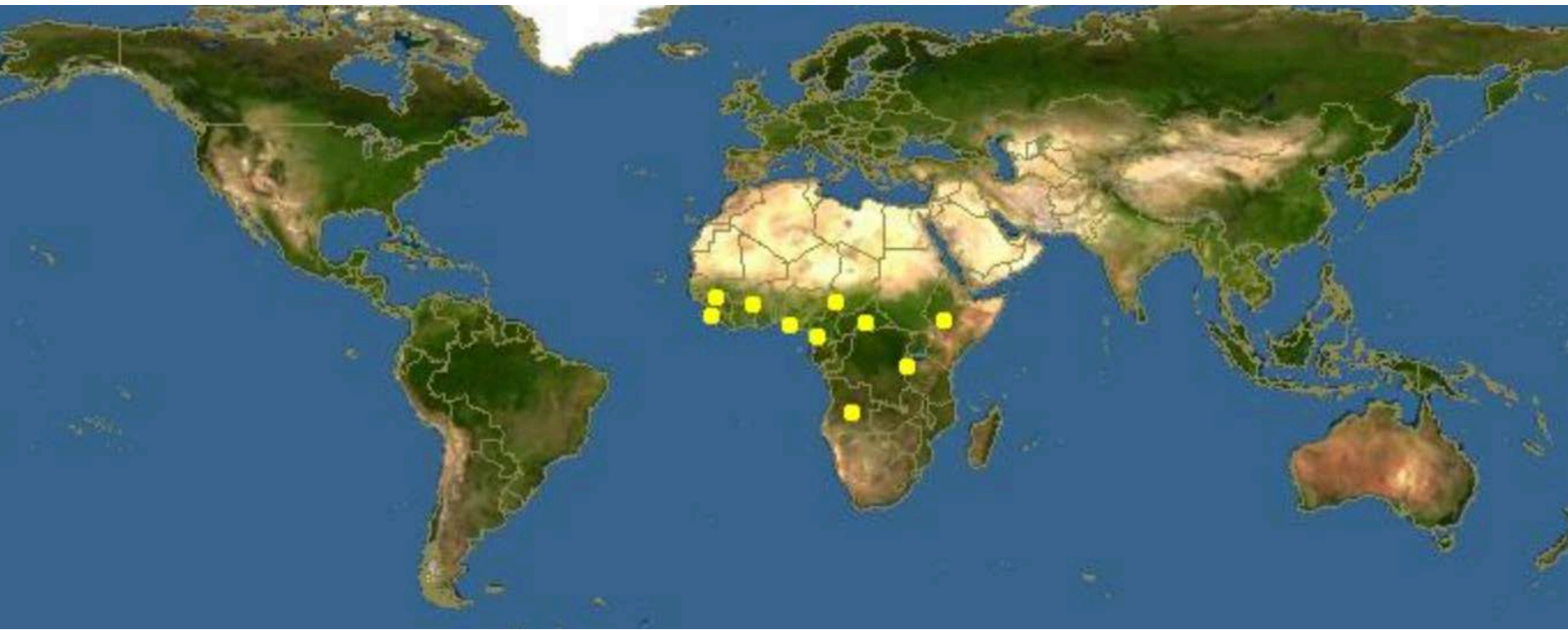


N  
G. W. Hooper  
California, and

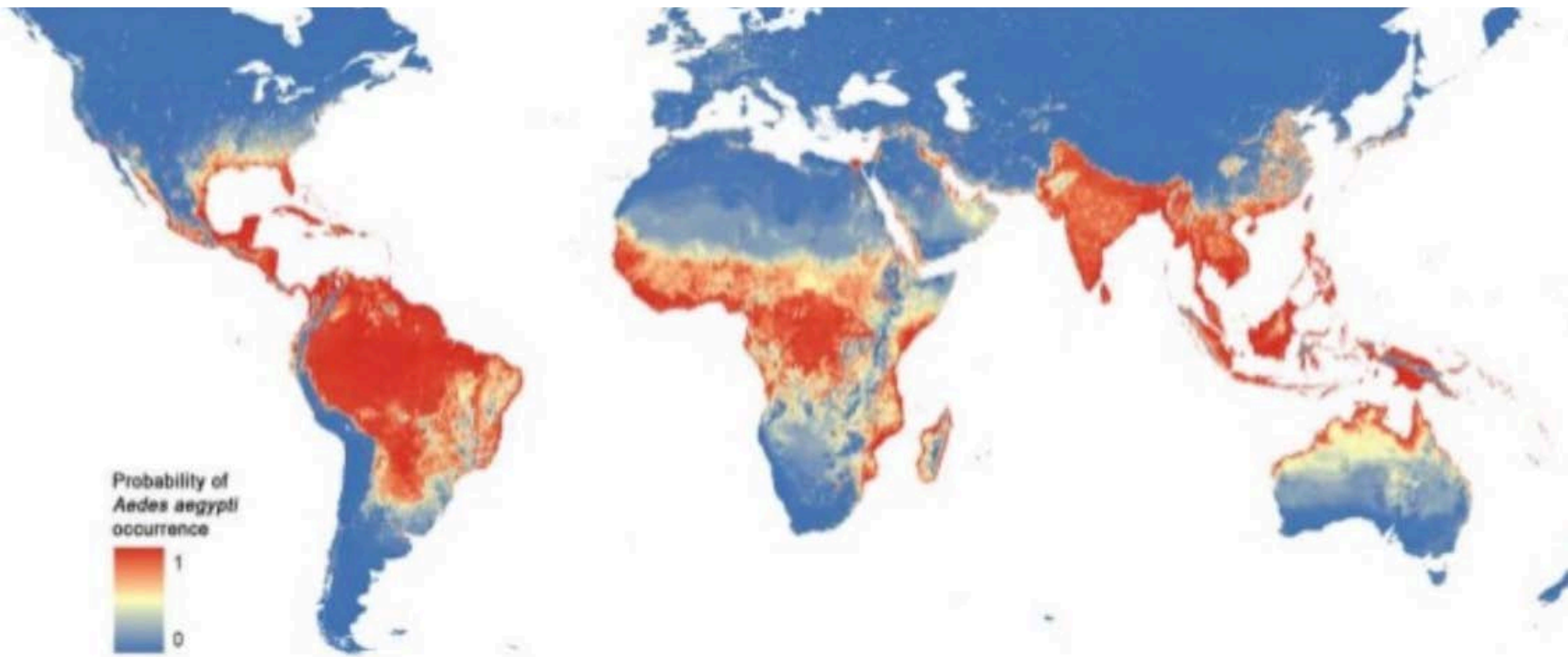


CK  
r, San Francisco,  
umpur, Malaysia

# Distribution of *Aedes africanus*



# Distribution of *Aedes aegypti*



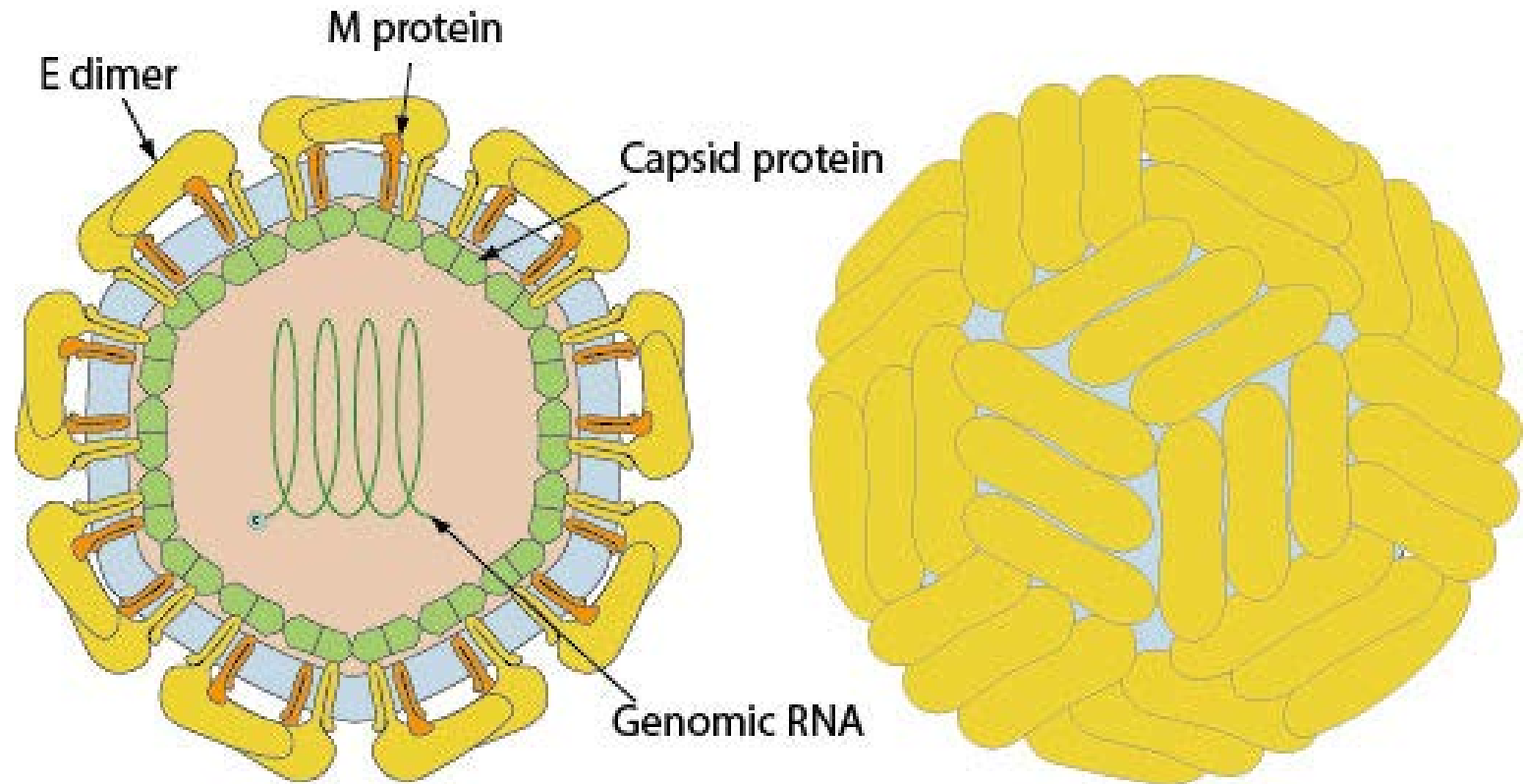
Temp. suitability 58%; Urban accessibility 18%; NDVI 12%



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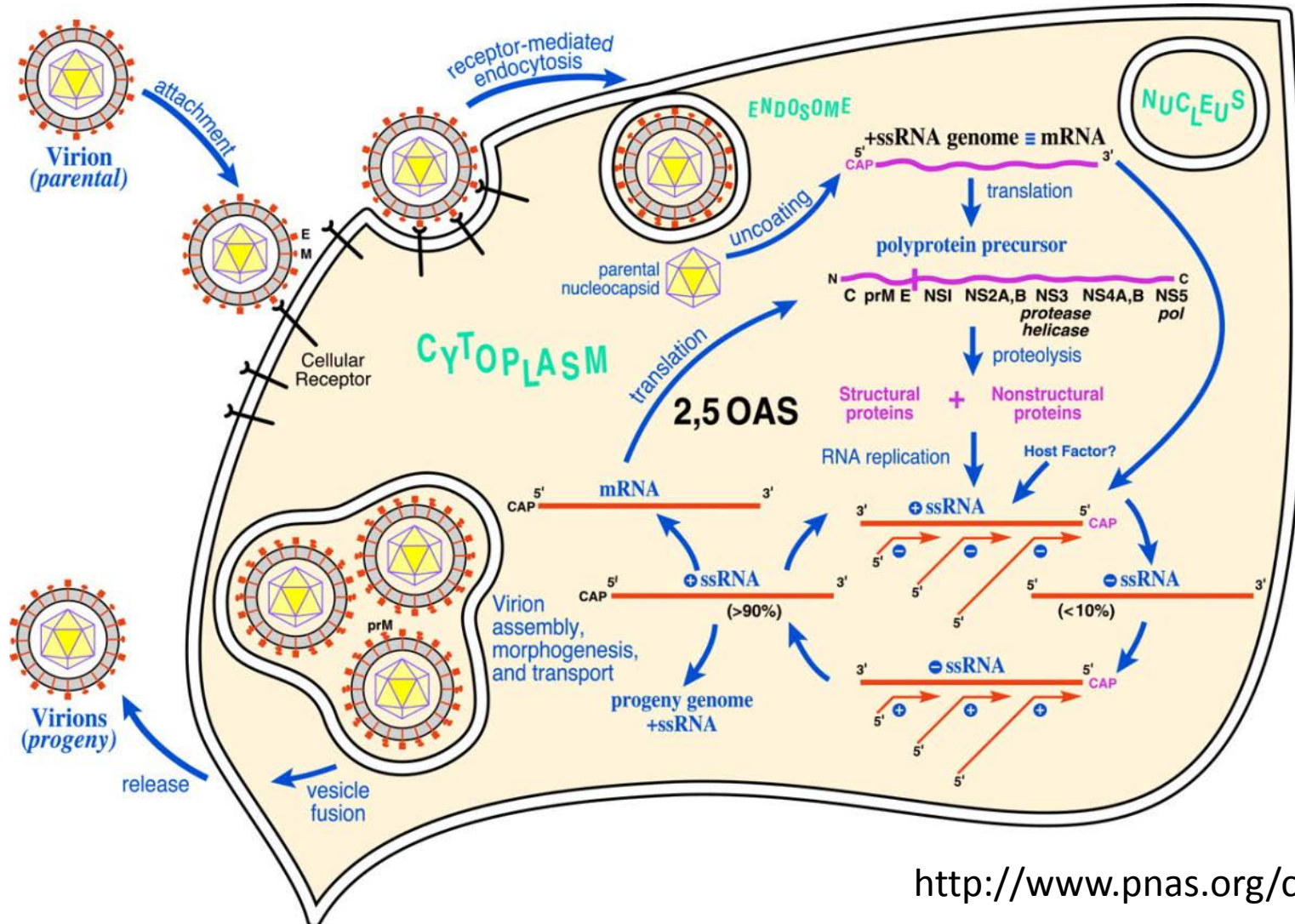
# Zika Virus: Structure



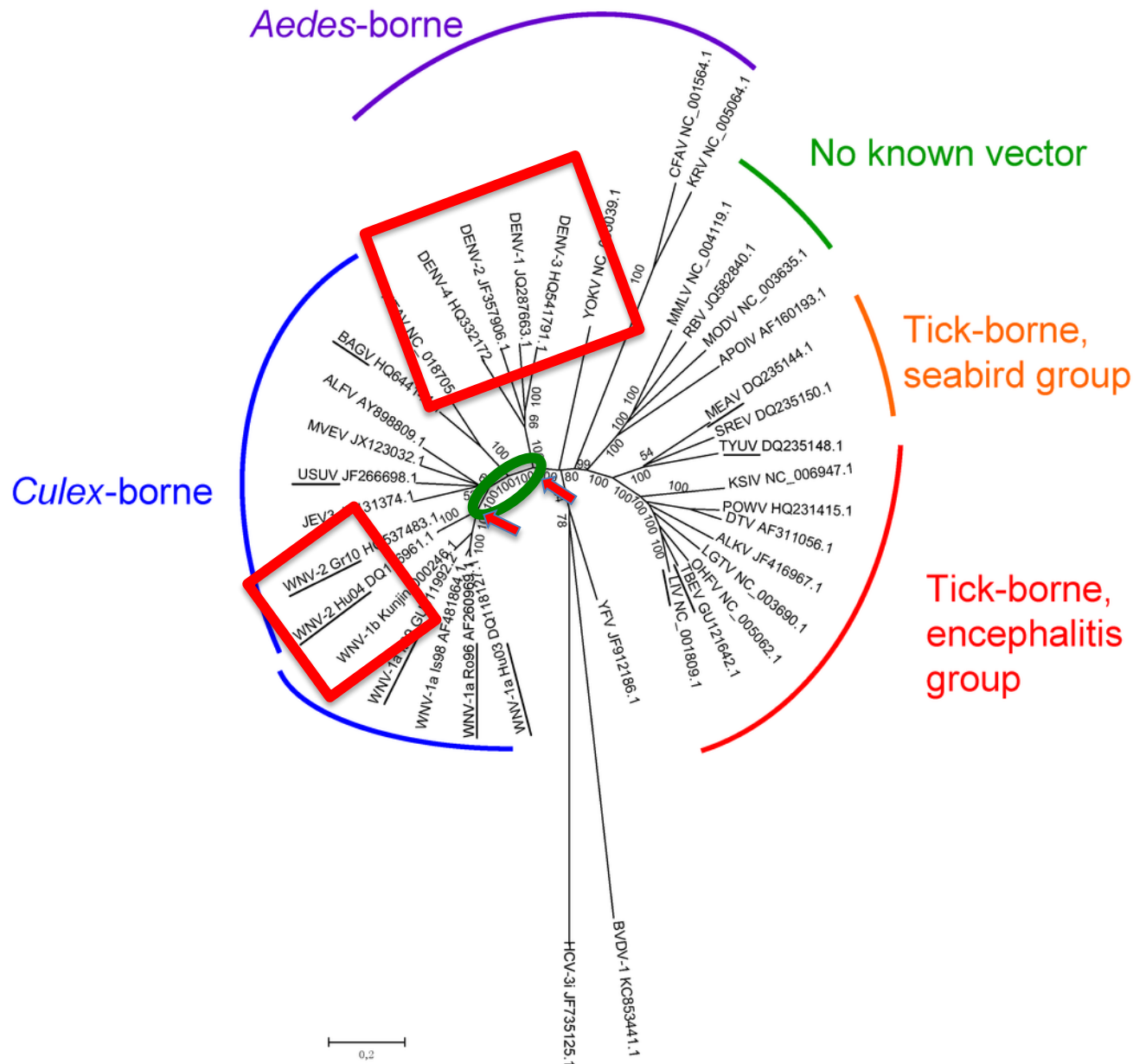
© ViralZone 2011  
Swiss Institute of Bioinformatics

**T=3-like organization  
of surface dimers**

# Life Cycle of a Flavivirus

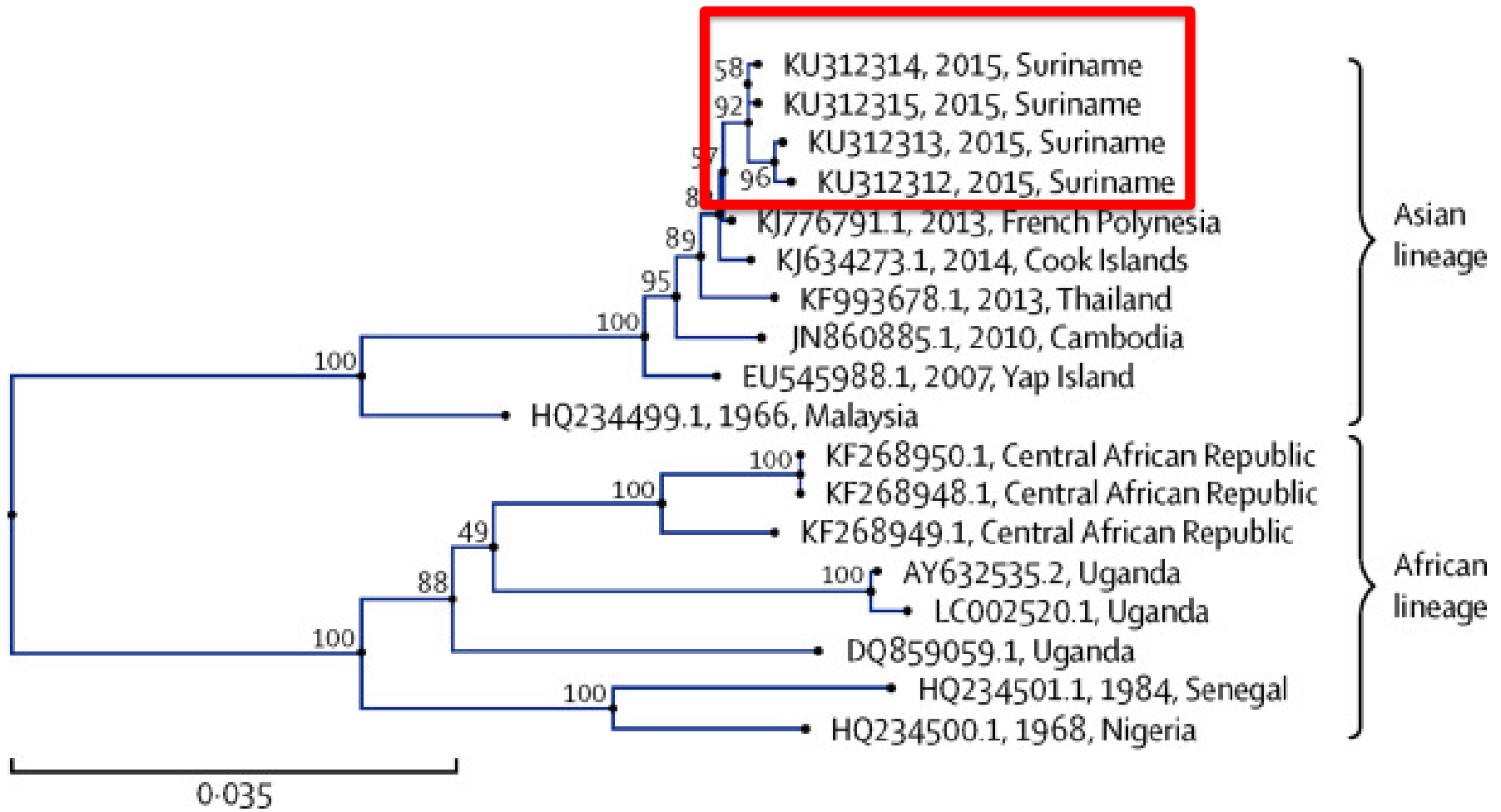


# Flaviviridae: Taxonomy





# Zika In the Americas

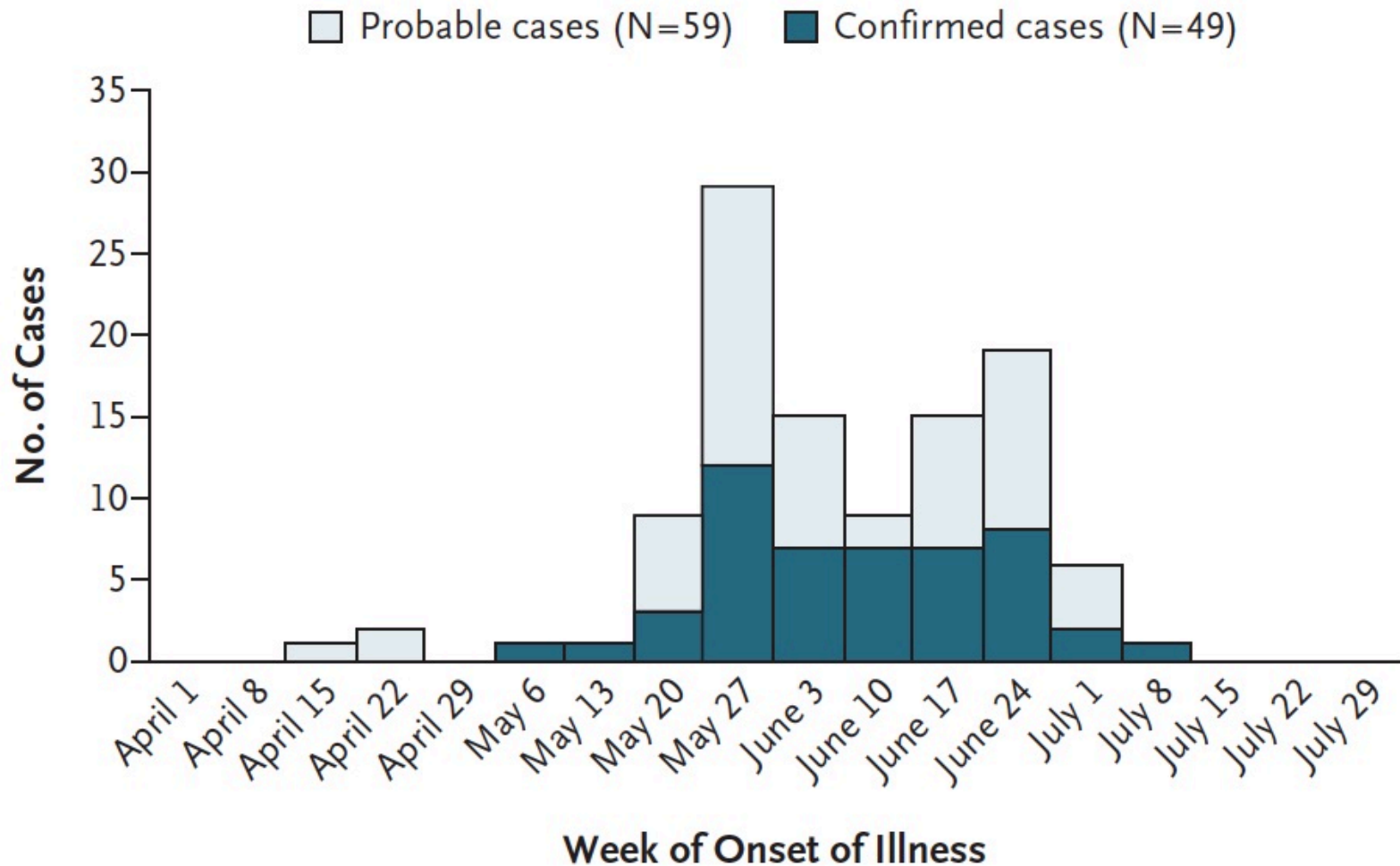


Antoine Enfissi, John Codrington, Jimmy Roosblad, Mirdad Kazanji, Dominique Rousset

# **Zika Virus: An Introduction**

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# Zika on Yap: 2007



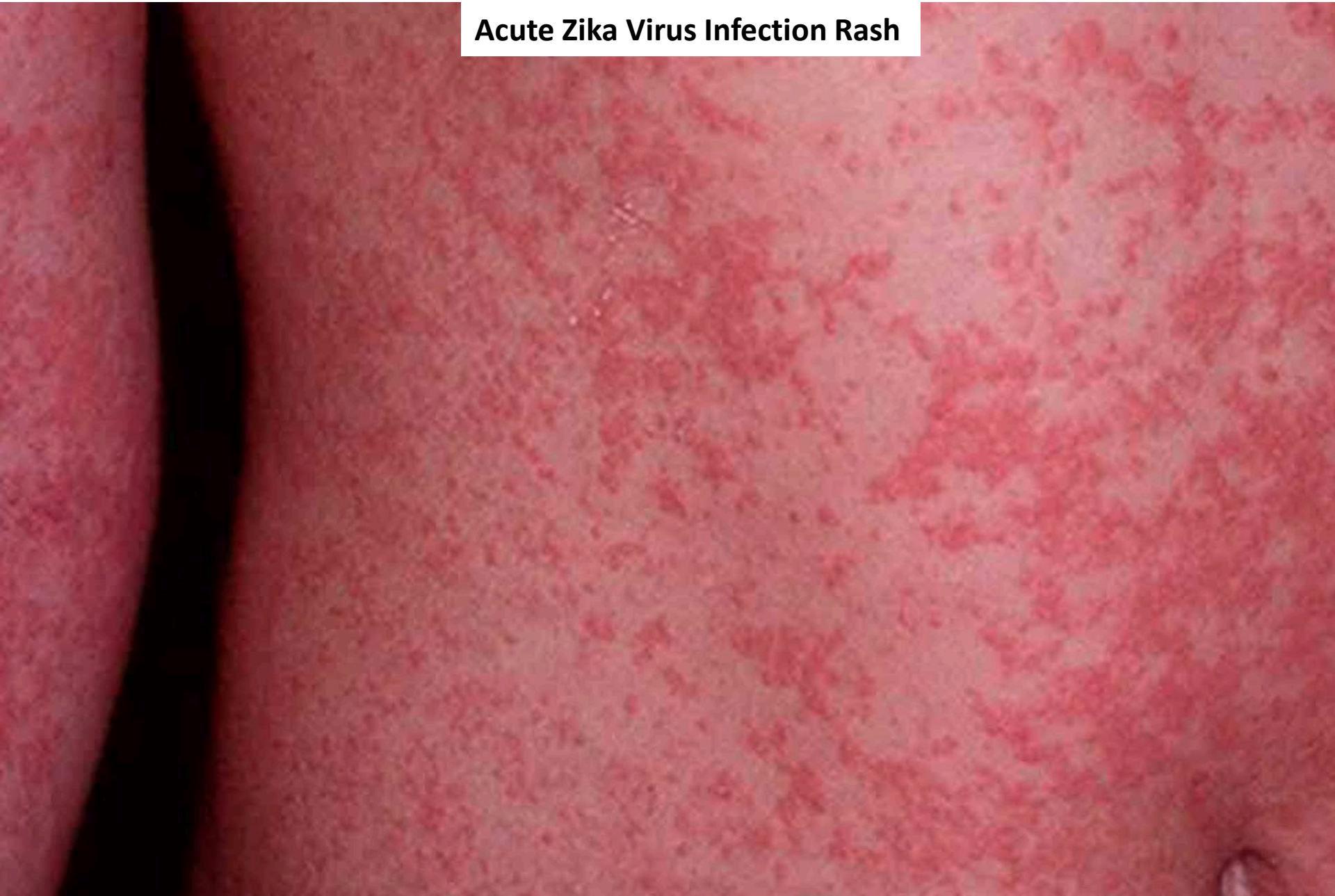
# Clinical Symptoms: Yap 2007

**Table 1.** Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.

Sign or Symptom	No. of Patients (%)
Macular or papular rash	28 (90)
Fever*	20 (65)
Arthritis or arthralgia	20 (65)
Nonpurulent conjunctivitis	17 (55)
Myalgia	15 (48)
Headache	14 (45)
Retro-orbital pain	12 (39)
Edema	6 (19)
Vomiting	3 (10)



## Acute Zika Virus Infection Rash



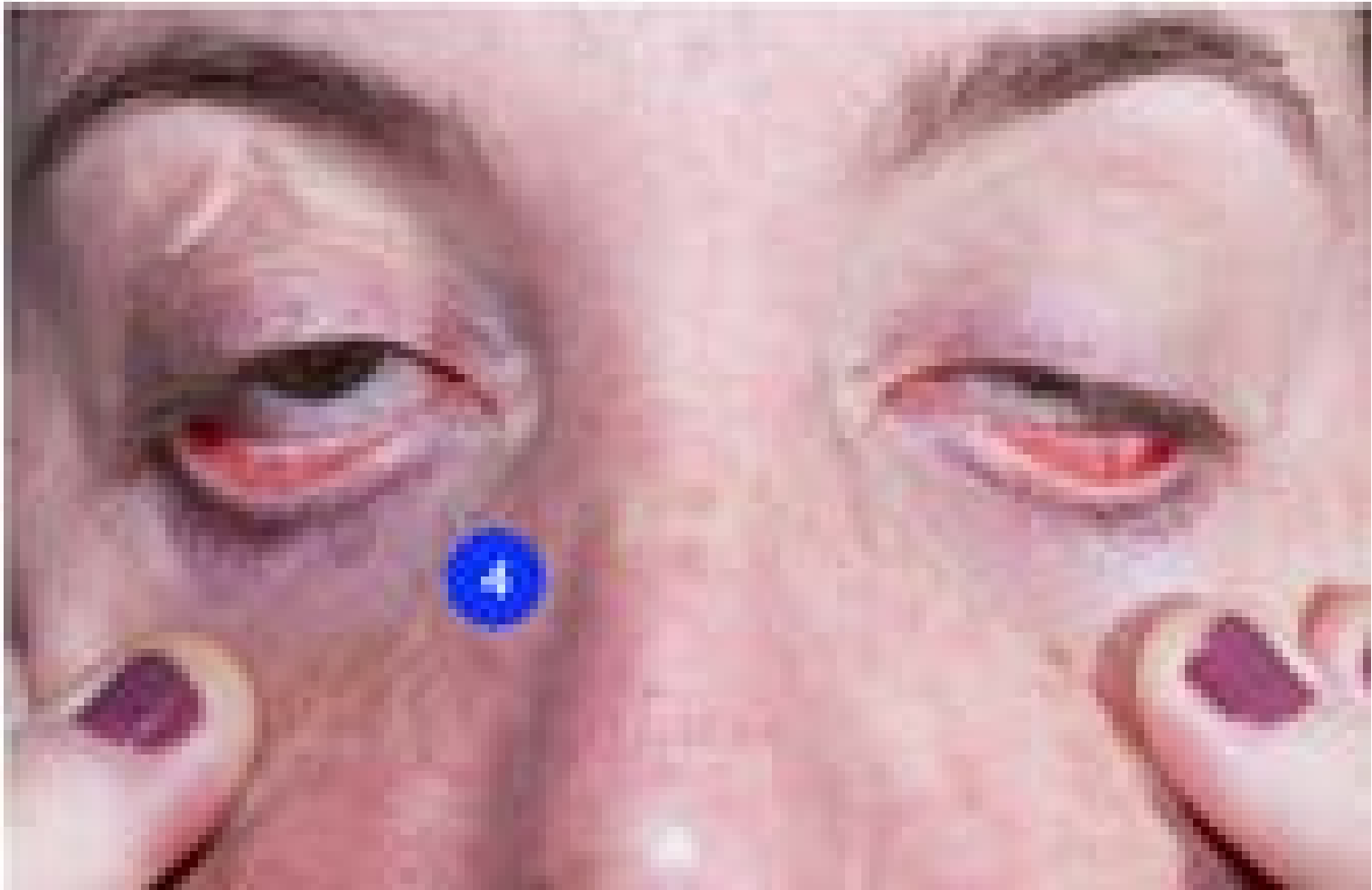
Courtesy of [drealimgrenada.com](http://drealimgrenada.com)

**Acute Zika Virus Infection Rash**





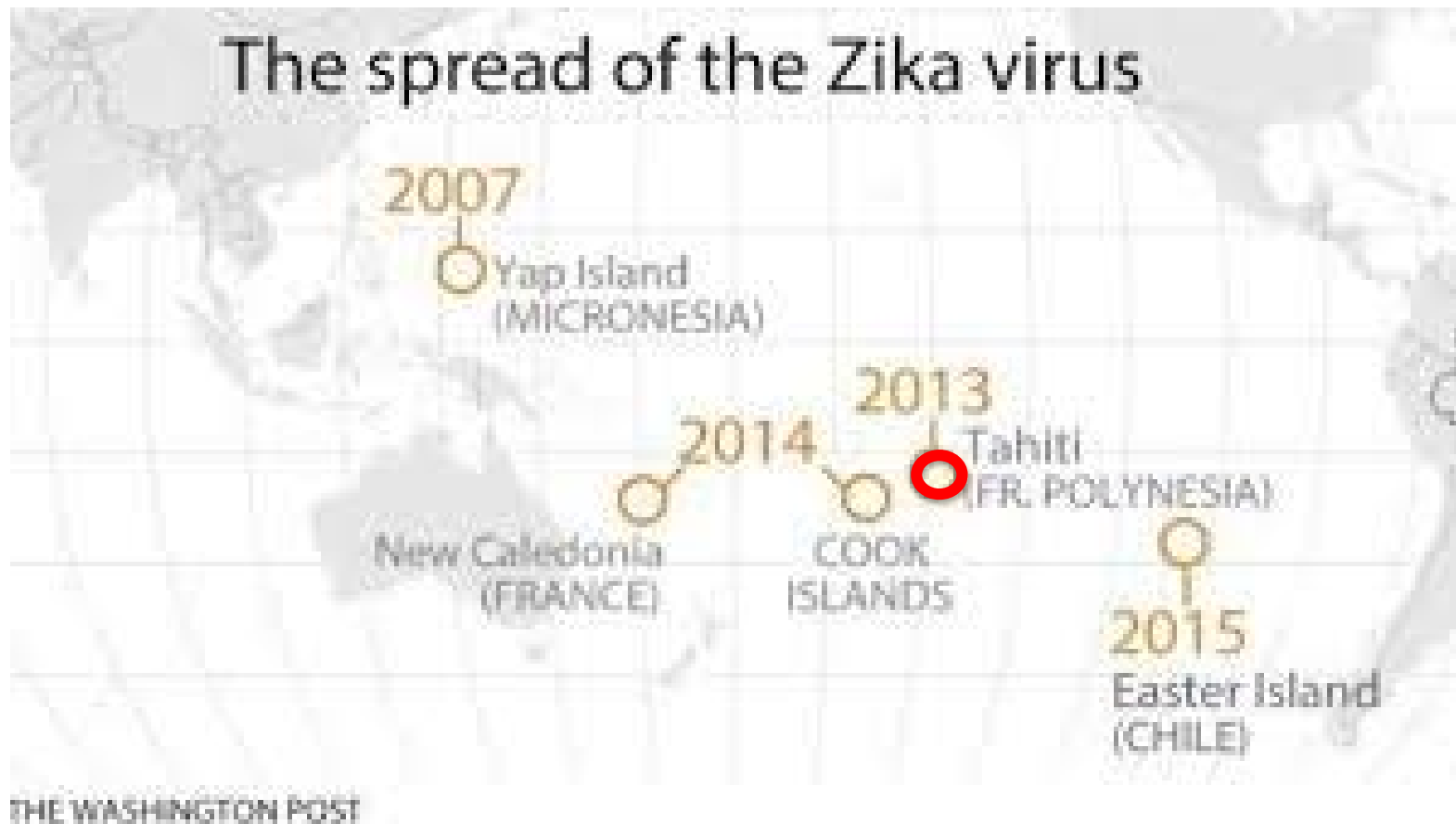




Conjunctivitis in a 30-year old woman with Zika from Rio Grand do North



# Spread of Zika Virus across the Pacific Ocean



# Guillain Barre Syndrome and Zika

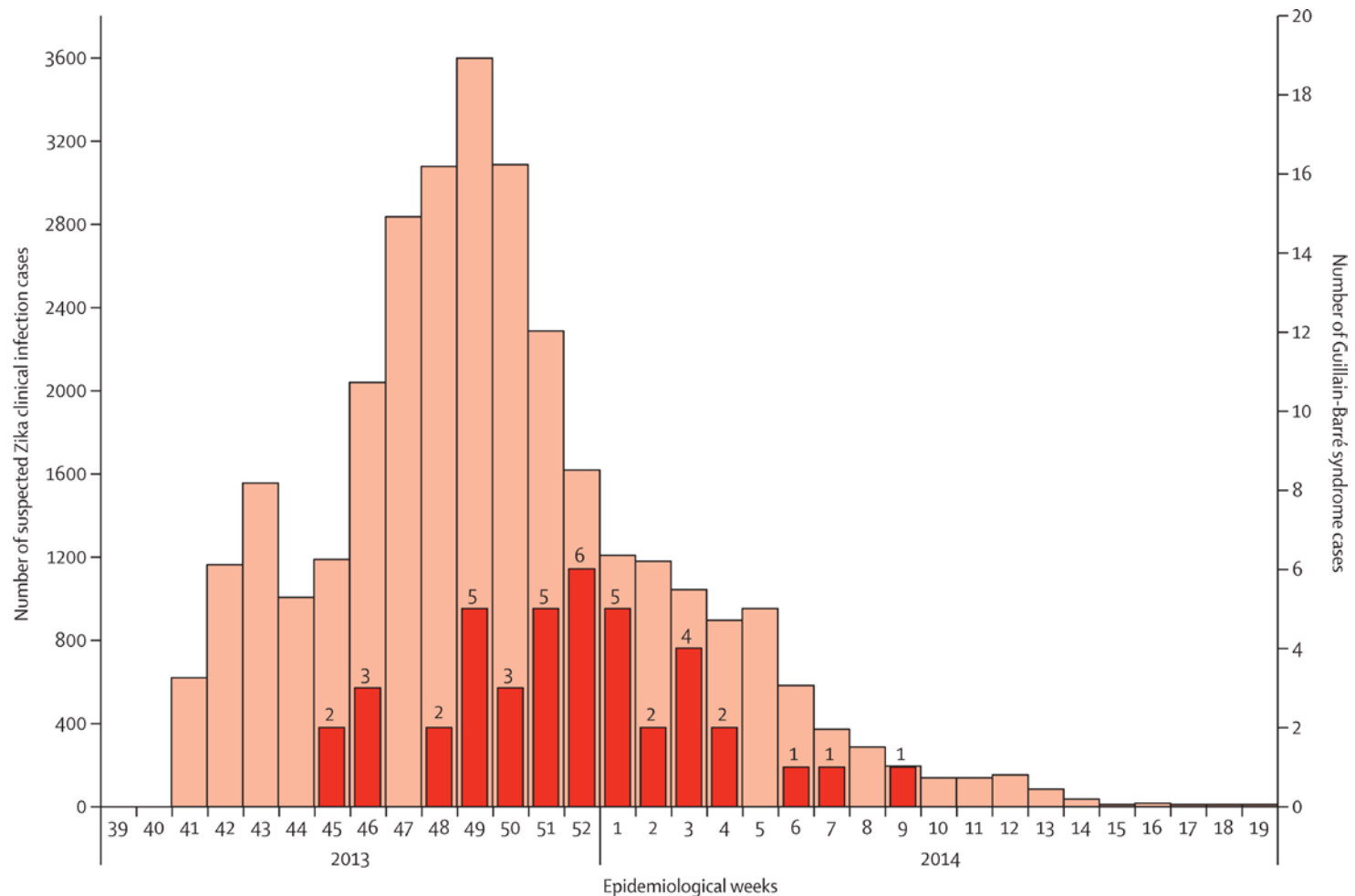
## RAPID COMMUNICATIONS

### Zika virus infection complicated by Guillain-Barré syndrome – case report, French Polynesia, December 2013

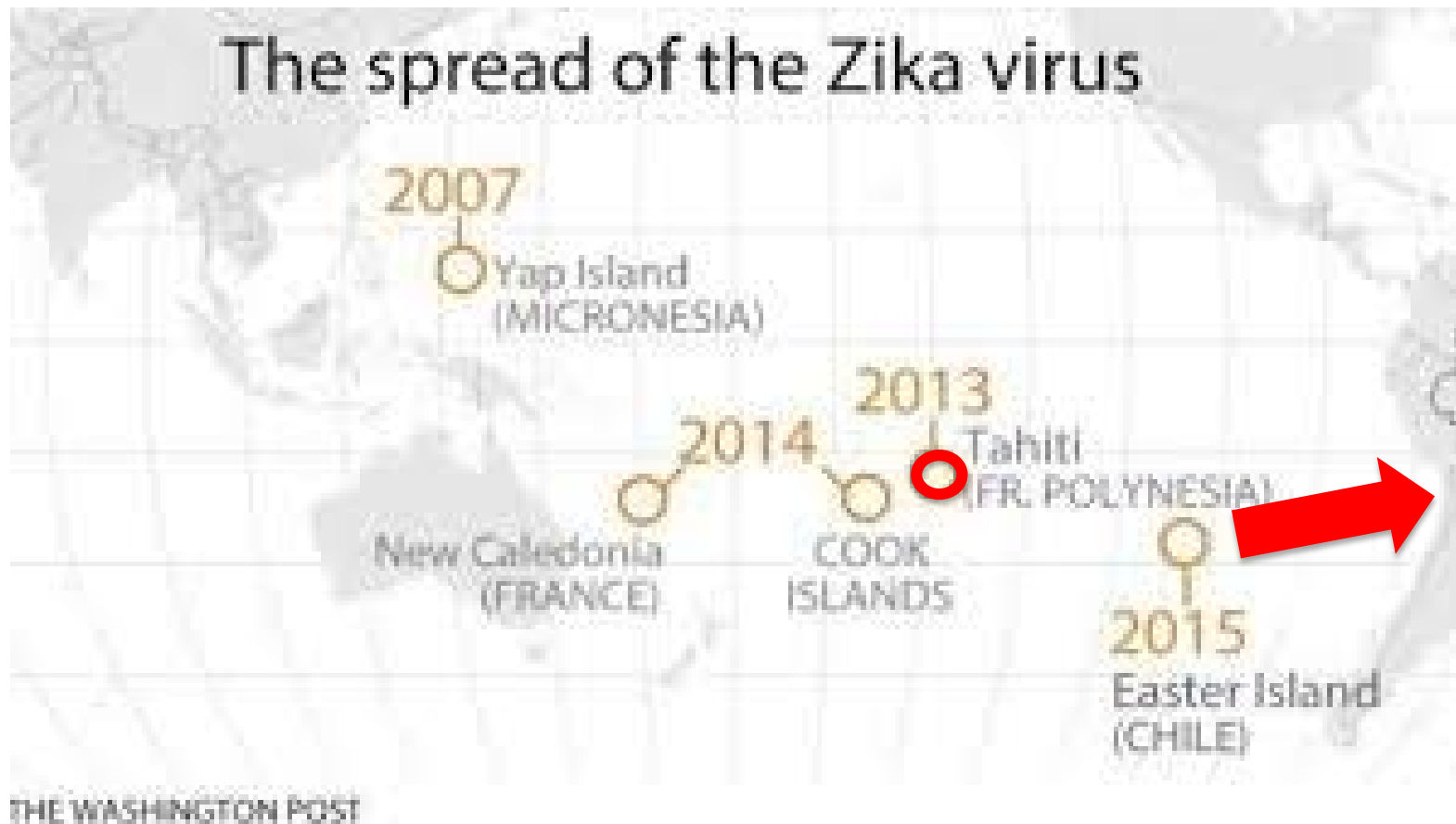
**E Oehler (erwan.oehler@cht.pf)<sup>1</sup>, L Watrin<sup>2</sup>, P Larre<sup>2</sup>, I Leparç-Goffart<sup>3</sup>, S Lastère<sup>4</sup>, F Valour<sup>1</sup>, L Baudouin<sup>5</sup>, H P Mallet<sup>6</sup>, D Musso<sup>7</sup>, F Ghawche<sup>2</sup>**

1. Internal medicine department, French Polynesia Hospital Center, Pirae, Tahiti, French Polynesia
2. Neurology department, French Polynesia Hospital Center, Pirae, Tahiti, French Polynesia
3. Institut de Recherche Biomédicale des Armées, National Reference Laboratory for arboviruses, Marseille, France
4. Laboratory of virology, French Polynesia Hospital Center, Pirae, Tahiti, French Polynesia
5. Intensive care unit, French Polynesia Hospital Center, Pirae, Tahiti, French Polynesia
6. Bureau de veille sanitaire – Direction de la Santé, Papeete, Tahiti, French Polynesia
7. Louis Mallardé Institute, Papeete, Tahiti, French Polynesia

# Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study



# Spread of Zika Virus across the Pacific Ocean



# **Zika Moves to the Americas**

## **Zika Virus Outbreak, Bahia, Brazil**

**Gubio S. Campos, Antonio C. Bandeira,  
Silvia I. Sardi**

Authors affiliations: Federal University of Bahia, Salvador,  
Bahia, Brazil (G.S. Campos, S.I. Sardi); Hospital Aliança, Salvador

**24 patients from St. Helena Hospital, Camaciri**



# Camaciri, Brazil



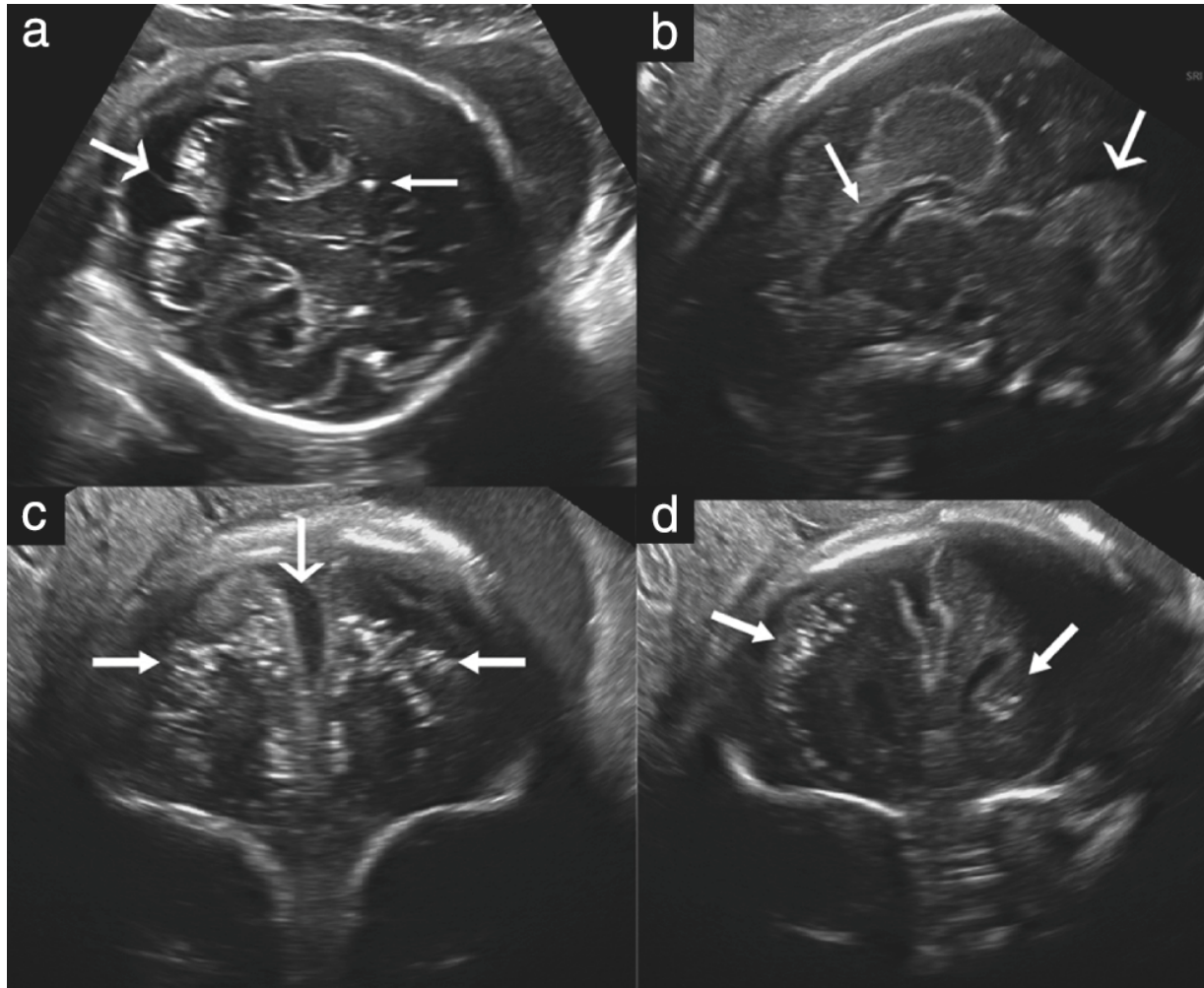
# Salvador, Bahia, Brazil



# Brazil 2015: Zika and Microcephaly



# Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?



# Zika Virus in Brazil

- 88 women with presumed Zika virus infection enrolled between Sept 2015 and Feb 2016
- Acute Zika virus between 5 and 38 weeks of gestation
  - Maculopapular rash: 44% vs 12% ( $p=0.02$ )
  - Conjunctival injection: 58 vs. 13% ( $p=0.002$ )
  - Lymphadenopathy: 40 vs 7% ( $p=0.02$ )



# Zika Virus In Pregnant Women: Brazil

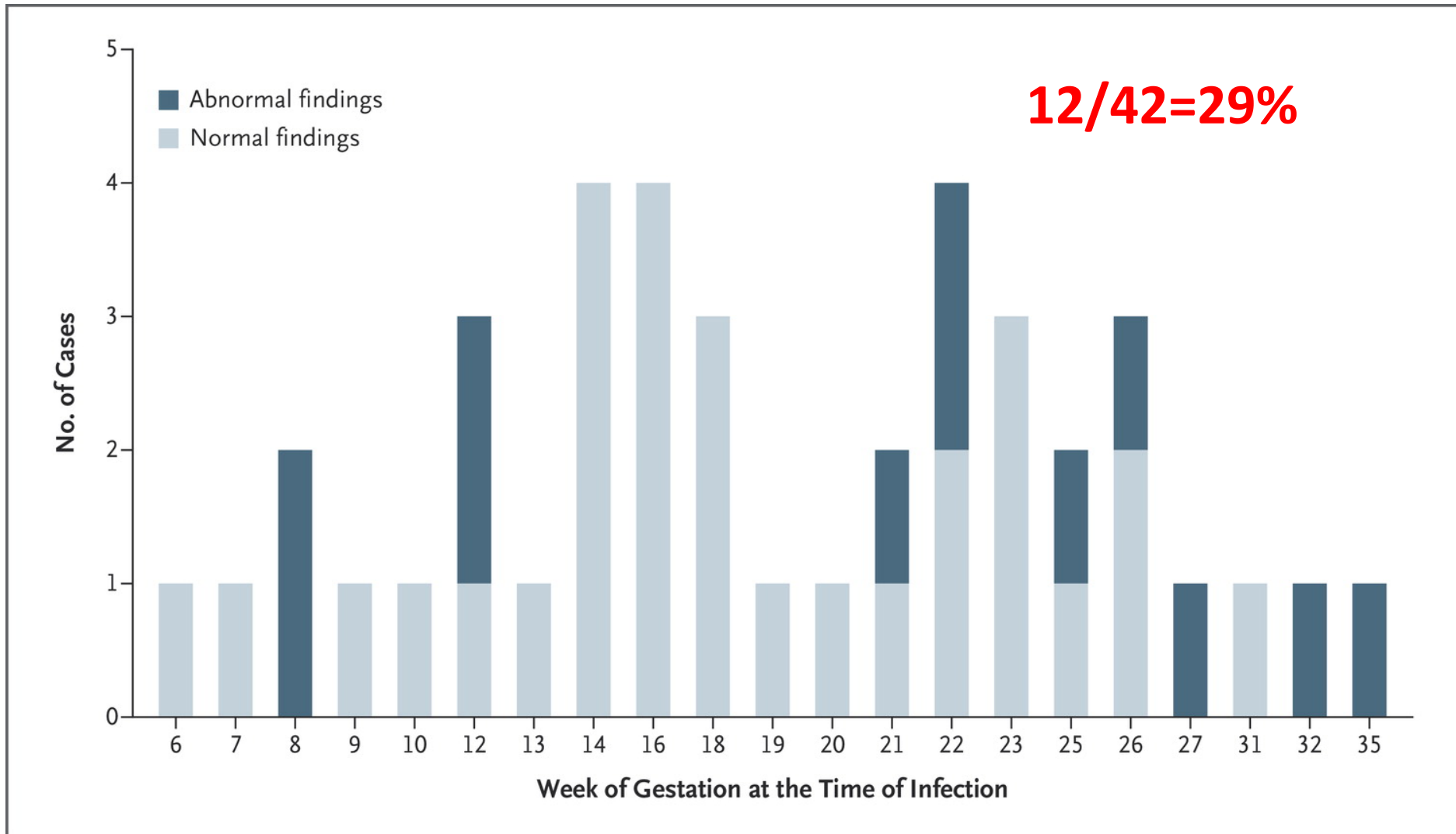


Brasil P et al. N Engl J Med 2016.  
DOI 10.1056 NEJMoa1602412

# Virologic Findings

- 60 women had positive PCR results in serum specimens
  - 34 of these were PCR + in Urine
- 46 had positive PCR results in urine samples
  - 12 women had positive results in urine specimens only

# Zika Virus In Pregnant Women: Brazil

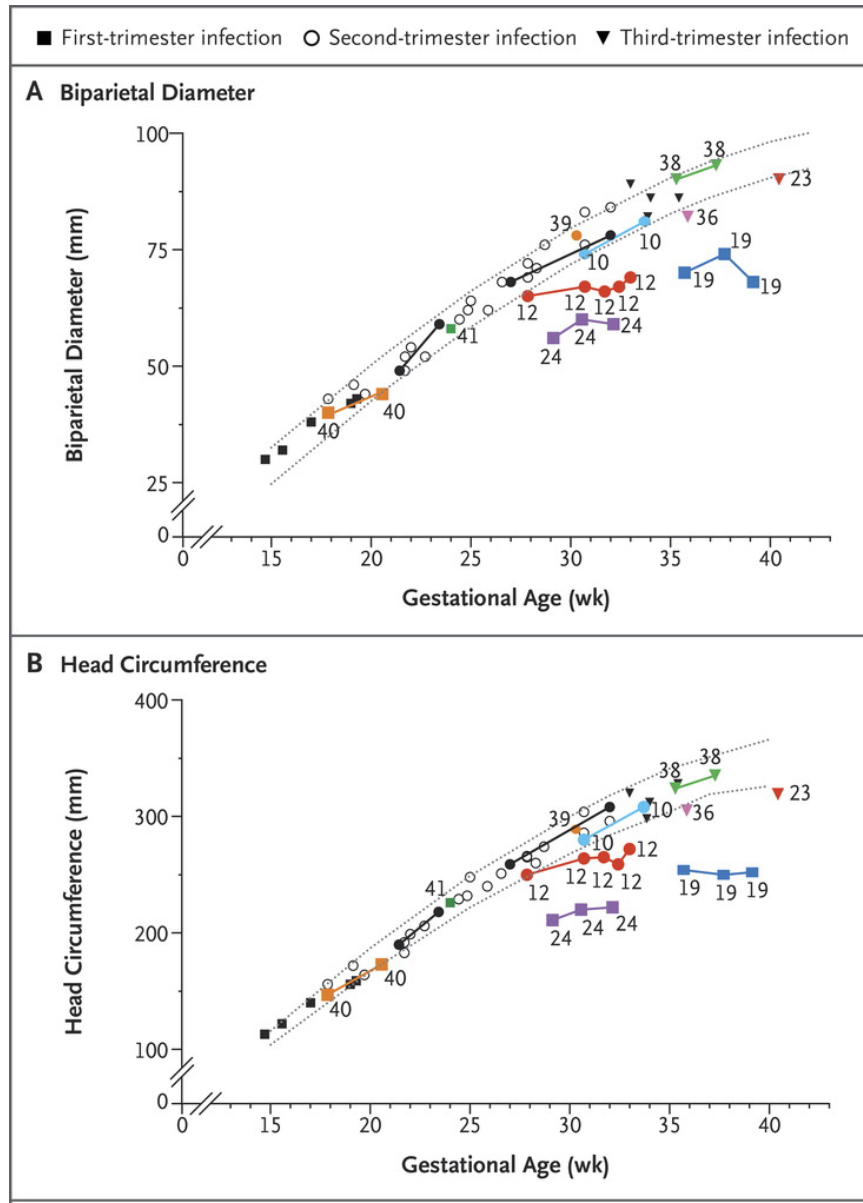


Brasil P et al. N Engl J Med 2016.  
DOI 10.1056 NEJMoa1602412

# Zika Virus in Brazil

- Fetal ultrasound performed in 42 Zika virus infected women
  - Fetal anomalies by Doppler in 12/42 (29%)
  - Fetal deaths: 2 (weeks 36 and 38)
  - In utero growth retardation  $\pm$  microcephaly: 5
  - Ventricular calcifications or other CNS malformations: 7
  - Abnormal umbilical fluid or umbilical artery flow: 7

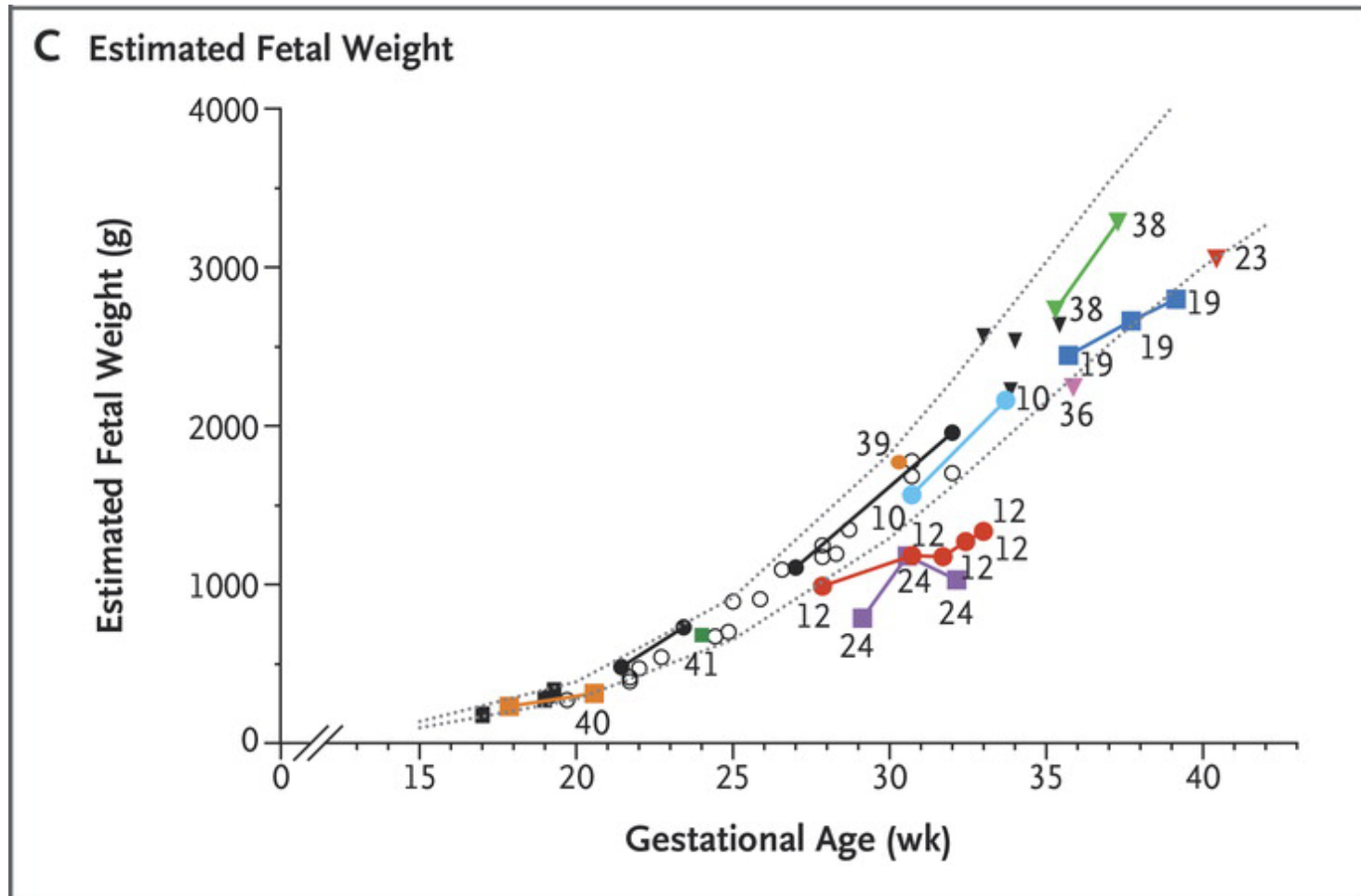
# Zika Virus In Pregnant Women: Brazil



Brasil P et al. N Engl J Med 2016.  
DOI 10.1056/NEJMoa1602412



# Zika Virus In Pregnant Women: Brazil





Courtesy of Miguel del Ca  
UCSD Division of Teratolo

# Zika Virus in Amnionic Fluid

- Two women with Zika virus infection during 10 and 18 weeks of gestation with acute Zika
  - Case 1: Zika @ 18 weeks-> microcephaly at week 21
  - Case 2: Zika @ 10 weeks-> fetal head circumference week 22 < 10<sup>th</sup> percentile
- Both underwent amniocentesis during week 28 of pregnancy
  - Amnionic fluid: PCR Positive for Zika in both women
  - Blood and Urine: both negative
- Both children born with severe microcephaly

# Zika in Neural Tissue of a Stillborn Infant

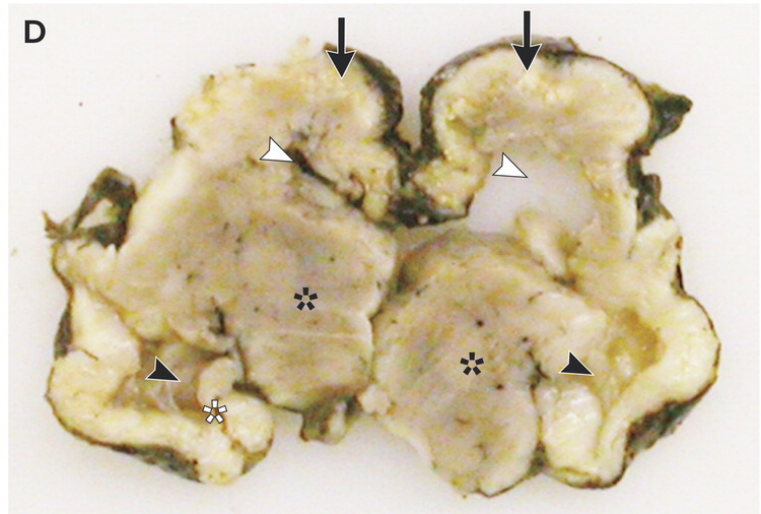
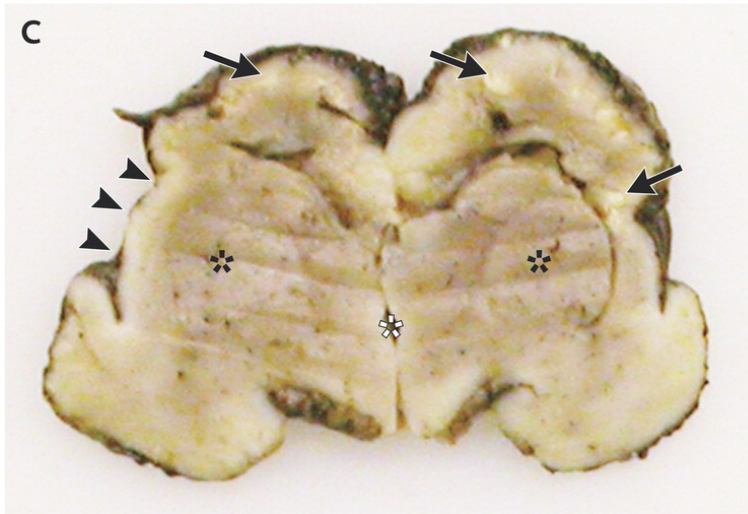
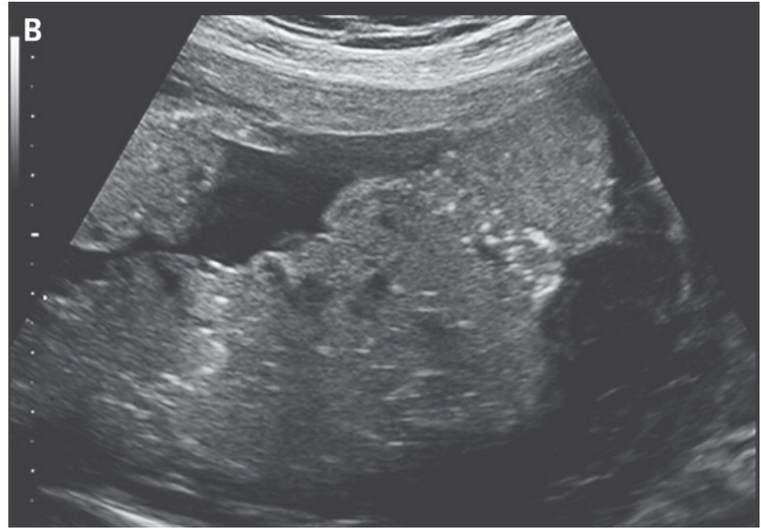
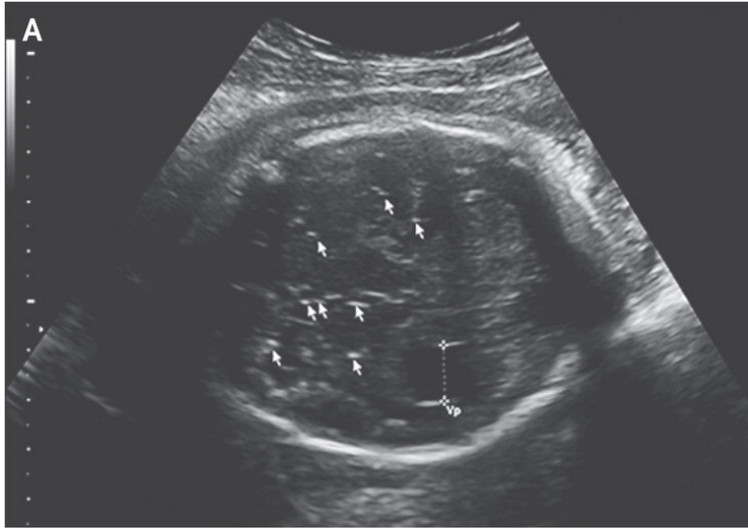
- Febrile illness with rash at the end of the first trimester of pregnancy in a woman who had been living in Brazil
- Ultrasonography performed at 29 weeks of gestation revealed microcephaly with calcifications in the fetal brain and placenta.

# Ultrasonographic findings at 32 Weeks

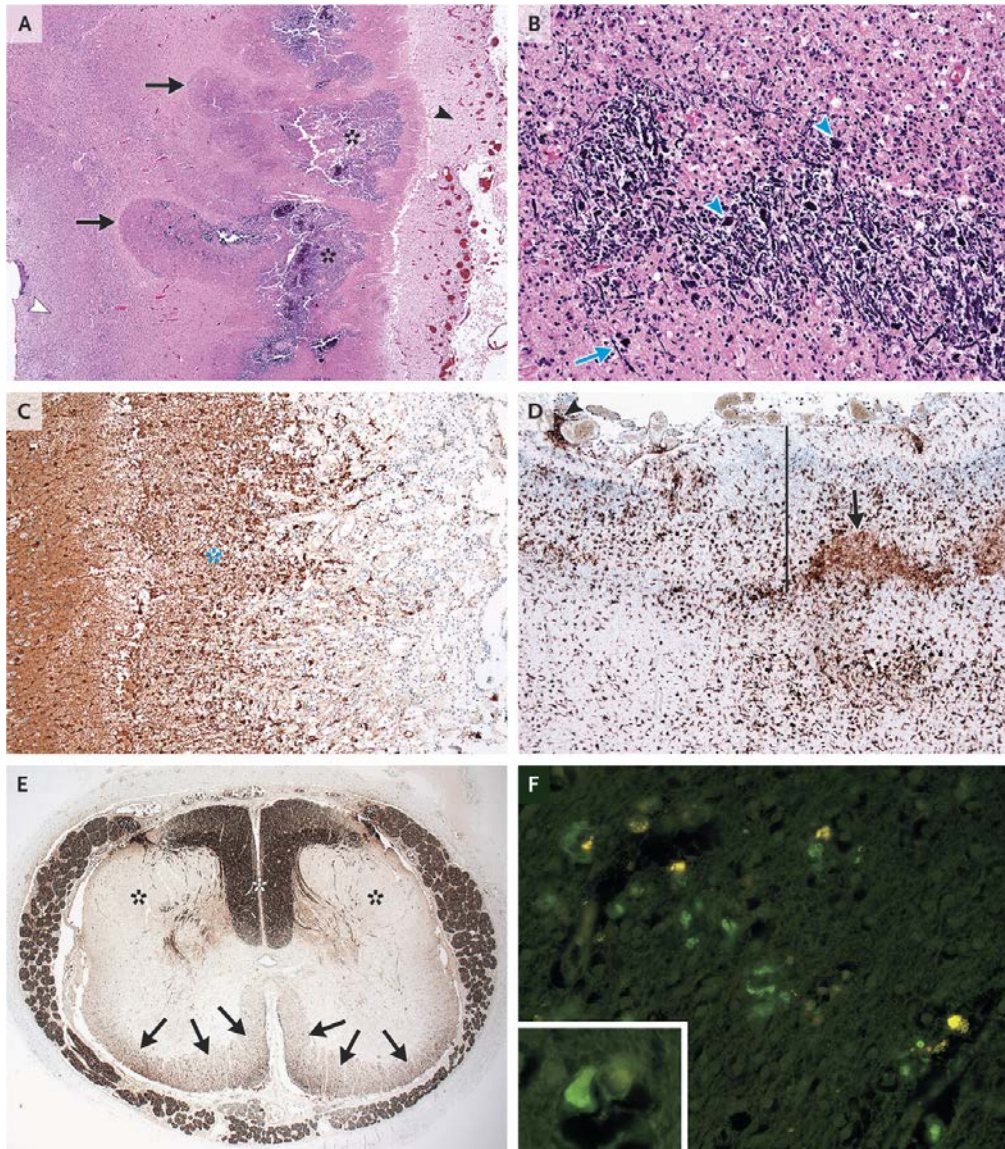
- Intrauterine growth retardation (estimated 3rd percentile of fetal weight) with normal amniotic fluid
- Normal thickness placenta with numerous calcifications
- Head circumference below the second percentile for gestation
- Moderate ventriculomegaly
- Brain structures blurred with numerous calcifications in various parts of the brain.



# Zika Virus in Brain of a Stillborn Baby

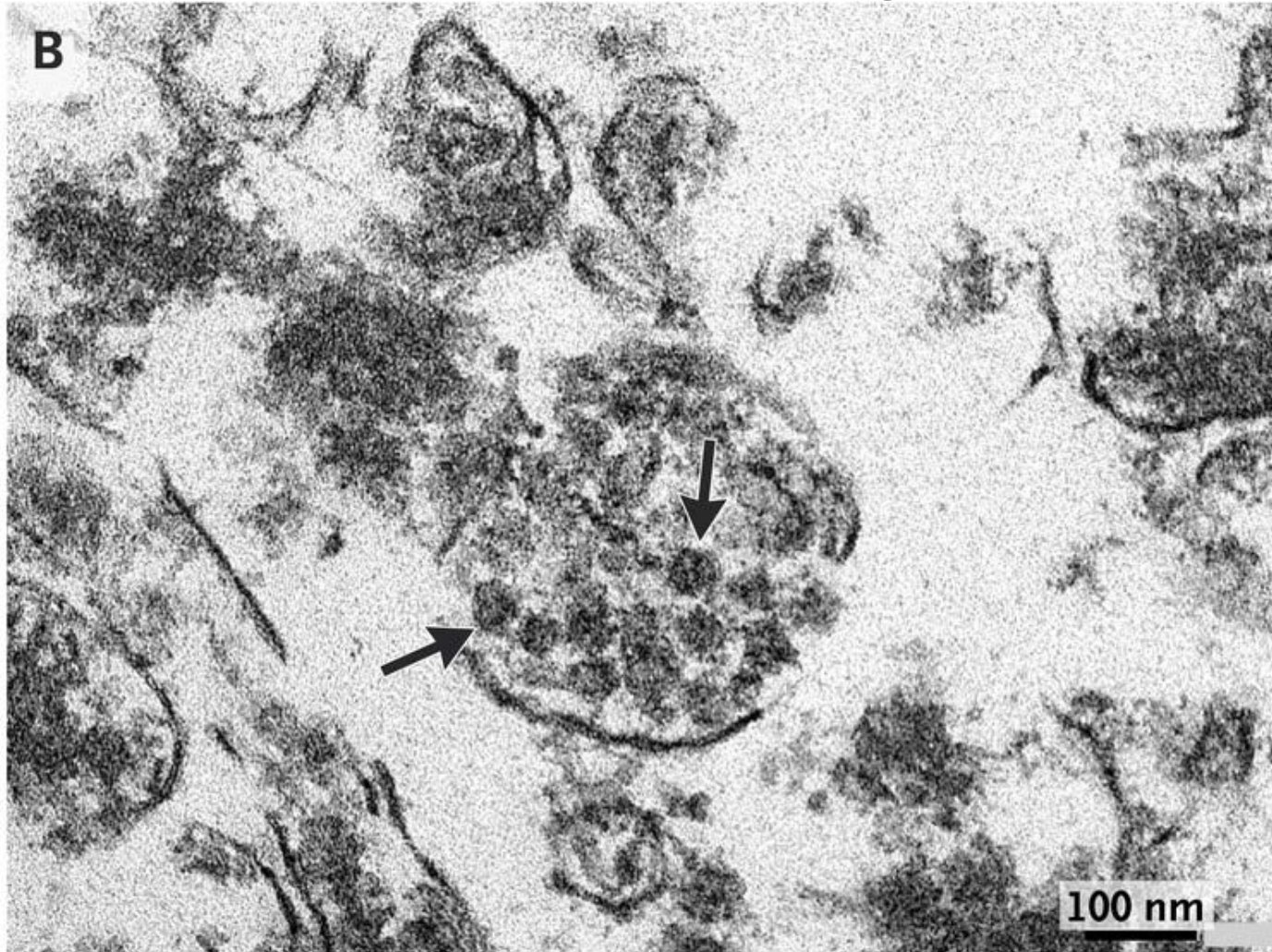


# Microscopic Analysis of Brain Tissue

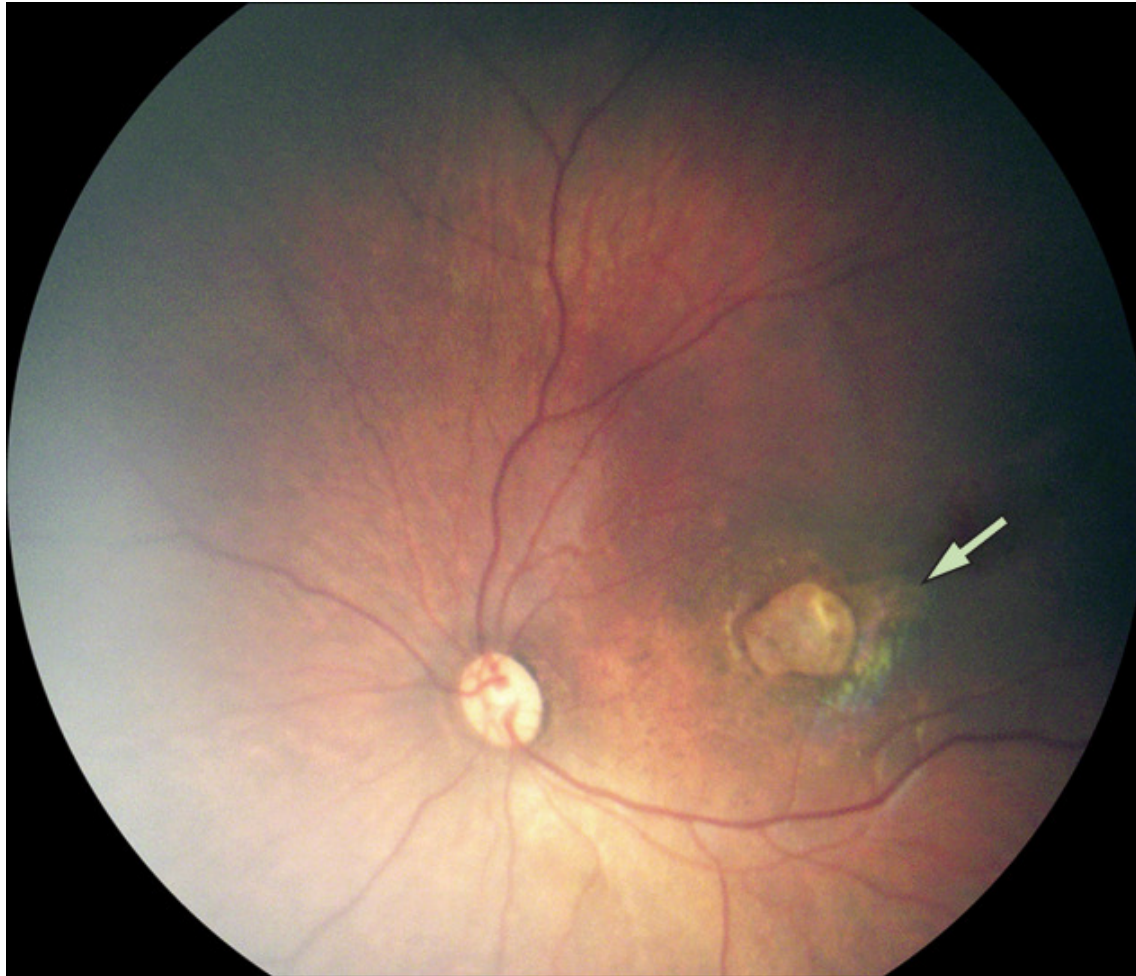




# Flavivirus Particles by EM in Brain of Stillborn Baby



# Severe macular neuroretinal atrophy in an infant with microcephaly

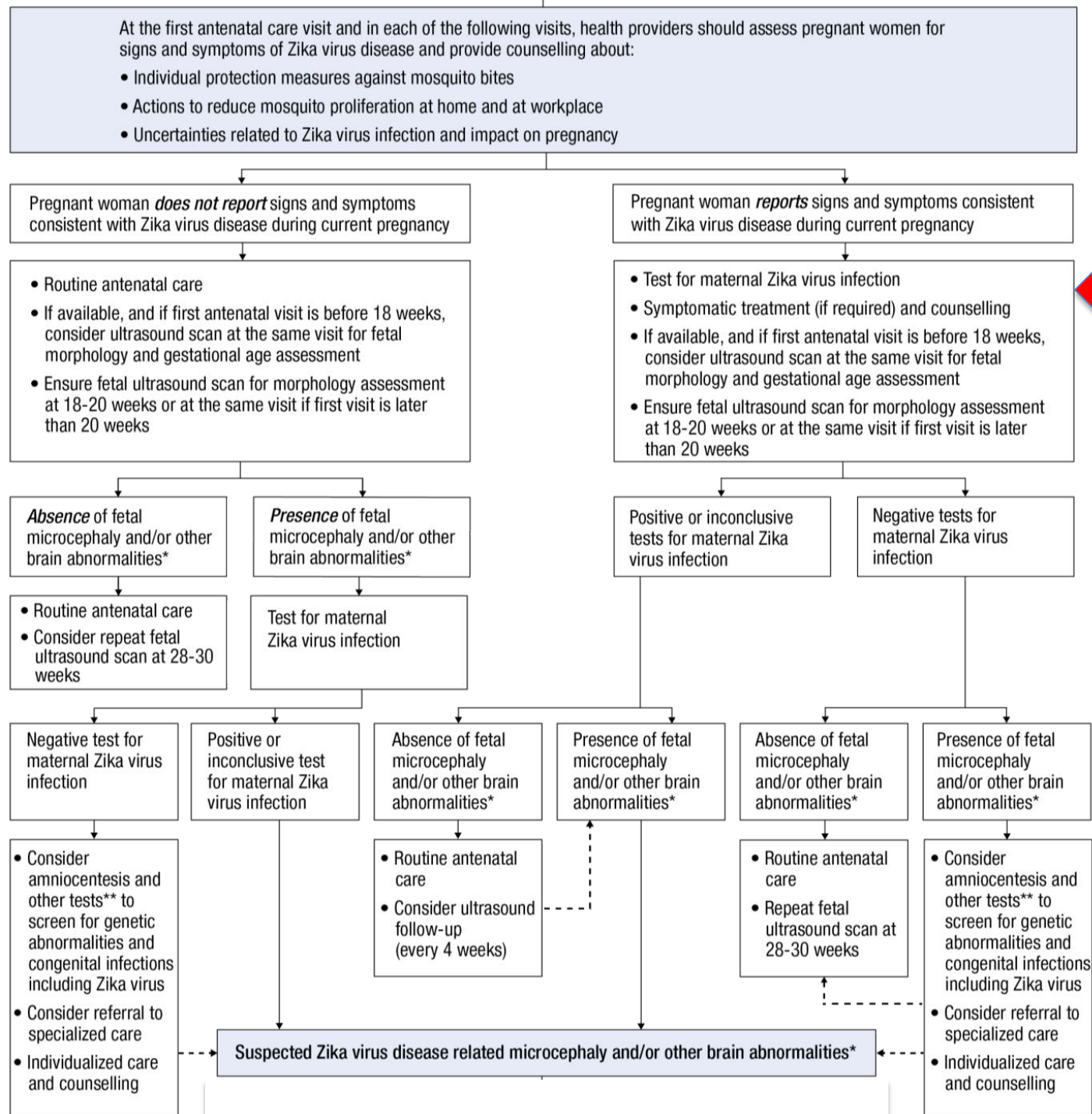


Camila V Ventura, Mauricio Maia, Vasco Bravo-Filho, Adriana L Góis, Rubens Belfort Jr

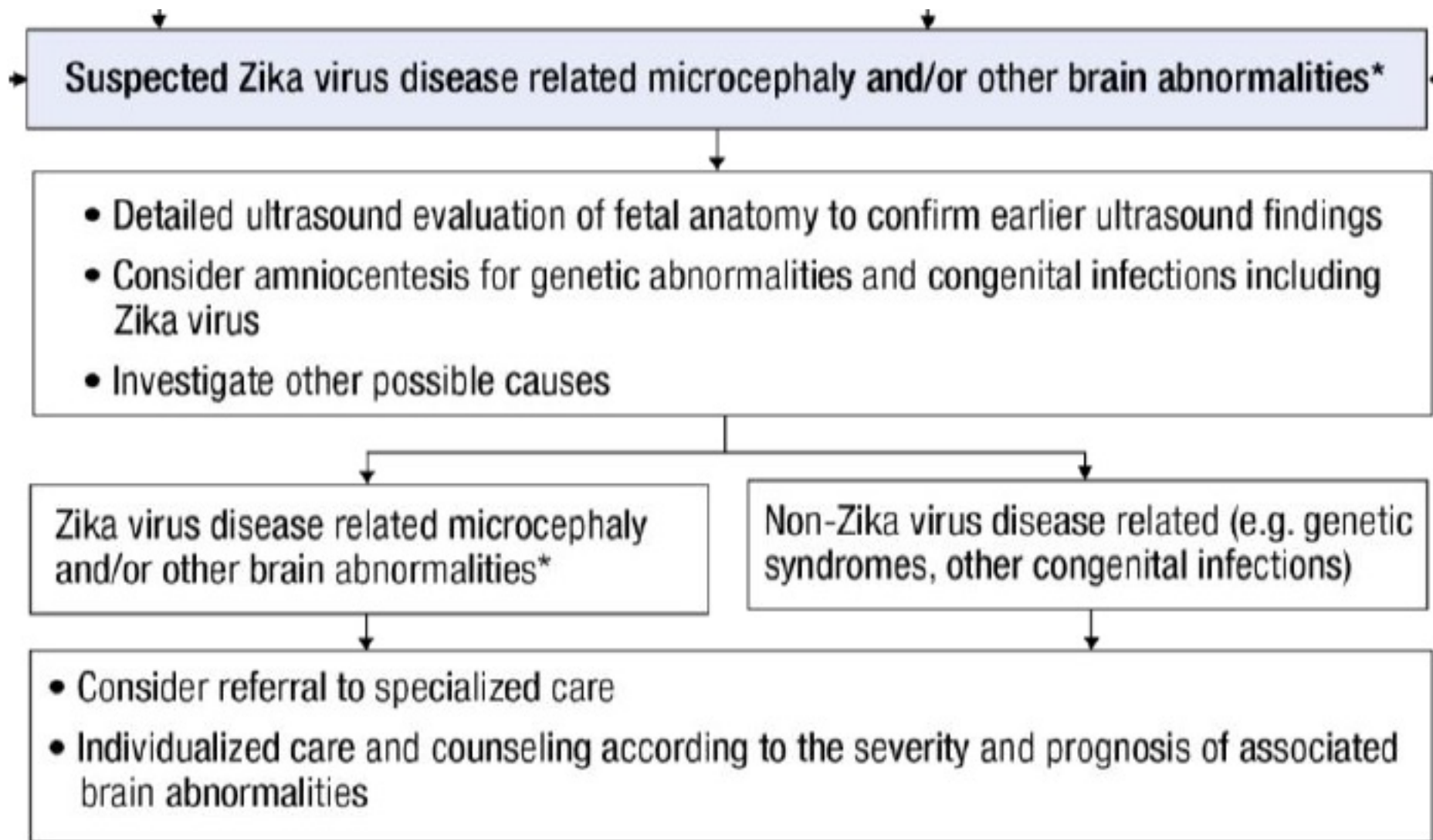
**Lancet 2016, 387; 228**



# WHO Interim Guidance Regarding Zika Virus infection in Pregnancy, March 2, 2016







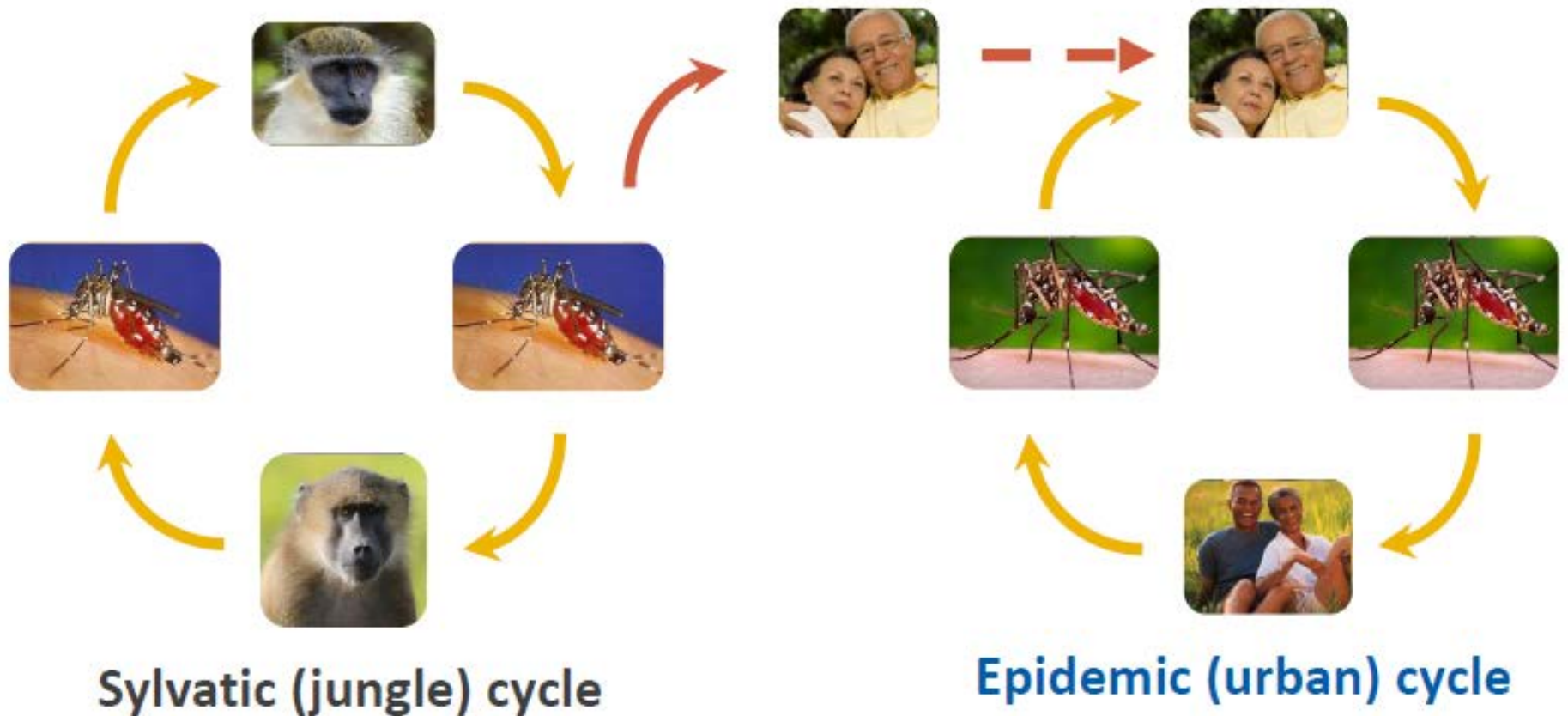
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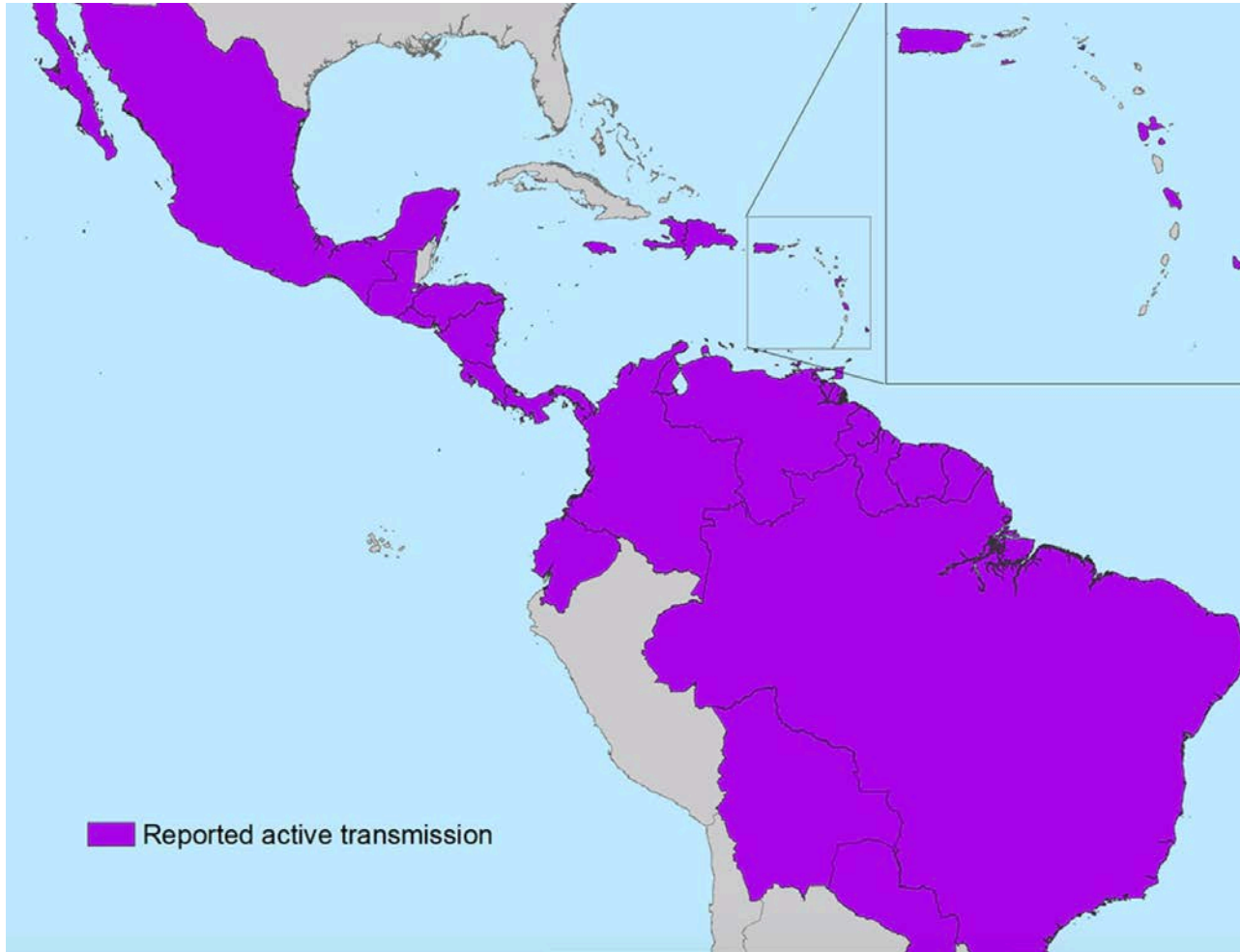
# Zika: Modes of Spread

- Mosquito
  - Within affected locations: vector control
  - Outside affected locations: prevention of mosquito transport and prevention of “seeding” local populations
- Travel
- Sexual transmission
- Transfusion

# Zika Virus Transmission Cycles



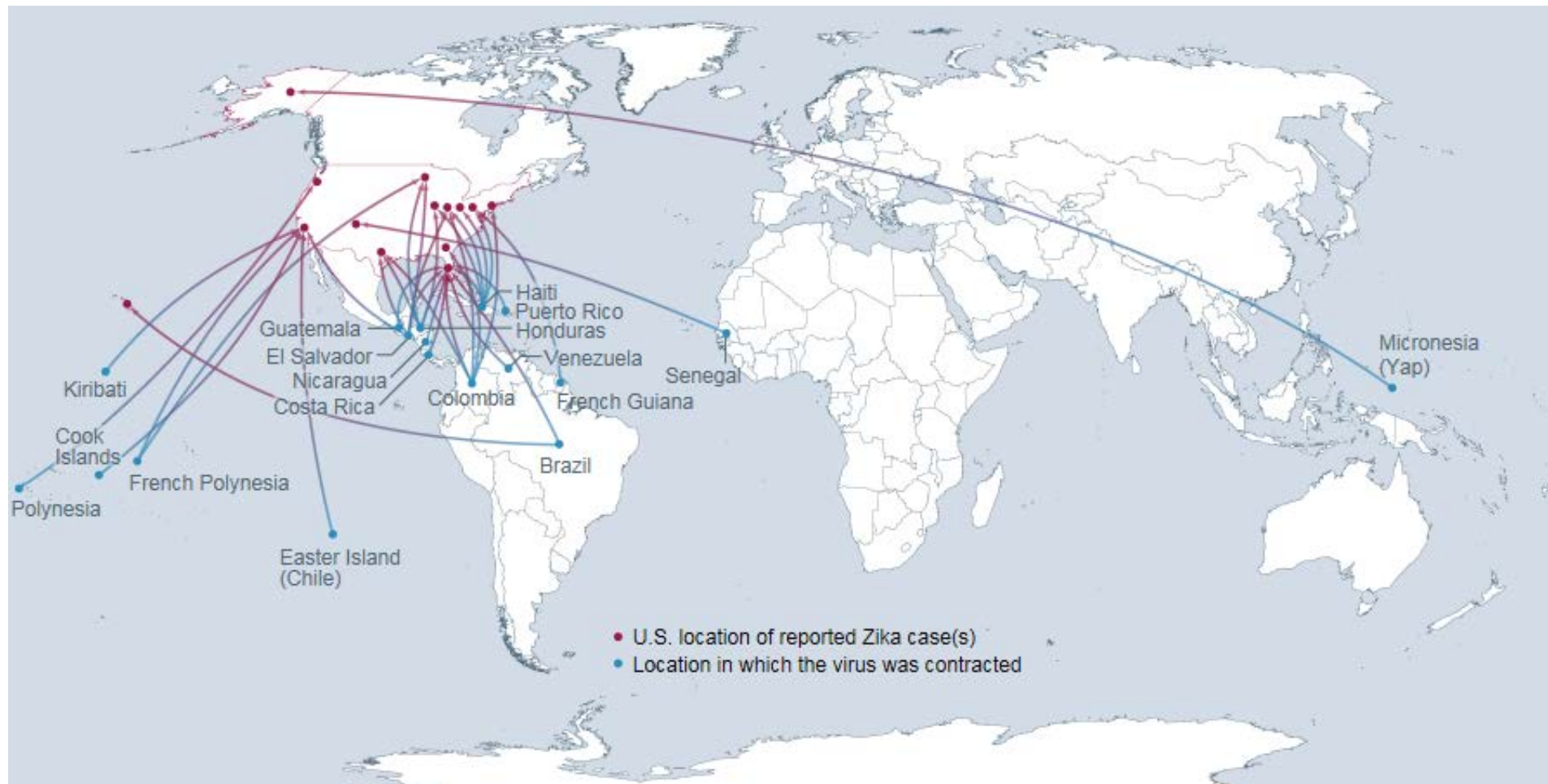
# Zika: Active Transmission 2016



Source: CDC



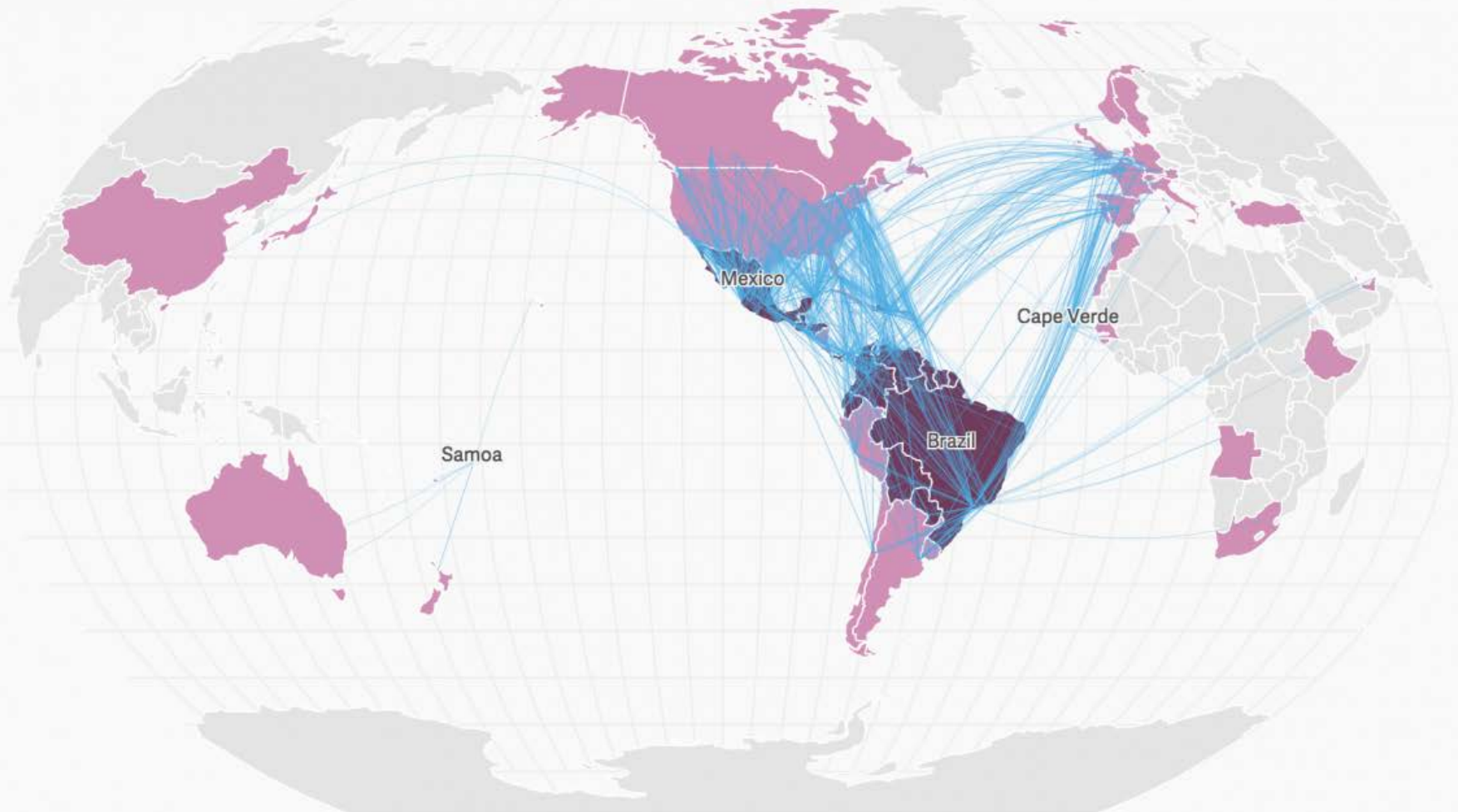
# How has Zika been getting to the U.S.?



**Source: Scientific American.** Downloaded 2.29.16 from  
<http://www.scientificamerican.com/article/zika-virus-threatens-u-s-from-abroad1/>  
Updated with cases reported through 2/23/16

Places that are just one flight away from Zika

■ Active Zika transmission ■ One flight away – Flights



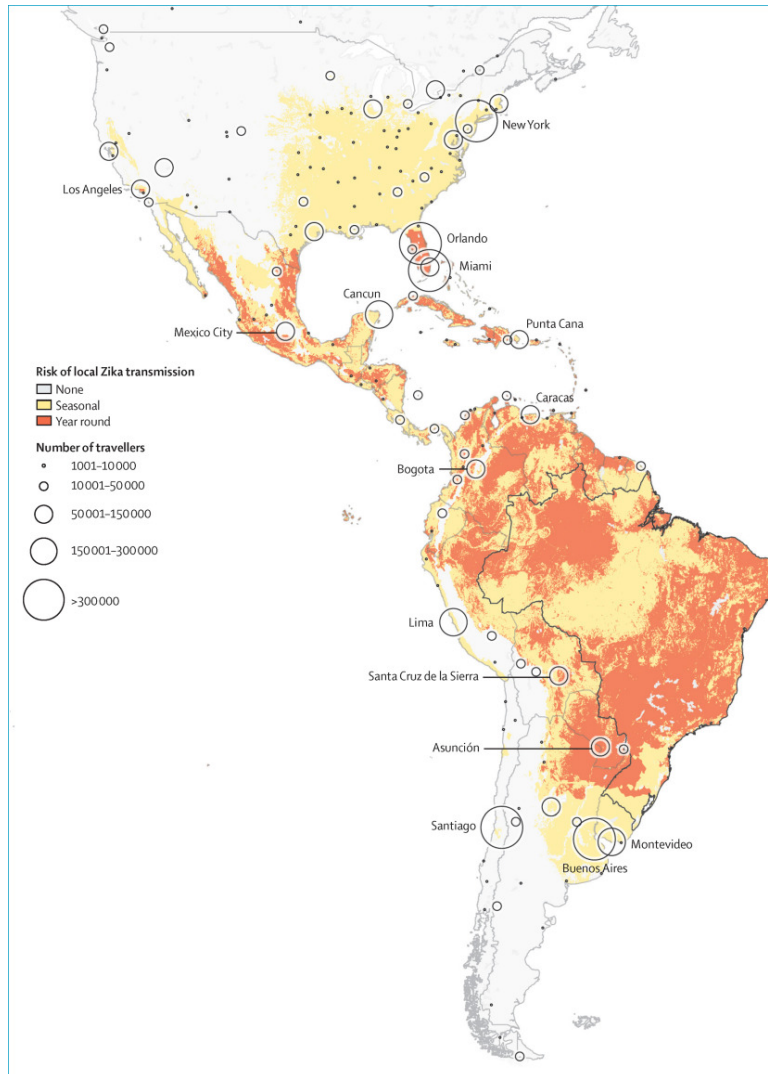
Note: Flights are based on published airline schedules for January 2016. Data: CDC, PlaneStats.com

Source: NWU Downloaded 2/29/16 from <http://www.storybench.org/spread-zika-virus-roundup-visualizations/> data from CDC, planestats.com

# Travel Destinations from Brazil

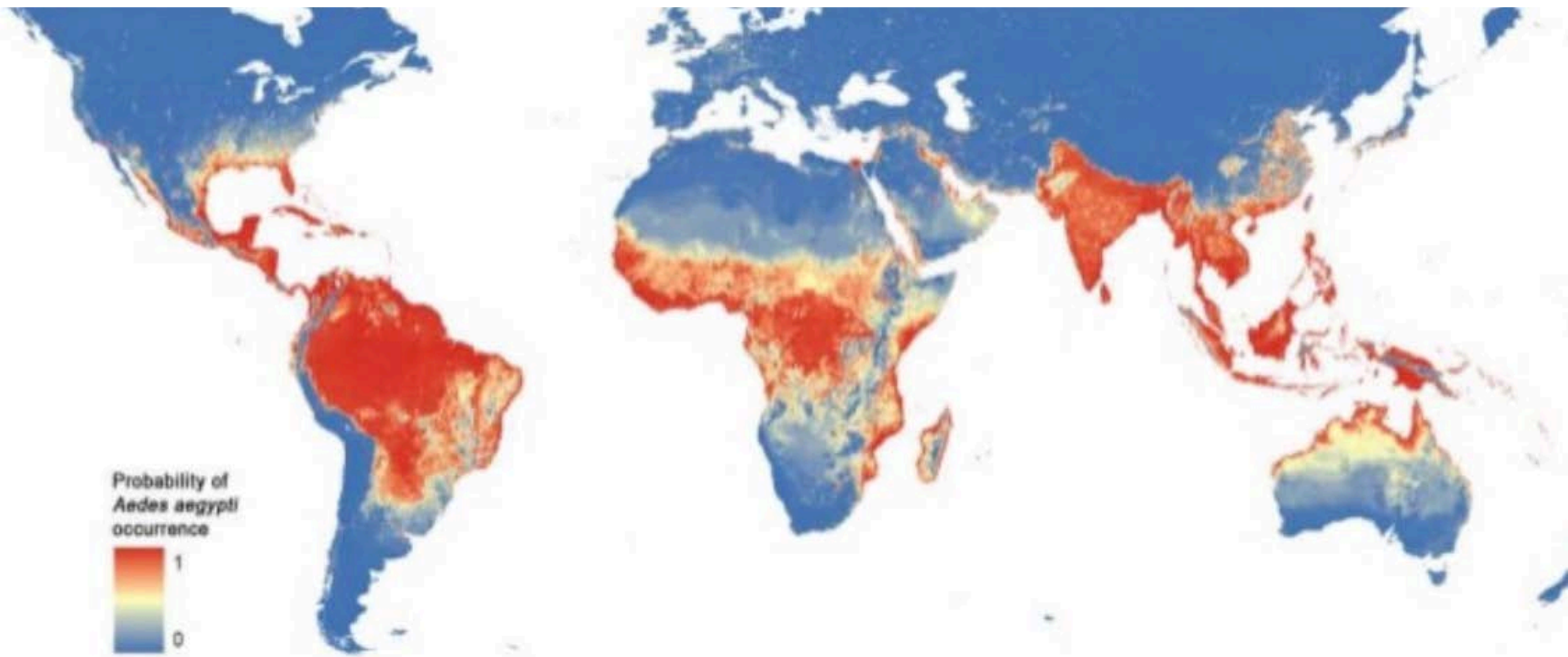
- Destinations from Brazilian airports within 50 km of areas conducive to year-round Zika virus transmission September, 2014, to August, 2015
  - Americas: 65%
  - Europe: 27%
  - Asia: 5%
  - Africa 1% (Angola #1 in Africa)

# Anticipating the international spread of Zika virus from Brazil



Final destinations of travellers departing Brazil by potential for autochthonous Zika transmission

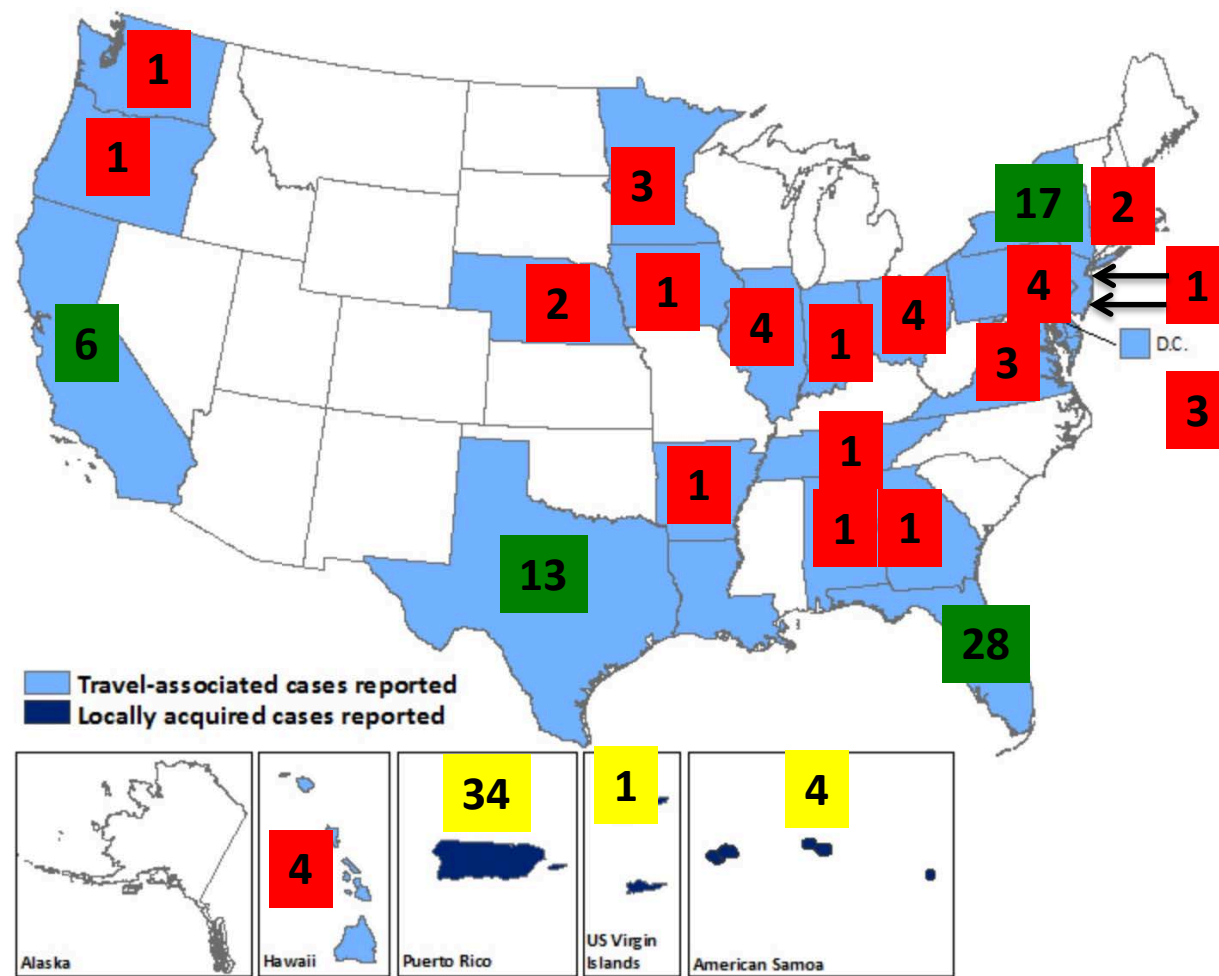
# Distribution of *Aedes aegypti*



Temp. suitability 58%; Urban accessibility 18%; NDVI 12%



# Zika in the US: February 2016



Laboratory-confirmed Zika virus disease cases reported to ArboNET by state or territory – United States, 2015–2016 (as of February 24, 2016)

Source: CDC

# Zika: Modes of Spread

- Mosquito
  - Within affected locations: vector control
  - Outside affected locations: prevention of mosquito transport and prevention of “seeding” local populations
- Travel
- Sexual transmission
- Transfusion

# Non–Vector-borne Transmission of Zika Virus, Colorado, USA

- Two male scientists returned to the Colorado from Bandafassi, Senegal on August 21
- Patient 1
  - August 30: maculopapular rash, swollen feet, extreme fatigue but no fever
  - August 31: Dysuria and peroneal pain
  - September 3: hematospermia
- Patient 2
  - August 29 –September 1: maculopapular rash, fatigue, headache and arthralgias

# Non–Vector-borne Transmission of Zika Virus, Colorado, USA

- Patient 3
  - September 3 – 6: malaise, chills, extreme headache, photophobia, and muscle pain that continued
  - September 7: maculopapular rash developed on her torso
  - September 8: expanded to neck and thighs

# Rash in Patient 3



Foy et.al., Emerg Infect Dis. 2011; 17): 880–2.

# Zika in Semen

- 32 year old man who developed a clinical syndrome c/w arbovirus 2 days after returning to Toulouse from Brazil and French Guyana
- Peripheral blood PCR positive for Zika virus RNA
- Further samples collected 2 weeks after diagnosis revealed Zika in
  - Plasma  $2.8 \log_{10}$  copies per mL
  - Urine  $3.1 \log_{10}$  copies per mL
  - Semen  $8.6 \log_{10}$  copies per mL



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# Zika: Research Questions

- Are the neurotropic complications (GBS, microcephaly) new or just not previously noted?
  - If new, what has changed
- How can we best control vectors and prevent transmission in affected areas?
- Is a vaccine feasible?
- What about drugs?
  - If so, how would you use them?

# Zika Introduction: Summary

- First isolated from mildly symptomatic *Rhesus macaque* monkey in Uganda in 1947
- For many years thought to be a mild to asymptomatic infection of primates and, accidentally, humans.
- Detected in *Aedes aegypti* mosquitos in Malaysia in 1969 on its march out of Africa
- Associated with Guillain Barre syndrome in 2013 in French Polynesia
- Spreads to Brazil in 2015 where it is first associated with microcephaly
- We will see more of it and other, as yet unidentified pathogens in the human population as the world becomes a more global community.



**Ngiyabonga!**