Zika Virus

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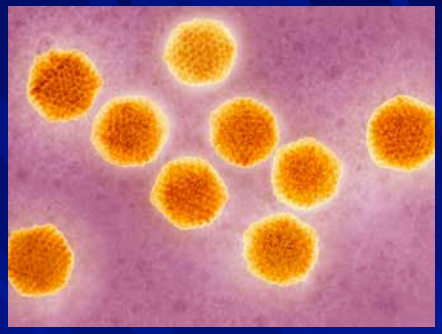
GeoSentinel (CDC/ISTM)

Objectives

- Understand recent epidemiology of Zika virus including modes of transmission
- Describe common clinical manifestations and complications of Zika virus disease
- Review strategies for prevention of Zika infection

Zika Virus



- Single stranded RNA virus of *Flavivirus* genus
- Closely related to dengue, West Nile, yellow fever, and Japanese encephalitis viruses
- Arbovirus: arthropod-borne virus
- Primary vector - *Ae. aegypti* but several other *Aedes* spp. and *Culex* spp. capable of transmission (in laboratory)

Two Distinct Zika Lineages – Only One Serotype

- African
- Asian

- All strains have 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 - Americas Outbreak

Enfissi A et al Lancet 2016

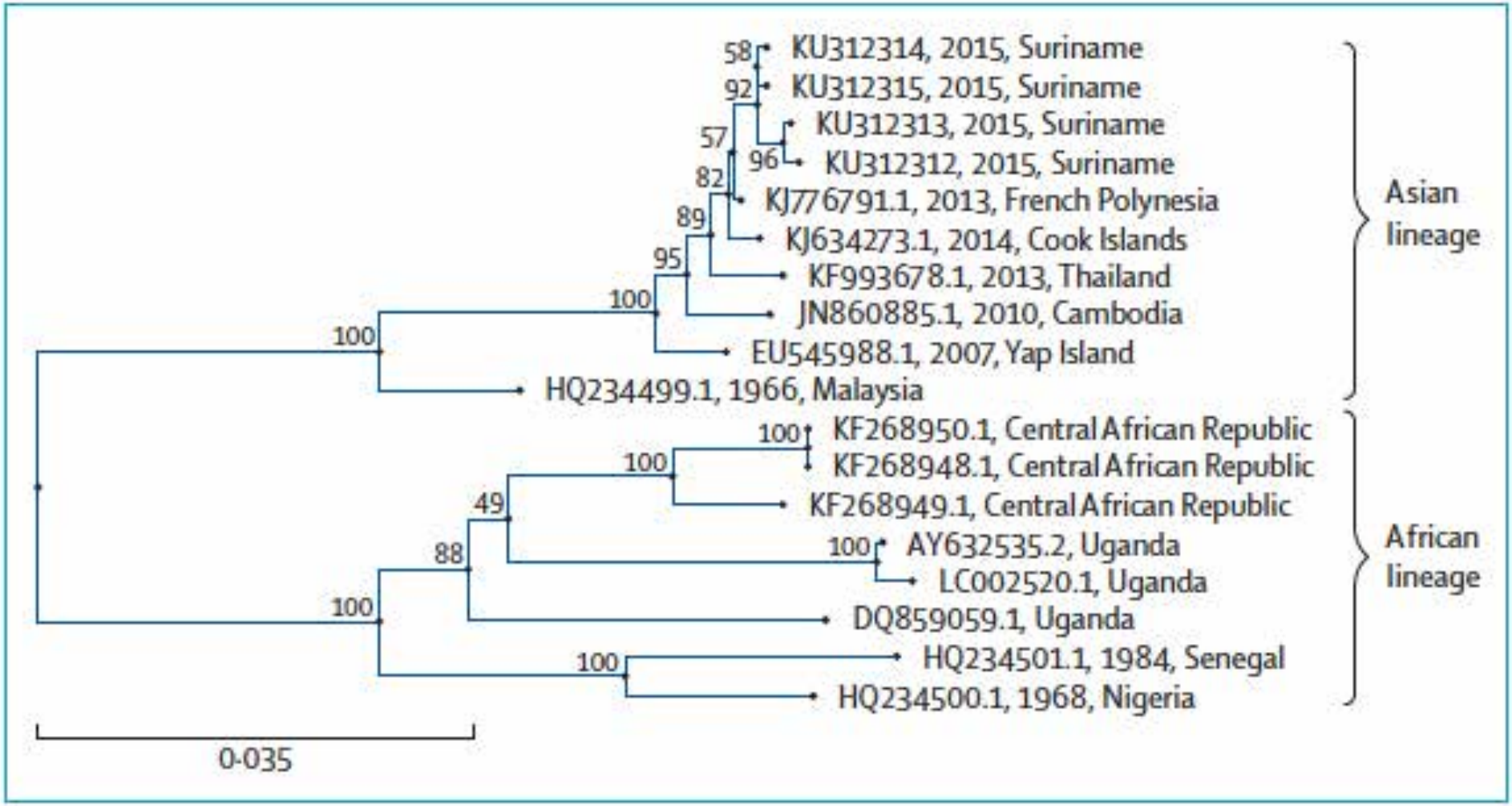


Figure: Phylogenetic relations between the envelope gene sequences of Suriname ZIKV and other ZIKV

Epidemiology

Discovered in Zika Forest, Uganda 1947

Epidemiology

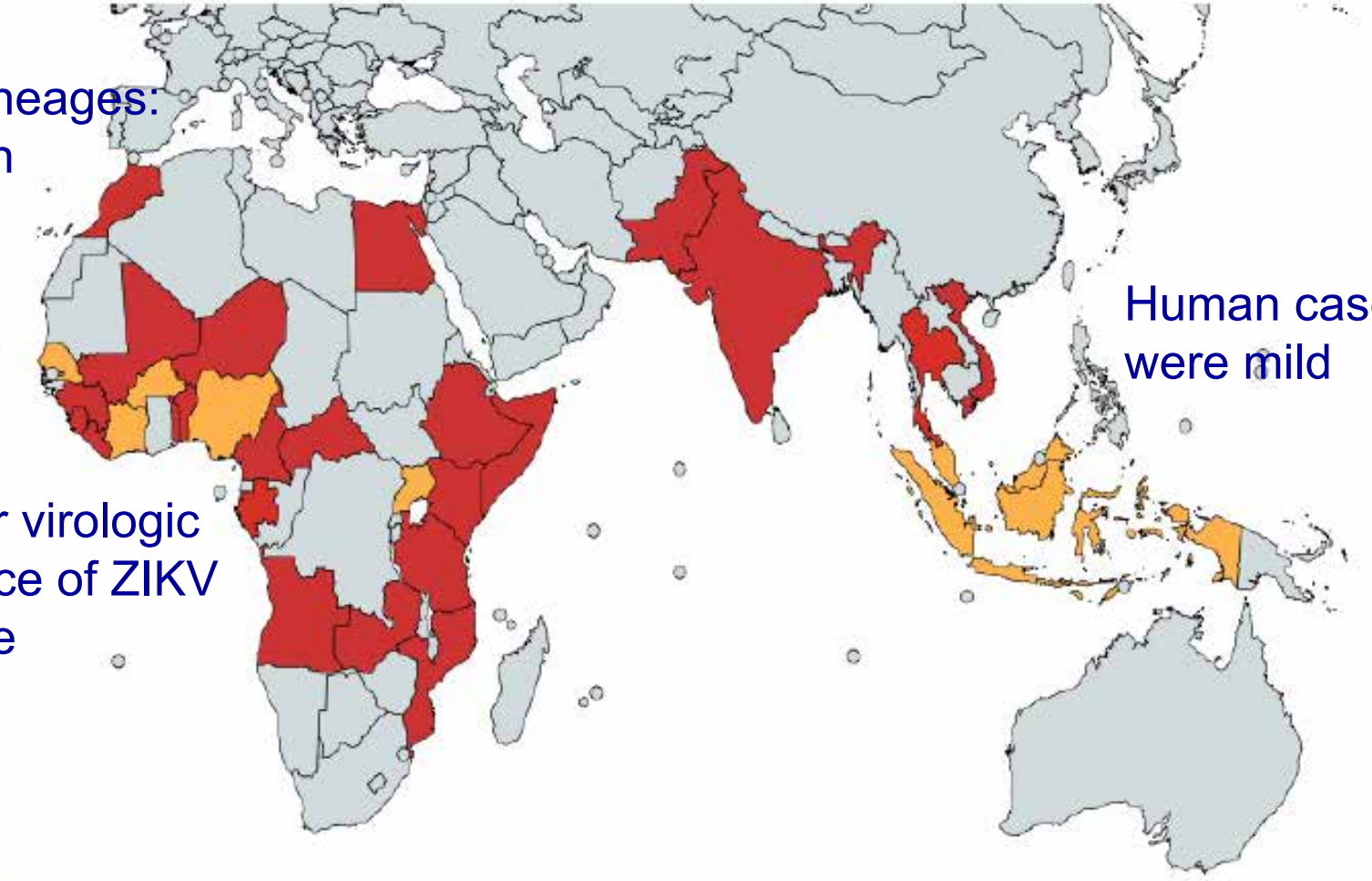
- First human case diagnosed 1962-3 in Uganda
- Serosurveys – neutralizing antibodies in East and West Africa, India, and SE Asia
  - Late 1940s to late 1990s
- Outbreaks in Yap, Micronesia in 2007; French Polynesia 2013, Easter Island 2014
- Brazil early 2015 then spread in the Americas
  - Chen & Hamer. Ann Int Med 2016
  - Musso & Gubler. Clin Microbiol Rev July 2016

Serologic Evidence of ZIKV Distribution until 2007

Two lineages:
African
Asian

Human cases were mild

Sero or virologic evidence of ZIKV multiple



Serologic evidence

Virus detection or confirmed human case

Pan American Health Organization

World Health Organization Americas

Historical Transmission of Zika Virus (human cases and/ or mosquito carriage reports)

1947

Humas cases and / or mosquito carriage have been reported in

Africa - Burkina Faso, Cameroon, Central African Republic, Gabon, Ivory Coast, Nigeria, Senegal, Sierra Leone and Uganda. Asia - Cambodia, Indonesia, Malaysia, Pakistan and Thailand. The Pacific Region - Cook Islands, French Polynesia, Guam , Micronesia and New Caledonia, Easter Island (Chile). Americas: Brazil, Barbados, Bolivia,Colombia, Dominican Republic, Guadelcupe, Guatemala, Guyana, French Guiana, Haiti, Honduras, Ecuador, El Salvador, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, US Virgin Islands, Venezuela

Data Sources: IHR National Focal Points of PAHO-WHO CHA IR MIC are through the Ministry of Health websites, 2014-2016; ECDC, 2016. Report Production: PAHO-WHO AD CHA IR MIC

Pan American Health Organization

World Health Organization Americas

Historical Transmission of Zika Virus (human cases and/ or mosquito carriage reports)

1978

Human cases and / or mosquito carriage have been reported in

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Pan American Health Organization

World Health Organization Americas

Historical Transmission of Zika Virus
(human cases and/ or mosquito carriage reports)

2007

Yap Island (Micronesia) and Guam, 2007

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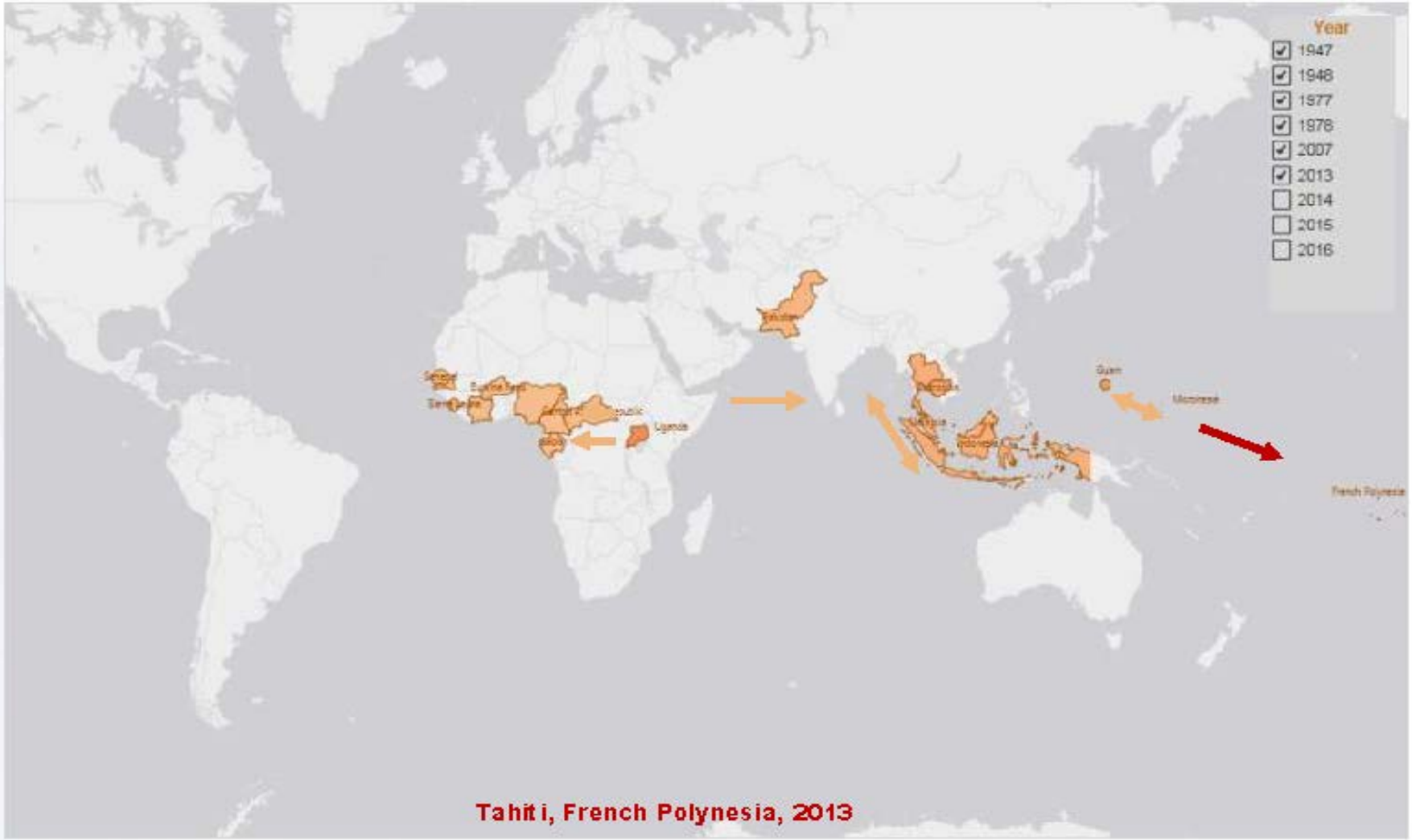
Data Sources: IHR National Focal Points to PAHO-WHO CHA IS ARC and through the Ministry of Health websites, 2014-2016; ECDC, 2016; Report Production: PAHO-WHO AD CHA IS ARC

Pan American Health Organization

World Health Organization Americas

Historical Transmission of Zika Virus (human cases and/ or mosquito carriage reports)

2013



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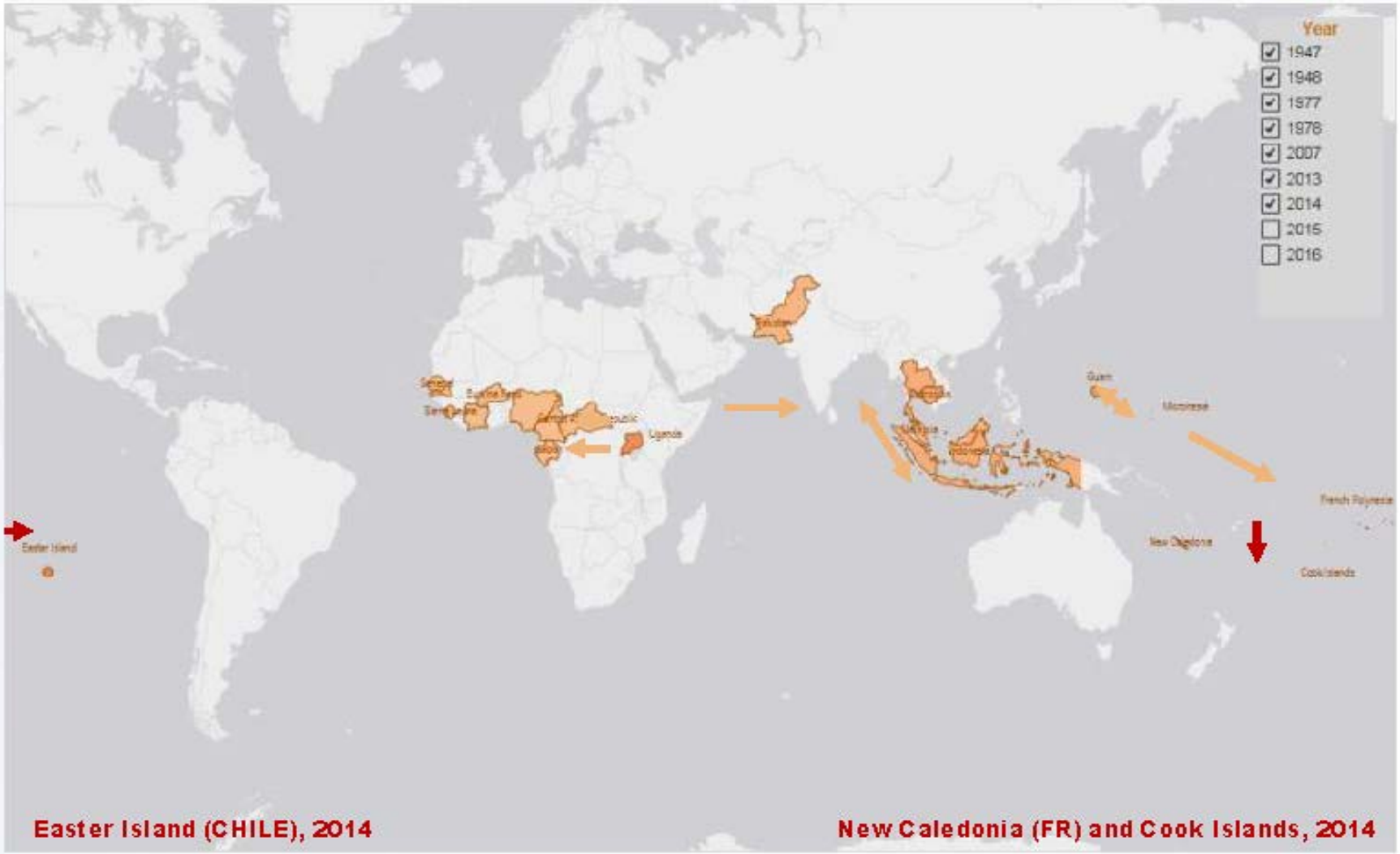
World Health Organization Americas

Historical Transmission of Zika Virus (human cases and/ or mosquito carriage reports)

2014



Easter Island (CHILE), 2014

New Caledonia (FR) and Cook Islands, 2014

Human cases and / or mosquito carriage have been reported in

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Pan American Health Organization

World Health Organization Americas

Historical Transmission of Zika Virus (human cases and/ or mosquito carriage reports)

2015

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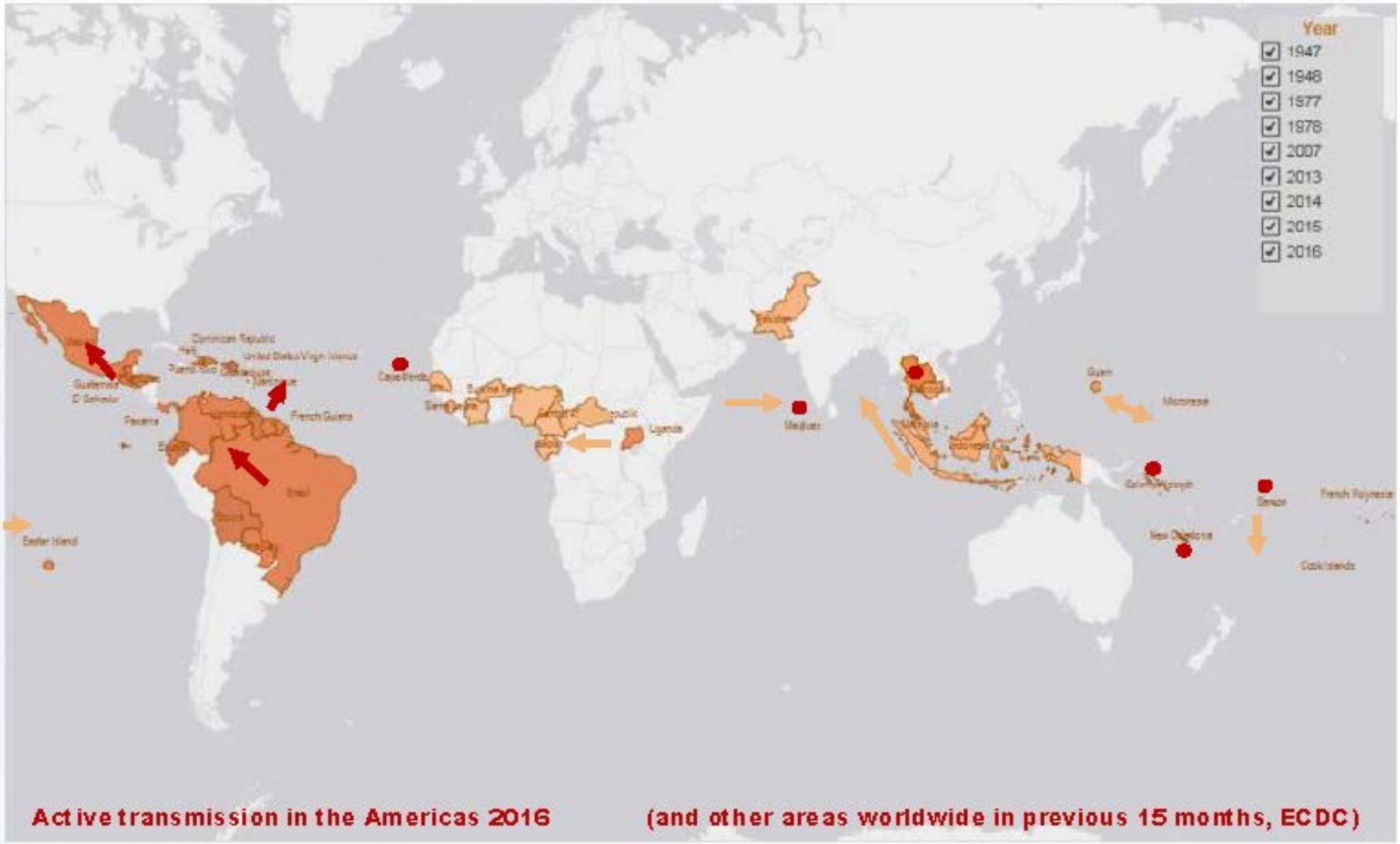
Pan American Health Organization

World Health Organization Americas

Historical Transmission of Zika Virus (human cases and/ or mosquito carriage reports)

2016



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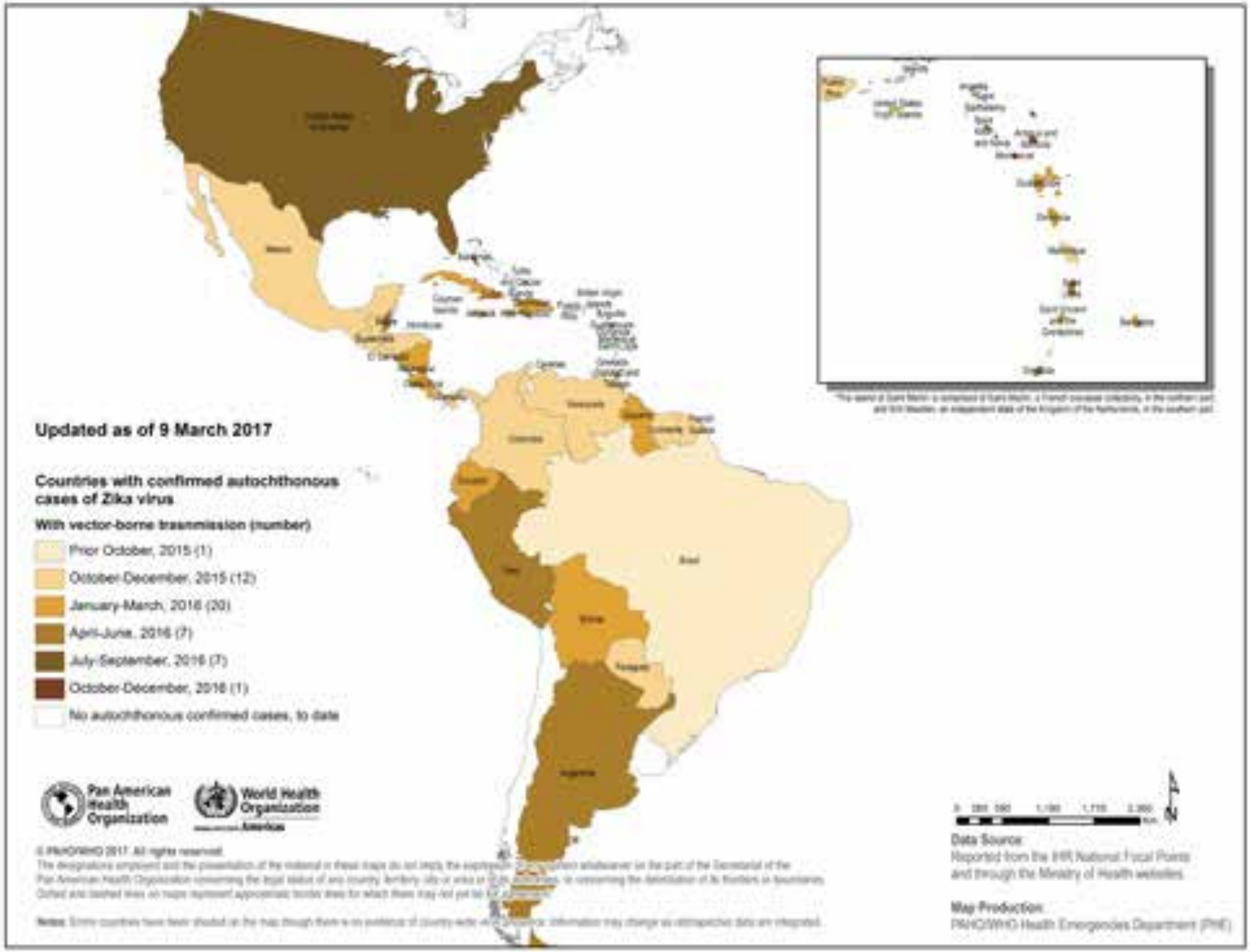
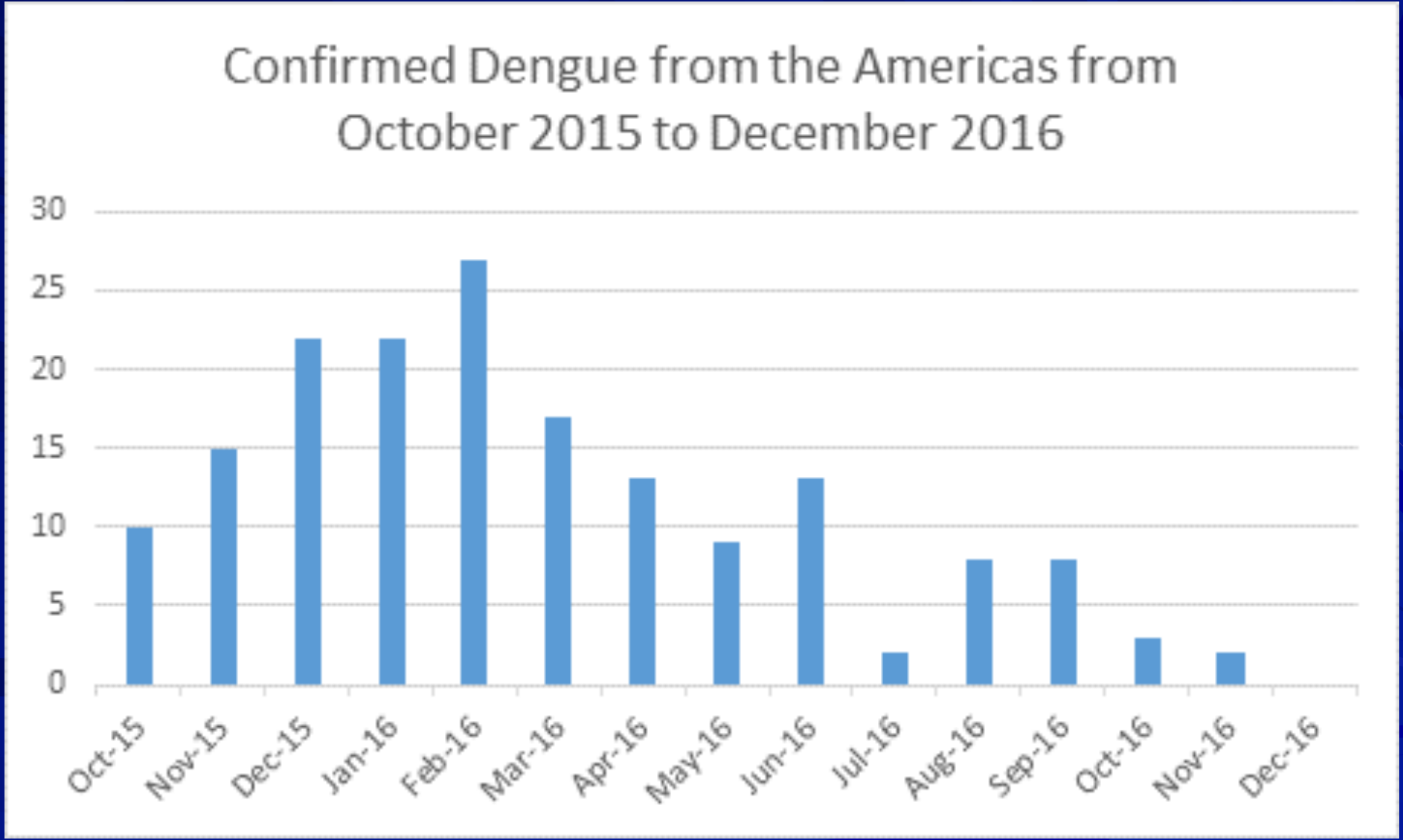
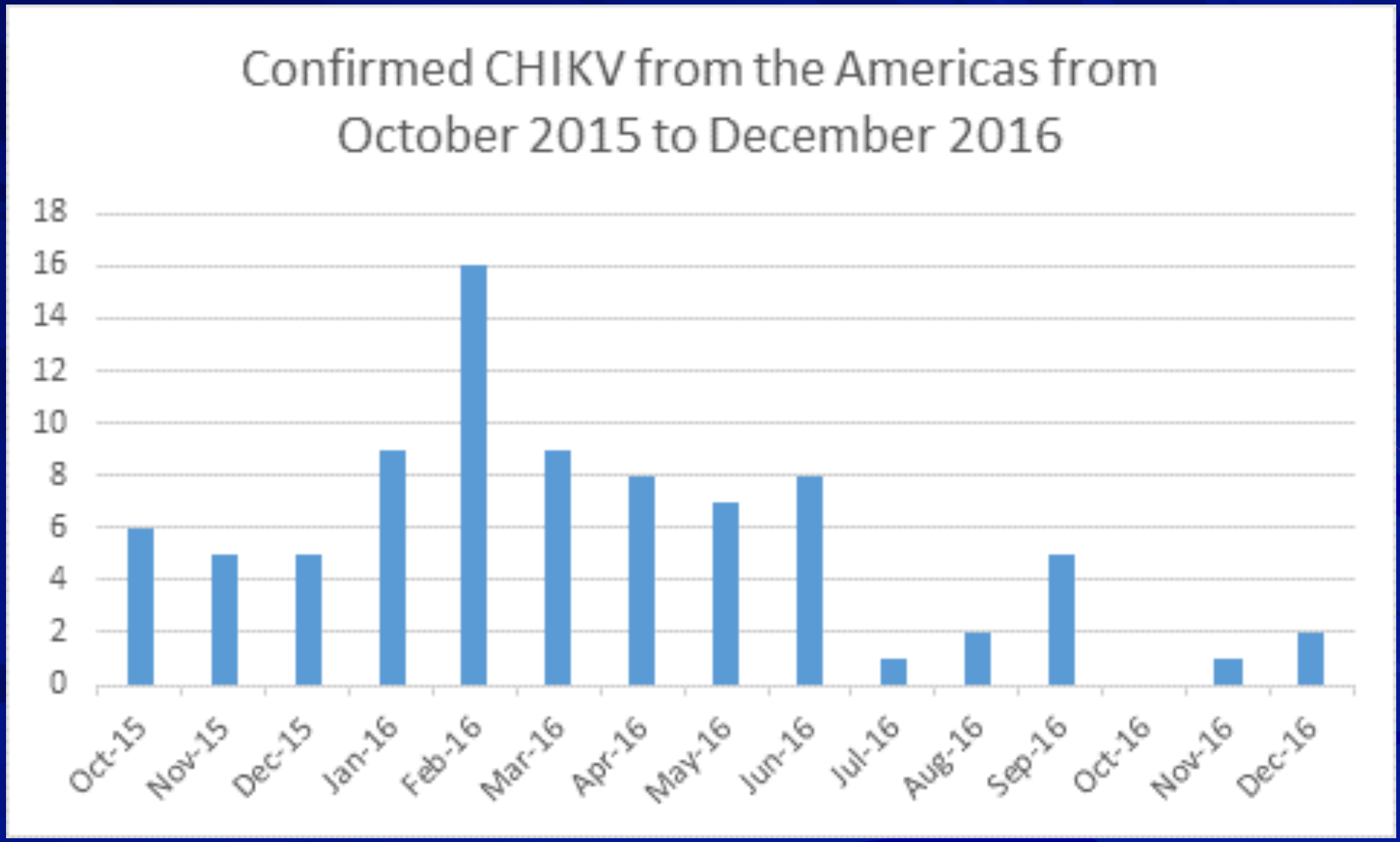
Data Sources: IHR National Focal Points of PAHO/WHO CHA IR MRC and through the Ministry of Health websites, 2014-2016, ECDC, 2016. Report Production: PAHO/WHO AD CHA IR MRC


Updated as of 9 March 2017
Countries with confirmed autochthonous cases of Zika virus
With vector-borne transmission (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
Pan American Health Organization
World Health Organization
Data Source
Reported from the IHR National Focal Points and through the Ministry of Health websites
Map Production
PAHO/WHO Health Emergencies Department (PHE)

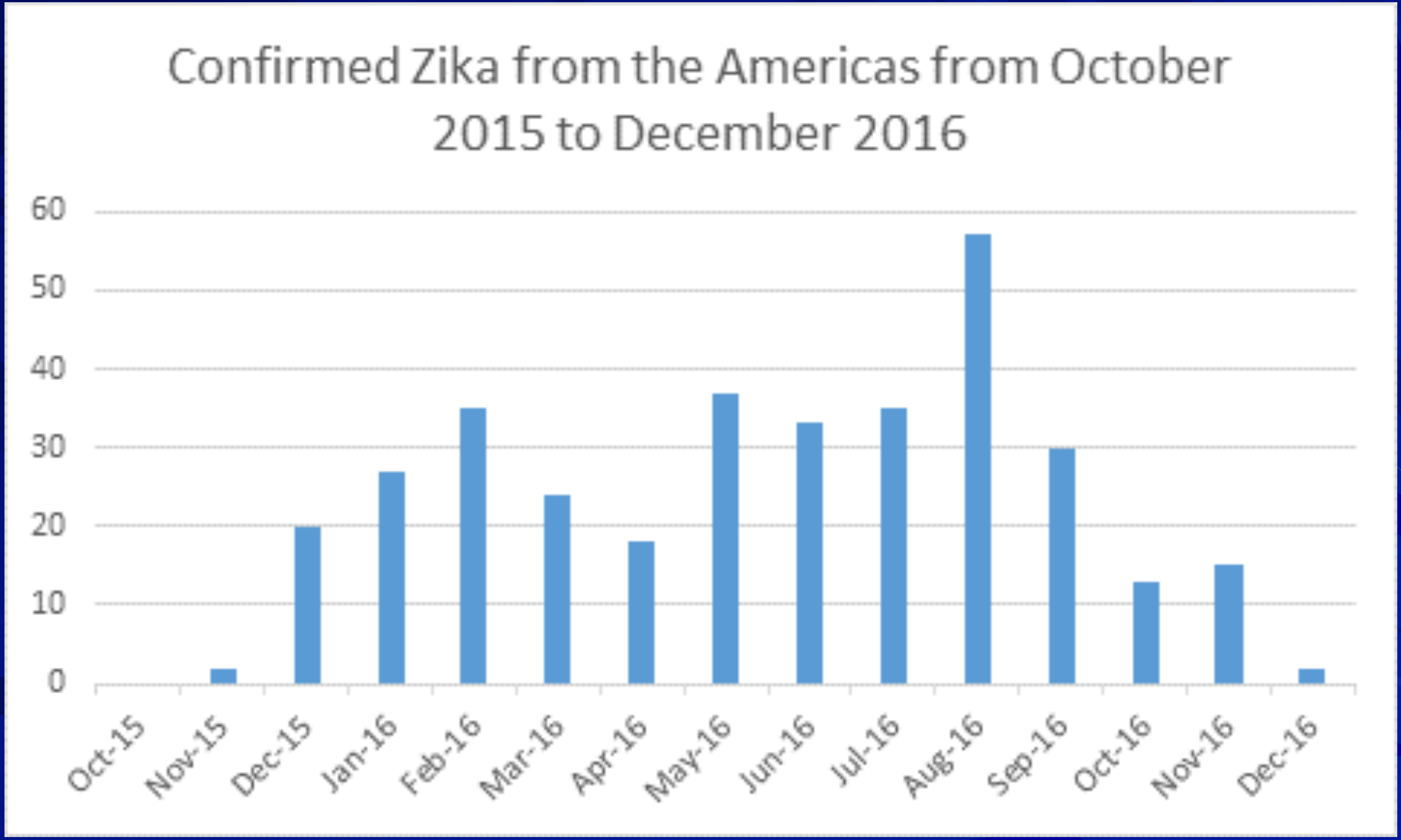
GeoSentinel Dengue Epi Curve



GeoSentinel Chikungunya Epi Curve



Zika Epi Curve GeoSentinel Reports

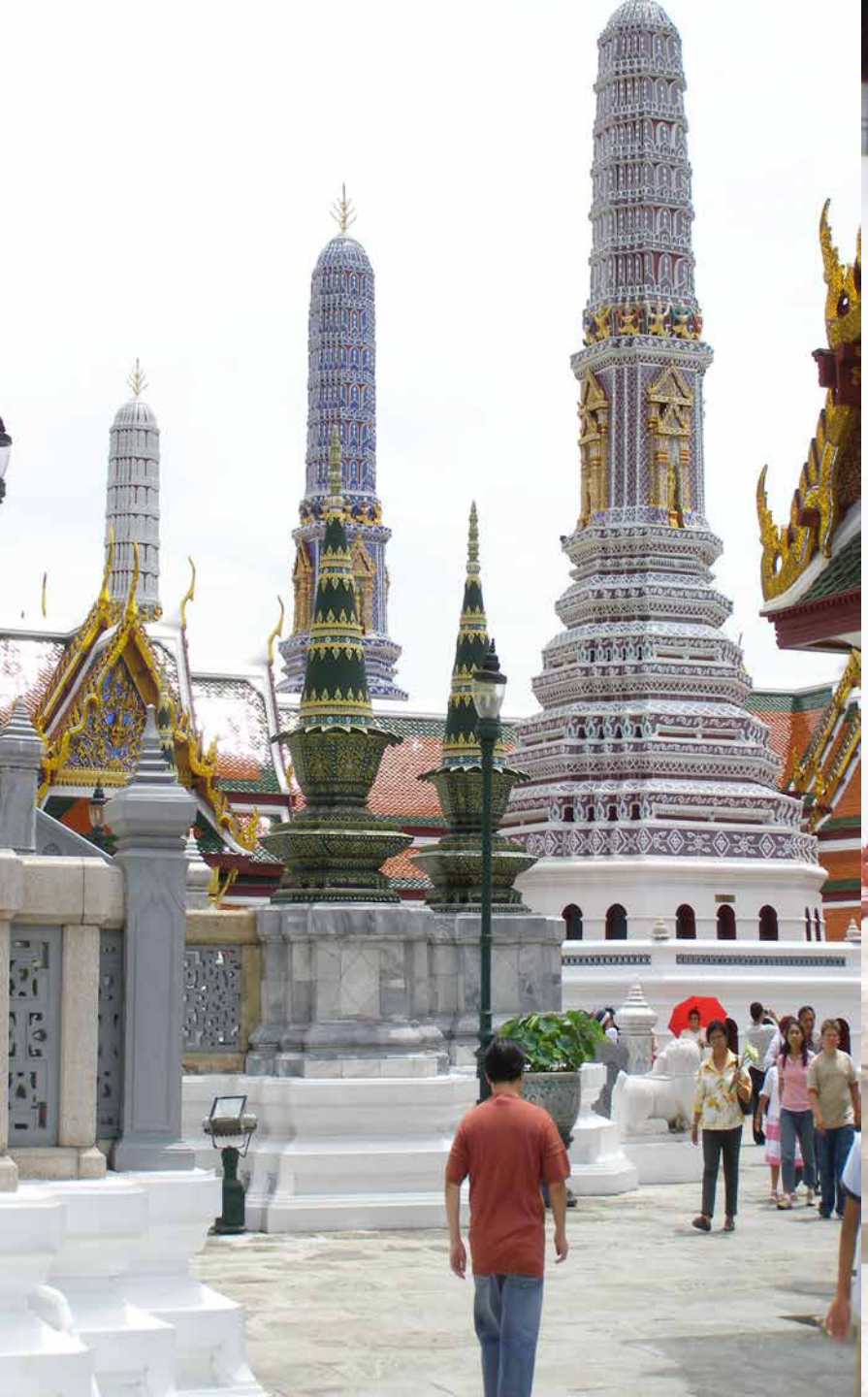


Theories on How Zika Was Introduced into Brazil

- 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 – higher human viremia and improved transmission efficiency

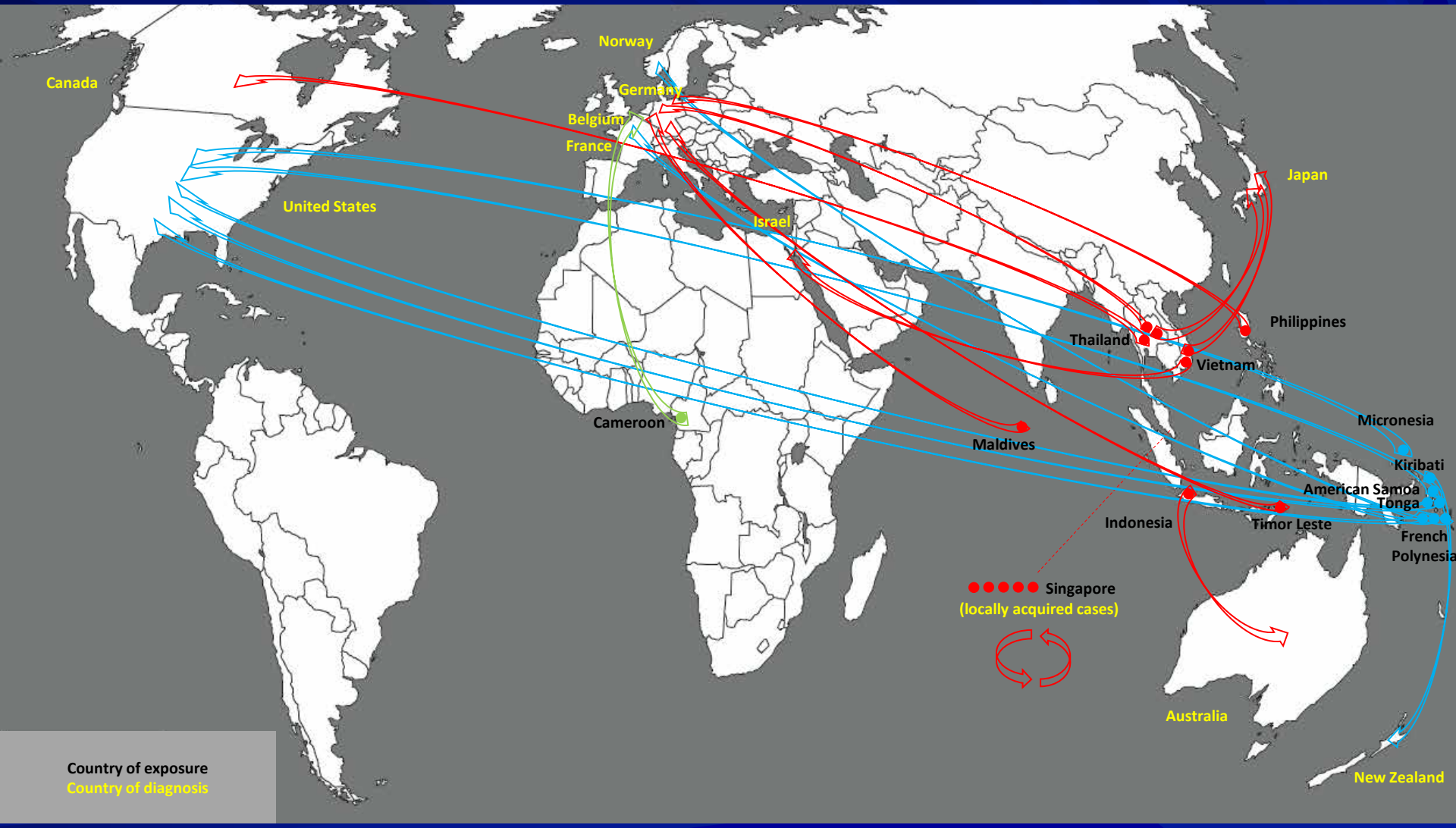



NGÂN HÀNG CÔNG THƯƠNG VIỆT NAM
INCOMBank
ATM
ATM

Zika in SE Asia, South Pacific and Africa: GeoSentinel Analysis

- Database reviewed for reported Zika cases from 1995 to December 2016
- Cases classified using modified CSTE definitions – confirmed and probable
- Comprehensive search of PubMed, ProMED and other outbreak sites to identify reported cases and timing of reporting

Zika Countries of Exposure and Diagnosis



Probable Sentinel Cases

- 2012: Indonesia (diagnosed in Australia)
  - Kwong JC et al. AJTMH 2013
- 2014: the Philippines (dx in Germany)
  - First case since 2012 for this country
- 2013: Thailand (dx in Canada)
  - Serological data in Thailand from the 1950s
    - Fonseca C et al. AJTMH 2014
- 2015: Vietnam (dx in Israel)
  - Serological data in Vietnam from the 1950s
    - Pond WL. Trans R Soc Trop Med Hyg 1963

Sentinel Cases

- 2010: Cameroon (diagnosed retrospectively in Belgium)
  - Only reported case in Cameroon since 2010
- 2015: Kirabati (dx in New Zealand)
  - First known report
- April 2016: East Timor (dx in Germany)
  - First known report although only probable

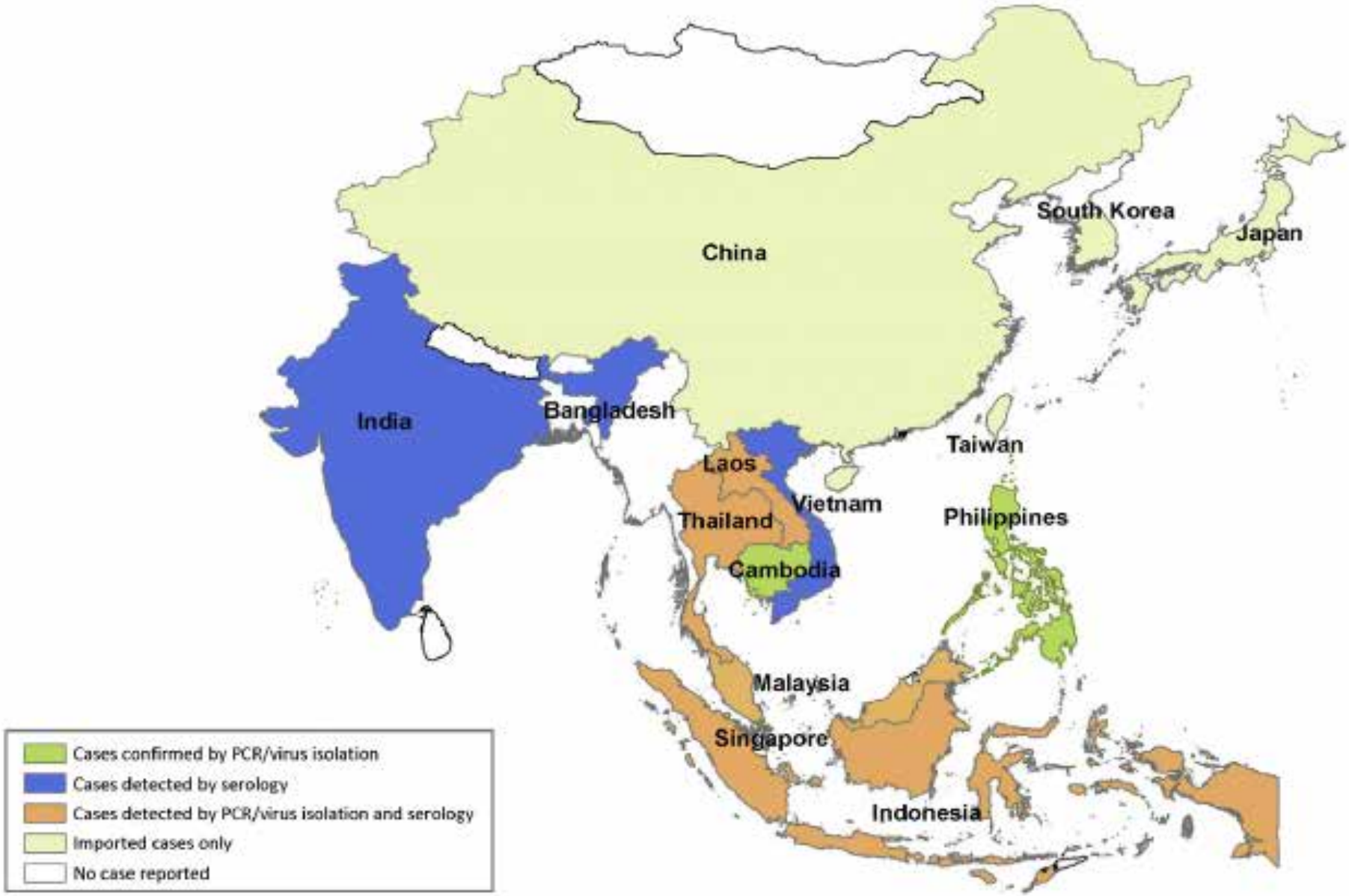
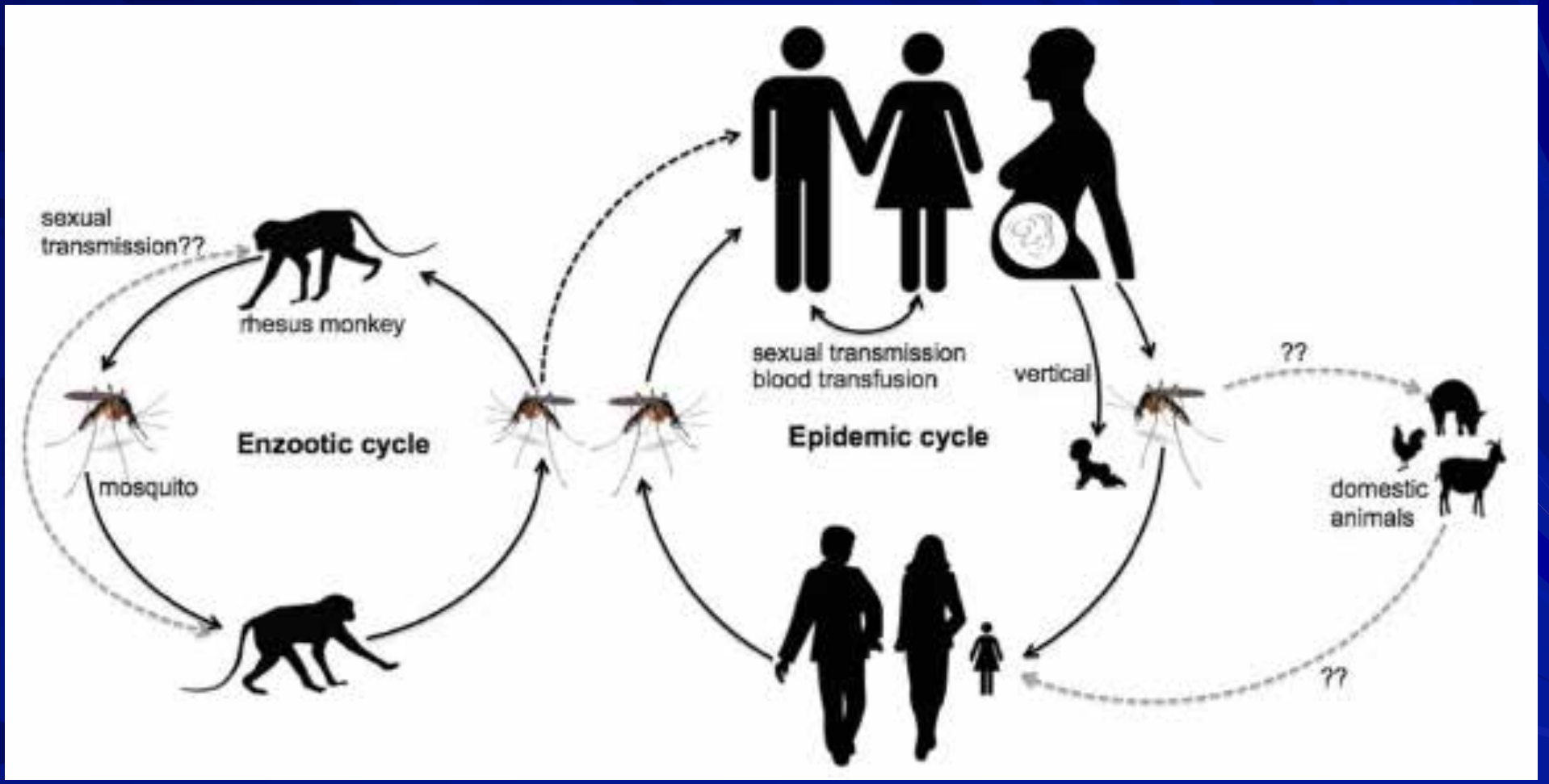


Figure 2. Map of Asian countries in which Zika virus circulation has been reported up to September 1, 2016.

Zika Virus Transmission Cycles



Basu & Tumban Virol J 2016

Mosquito Vectors

Aedes aegypti **-**
main vector
Multiple blood meals
Humans preferred host

Ae. albopictus **-**
potential vector
Single blood meal
Humans and other mammals

CDC
Centers for Disease Control and Prevention

Transmission – Other Modes

Proven:

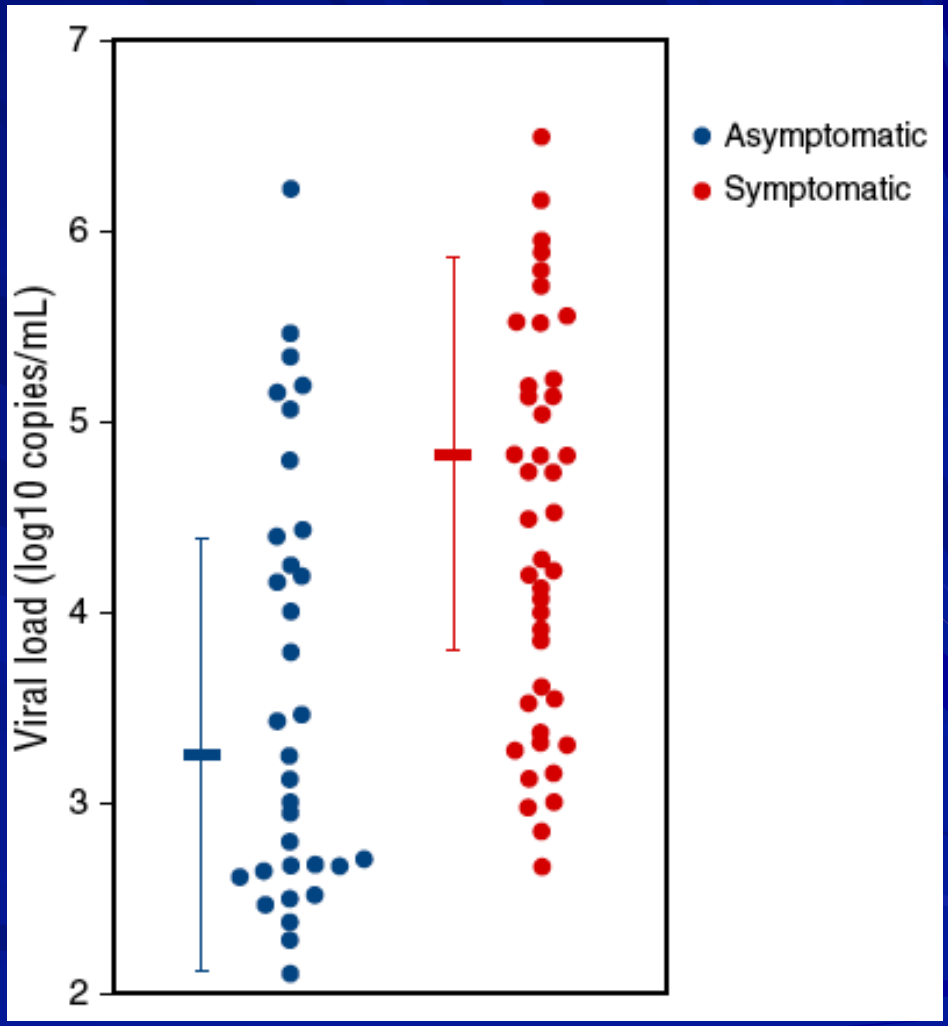
- Sexual
  - Male to female; male to male; female to male
- Blood products
  - Documented in Brazil and French Polynesia

Theoretically possible:

- Breast milk
  - 1 report (Mar 2016) infectious (VL 850k/ml) day 4 postpartum
- Saliva or tears
- Transplantation

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



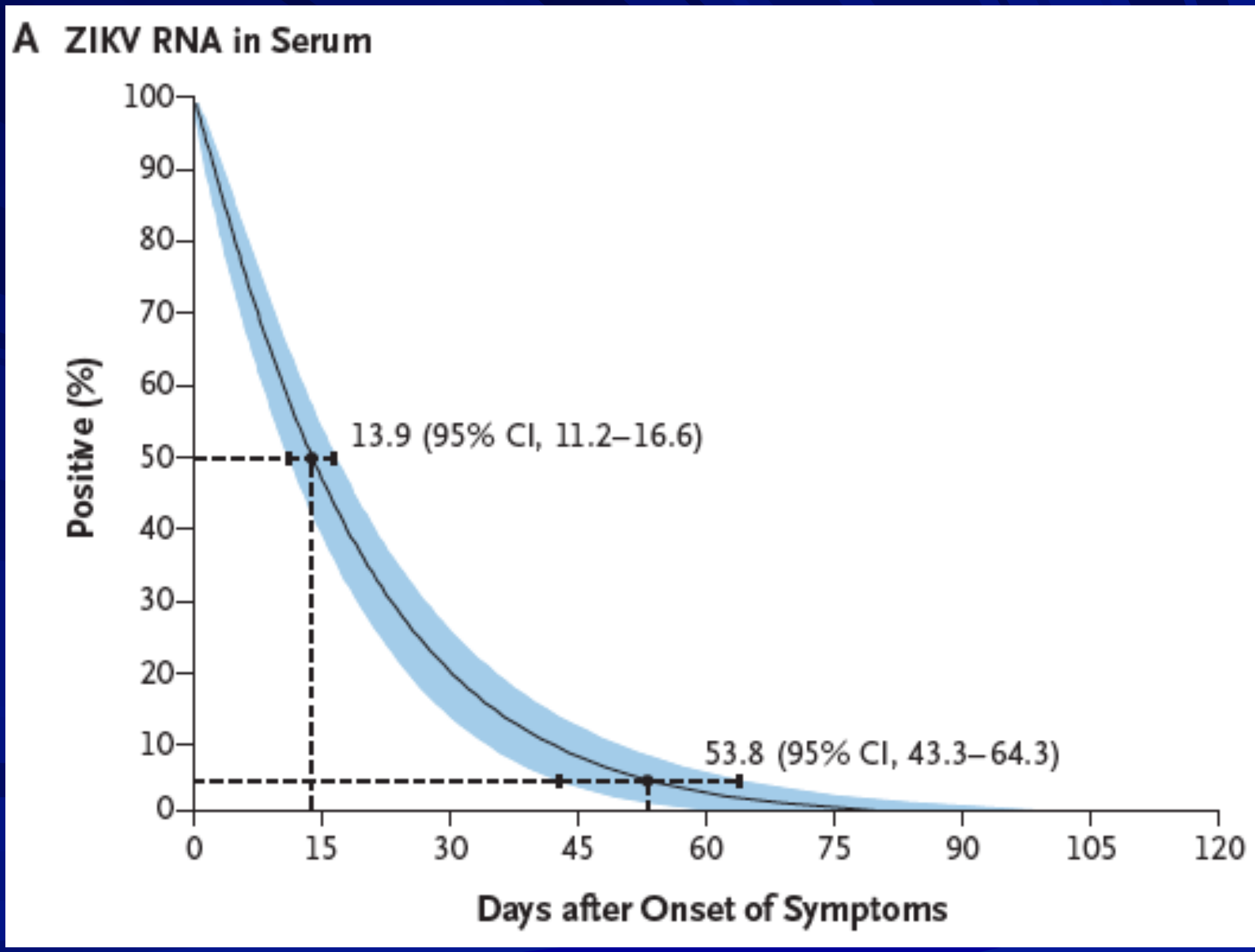
Sexual Transmission

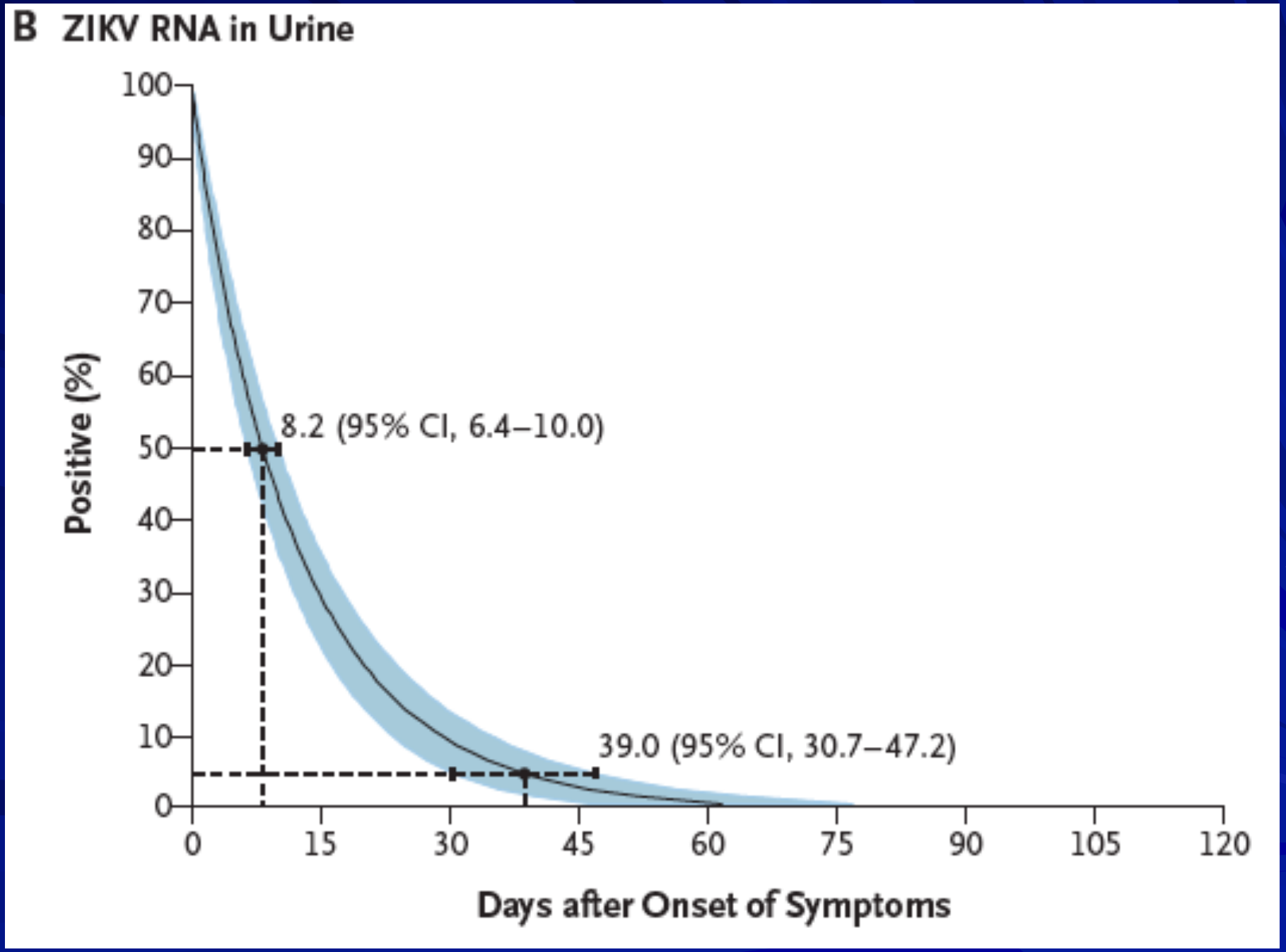
- Preliminary semen carriage studies:
  - Up to 188 days by PCR
  - Replication competent Zika in semen for 69 days
- High viral load in semen (and urine)
- Rarely hematospermia or microhematospermia
- Viral shedding in vaginal secretions to 14 days and in cervical mucus to day 11 post-symptom onset
- 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

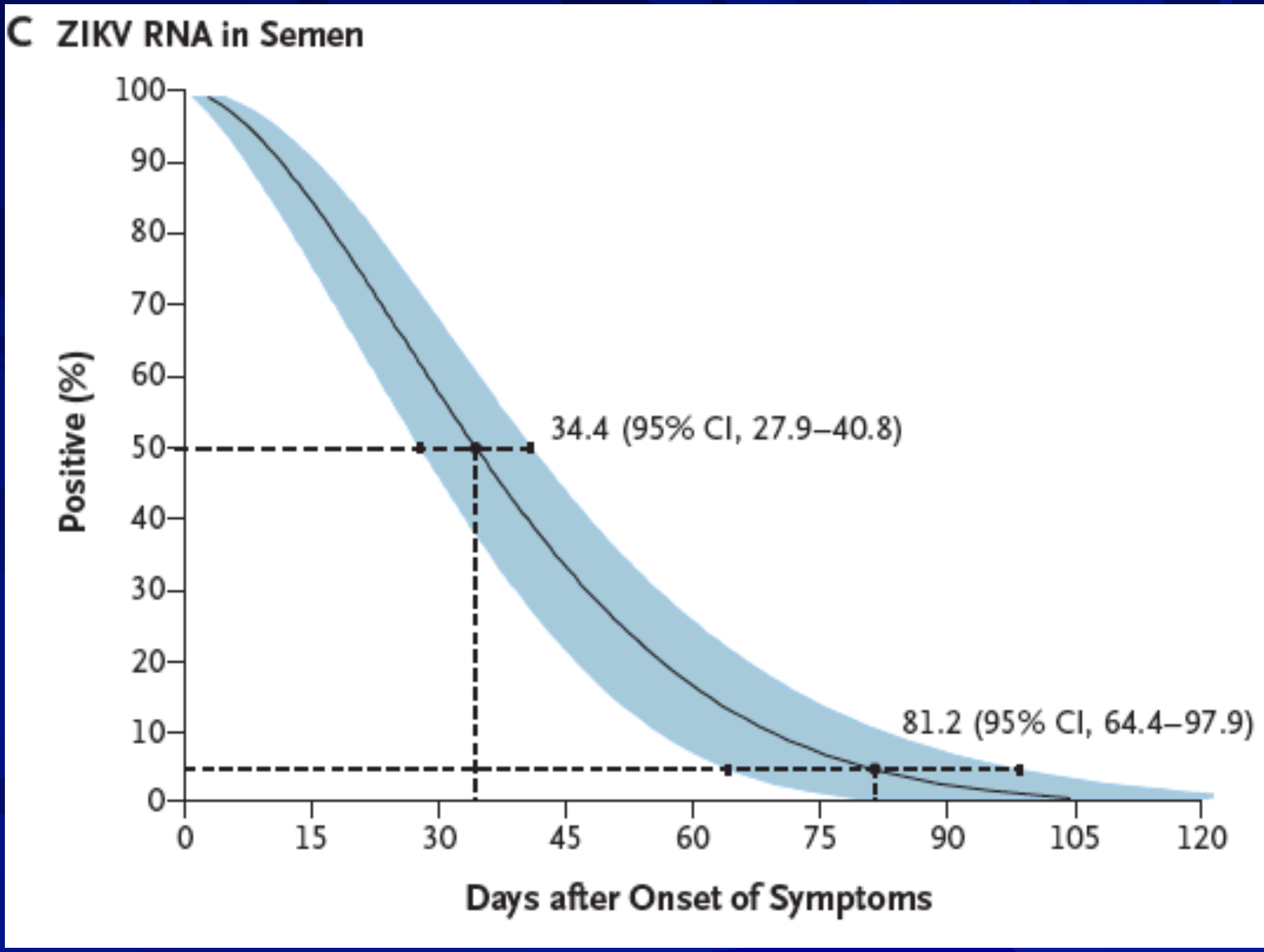
Persistence of Zika Virus in Body Fluids — Preliminary Report

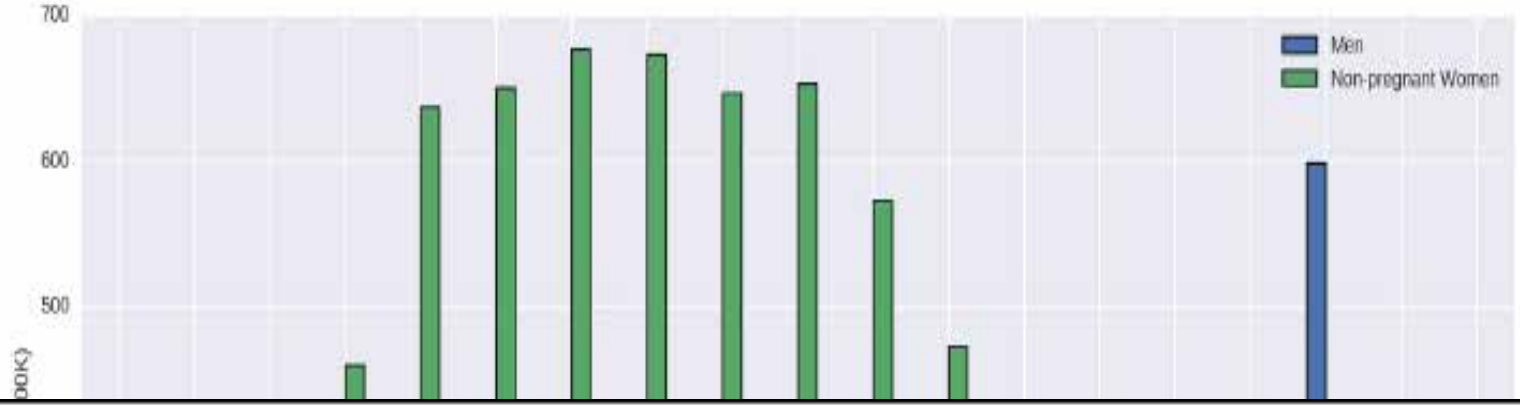
Gabriela Paz-Bailey, M.D., Ph.D., Eli S. Rosenberg, Ph.D., Kate Doyle, M.P.H., Jorge Munoz-Jordan, Ph.D., Gilberto A. Santiago, Ph.D., Liore Klein, M.S.P.H., Janice Perez-Padilla, M.P.H., Freddy A. Medina, Ph.D., Stephen H. Waterman, M.D., M.P.H., Carlos Garcia Gubern, M.D., Luisa I. Alvarado, M.D., and Tyler M. Sharp, Ph.D.

- 150 participants enrolled in Puerto Rico (55 men; 95 women)
- Collected serum, urine, saliva, semen, and vaginal secretions weekly for 1 month then at 2, 4, and 6 months
- Median and 95th percentile longest in semen; few positive vaginal or saliva samples
  - Paz-Bailey G et al. NEJM 2017


A ZIKV RNA in Serum
Positive (%)
100
90
80
70
60
50
40
30
20
10
0
13.9 (95% CI, 11.2–16.6)
53.8 (95% CI, 43.3–64.3)
0
15
30
45
60
75
90
105
120
Days after Onset of Symptoms


B ZIKV RNA in Urine
Positive (%)
100
90
80
70
60
50
40
30
20
10
0
8.2 (95% CI, 6.4–10.0)
39.0 (95% CI, 30.7–47.2)
0
15
30
45
60
75
90
105
120
Days after Onset of Symptoms


C ZIKV RNA in Semen
Positive (%)
100
90
80
70
60
50
40
30
20
10
0
34.4 (95% CI, 27.9–40.8)
81.2 (95% CI, 64.4–97.9)
0
15
30
45
60
75
90
105
120
Days after Onset of Symptoms



Disease	Incidence in women	Incidence in men	Ratio, women/men
Zika	5382.58	2854.85	1.88
Dengue 2015–16	16 628.04	13 941.05	1.19
Dengue 2013	32 201.37	25 410.52	1.27

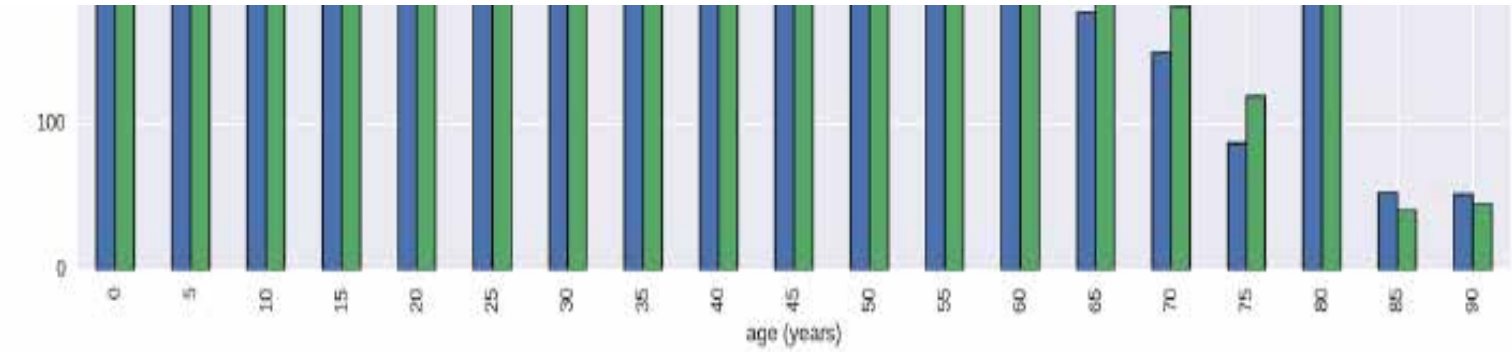


Figure 3. Incidence of Zika in men and women by age group, excluding pregnant women. Pregnant women are excluded because extra efforts were made by the health services to identify all possible Zika cases in this group due to their babies being at high risk of developing neurological complications.

Coelho FC et al. Incidence by sex Zika and dengue in Rio. IJID 2016

Clinical Manifestations

- Estimated 80% asymptomatic
  - Duffy MR et al. NEJM 2009
- Incubation period: 2-7 d (7-14 d in mosquitos)
  - Similar to other flaviviruses
- Typical presentation:
  - Maculopapular rash (duration 2-14 d; median 6 d)
  - Fever (65%)
  - Arthralgias (duration 1-14 d; median 3.5 d)
  - Conjunctivitis

rash

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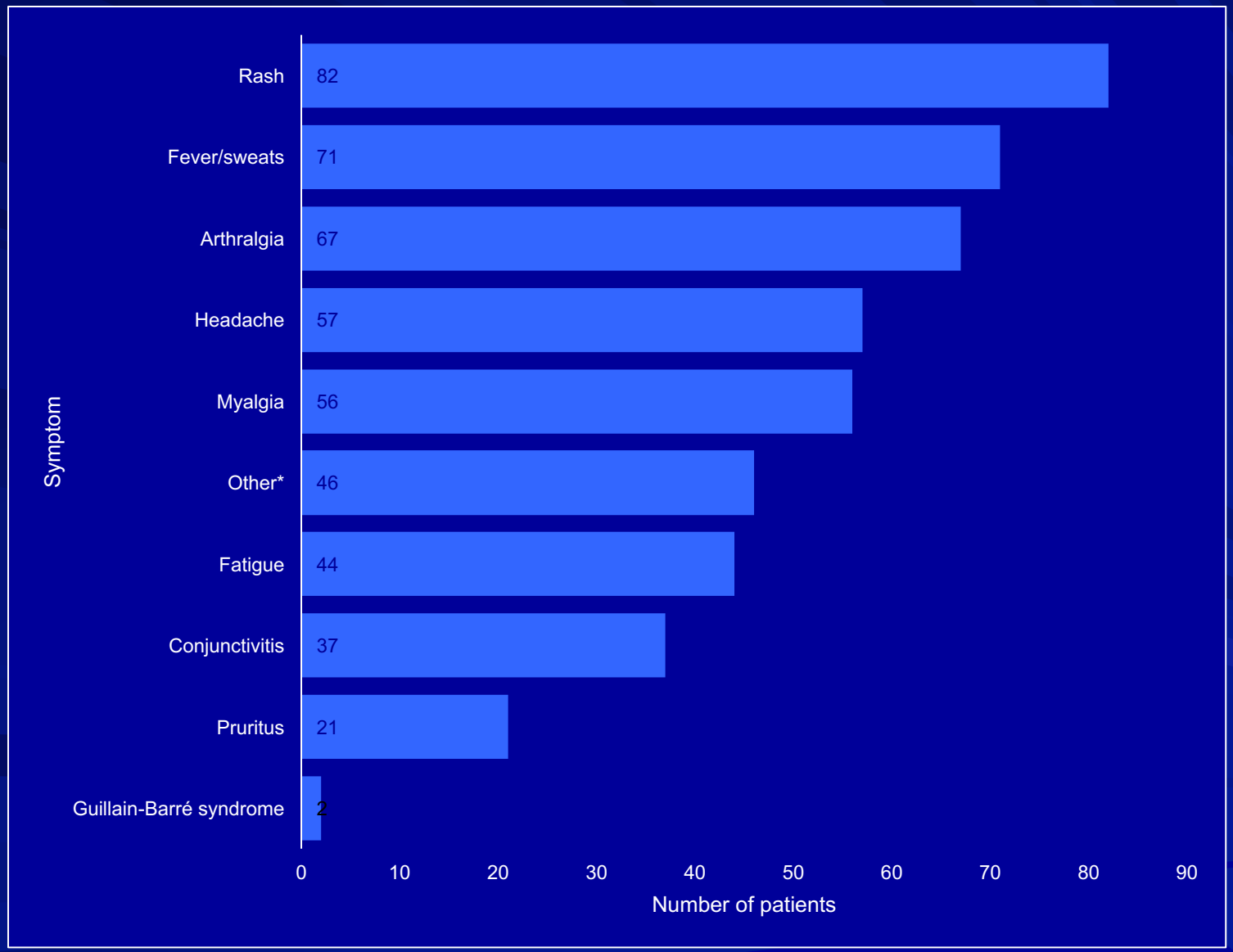
land,

Maculopapular rash after travel to Haiti

Clinical symptoms and signs in 93 patients with Zika virus disease acquired in the Americas



Hamer DH et al. GeoSentinel case series Ann Int Med 2016

Less Common Signs

- Joint swelling
- GI: diarrhea, nausea, vomiting
- Paraesthesias
- Retro-orbital pain
- Pharyngitis
- Dysgeusia
- Subcutaneous hematomas

Substantial Clinical Overlap Among Common Arboviruses

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

Co-infection Data for 346 Nicaragua Children 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.

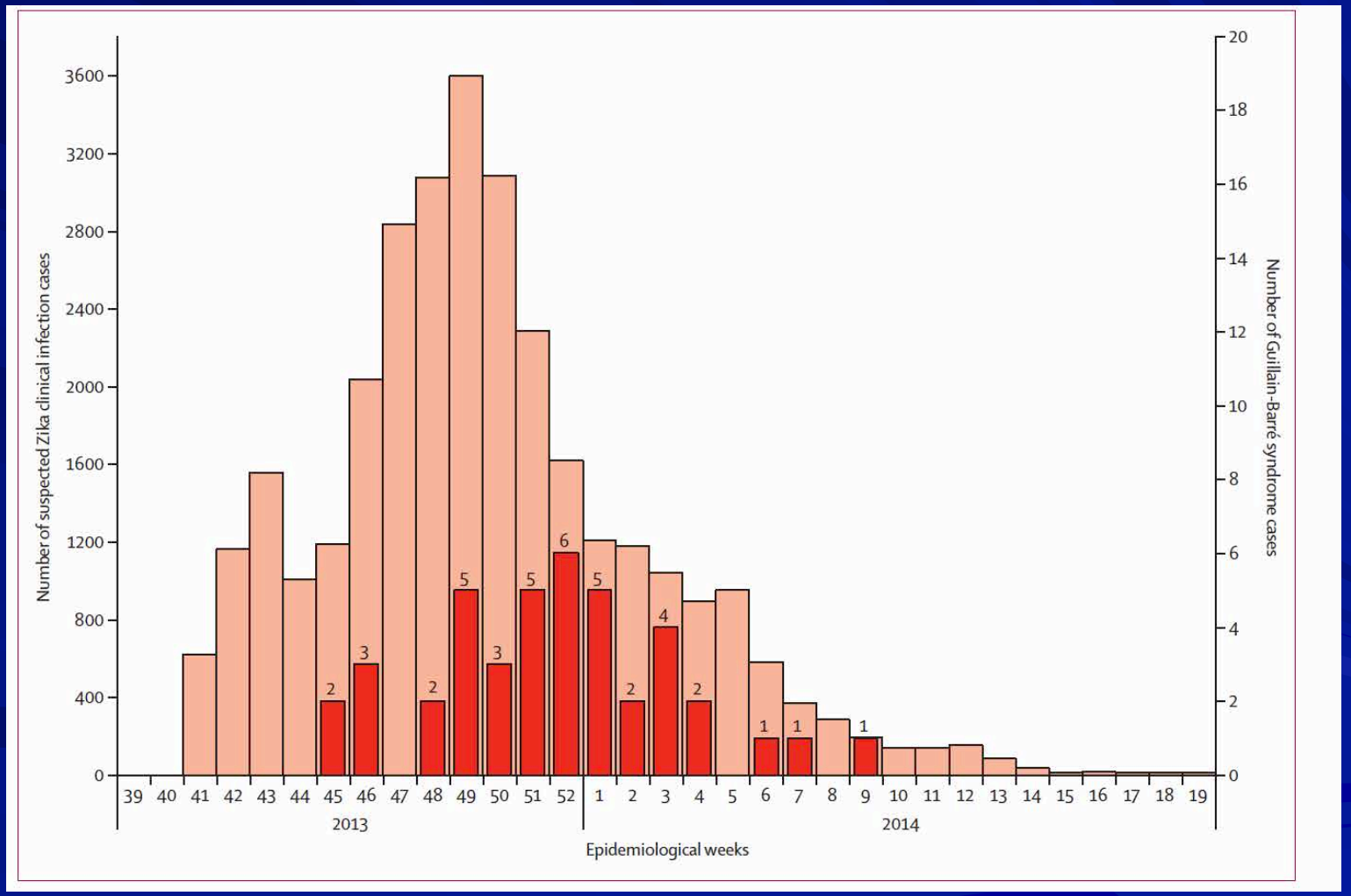
[a] Serotypes of 109 DENV-positive samples: DENV-2, 107; DENV-1, 1; DENV-4, 1.

Zika Complications

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

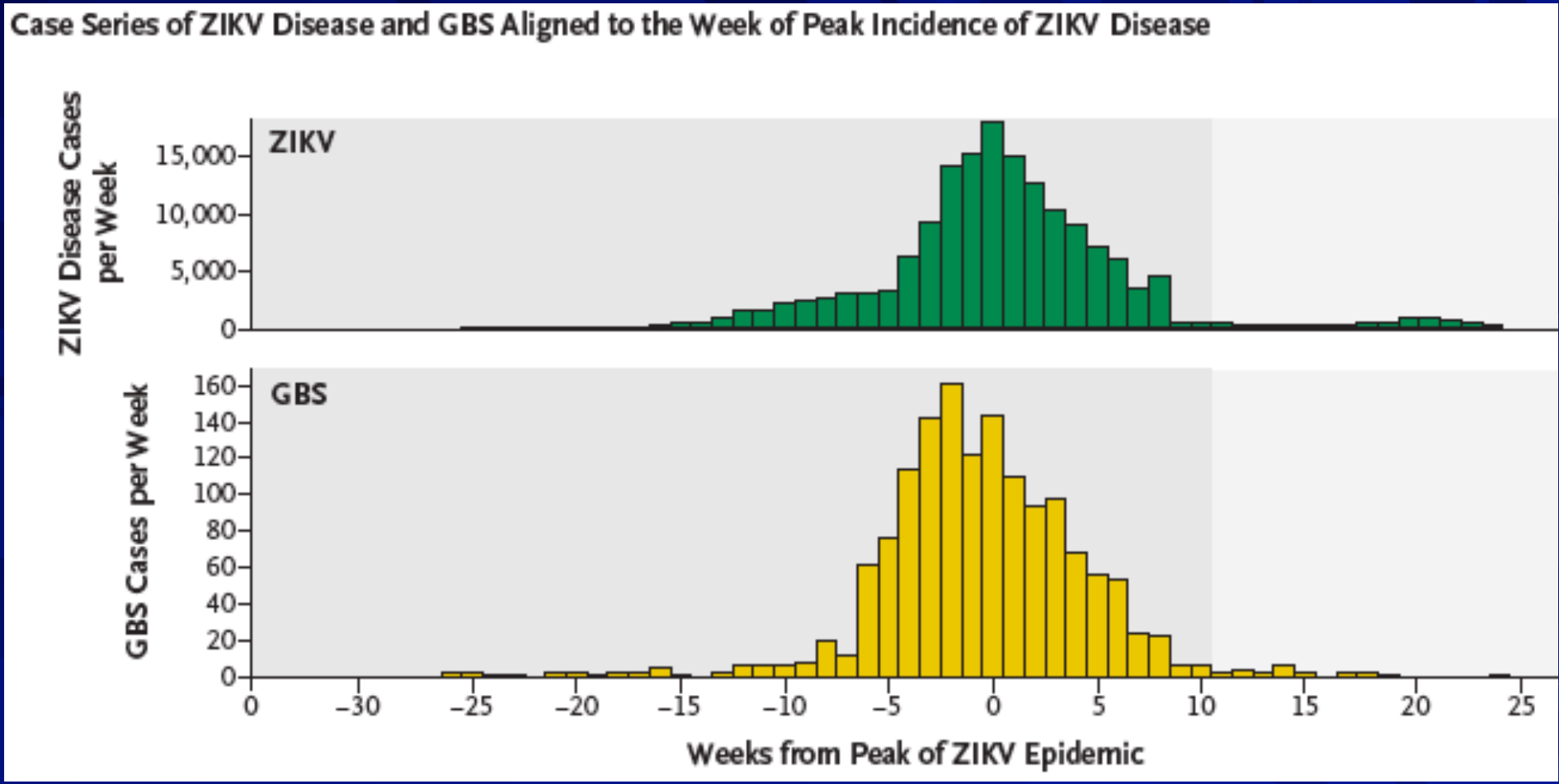
ZIKV-Associated GBS in French Polynesia

- 42 patients – median age 42 y; 74% men; 100% with neutralizing antibodies to Zika
- Estimated 0.24 cases per 1000 ZIKV infections
- Neurological symptoms median 6 d after recent acute illness (Zika)
- Rapid progression to nadir (median 6 d from onset neurological symptoms)

Cao-Lormeau et al. Lancet 2016

ZIKV-Associated GBS

- No difference past dengue infection
- Clinical presentation:
  - Generalized muscle weakness: 74%
  - Inability to walk: 44%
  - Facial palsy: 64%
  - Required respiratory assistance: 29%
- EPS findings compatible with acute motor axonal neuropathy type
  - Cao-Lormeau VM et al Lancet 2016



- Increased incidence GBS 2 to 9.8 times baseline

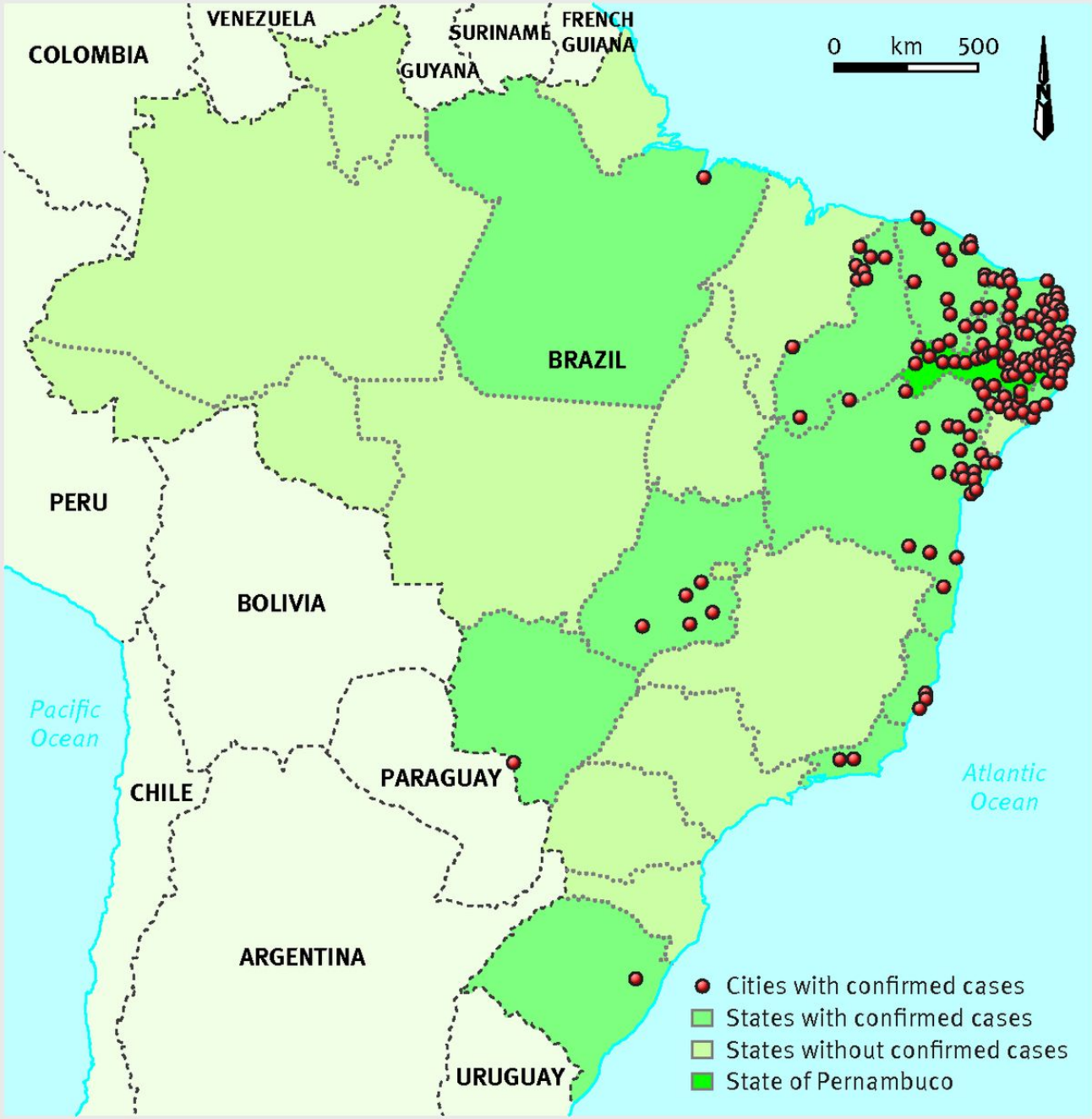
Dos Santos T et al. Case series from 7 countries. NEJM 2016.

Congenital Zika Syndrome

Courtesy of NBC News

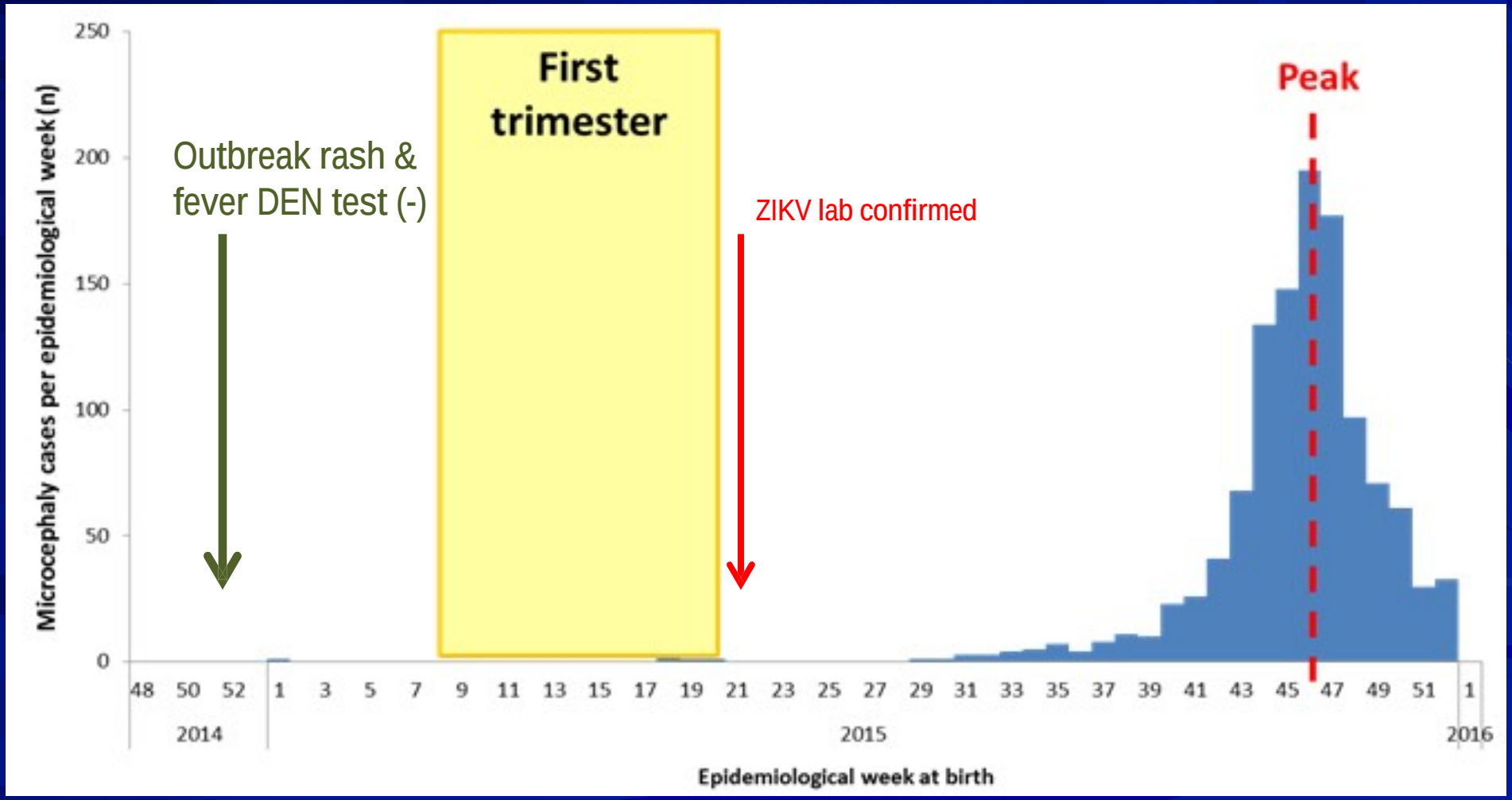
Notified cases of micro-cephaly up to 3 Feb 2016

Vasco Aragao MF et al. BMJ 2016



Epidemic curve of microcephaly cases among at-term newborns

Pernambuco State, Brazil, 2015



Trimester and Risk of Congenital Zika Infection

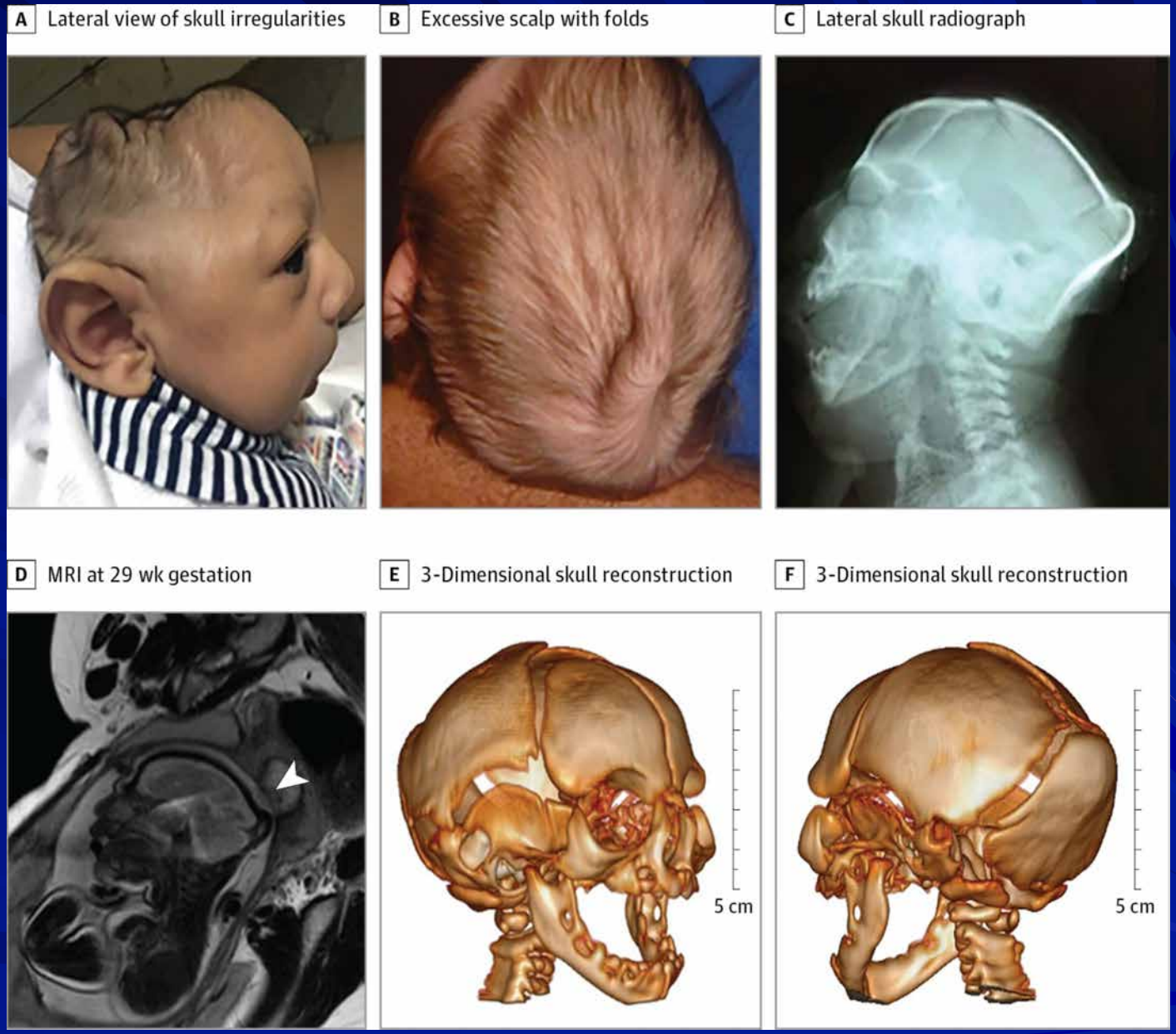
- Municipality-level data indicate suspected microcephaly reports in Brazil correlate best with ZIKV incidence around week 17 of pregnancy
  - Faria NR et al Science 2016
- Risk greatest first trimester
  - Johansson MA et al. NEJM 2016
- Low risk third trimester in Colombia
  - Pacheco O et al NEJM 2016

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.



Shepard's criteria for teratogenicity: 1. Proven exposure during a critical time in development

- First/second trimester
  - Microcephaly
  - Brain anomalies – calcifications, lissencephaly, cerebellar hypogenesis, ventriculomegaly
- Third trimester
  - Growth restriction
  - Stillbirth (without gross anomalies)

Shepard. "Proof" of human teratogenicity. Teratology, 1994.
Rasmussen et al. Zika virus and birth defects – reviewing the evidence for causality. NEJM May 2016

2. Consistency across ≥ 2 high quality epidemiologic studies

- Brasil et al, NEJM (Brazil)
  - 88 symptomatic women, 72 with + serology
    - 7 fetuses with CNS lesions
    - 5 IUGR +/- microcephaly
    - 2 stillbirths
- Cauchemez et al, Lancet (French Polynesia)
  - Time analysis of cases of microcephaly, 88% occurred shortly after the 7 month outbreak

Brasil et al, Zika virus infection in pregnant women in Rio de Janeiro – Preliminary Report. NEJM 2016.

Cauchemez, et al. Association between Zika virus and microcephaly in French Polynesia, 2013-2015: a retrospective study. Lancet May 2016.

3. Characterized phenotype

- Congenital Zika syndrome
  - Microcephaly – not a necessary feature
    - Reduced brain volume
  - Intracranial calcifications
  - Ventriculomegaly, lissencephaly, pachygyria
  - Ocular manifestations
- Fetal brain disruption sequence

Ventura, Zika: neurological and ocular findings infant without microcephaly. Lancet 2016.

Franca et al, Congenital Zika virus syndrome in Brazil: a case series of the first 1501 live births with complete investigation. Lancet August 2016.

4. Rare exposure - rare phenotype

- Repeated reports of congenital Zika syndrome in fetuses of women who have traveled to affected areas
  - Brazil
  - Haiti
  - Puerto Rico
  - Cape Verde
  - El Salvador

Meaney-Delman et al. Zika virus infection among U.S. pregnant travelers – August 2015-Febrary 2016. MWMR 2016.

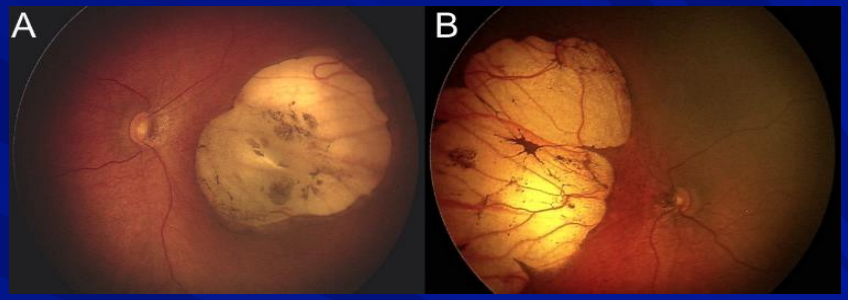
Criteria for Proof of Teratogenicity of Zika Virus in Pregnancy

Criterion	Evidence	Criterion Met?
Proven exposure to agent during critical prenatal development	Case series and epi studies suggest late 1st to early 2nd trimester	Yes
Consistent findings 2+ high quality epi studies	Brazil and Columbian data	Partially
Specific deficit or syndrome	Phenotype well characterized in fetuses	Yes
Rare environmental exposure	Microcephaly cases post-travel to endemic areas	Yes
Animal teratogenicity	No good animal models	No
Association makes biological sense	Congenital syndrome similar to TORCH, Zika neurotropism	Yes

Rasmussen S et al. NEJM 2016

Congenital Zika Syndrome Common Manifestations

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



Pictures from
http://www.telegraph.co.uk/news/picturegalleries/worldnews/12125010/Zika-virus-outbreak-spreads-across-South-and-Central-America-in-pictures.html?frame=3561550

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

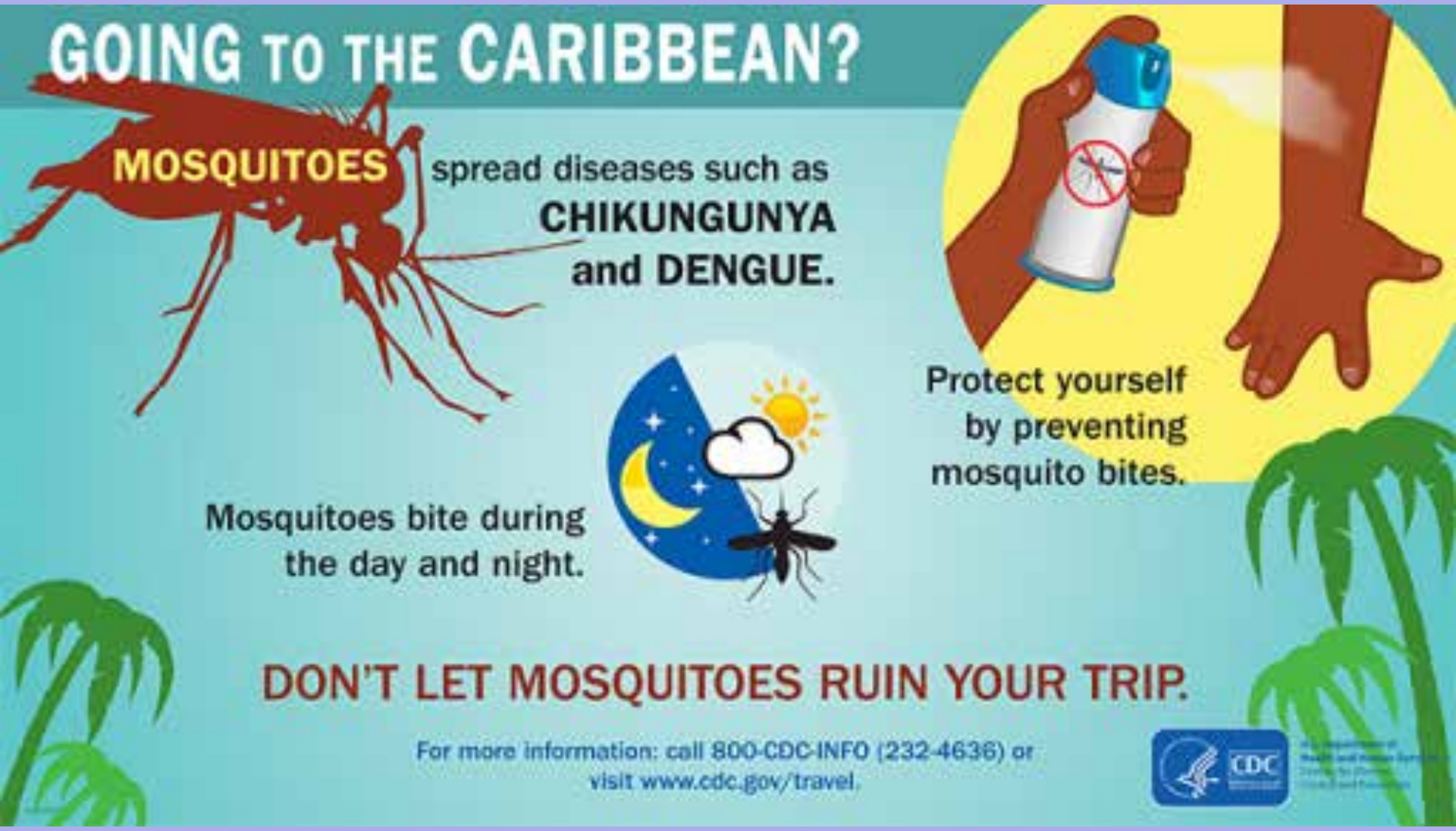
Zika Diagnostic Options

- Monoplex RT-PCR serum, urine, CSF, or amniotic fluid
- Trioplex Real Time RT PCR (Zika, dengue, and chikungunya
- MAC ELISA for anti-Zika IgM
- Euroimmun for anti-Zika IgM and IgG
- PRNT confirmation of IgM and IgG
- Anti-Zika IgG available in Europe
- New assays under development (NS-1 Ag)

Treatment of Zika Virus Disease

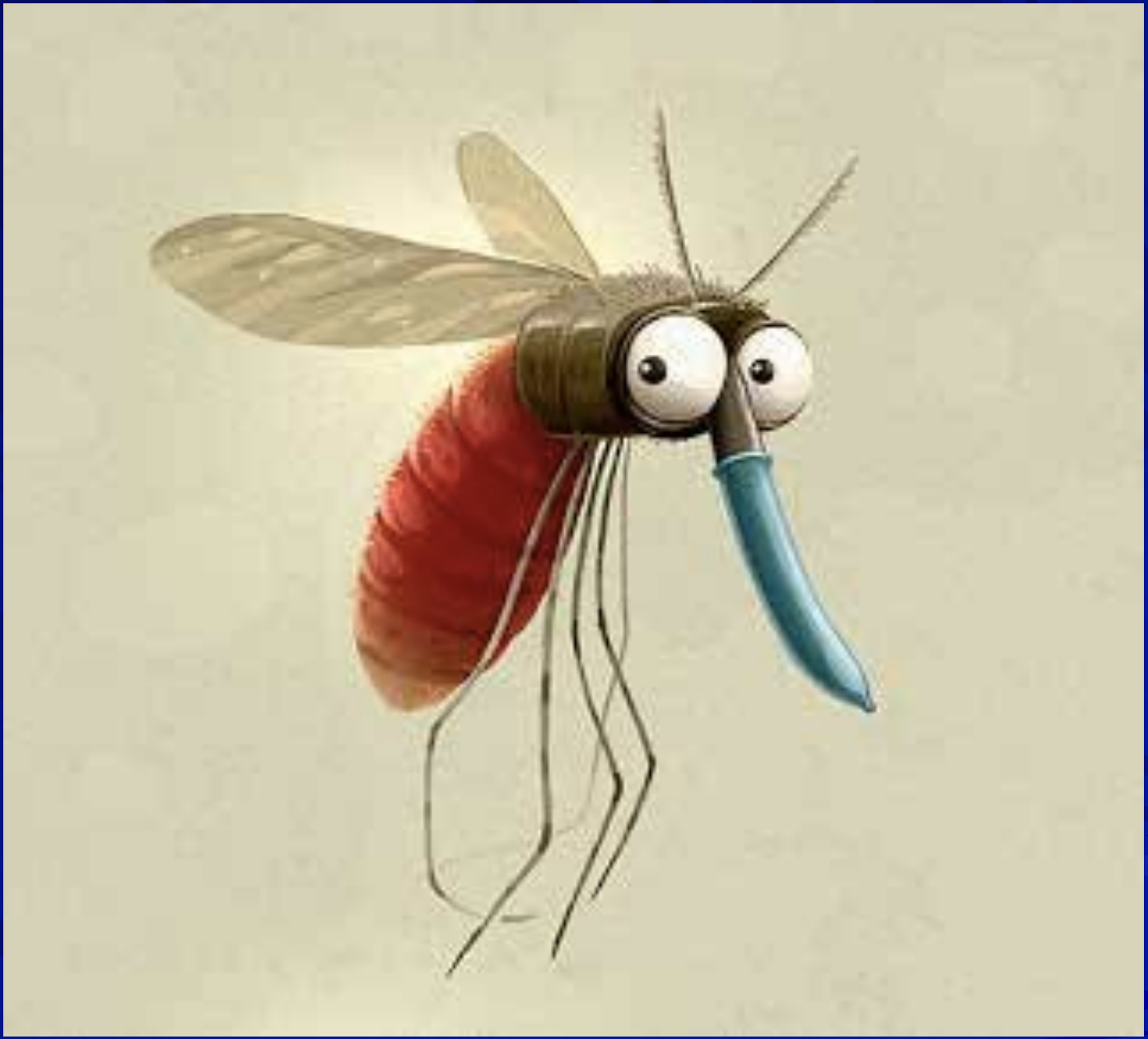
- Supportive treatment with acetaminophen, hydration, and rest
- Avoid aspirin and NSAIDs until dengue has been ruled out
- Urgent medical care needed if symptoms of GBS develop
- No specific antiviral therapy available
  - In vitro data suggest sofosbuvir, chloroquine, and azithromycin active against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

Dengue, Chikungunya, and Zika



Zika Public Health Control Measures

- Screening blood products
- Reduce mosquito breeding sites by emptying standing water from containers (community mobilization)
- Genetically modified mosquitoes
- Vaccines – under development



The Zika Virus Is Spreading in Miami, CDC Issues Travel Warning ...Us Weekly

Carlos Varas, a Miami-Dade County mosquito inspector, sprays around homes in the Wynwood area of Miami on August 2, 2016
Credit: Emily Michot/Miami

Zika Vaccines

- Two DNA vaccines completed Phase 1
  - Phase 2 started June in Puerto Rico for one
  - Phase 2 starting Jan 2017 for the other
- Whole inactivated vaccine with alum Phase 1 starting soon
- WHO website has about 20 different vaccines (live attenuated, chimeric, recombinant subunit, mRNA, VSV)
- Target populations: WORA, their sexual partners, travelers

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

Travel and Pregnancy

- 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
- Screen pregnant women after travel to Zika-infected areas

Personal Protection Measures

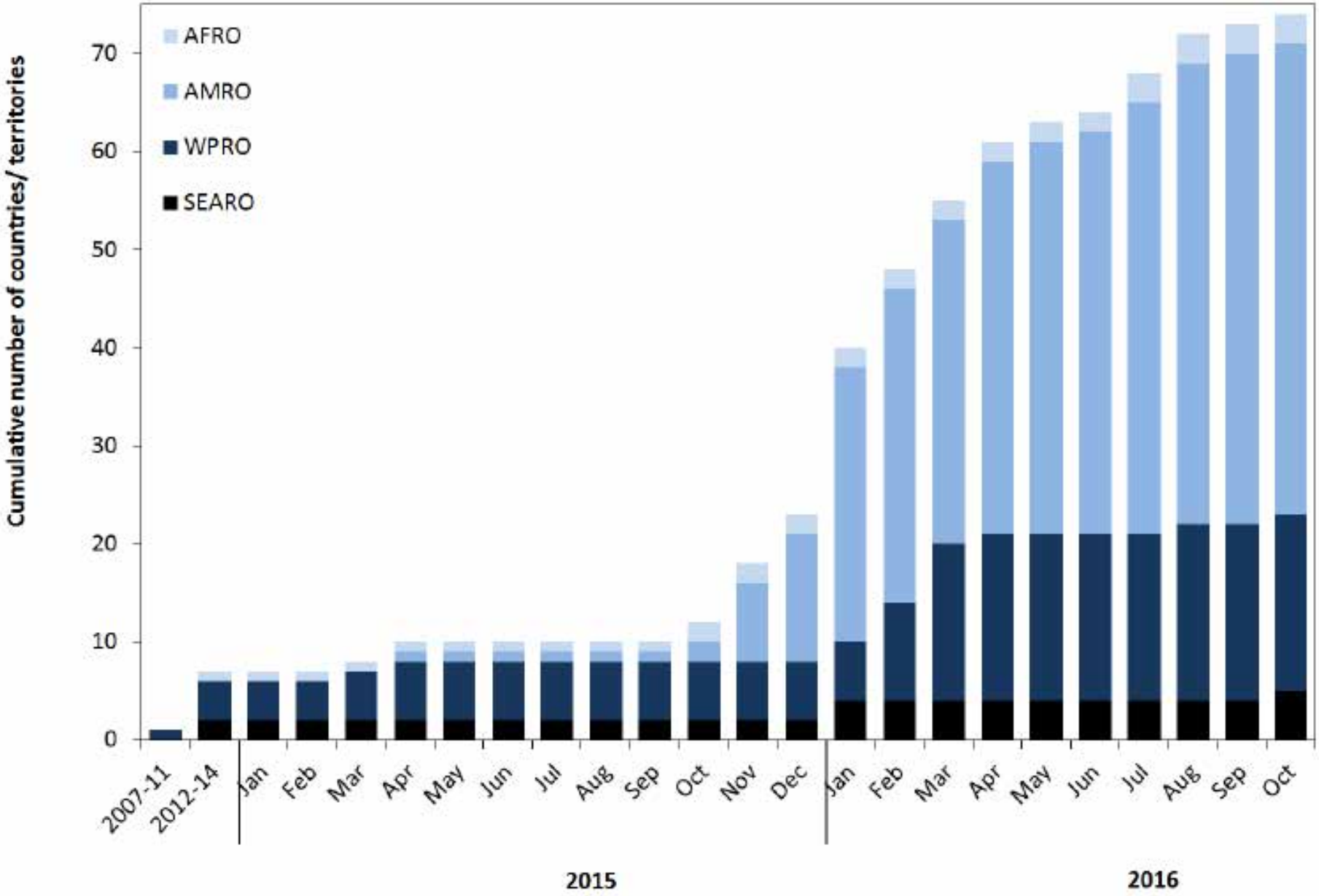
- Dark colors and strong scents attract mosquitoes
- Insect repellents providing long lasting protection:
  - DEET (20-30%)
  - Picaridin (icaridin) (20%)
  - IR3535
  - Oil of lemon eucalyptus and para-menthane-diol
  - If using both sunscreen and insect repellent, apply sunscreen first and then repellent
- Permethrin treatment of clothing

Prevention of Sexual Transmission of Zika

After visiting areas with local Zika transmision:

- Sexual partners of pregnant women should practice safe sex or abstain from sexual activity for duration of pregnancy
- Men, both symptomatic and asymptomatic, should wait at least 6 months before attempting conception
- Asymptomatic and symptomatic women returning should wait at least 8 weeks before attempting conception

Figure 1. Cumulative number of countries and territories by WHO region[3] reporting mosquito-borne Zika virus transmission for the first time by year (2007–2014), and by month from 1 January 2015 to 26 October 2016



WHO Classifications of Zika Transmission

- Category 1: Countries with a reported outbreak from 2015 onwards
  - e.g. Angola, Brazil, Maldives
- Category 2: Countries with evidence of transmission before 2015 and ongoing transmission
  - e.g. Haiti, Viet Nam
- Category 3: Countries with evidence of local mosquito-borne Zika infections in or before 2015, but without documentation of cases in 2016, or outbreak terminated (interrupted transmision)

  e.g. Easter Island, French Polynesia

Conclusions

- Zika virus responsible for large outbreak in the Americas
- Clinical overlap with dengue and chikungunya
- Substantial morbidity due to congenital Zika syndrome and, to lesser extent, other neurological complications
- PCR preferred for diagnosis
- Improved diagnostics, Zika vaccine and potential therapeutics in near future
- Useful resources: CATMAT guidelines, CDC, PAHO and WHO web sites

Acknowledgments

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GeoSentinel Surveillance Network Site Directors and CDC team

Tina Yarrington

Thank You for Your Attention!