Emerging Arboviral Threats: Dengue, Chikungunya, and Zika

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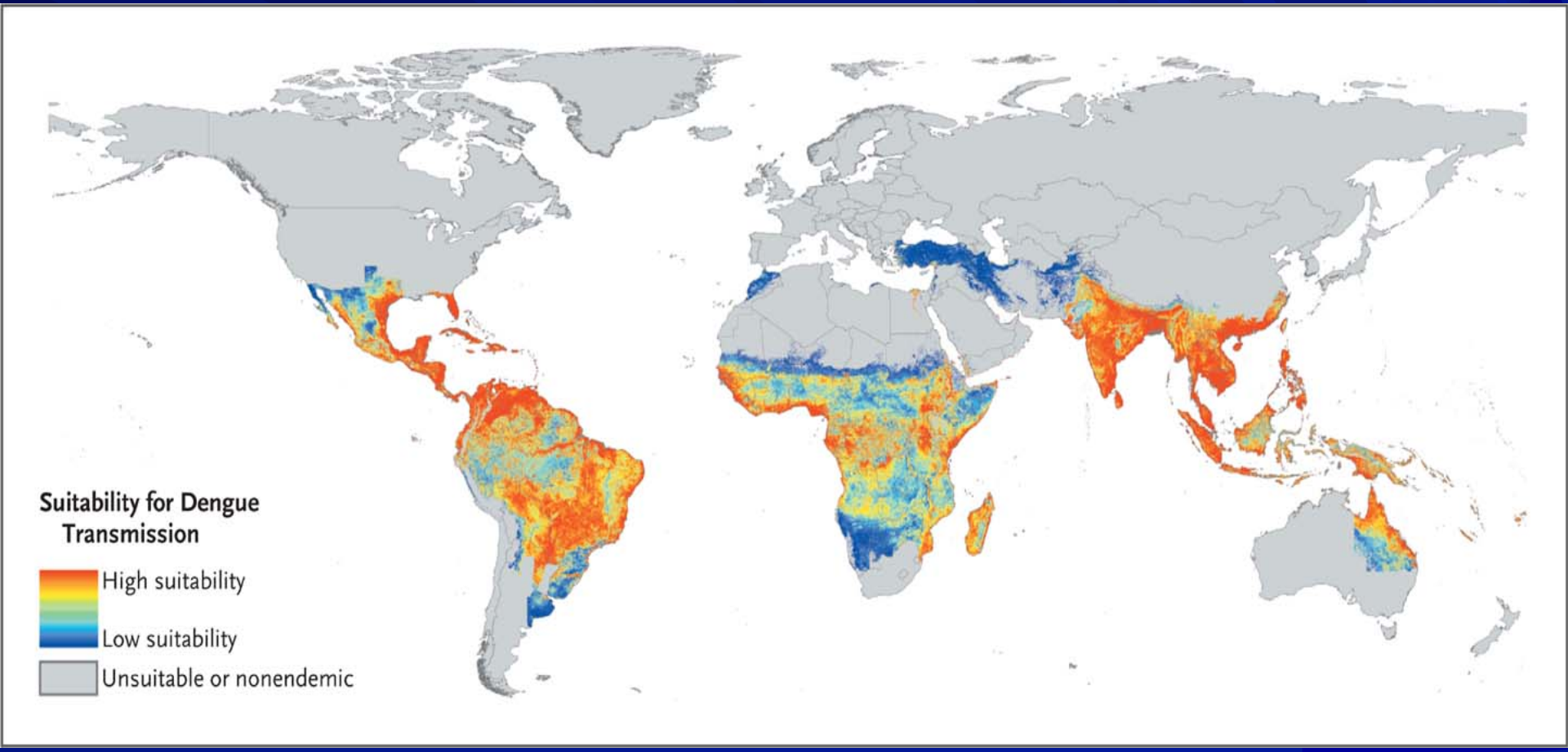
Talk Outline

- Describe epidemiology, clinical manifestations, and diagnosis of dengue, chikugunya and Zika
- Analyze factors responsible for recent outbreaks of chikungunya and Zika
- Options for prevention including vaccines

Global Dengue Risk



Simmons CP et al. N Engl J Med 2012;366:1423-1432

WHO Dengue Estimates

3.6 billion people at risk
worldwide for dengue infection

120 endemic countries

390 million infections per year
About 100 million DF/DHF cases annually

~500,000 DHF/DSS cases per year
require hospitalization
~5% die

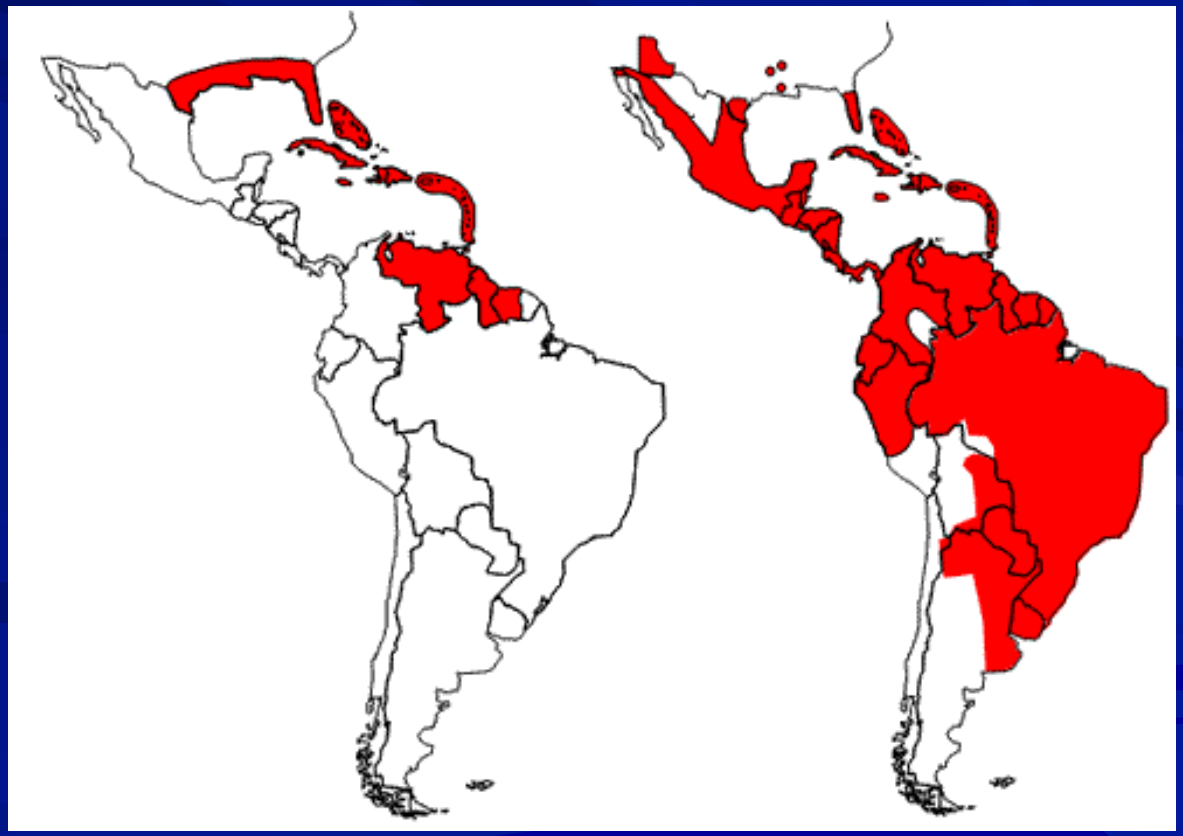
Factors Contributing to Dengue Emergence

Lack of effective mosquito vector control

Distribution of *Aedes aegypti*

1970

(end of global eradication program)



2002

DENGUE ± WARNING SIGNS

CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

Dengue Hemorrhagic Manifestations

Simmons CP et al. N Engl J Med 2012;366:1423-1432

Dengue Hemorrhagic Manifestations

SEVERE DENGUE

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

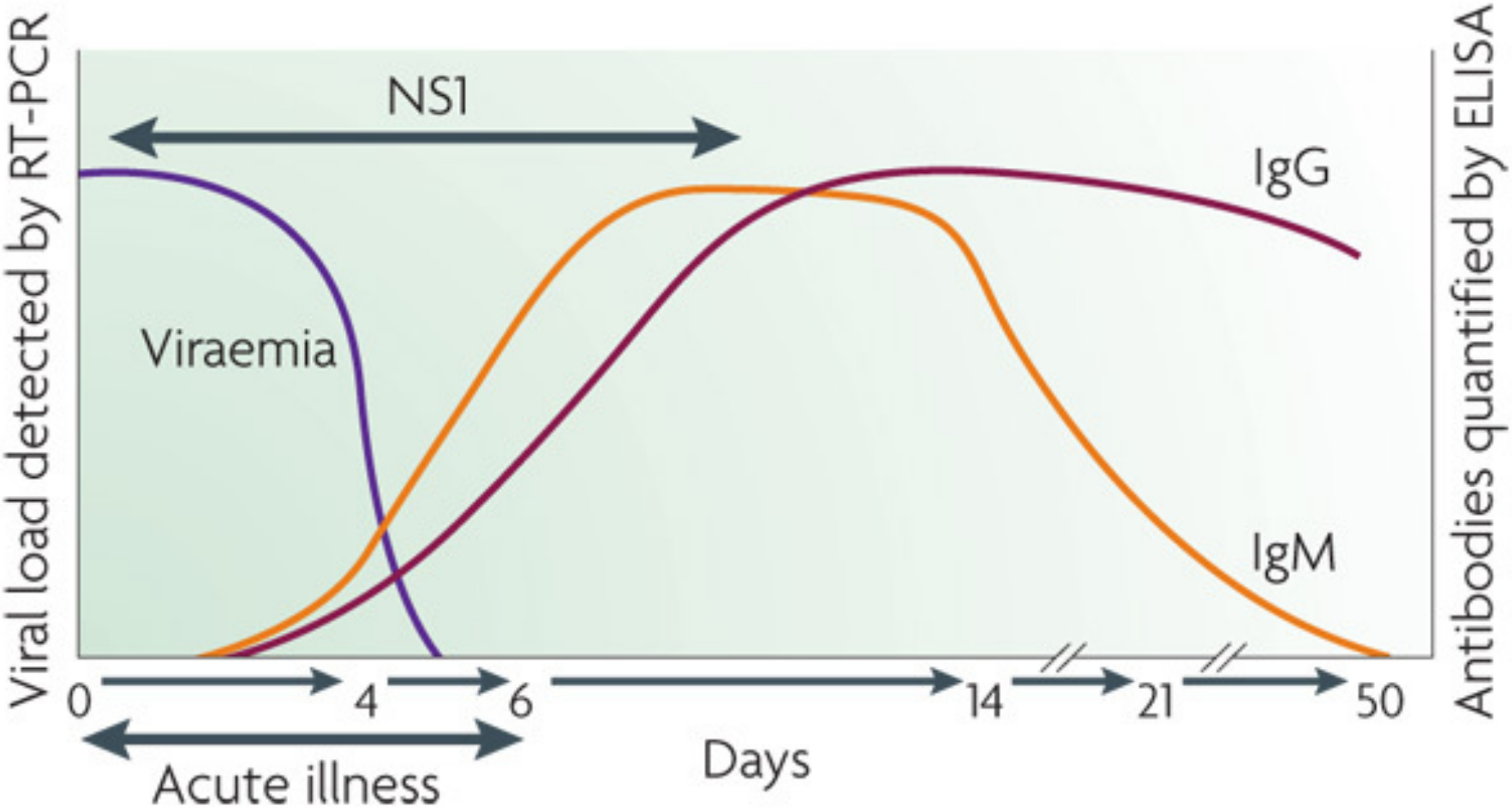
Severe bleeding

as evaluated by clinician

Severe organ involvement

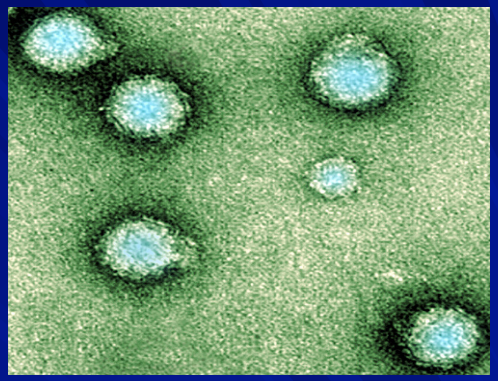
- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

Immune Response to Dengue Infection



Guzman, M. G. *et al.* Dengue: A continuing global threat. *Nature Reviews Microbiology* 8, S7–S16 (2010).

Chikungunya Virus



- Genus *Alphavirus*, family *Togaviridae*: ssRNA virus
- Identified in the 1950s in Africa (Southern Province, Tanganyika)
- Disease given a Kimakonde name: chikungunya
  - According to an educated local chief, term derived from a root verb—kungunyala—meaning to dry up or become contorted
    - Lumsden WHR. TRSTM 1955

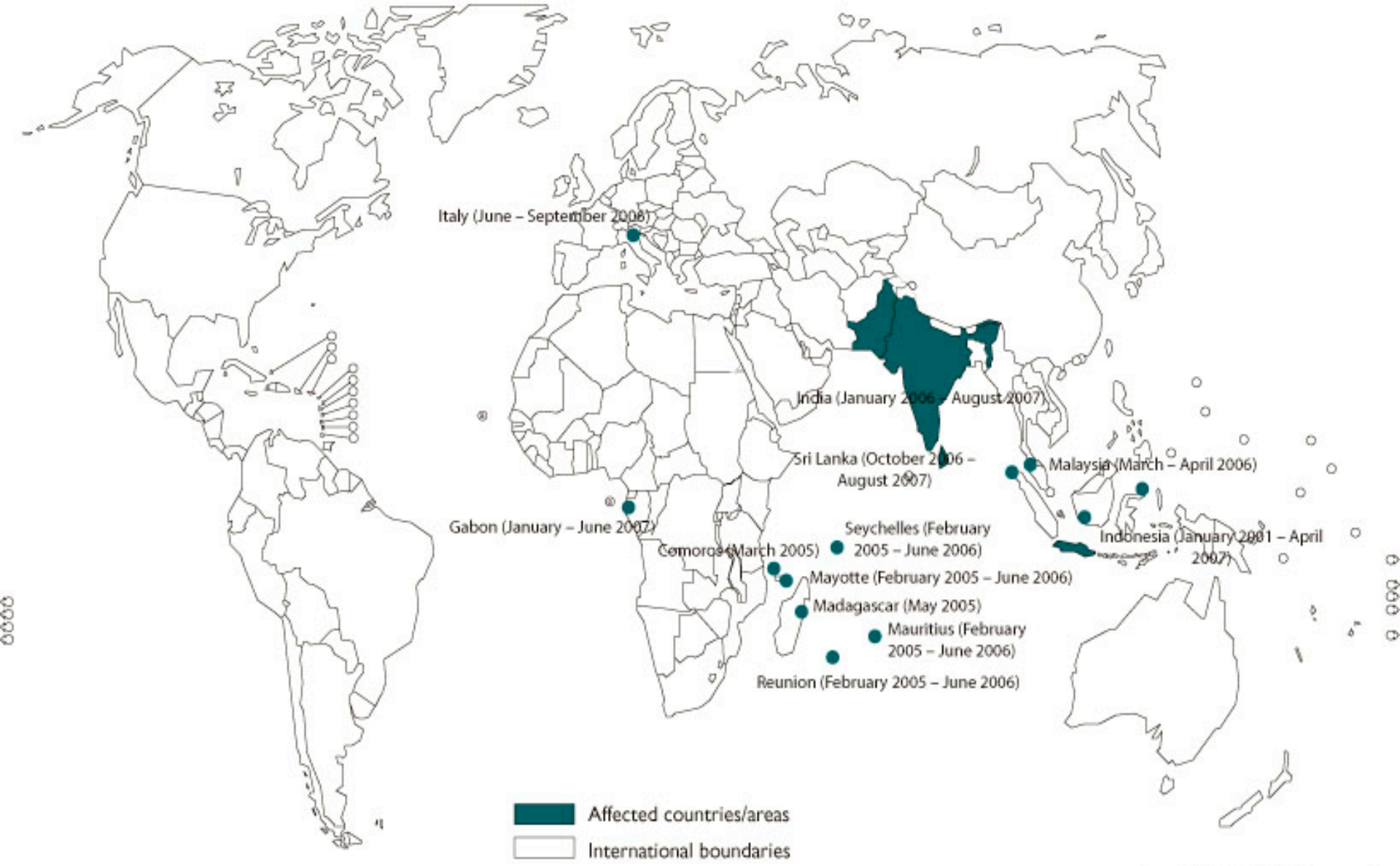
Chikungunya Virus Epidemiology

- Maintained in sylvatic cycle involving wild primates and forest-dwelling mosquitoes
- Increasing prevalence in Asian countries where it established an urban cycle 2005: >5,000 cases Comoros Islands then
  - Explosive outbreak in Reunion during Southern Hemisphere summer
  - Estimated 266,000 residents affected (pop. 770K)
  - 248 possible deaths due to CHIKV
  - *Ae. albopictus* implicated as local vector

Modes of Transmission and Reservoirs

- Primarily spread by bite of infected *Aedes* spp. mosquitoes
- Mother-to-child transmission documented in context of intrapartum maternal viremia
  - 49% of women with peripartum viremia had vertical transmission
  - Overall 2.5% of exposed neonates became infected
    - Gerardin P et al. PLoS Med 2008;5:e60
- Reservoirs = humans during epidemics and monkeys, rodents, and birds during non-epidemic periods

Chikungunya, 2001–2007



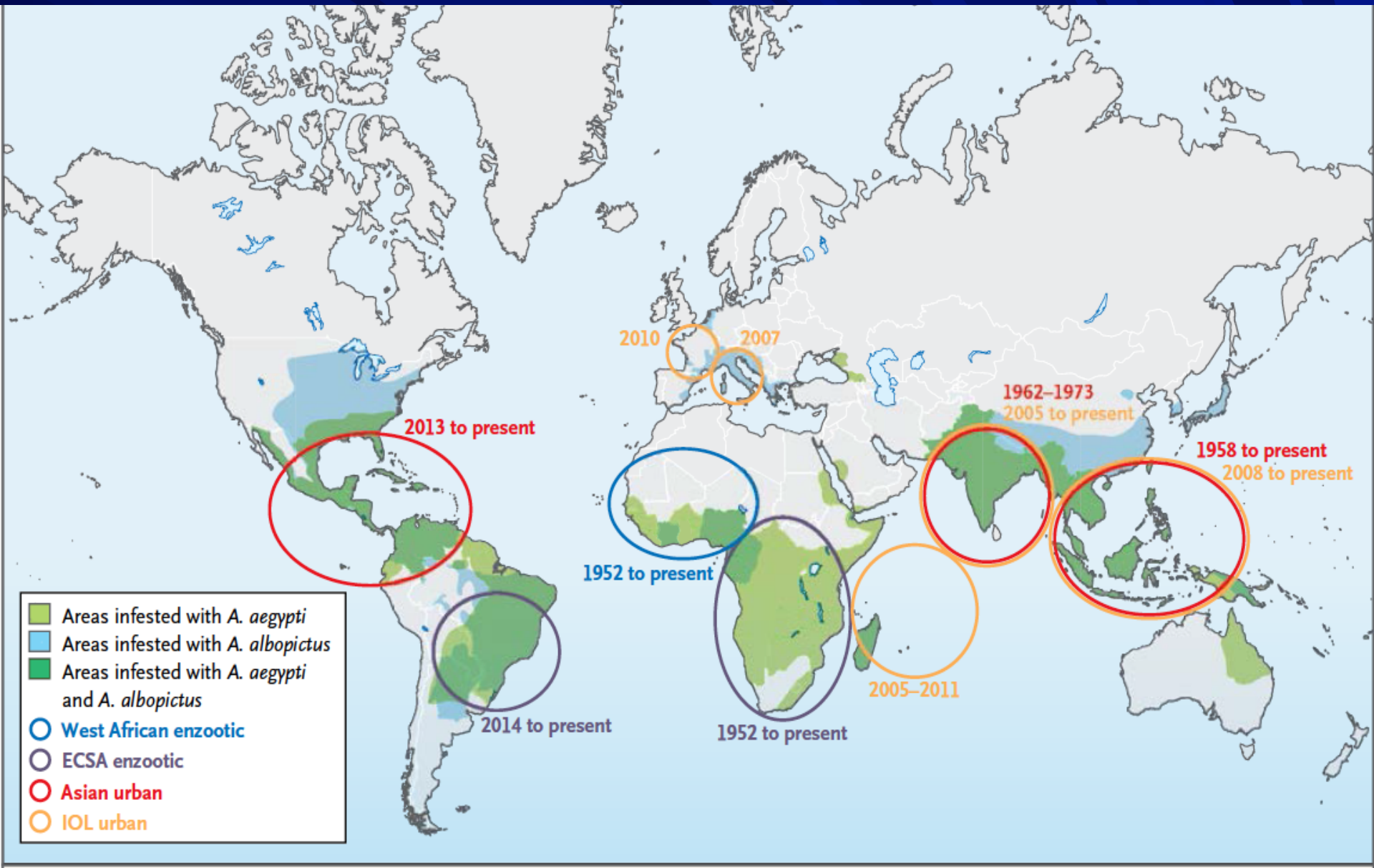


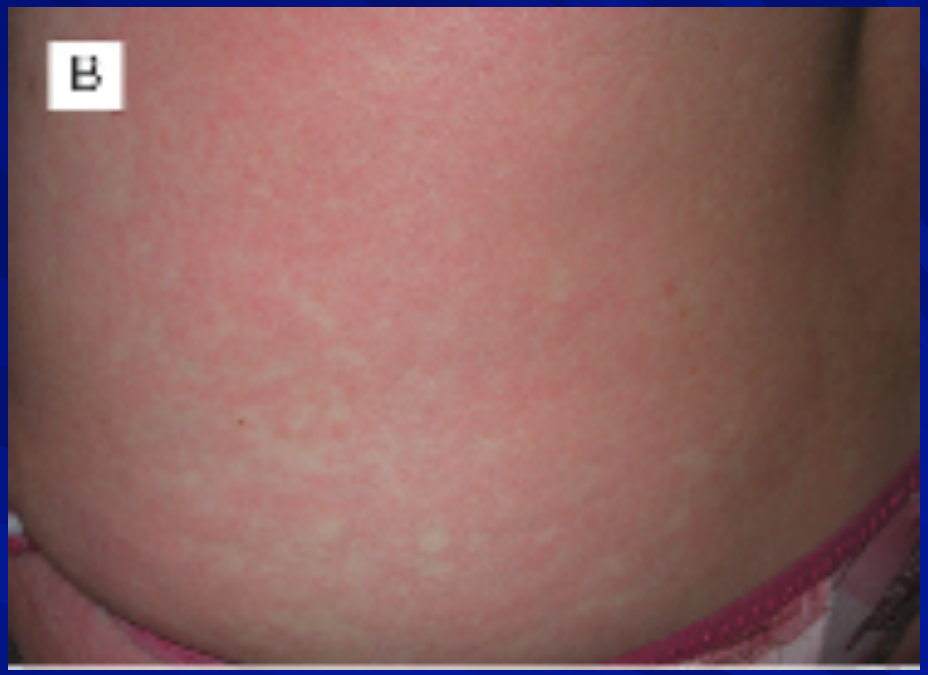
Figure 2. Origin, Spread, and Distribution of Chikungunya Virus and Its Vectors.

Weaver and Lecuit NEJM 2015

Clinical Manifestations

- Mean incubation period of 2-4 d (range 1-12 d)
- Abrupt onset of symptoms including high fever (up to 40ºC), HA, back pain, myalgias, and arthralgias
- Joint pains can be intense, affecting mainly extremities (ankles, wrists, phalanges) and large joints (knees, hips)
- Rash present in 40-50% of cases
  - Pialoux G. et al. Lancet Infect Dis 2007;7:319-327.

Skin Manifestations



Facial and abdominal rash with edema of the face and hand

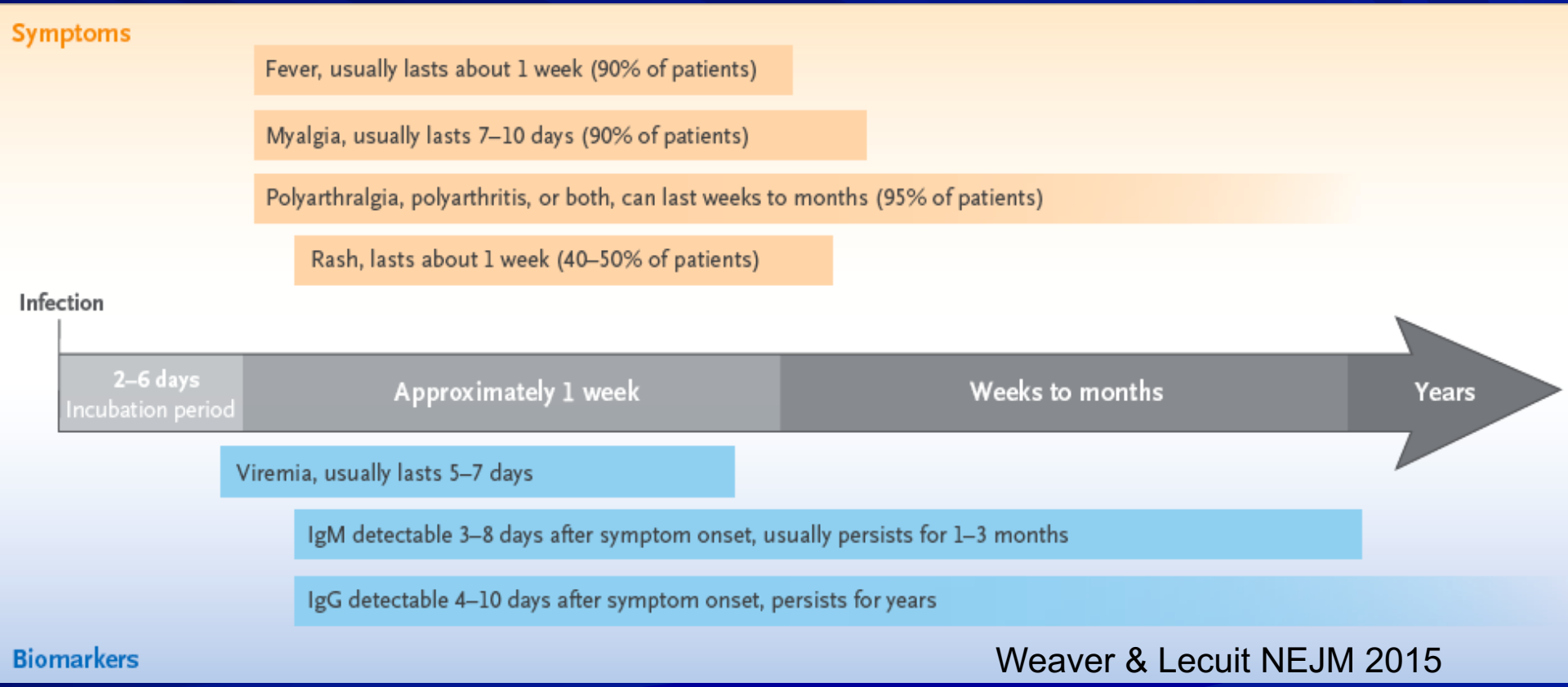
•Simon F et al. Medicine 2007;86:123-137.

Arthralgias and Arthritis

- Relapsing, incapacitating joint pains = hallmark of chikungunya
- Often have initial severe febrile polyarthritis followed by disabling peripheral rheumatism lasting for months
- Arthralgias or arthritis can persist for 4 mo in 33% of patients, 20 mo in 15% and 3-5 years in 10%
- May cause decreased ability to ambulate and carry out activities of daily life

Diagnosis of CHIKV Infection

- Two main diagnostic methods:
  - RT-PCR: useful during initial viremic phase
  - Serology (IgM, IgG)
- Virus isolation - inoculation of mosquito cell cultures, mosquitos, mammalian cell culture, or mice



Weaver & Lecuit NEJM 2015


NUEVO
VIRUS!
ZIKA


ZIKAVIRUS

Zika Virus

- Single stranded RNA virus of *Flavivirus* genus
- Closely related to dengue, West Nile, yellow fever, and Japanese encephalitis viruses
- Primarily vector is *Ae. aegypti* but several other *Aedes* spp. capable of transmission

Two Distinct Zika Lineages – Only One Serotype

- African and Asian
- 3 genotypes: West African, East African, and Asian
  - Baud D et al. Lancet 2017
- All strains same serotype
  - Identical surface antigens
  - Antibodies elicited after infection with Asian lineage potently inhibit both lineages *in vitro*
    - Dowd K et al. Cell Reports 2016

Asian Viral Lineage

Enfissi A et al EID 2006

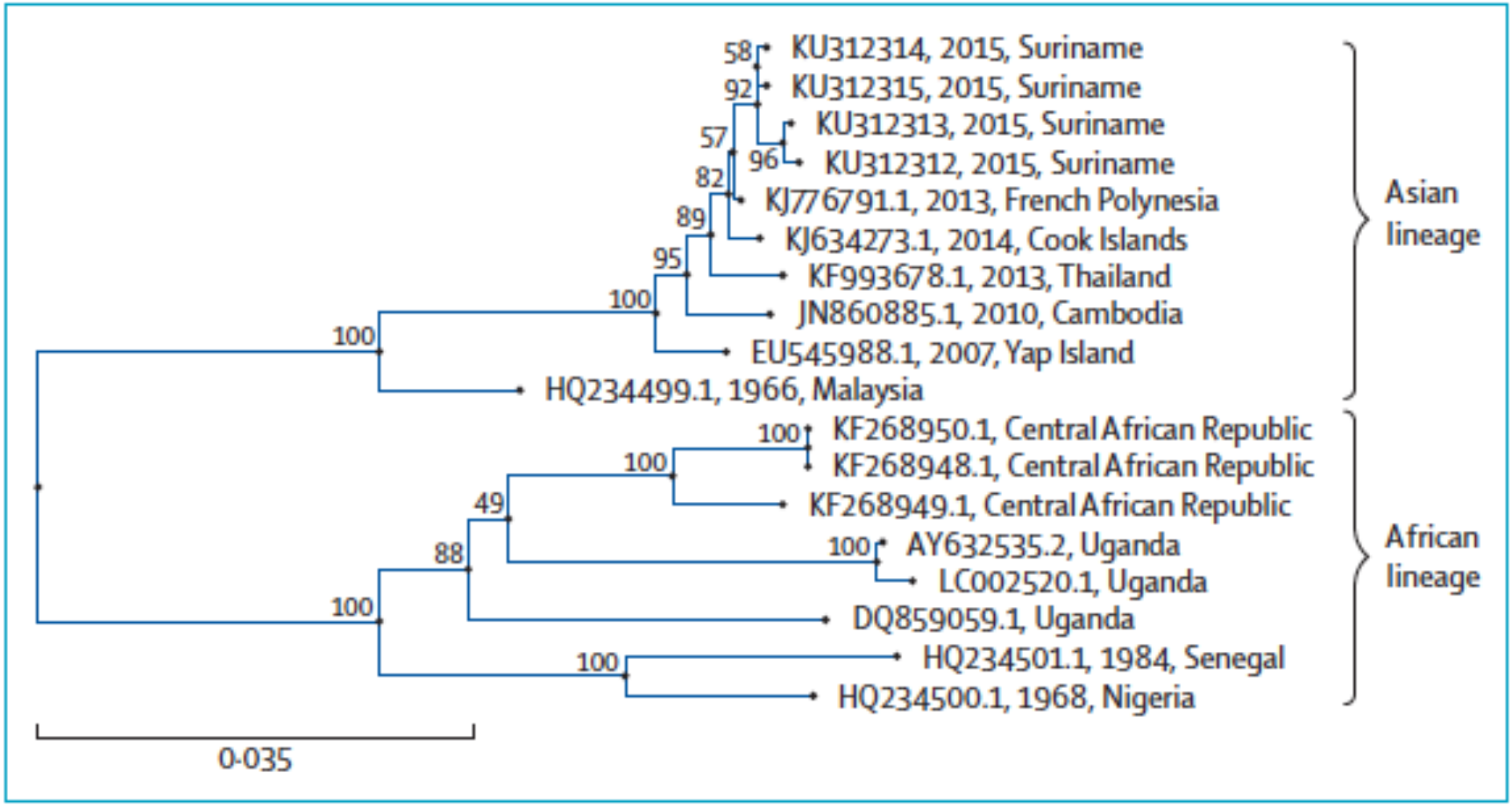
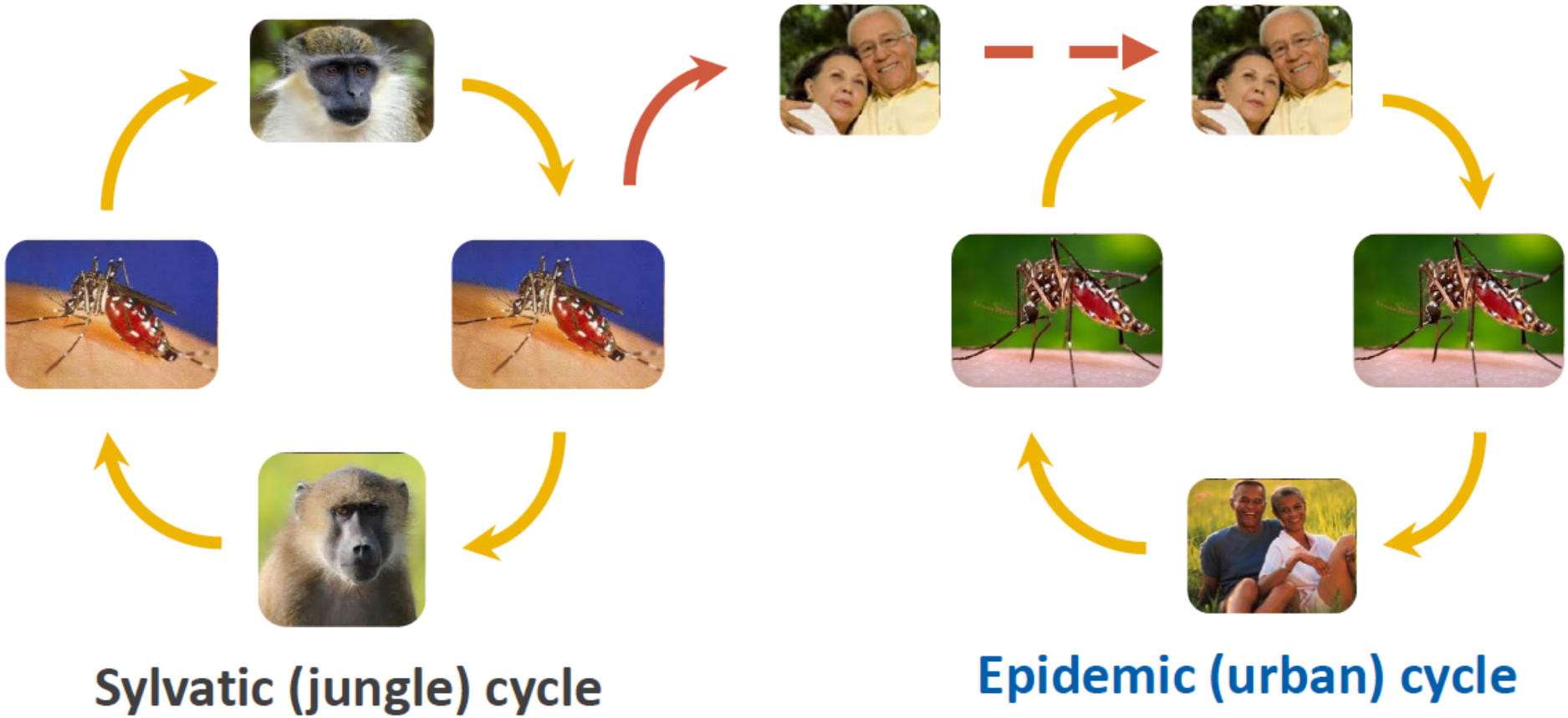


Figure: Phylogenetic relations between the envelope gene sequences of Suriname ZIKV and other ZIKV

Zika Virus Transmission Cycles



Rabe I & Meaney-Delman D. CDC Zika presentation January 2016

Non-Vector Transmission

Proven:

- Sexual
  - Male to female; male to male; female to male
- Transfusion
  - Documented in Brazil, Martinique, French Polynesia

Theoretically possible:

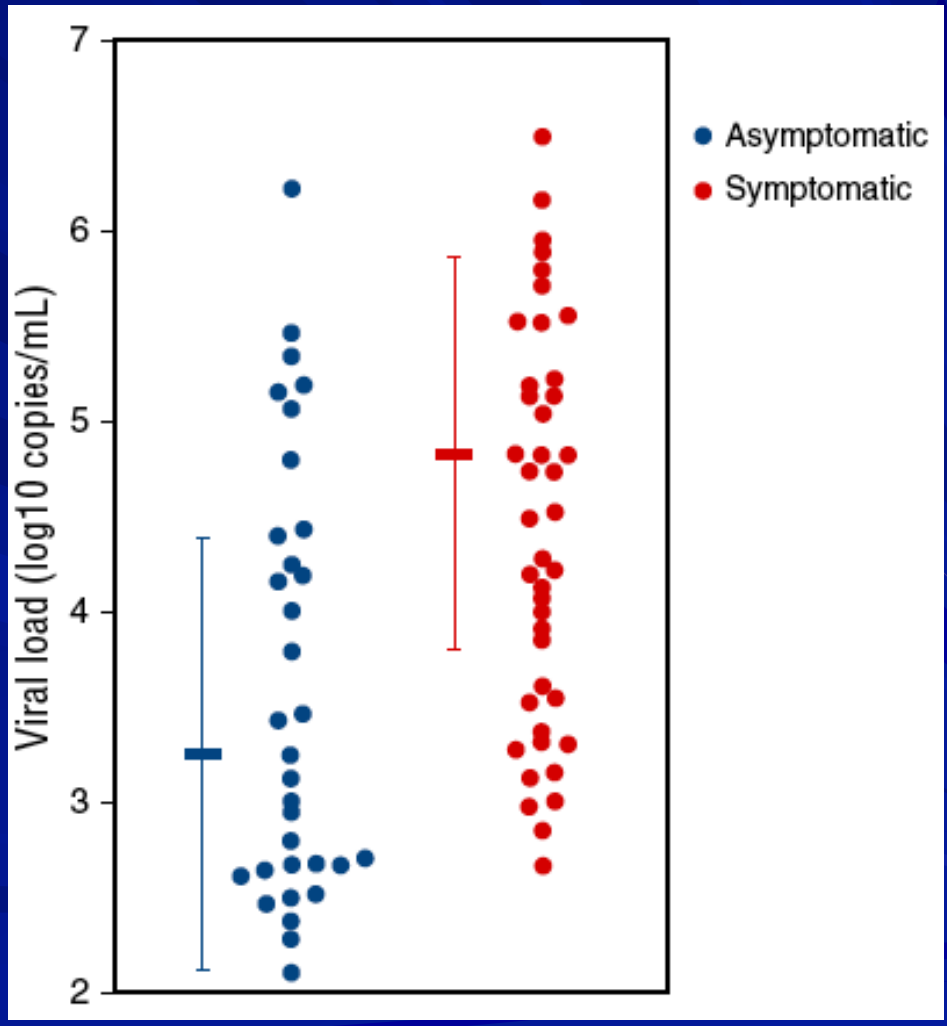
- Breast milk
  - 2+ reports of moderate to high VL in breast milk (cultured in one case but no MTCT)
- Saliva (?)
- Tears (?)

Sexual Transmission

- Preliminary semen carriage studies:
  - Up to 188 days by PCR
  - Replication competent Zika in semen for 69 days
- High viral load in semen (and urine)
- Rarely hematospermia or microhematospermia
- Viral shedding in vaginal secretions to 14 days and in cervical mucus to day 11 post-symptom onset
- Time from sexual contact to symptom onset 8-21 days
  - Hamer DH et al. Curr Infect Dis Rep 2017
  - Russell K et al. Clin Infect Dis 2016

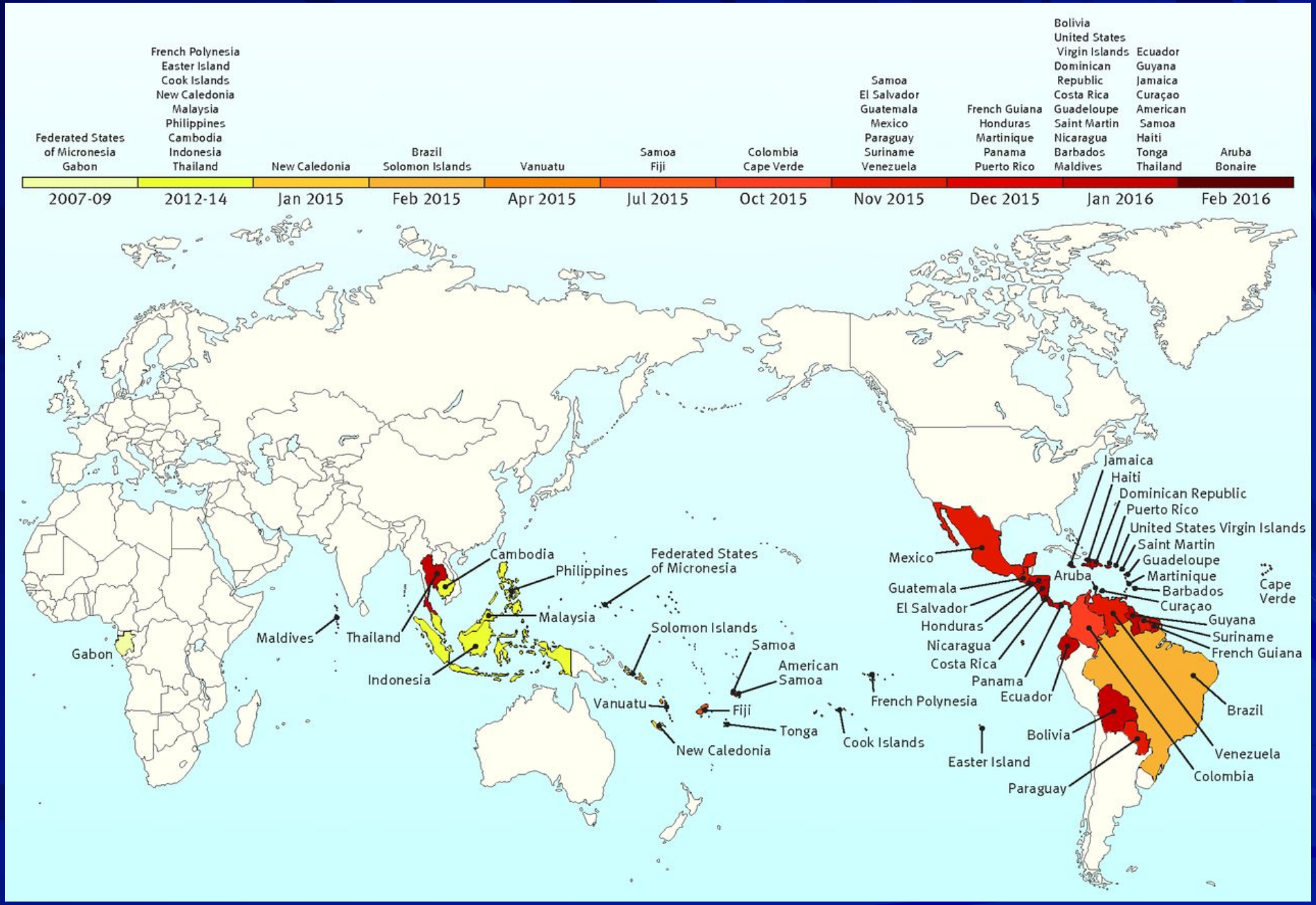
Transmission – Transfusion

- Martinique January to June 2016
  - Screened 4129 blood donations
  - 1.84% positive by nucleic acid testing
- Contacted donors to determine whether they were or became symptomatic
  - Mean $\log_{10}$ RNA higher if symptomatic (P = .0013)
    - Gallian P et al. Blood 2017

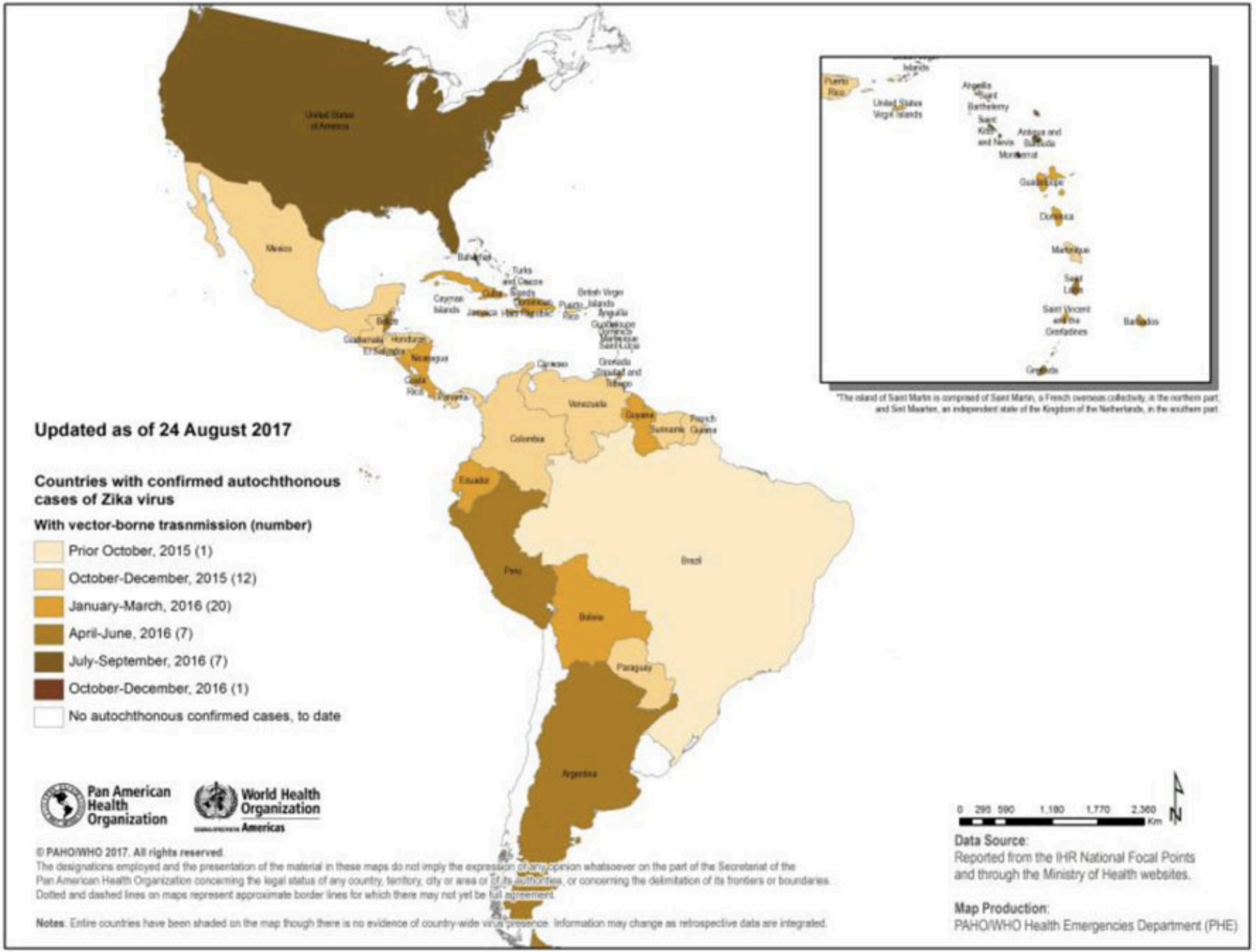


Epidemiology

- First human case diagnosed 1962 in Uganda
- Serosurveys – neutralizing antibodies in East and West Africa, India, and SE Asia
  - Late 1940s to late 1990s
- Outbreaks in Yap, Micronesia in 2007; French Polynesia 2013, Easter Island 2014
- Brazil early 2015 then spread in the Americas
  - Chen & Hamer. Ann Int Med 2016
  - Musso & Gubler. Clin Microbiol Rev July 2016



Basarab M et al. Zika virus. BMJ 2016


Updated as of 24 August 2017
Countries with confirmed autochthonous cases of Zika virus
With vector-borne trasnmission (number)
Prior October, 2015 (1)
October-December, 2015 (12)
January-March, 2016 (20)
April-June, 2016 (7)
July-September, 2016 (7)
October-December, 2016 (1)
No autochthonous confirmed cases, to date
*The island of Saint Martin is comprised of Saint Martin, a French overseas collectivity, in the northern part, and Sint Maarten, an independent state of the Kingdom of the Netherlands, in the southern part
Pan American Health Organization
World Health Organization
Americas
0 295 590 1,180 1,770 2,360 Km
N
Data Source:
Reported from the IHR National Focal Points and through the Ministry of Health websites.
Map Production:
PAHO/WHO Health Emergencies Department (PHE)
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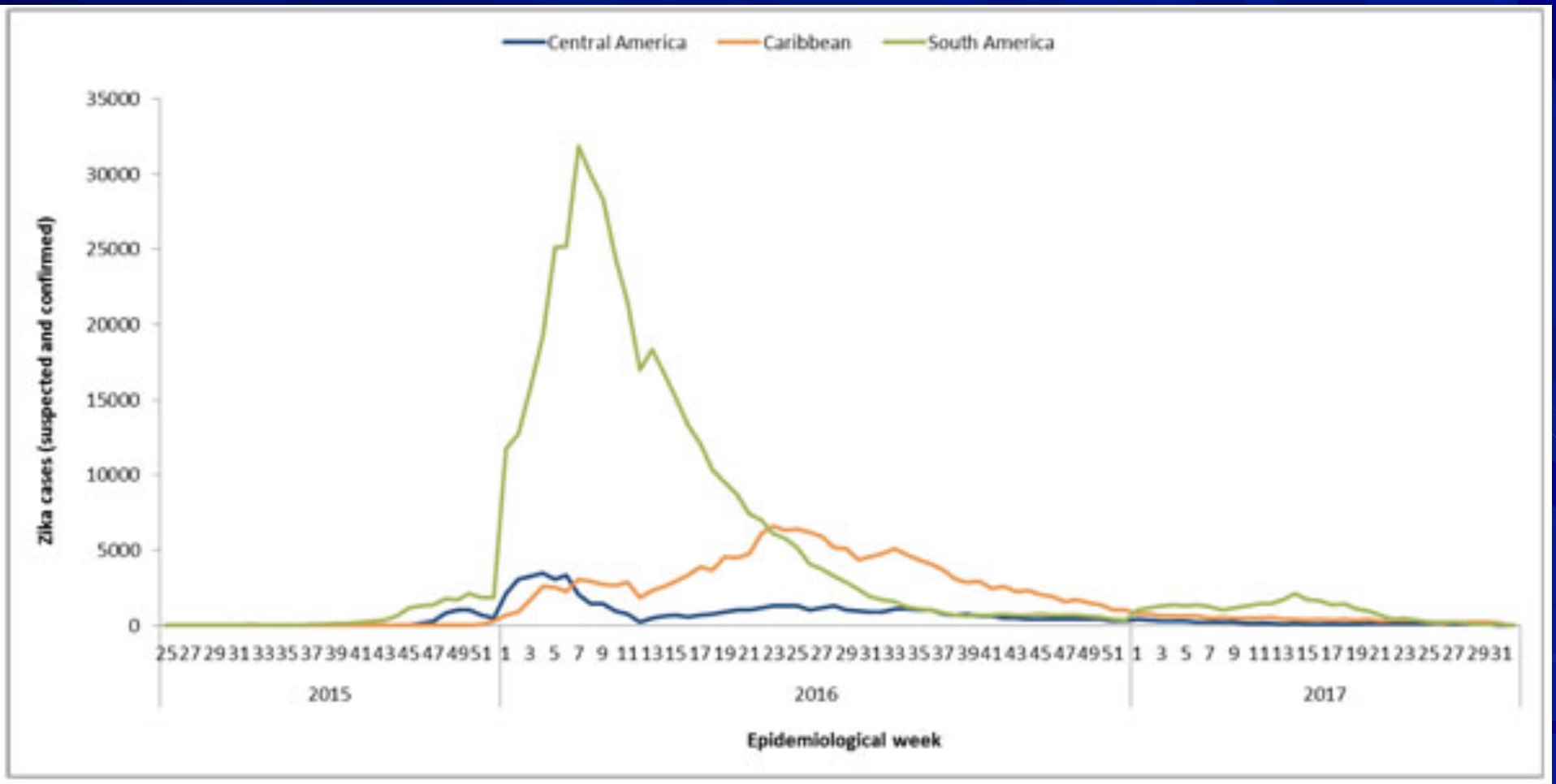
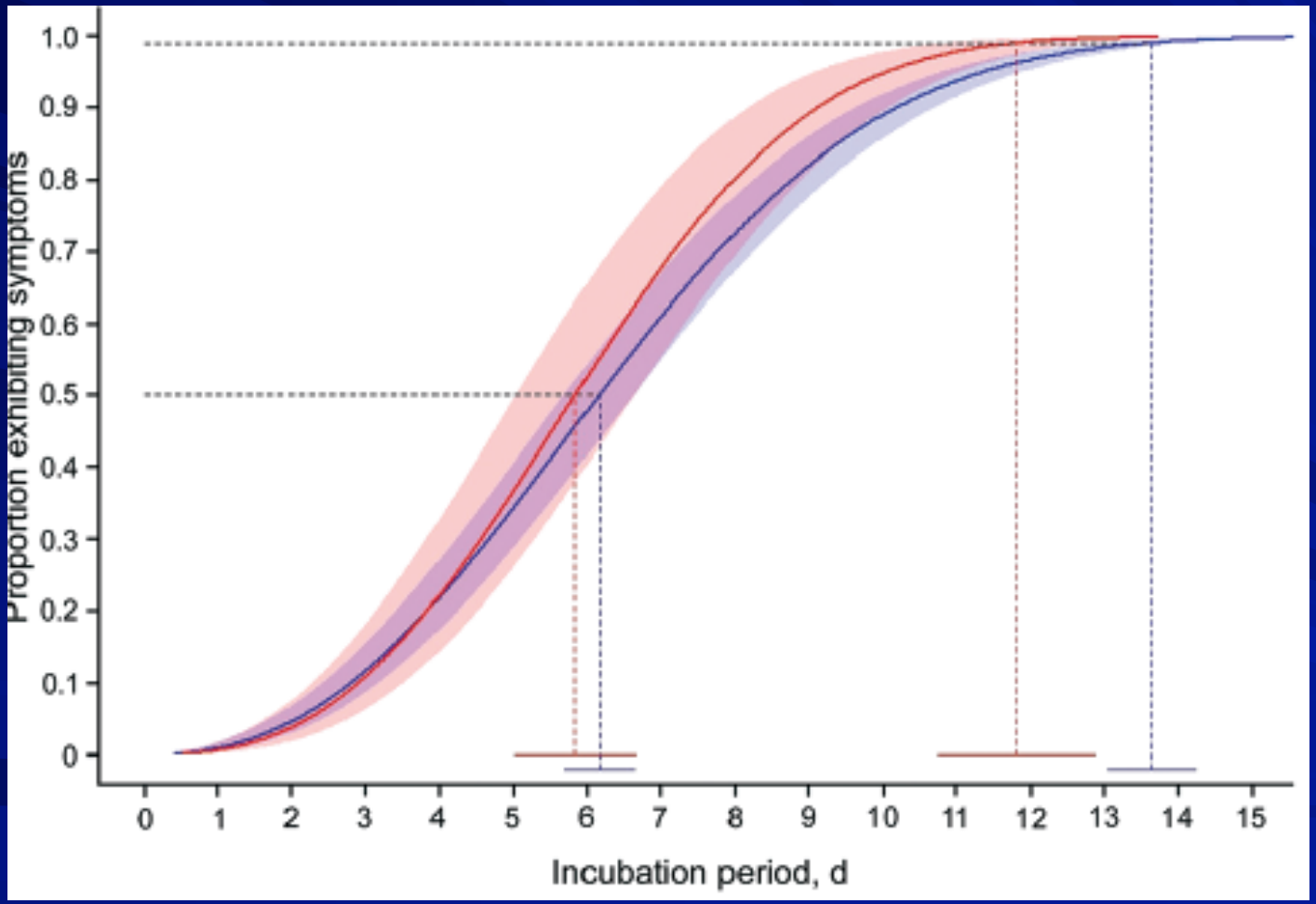
The designations employed and the presentation of the material in these maps do not imply the expression of any opinion whatsoever on the part of the Secretariat of the Pan American Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
Notes: Entire countries have been shaded on the map though there is no evidence of country-wide virus presence. Information may change as retrospective data are integrated.

PAHO/WHO Data for the Americas 2015-2017



Estimated Incubation Period

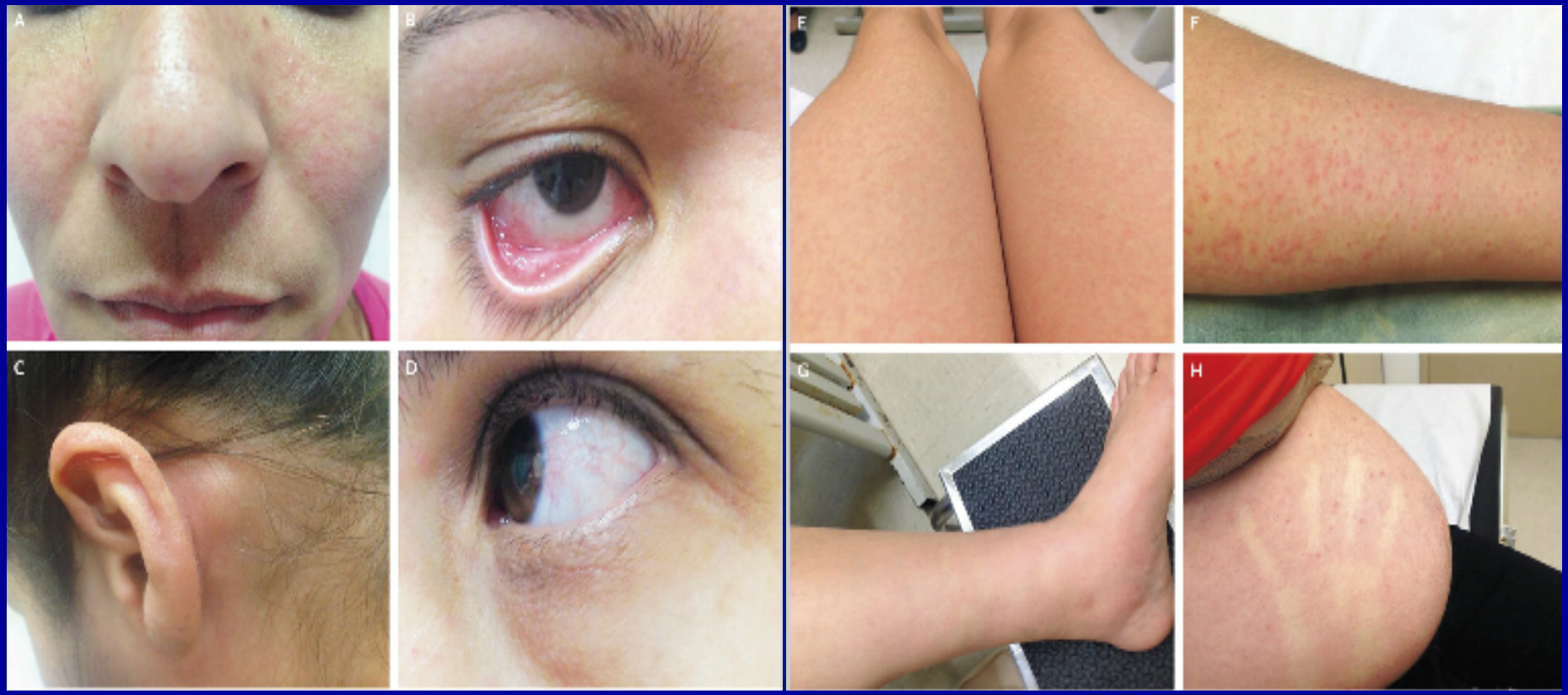


- Median = 6.2 days
- Estimated range 3-14 days
- Krow-Lucal ER et al. EID 2017

Clinical Manifestations

- Estimated 80% asymptomatic
  - More recent data suggest 40-60% asymptomatic
- Typical presentation:
  - Fever (65%)
  - Maculopapular rash (duration 2-14 d; median 6 d)
  - Arthralgias (duration 1-14 d; median 3.5 d)
  - Conjunctivitis
  - Less commonly, myalgias, headache, retro-orbital pain, joint swelling, vertigo, vomiting, paraesthesias, dysguesia, subcutaneous hematomas

ZIKV Clinical Features



Brasil P et al. NEJM 2016

Chen

Mass

Rica:

osta

Substantial Clinical Overlap

Feature	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Arthralgia/ arthritis	++	+	+++
Conjunctivitis	++	-	-
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	Rare	++	-
Shock	-	+	-

Assay Results 346 Patients Nicaragua

Waggoner JJ et al. CID 2016

ZCD Assay Result	Number, n (% of all Samples)
Positive	263 (76.0)
Monoinfections	*192 (55.5)*
ZIKV	47 (13.6)
CHIKV	91 (26.3)
DENV[a]	54 (15.6)
Coinfections	*71 (20.5)*
ZIKV-CHIKV	16 (4.6)
ZIKV-DENV[a]	6 (1.7)
CHIKV-DENV[a]	43 (12.4)
ZIKV-CHIKV-DENV[a]	6 (1.7)
Negative	83 (24.0)

Abbreviations: CHIKV, chikungunya virus; DENV, dengue virus; ZCD, multiplex real-time reverse-transcription polymerase chain reaction for the detection and differentiation of ZIKV, CHIKV, and DENV; ZIKV, Zika virus.

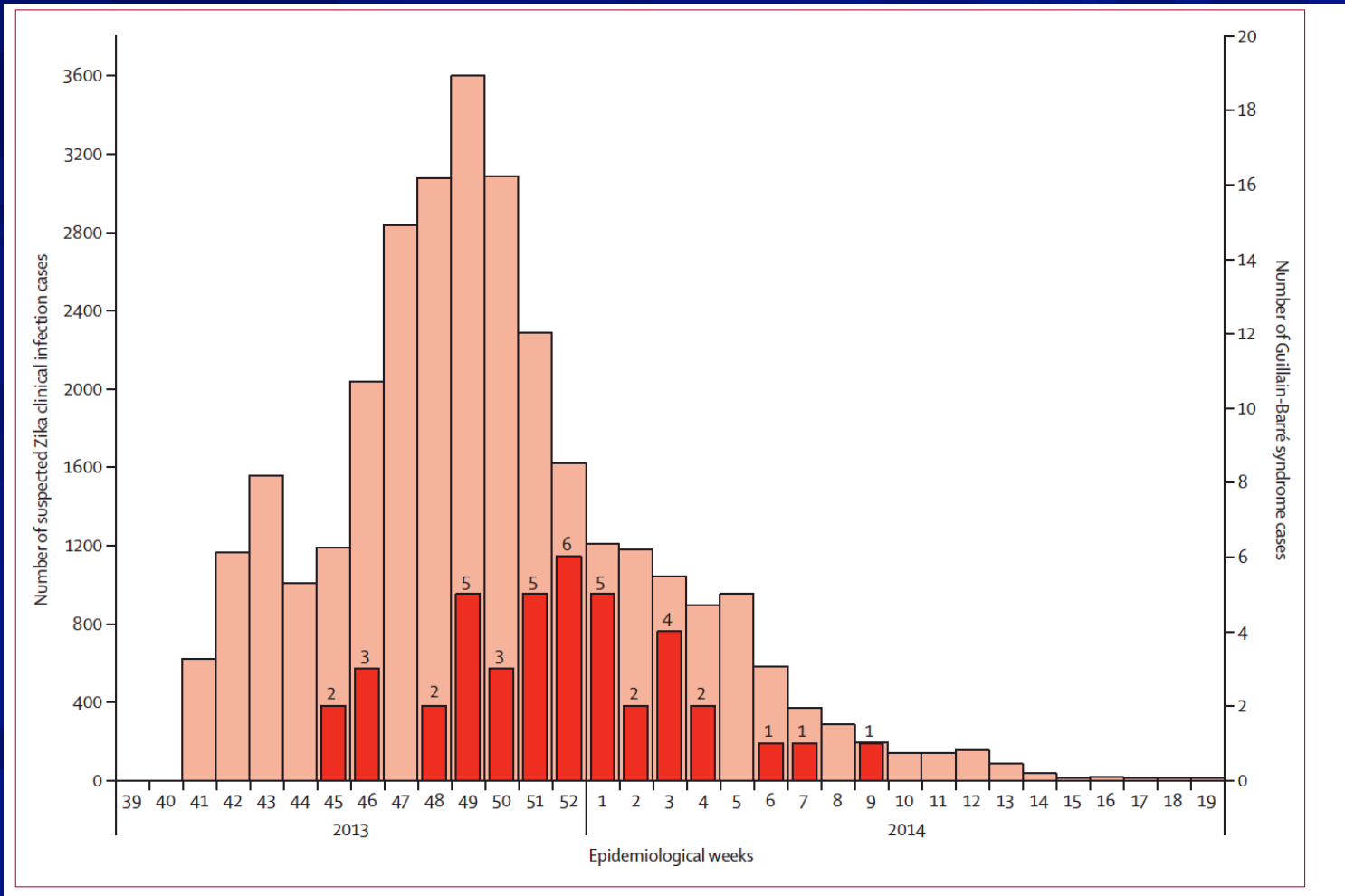
[a] Serotypes of 109 DENV-positive samples: DENV-2, 107; DENV-1, 1; DENV-4, 1.

Complications of Zika

Zika Neurological Complications

- Congenital Zika syndrome
- Guillain-Barré syndrome (GBS)
- Meningoencephalitis
- Acute myelitis
- Hearing loss
- Posterior uveitis

Weekly cases of suspected ZIKV infections and Guillain-Barre syndrome in French Polynesia between October 2013 and April 2014

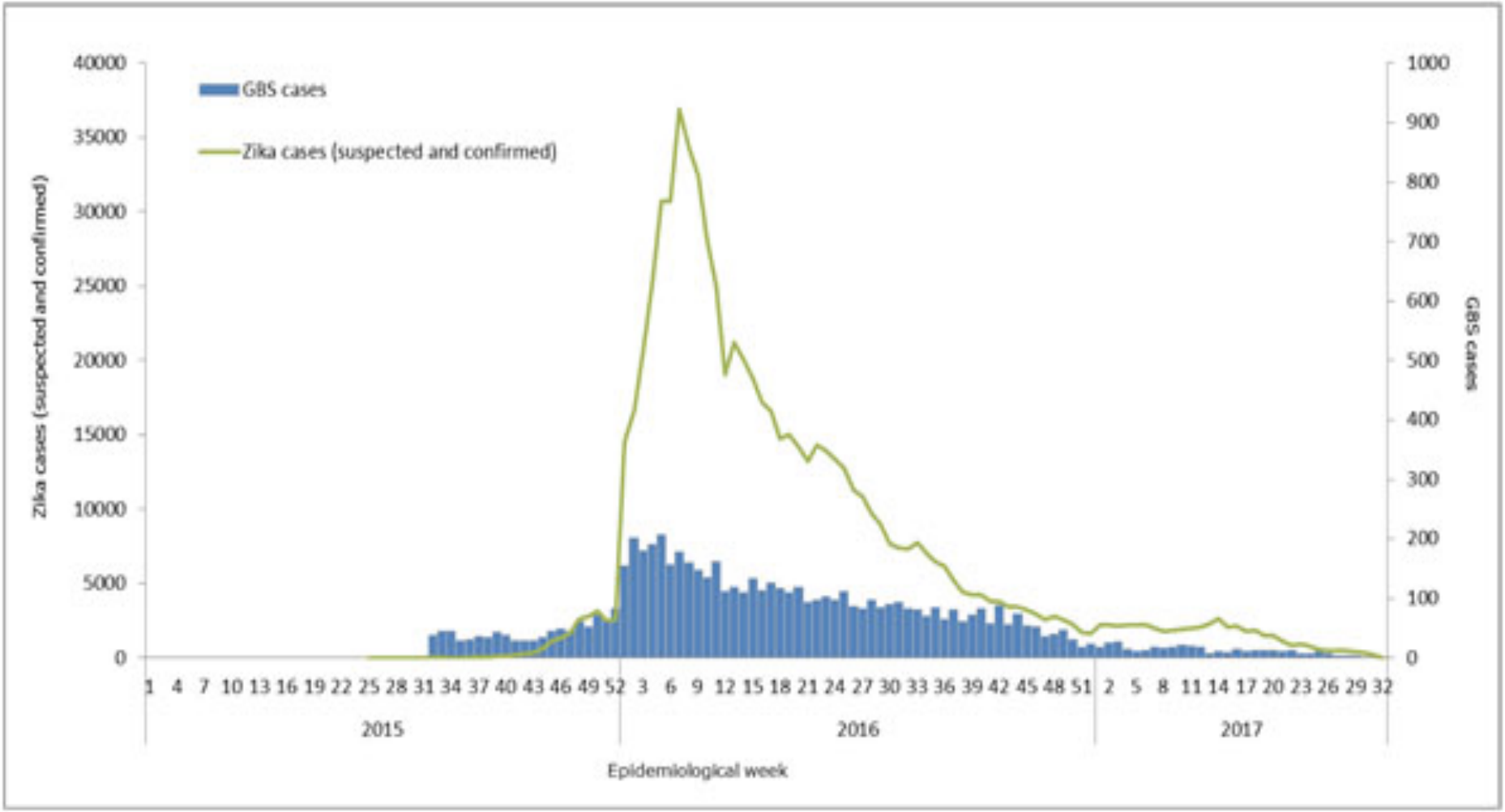


Cao-Lormeau, Lancet 2016

ZIKV-Associated Guillain-Barre Syndrome

- 42 patients – median age 42 y; 74% men; 100% with neutralizing antibodies to Zika
- Estimated 0.24 cases per 1000 ZIKV infections
- Rapid progression to nadir (median 6 d from onset neurological symptoms)
- Clinical presentation: generalized muscle weakness (74%), inability to walk (44%), and facial palsy (64%)
  - Cao-Lormeau VM et al Lancet 2016

Distribution suspected and confirmed Zika and GBS cases by EW Americas 2015-2017

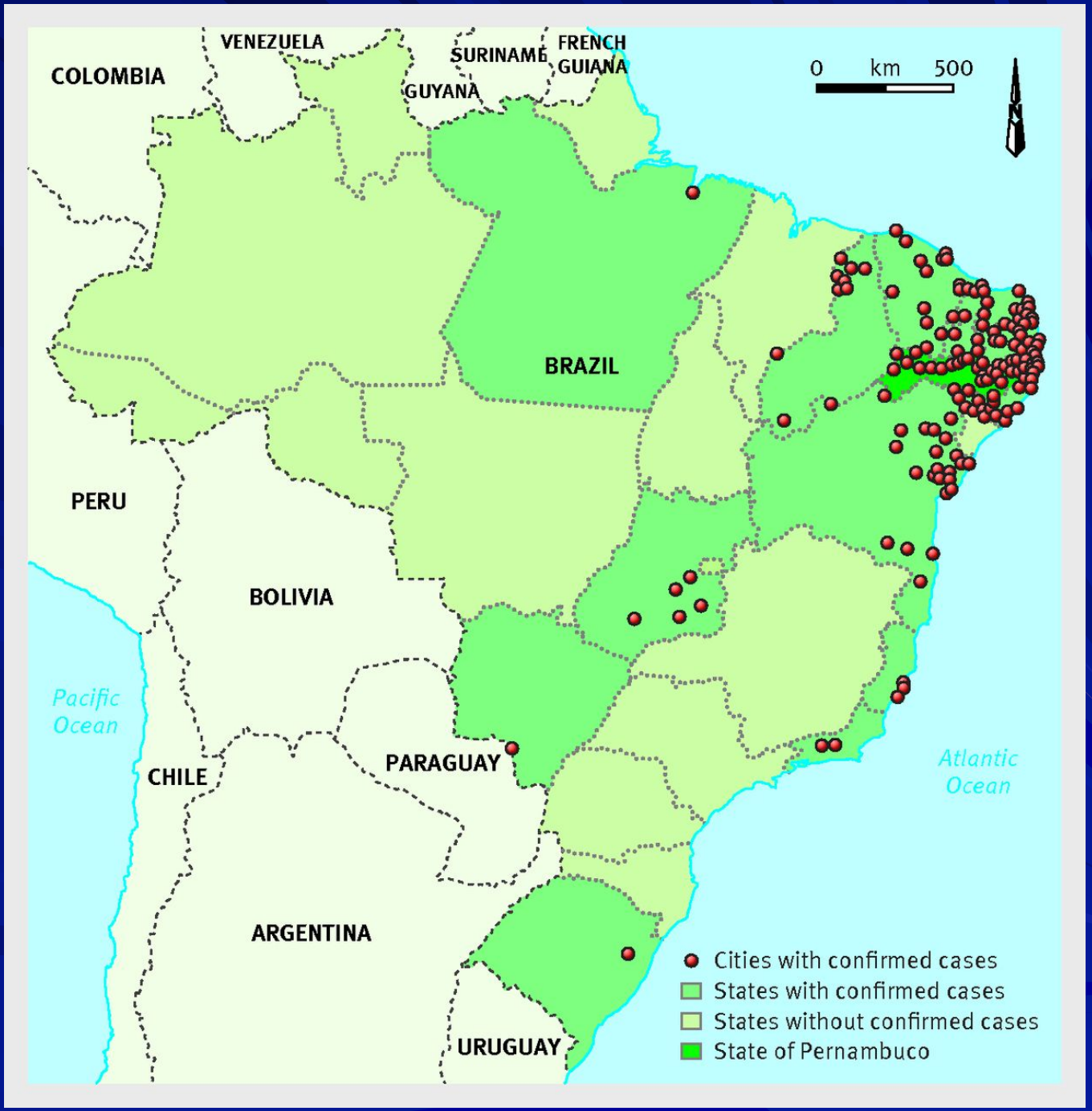


Congenital Zika Syndrome

Courtesy of NBC News

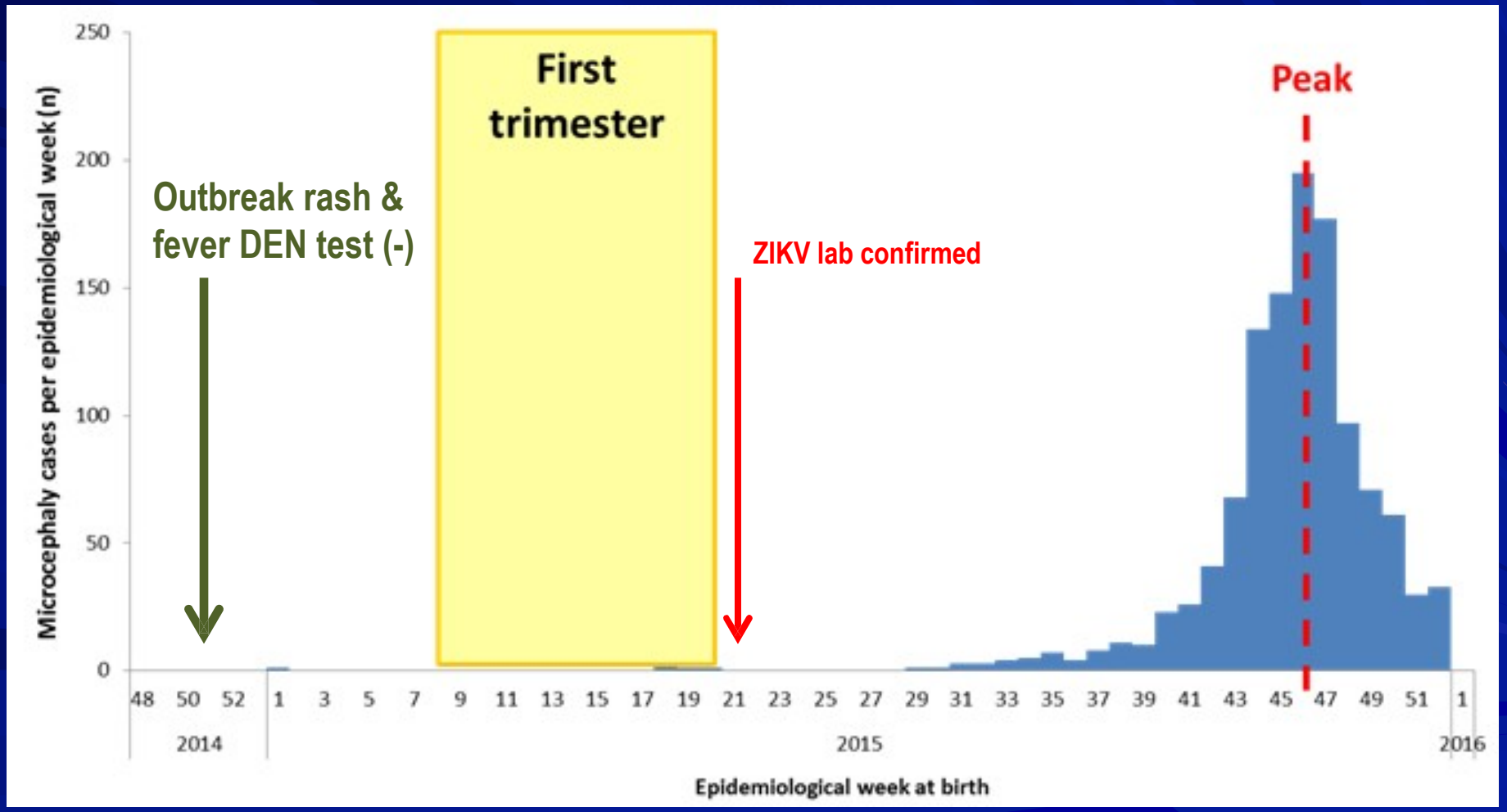
Notified cases of micro-cephaly up to 3 Feb 2016

Vasco Aragao MF et al. BMJ 2016

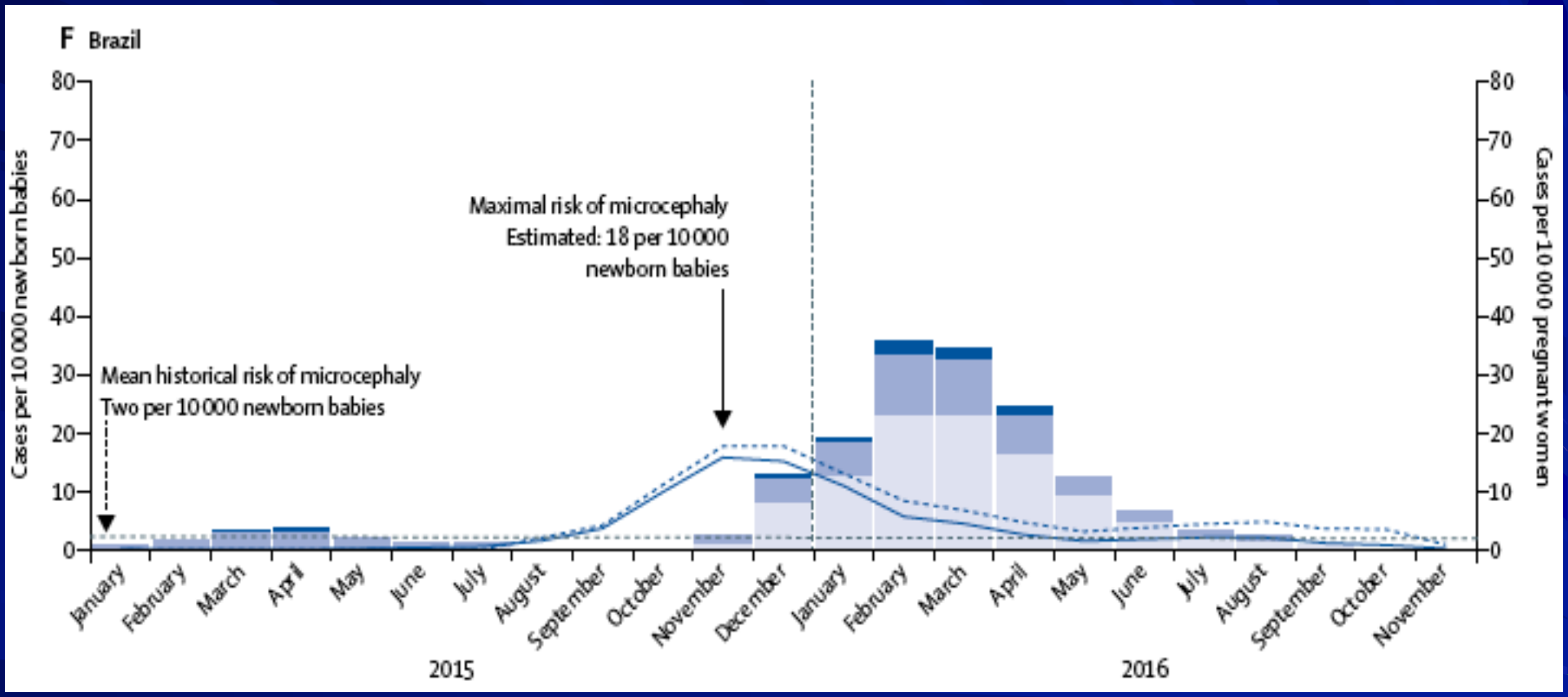


Epidemic curve of microcephaly cases among at-term newborns and preceding ZIKV circulation

Pernambuco State, Brazil, 2015



Zika Virus and Microcephaly in Brazil



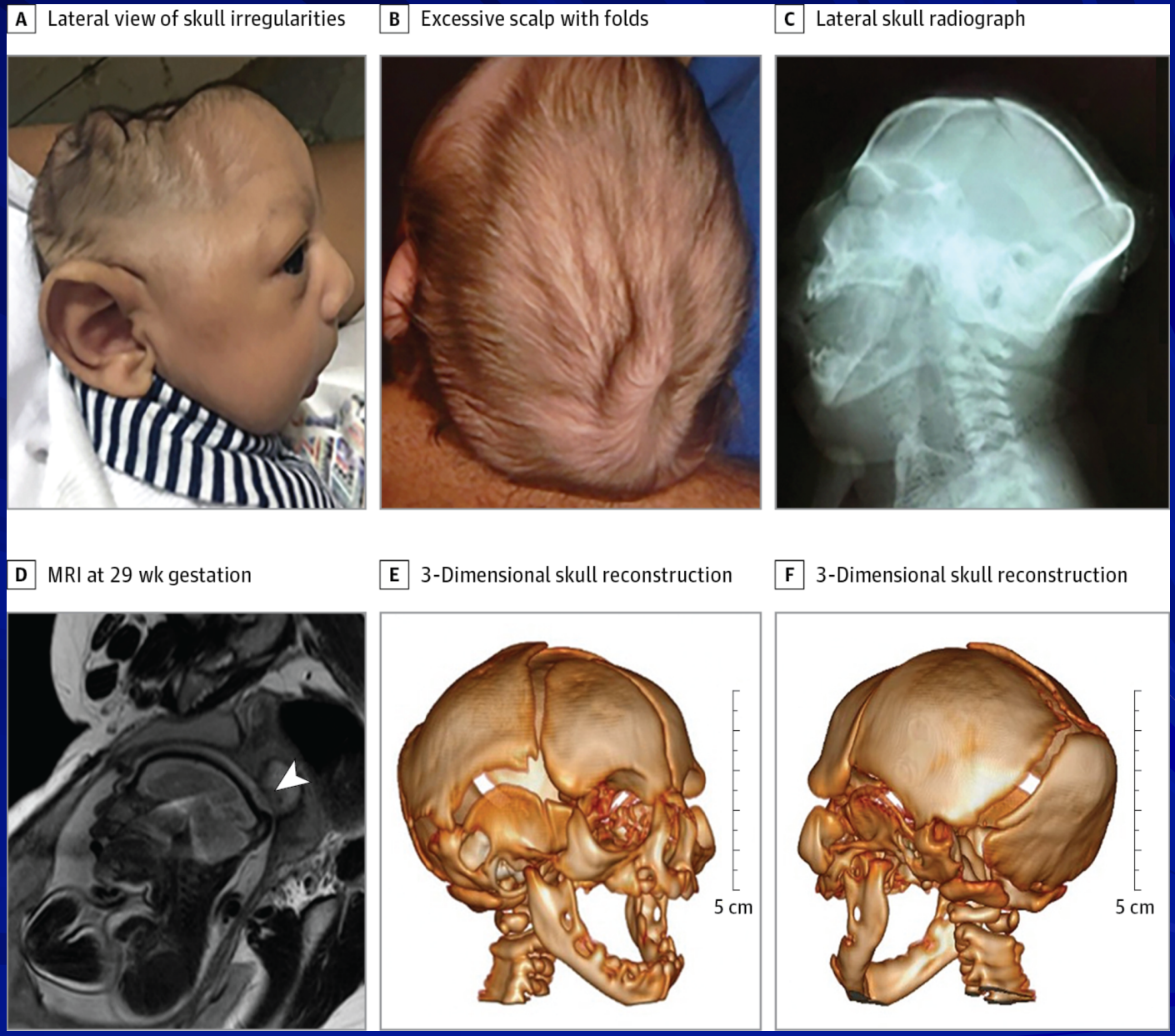
De Oliveira WK et al. Lancet 2017

Fetal Brain Disruption Sequence

- Extreme microcephaly
- Overlapping sutures
- Prominent occipital bone
- Scalp rugae*
- Marked neurological impairment

Corona-Rivera, et al. Report and review of the fetal brain disruption sequence. Eur J Pediatr. Nov 2001.

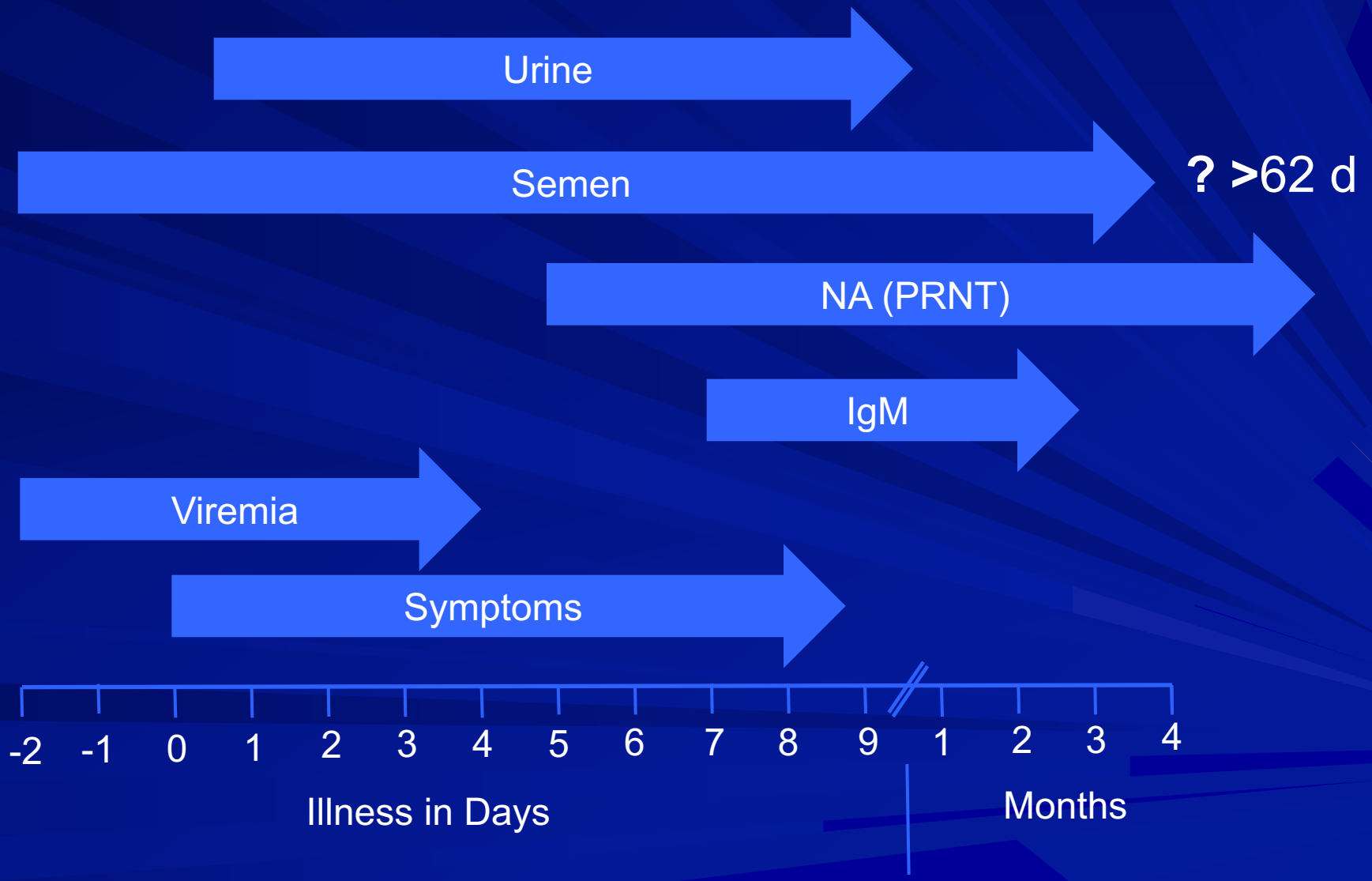
Moore CA et al. JAMA Pediatr. Published online November 03, 2016.



Congenital Zika Syndrome

- Early miscarriage
- Brain injury related problems
  - Eye abnormalities
  - Hearing impairment
  - Seizures
  - Swallowing impairment
  - Hydrocephalus
  - Limb abnormalities
  - Severe irritability
  - Developmental delay

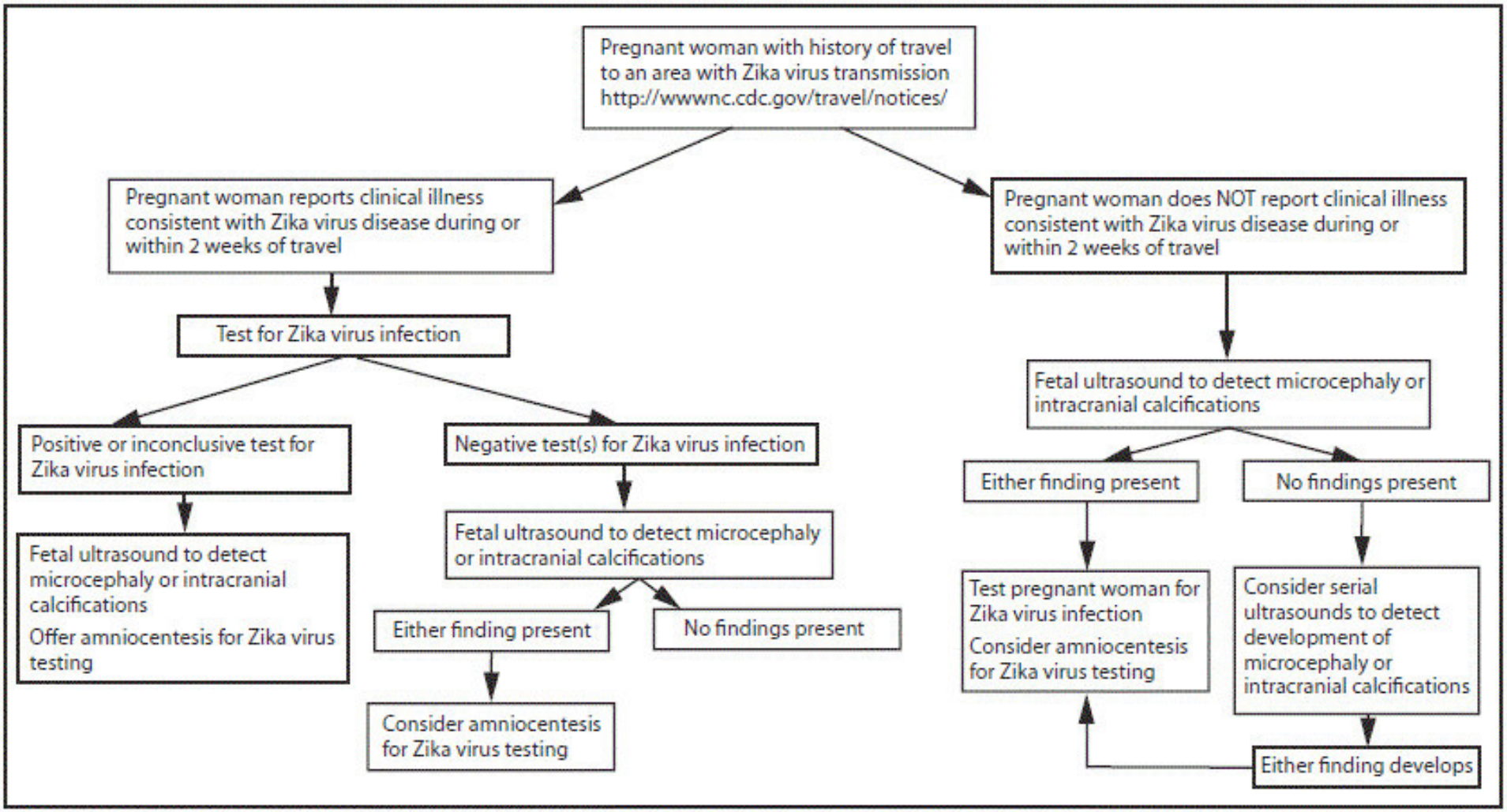
ZIKV Diagnostics



Zika Diagnosis

- Reverse transcriptase PCR of plasma (urine, saliva, CSF) in first 7 d post-symptom onset
  - Blood PCR may remain positive longer than urine or plasma
- IgM serology cross reacts with dengue—need negative dengue or 4X higher Zika titer plus ideally PRNT confirmation
- 4 fold rise titer by PRNT acute vs. convalescent sera
- Direct viral detection in amniotic fluid or tissue

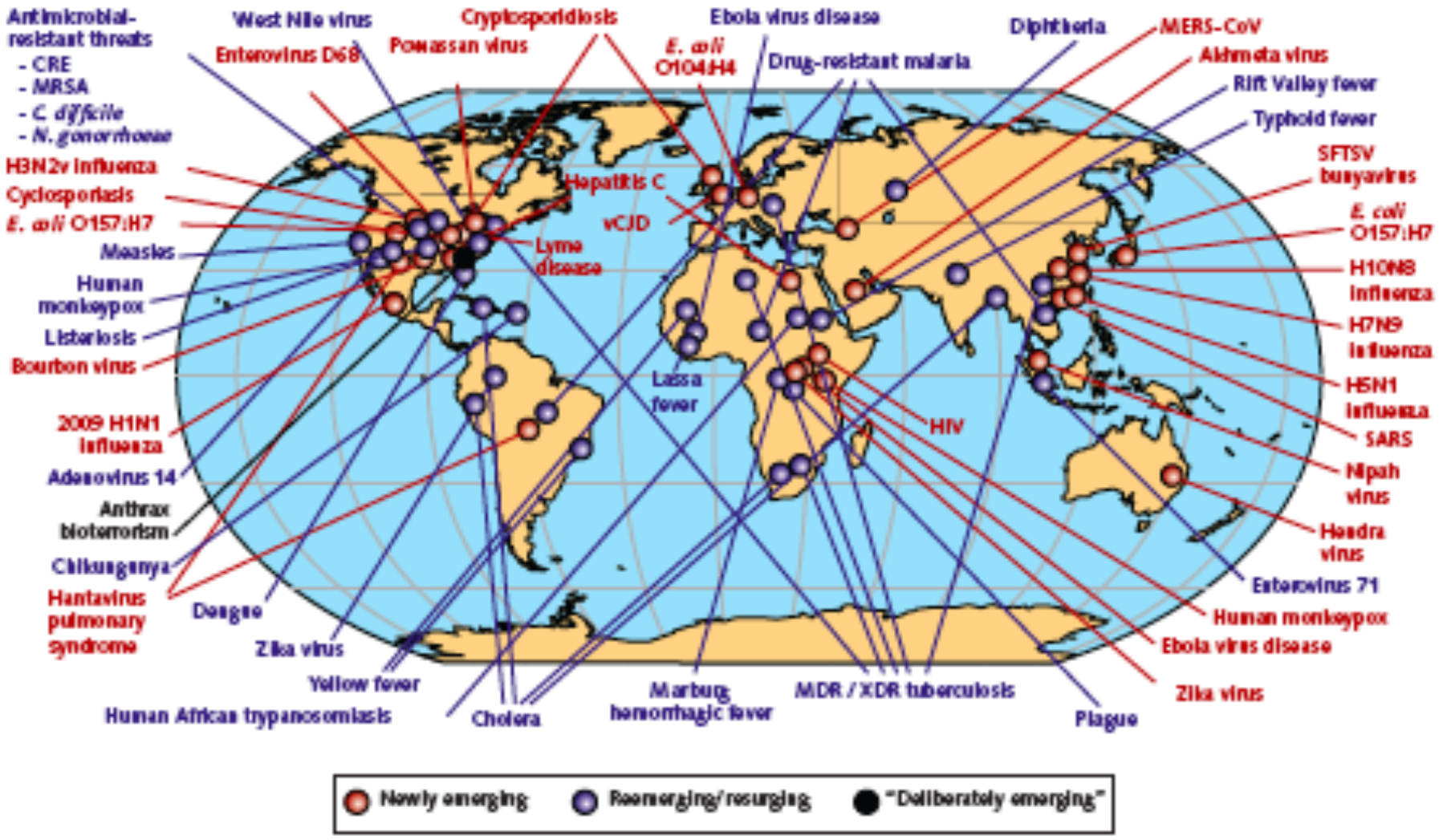
Screening of Pregnant Women with Zika Exposure



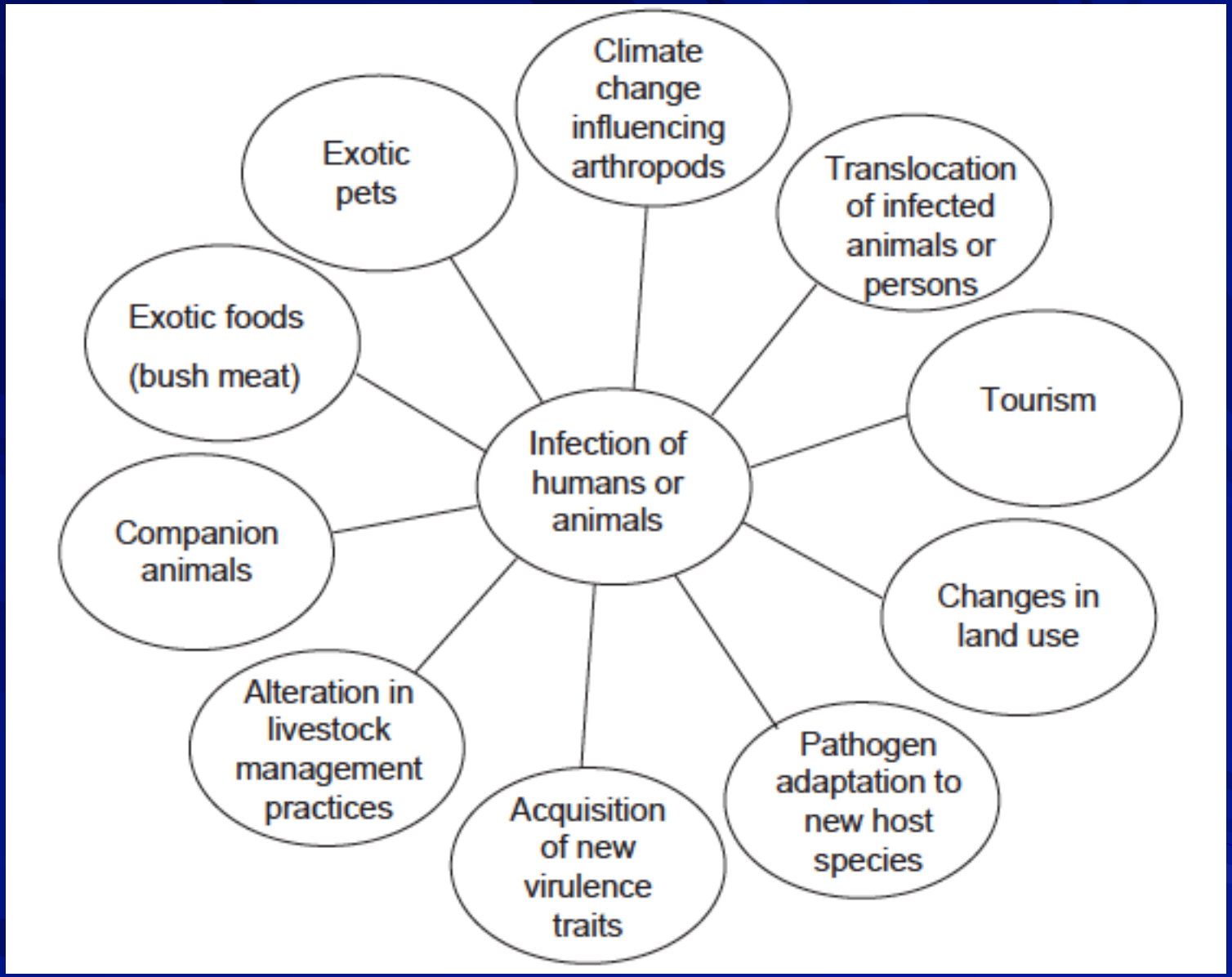
Treatment of Zika Virus Disease

- Supportive treatment with acetaminophen, hydration, and rest
- Avoid aspirin and NSAIDs until dengue has been ruled out
- Urgent medical care needed if symptoms of GBS develop
- No specific antiviral therapy available
  - In vitro data suggest sofosbuvir, chloroquine, and azithromycin active against Zika
    - Hamer DH et al. Curr Infect Dis Rep 2017

Recent Emerging Infectious Diseases



Paules CI et al. Ann Int Med 2017



Estimated 75% of EIDs are zoonoses

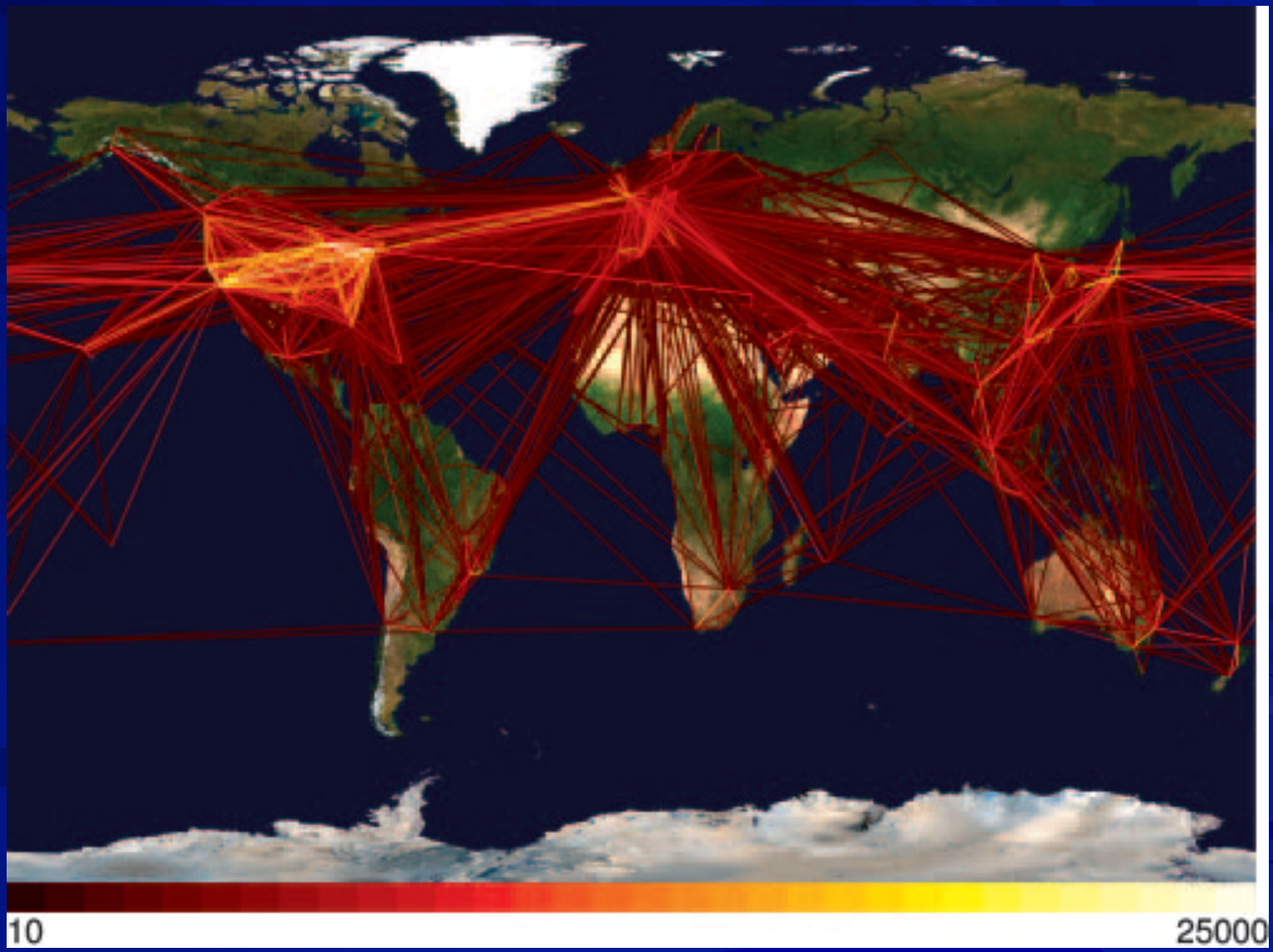
Cutler SJ et al. EID 2010

Factors Influencing Infectious Disease Emergence and Spread

- Demographic
- Social and behavioral
- Technology and industry
- Environment and land use changes
- International travel and commerce
- Microbial adaptation
- Breakdown in public health measures

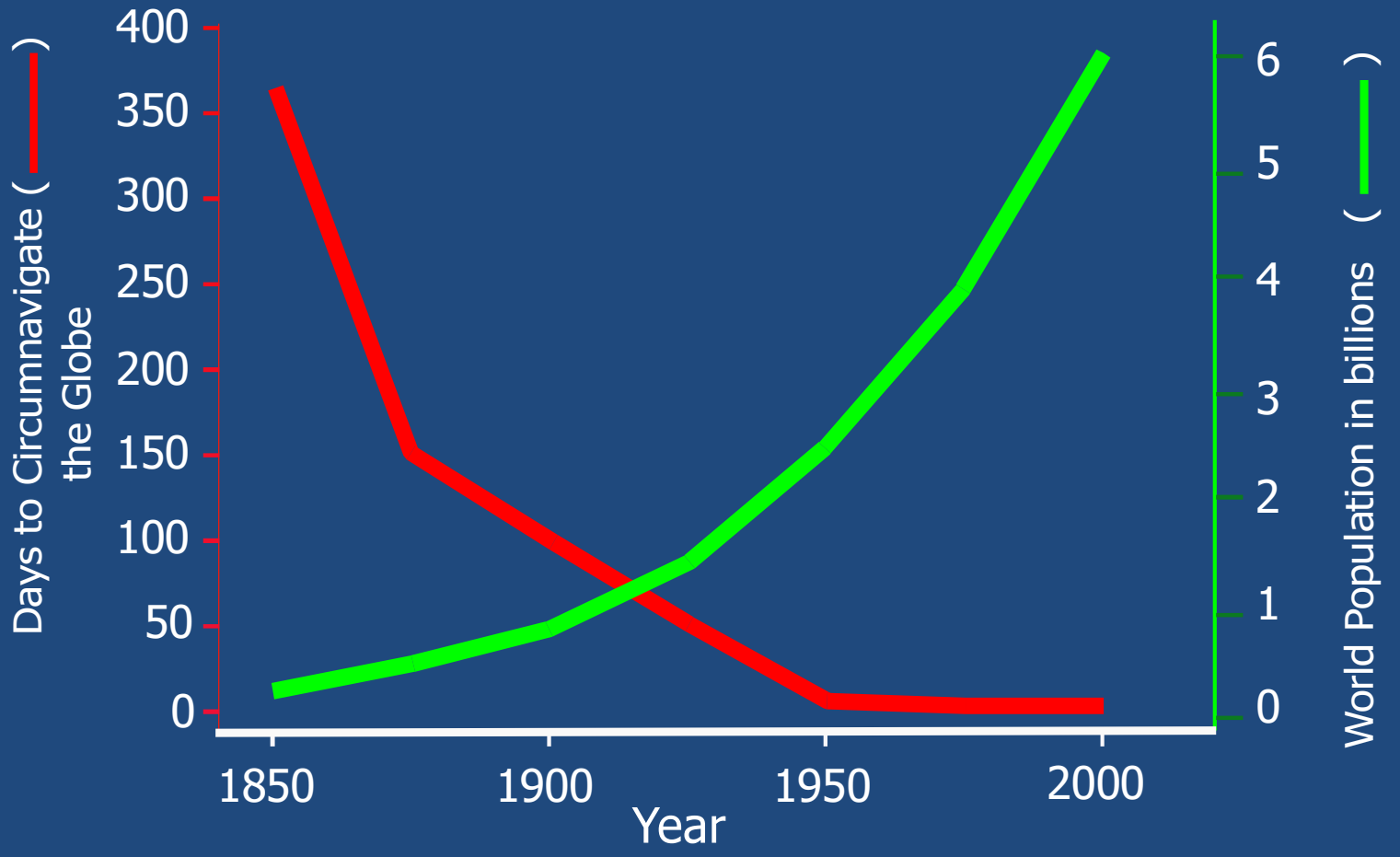
Global Aviation Network

(civil traffic, 500 largest airports, 100 countries)



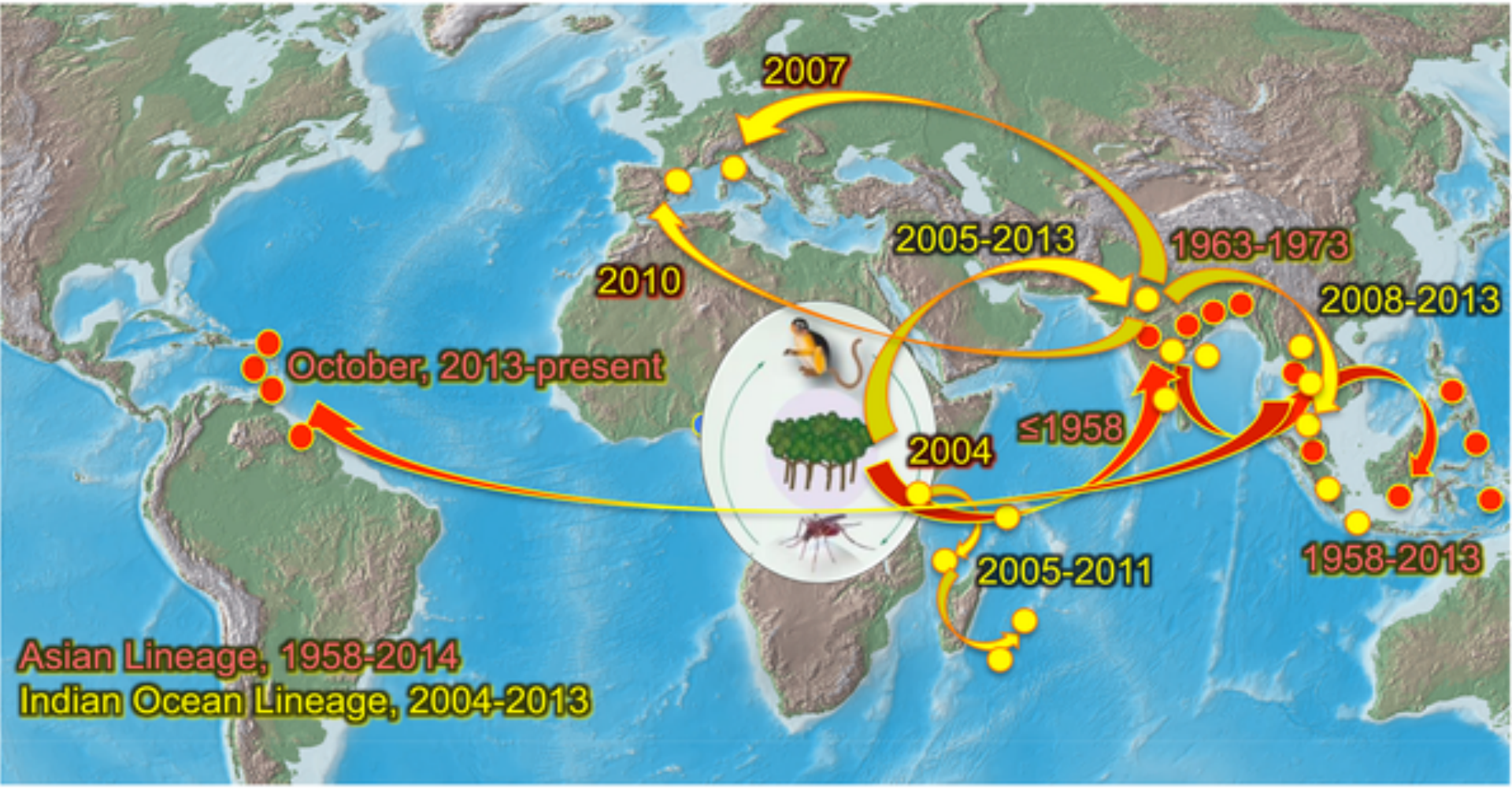
PNAS 2004;101:15125

Global Travel and World Population



From: Murphy and Nathanson Sems. Virol. 5, 87, 1994

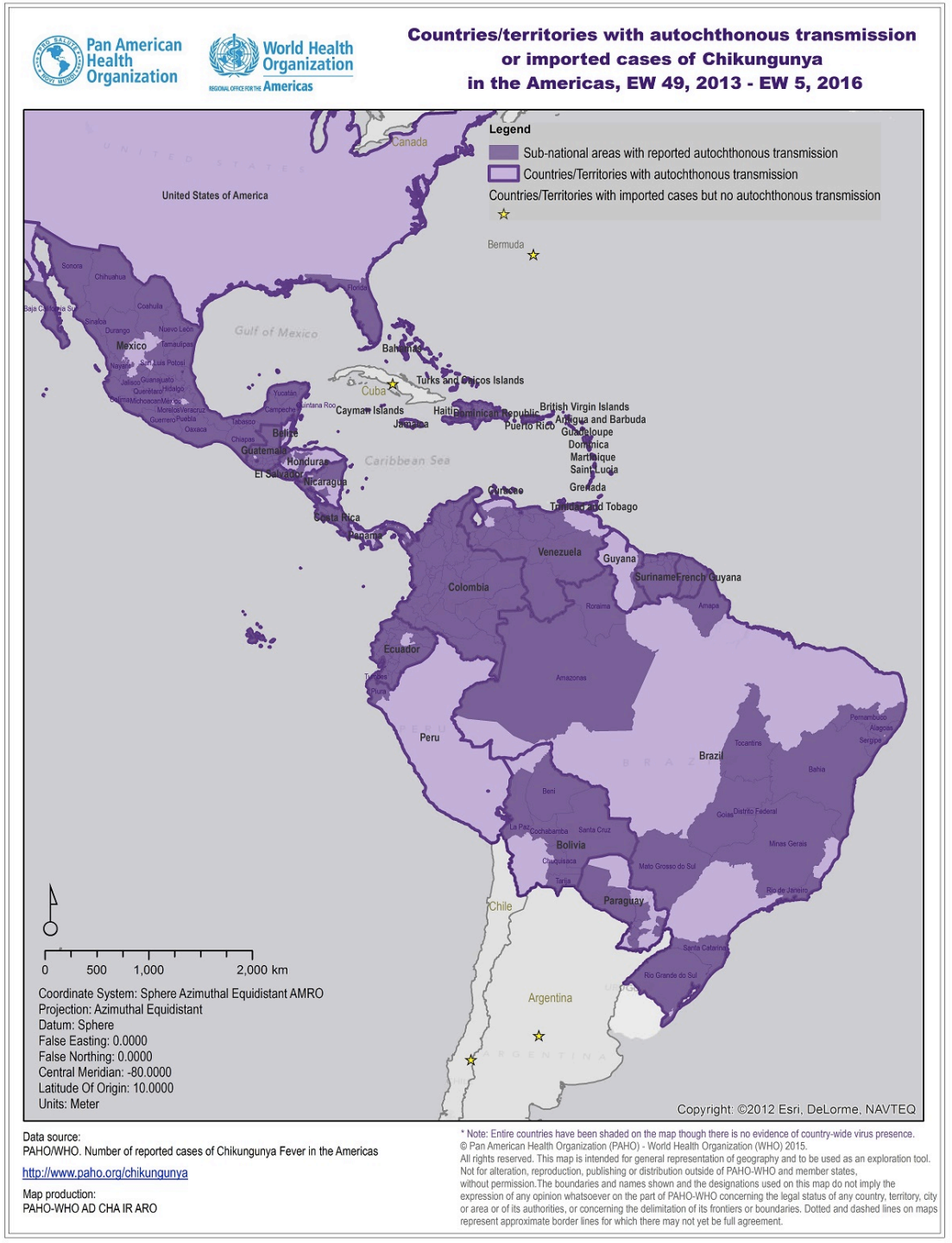
Emergence and Spread of Chikungunya Asian and Indian Ocean Lineages from Africa



Weaver SC (2014) Arrival of Chikungunya Virus in the New World: Prospects for Spread and Impact on Public Health. PLoS Negl Trop Dis 8(6): e2921. doi:10.1371/journal.pntd.0002921
http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0002921

Chikungunya in the Americas

More than 1.7 million estimated cases reported to PAHO



Factors Responsible for Chikungunya Emergence

- Biologic and genetic:
  - Virus adaptation: mutation at residue 226 of membrane fusion glycoprotein E1
    - May have resulted in improved virus adaptation to *A. albopictus*
- Ecological:
  - East Africa drought increased standing water and provided ideal conditions for vector breeding
  - Warm European summer with high vector abundance

Factors Responsible for Chikungunya Re-emergence (2)

- Physical environment:
  - Artificial vector breeding sites (household water stores, manholes, used tires)
  - Previous introduction of *A. albopictus* to Indian Ocean islands and Italy
- Social, political, and economic:
  - International and domestic travel
  - Human population migrations in the Indian Ocean region
  - Delayed identification and control of initial outbreaks

Three Theories on How Zika Was Introduced into Brazil

- 2014 World Cup in Brazil
- Va'a canoe event in Rio de Janeiro in August 2014 included participants from French Polynesia
- Confederation Cups soccer tournament in June 2013
  - Phylogenetic analyses suggest single introduction of Zika virus May-Dec 2013
    - **Faria NR et al Science 2016**

Why has Zika emerged now?

- Naïve populations in South Pacific amplified virus and facilitated spread via global mobility
- Abundance of competent vectors in the Americas
- Antibody-dependent enhancement in a heavily dengue-exposed population
- Mutational change (‘Asia strain’) - enhanced viral infectivity of *Aedes* vectors
- Mutational change
  - Enhanced human viremia and improved transmission efficiency
  - Increased infectivity to neural progenitor cells

nature immunology

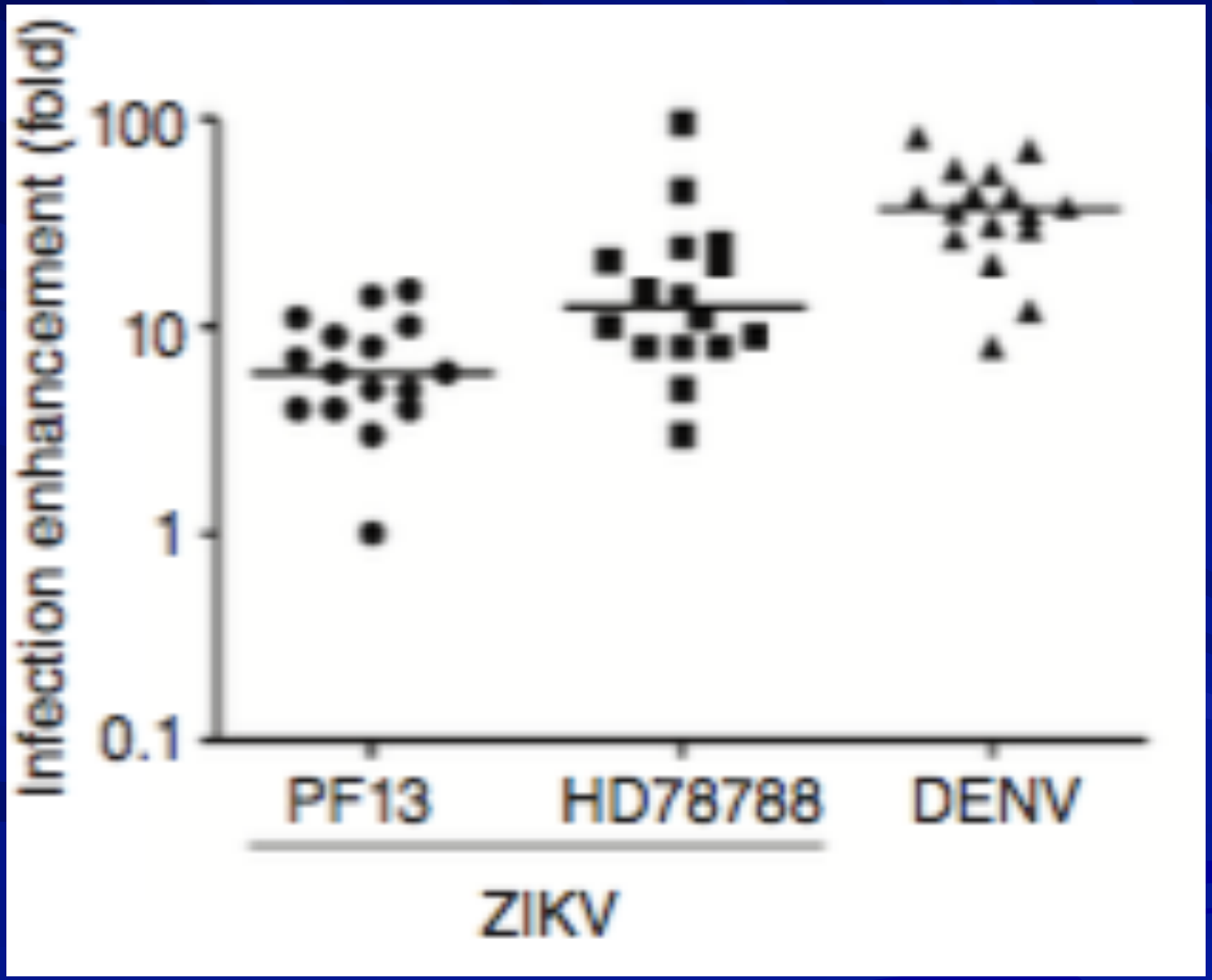
Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus

Wanwisa Dejnirattisai[1], Piyada Supasa[1–3], Wiyada Wongwiwat[1], Alexander Rouvinski[4,5], Giovanna Barba-Spaeth[4,5], Thaneeya Duangchinda[6], Anavaj Sakuntabhai[7,8], Van-Mai Cao-Lormeau[9], Prida Malasit[2,6], Felix A Rey[4,5], Juthathip Mongkolsapaya[1,2]& Gavin R Screaton[1]

- Previously established DENV infected cohort in NE Thailand
- Panel monoclonal antibodies generated from DENV-infected subjects
- Blood sample collection done during acute illness, convalescent phase (6m after hospital discharge) 2002-2004

DENV plasma potently induces ADE

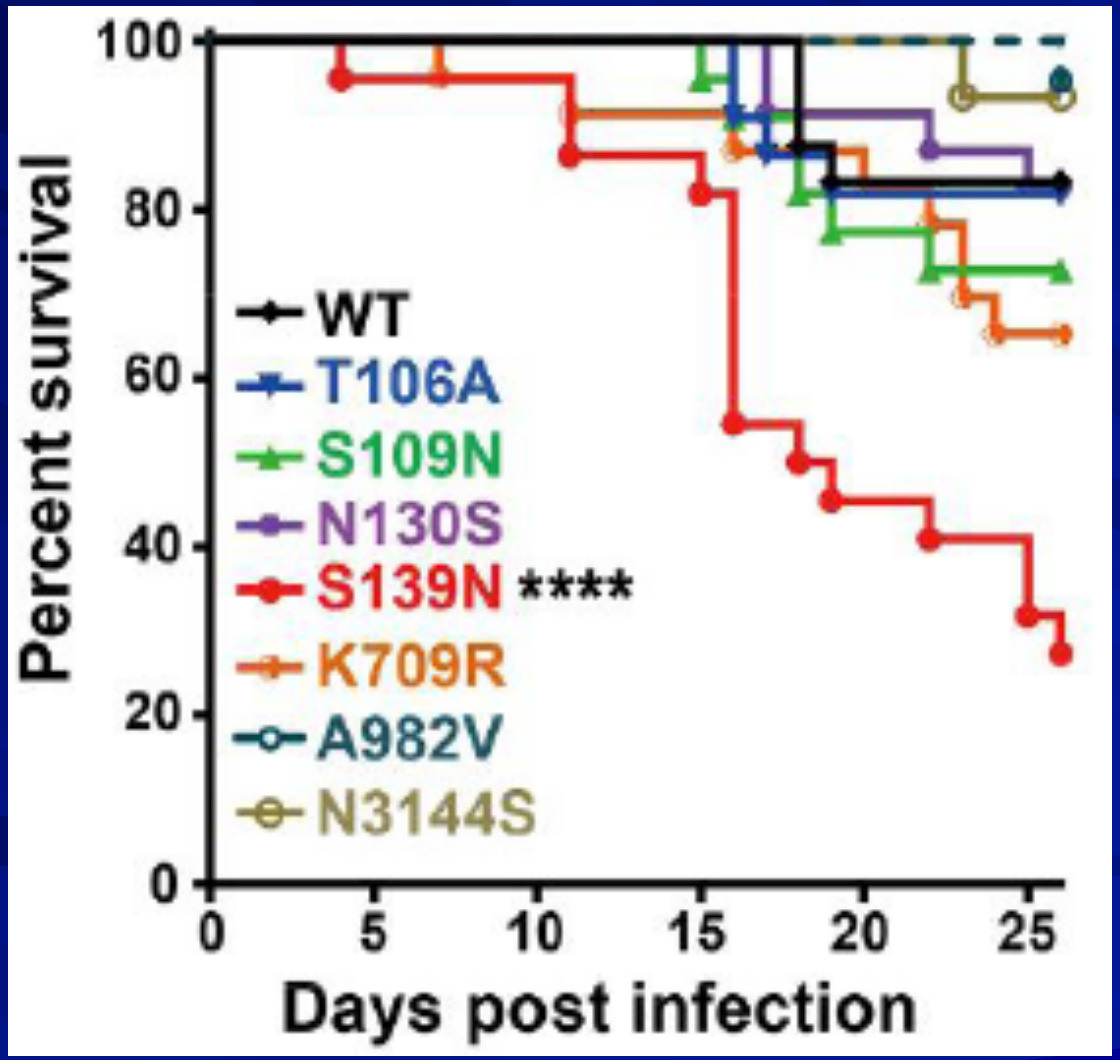
1-2 weeks after recovery

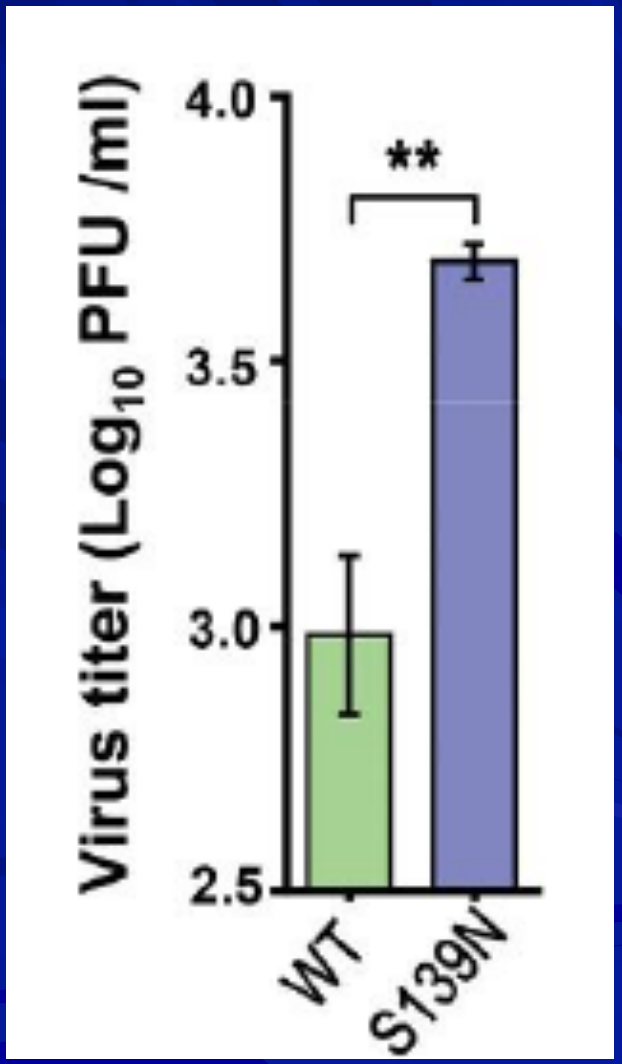


Mutation of the prM Protein of Zika Virus

- S139N mutant virus (Asian lineage) emerged in May 2013 shortly before the French Polynesia outbreak
  - Based on Bayesian phylogenetic tree estimates
- S139N mutant causes more robust infection of neuroprogenital cells of embryonic mouse brains
- Mutation associated with severe fetal microcephaly
  - Yuan L et al. Science 2017

S139N mutant virus enhanced virulence in neonatal mouse model



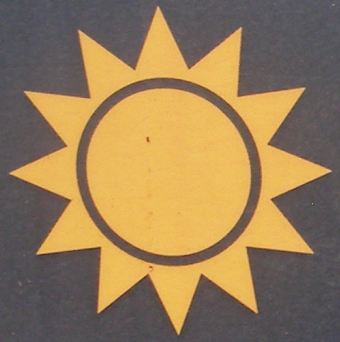


Pregnant?

Warning: Zika might be linked to birth defects

There is no vaccine to prevent Zika virus infection

Protect yourself from mosquito bites



Daytime is most dangerous

Mosquitoes that spread chikungunya, dengue, and Zika are aggressive daytime biters. They can also bite at night.

Use insect repellent

It works!

Look for the following active ingredients:

• DEET • PICARIDIN • IR3535

Wear protective clothes

Wear long-sleeved shirts and long pants and use insect repellent. For extra protection, treat clothing with permethrin.

Mosquito-proof your home

Use screens on windows and doors. Use air conditioning when available. Keep mosquitoes from laying eggs in and near standing water.

For more information:

www.cdc.gov/chikungunya • www.cdc.gov/dengue • www.cdc.gov/zika

CDC

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Mosquito Vectors – Most Common

Aedes aegypti

Aedes albopictus

Options for Prevention

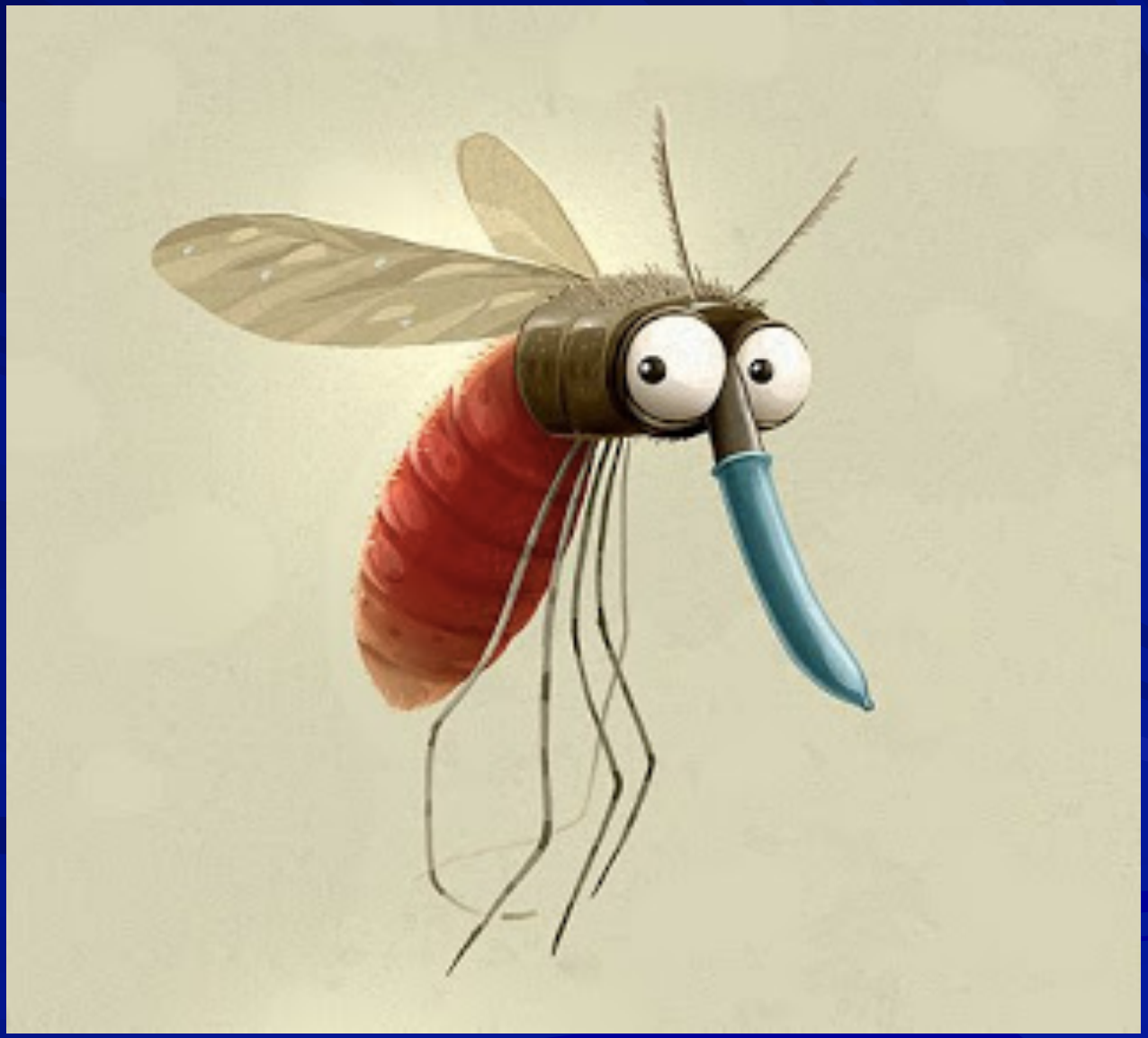
- As weather permits, wearing long-sleeved shirts and long pants
- Insect repellents
- Air conditioning or window/door screens to keep mosquitoes outside
  - If no screens, sleep under a mosquito bed net or in a tent (can treat with permethrin)
- Reduce number of mosquitoes outside by emptying standing water from containers (community mobilization)

Antivector Measures

- Insect repellents
  - Repellents containing DEET (30%), picaridin, IR3535, and oil of lemon eucalyptus and para-menthane-diol products provide long lasting protection
  - If you use both sunscreen and insect repellent, apply sunscreen first and then repellent
  - Treat clothing with permethrin
- Dark colors, strong smells, CO, PW attract
- Protected sex post-travel!
- Screening of blood products


159

Genetically modified mosquitoes?



Travel Precautions

- Women who are pregnant should avoid travel to areas with ongoing Zika transmission
  - Modified (based on epidemiological data on *Ae. aegypti* distribution and dengue risk) to avoid travel to elevations <2000 m
- Pregnant women who have traveled to Zika-infected areas should be screened for infection upon return
- Male partners of women who are pregnant should use barrier methods after travel to countries with Zika for 6 months

Dengue Vaccine (Dengvaxia)

Table 2. Vaccine Efficacy against Any Serotype of Dengue.

Analysis	Vaccine Group			Control Group			Vaccine Efficacy (95% CI)
	Cases/ Events*	Person-Yr at Risk†	Incidence Density (95% CI)‡	Cases/ Events*	Person-Yr at Risk†	Incidence Density (95% CI)‡	
	no.		*no./100 person-yr*	*no.*		*no./100 person-yr*	%
Per-protocol analysis	176/176	11,793	1.5 (1.3–1.7)	221/221	5,809	3.8 (3.3–4.3)	60.8 (52.0–68.0)
Intention-to-treat analysis	277/280§	26,883	1.0 (0.9–1.2)	385/388§	13,204	2.9 (2.6–3.2)	64.7 (58.7–69.8)

- Recombinant live attenuated tetravalent vaccine
- Protective efficacy varied from 42% for serotype 2 to 78% serotype (higher protection severe dengue – 95%)
  - Villar L et al NEJM 2014
- Much less effective in Thailand-only 30% (9% and 100% for serotypes 2 and 4)
  - Sabchareon A et al Lancet 2012

Dengvaxia - Challenges

- Pooled vaccine efficacy across both trials 59.2% in year following primary series (PP analysis)
  - 79% vs. severe dengue
- Efficacy varied by age at vaccination and serostatus at baseline (i.e., previous exposure to dengue prior to vaccination)
- Today Sanofi Pasteur announced risk of severe dengue in those seronegative at baseline
  - Excess of hospitalization and severe dengue in year 3 post vaccination
  - Excess mainly observed in those vaccinated aged 2-5 years in CYD14 in Asia, (RR hospitalized dengue in vaccinees 7.45 (95% CI 1.15, 313.80) in year 3)

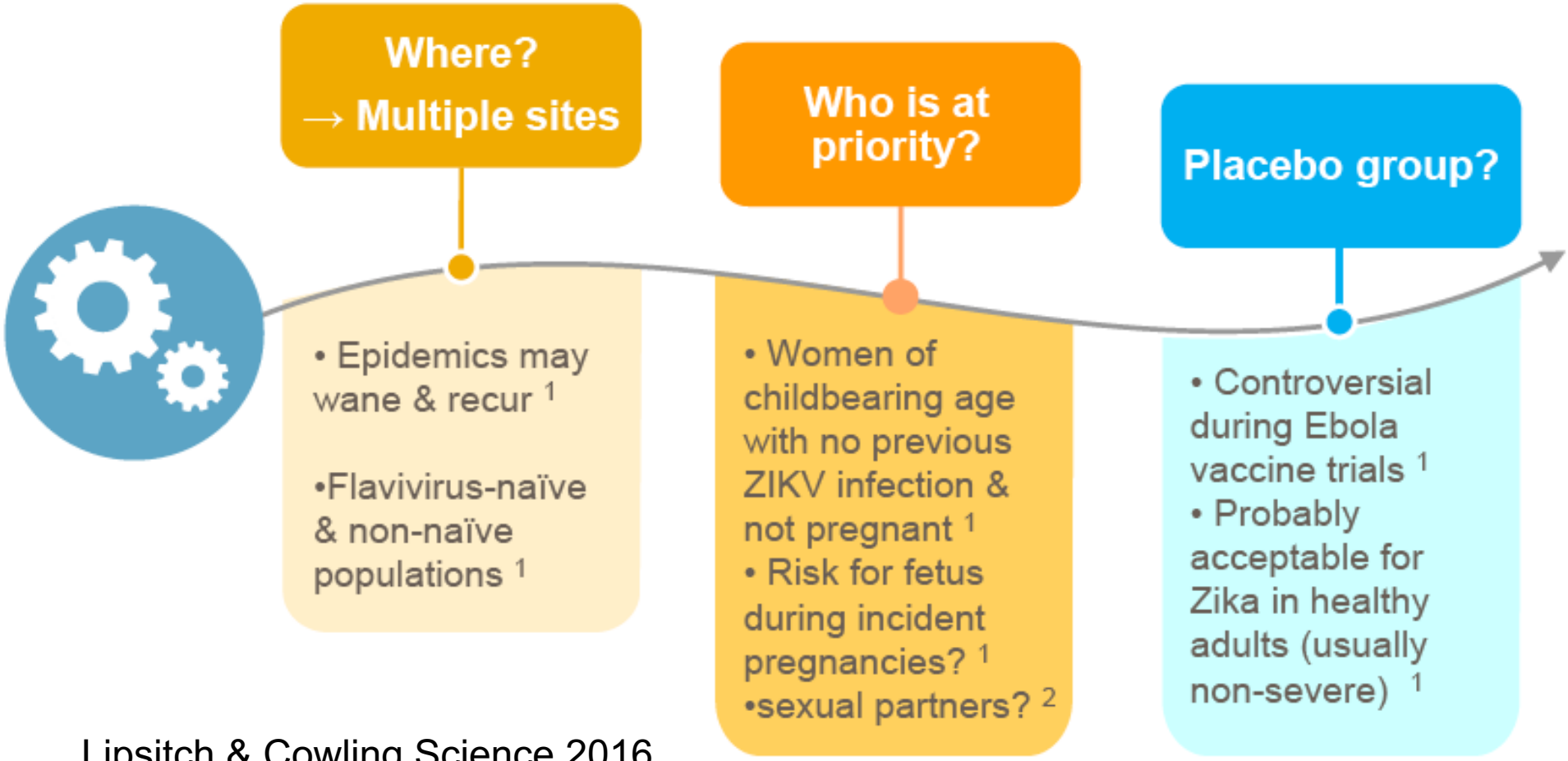
Chikungunya Vaccines

- CHIKV elicits long-lasting protective immunity
- Animal models show some cross-protection between CHIKV and other alphaviruses
- Candidate vaccines have been tested in humans
  - MV-CHIKV (measles vaccine modified to express CHIKV proteins; Themis Bioscience) beginning phase 1/2 trial
    - 2 dose vaccine; testing different intervals
  - Virus-like particle vaccine in phase 2

Zika Vaccine Strategies

- Live attenuated vaccine
  - Phase 1 soon in Baltimore and Burlington
- Purified inactivated virus
  - ZPIV (Walter Reed) in phase 1 trials
- DNA
  - DNA virus completed phase 1 trials 2016 (NIAID)
  - Phase 2 trial (VRC 705) ongoing – safety and immunogenicity
- mRNA
- Virus like particles
- Vesicular stomatitis virus
- Recombinant subunit

Zika Vaccines – Design Issues



Lipsitch & Cowling Science 2016
Marston et al. NEJM 2016

Any Questions?