

# Zika virus infection

Current epidemic outbreak in  
America

Jeong Youn Hong

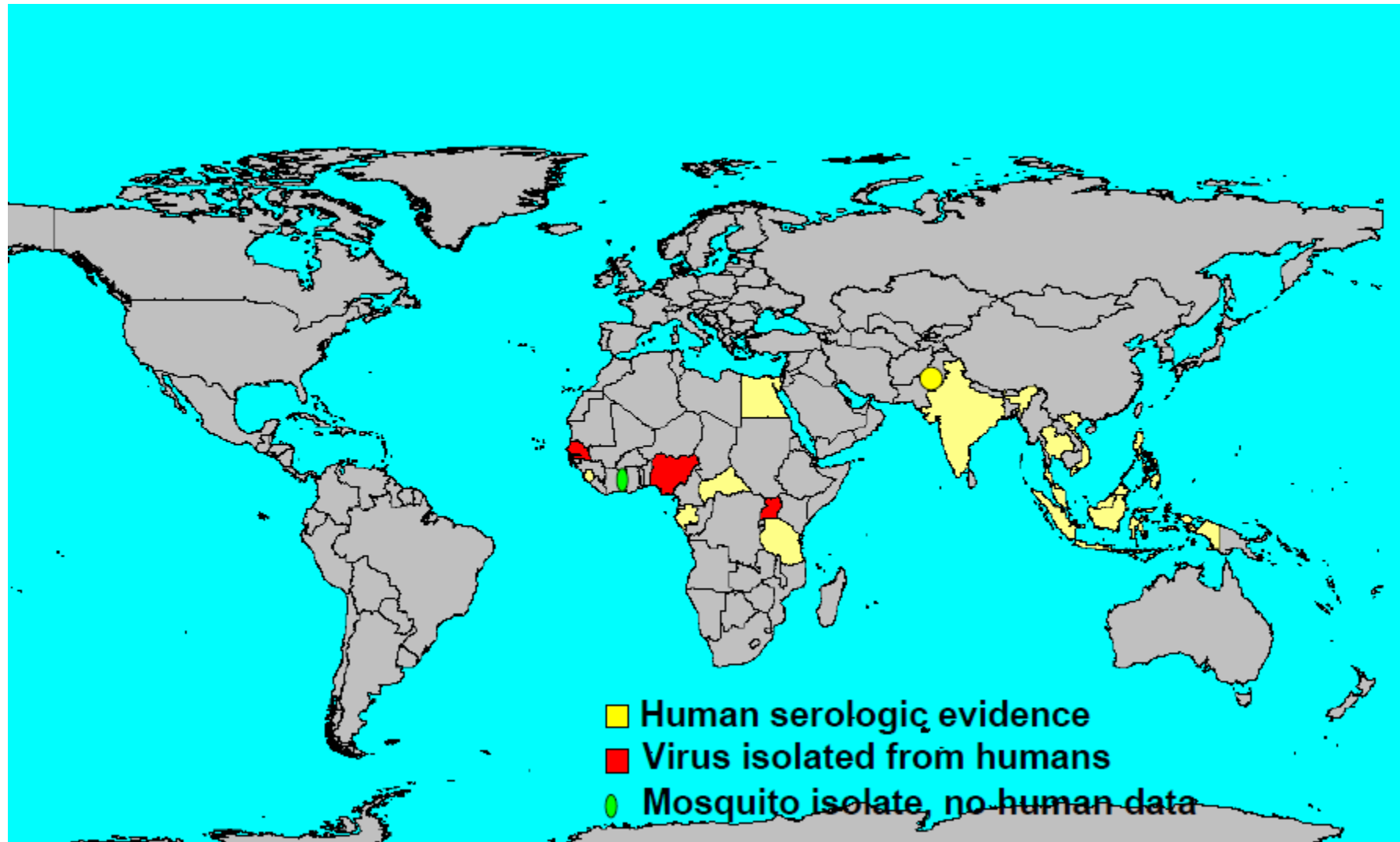
# What is Zika virus?

- Mosquitoes mediated flavivirus (like dengue, yellow fever, Japanese encephalitis viruses)
- Positive-sense, single-stranded RNA virus with 10,794-nt genome
- First isolated from a rhesus monkey in Uganda in 1947
- Phylogenetic analyses have revealed 2 major lineages: **Asian** and African

## Zika virus infection before 2007

- The first human infection was reported in Nigeria in 1954.
- Serologic evidences for human infections in 1950-1965 (Egypt, East Africa, Nigeria, India, Thailand, Vietnam, Philippines, and Malaysia)
- Sporadic infections (13 cases) reported before 2007 Yap Island outbreak.

# Zika virus distribution confined to Africa and Southeast Asia before 2007 Yap Island outbreak



## Zika virus infection from 2007 to early 2013

- **The first Epidemic outbreak (73% (95% confidence interval: 68-77%) of total population, 80% asymptomatic infection) in 2007 on Yap island** in the Federated States of Micronesia.
- Viruses were sporadically isolated in the patients to traveled to or lived in Cambodia (2010), Philippines (2012), Thailand (2013)

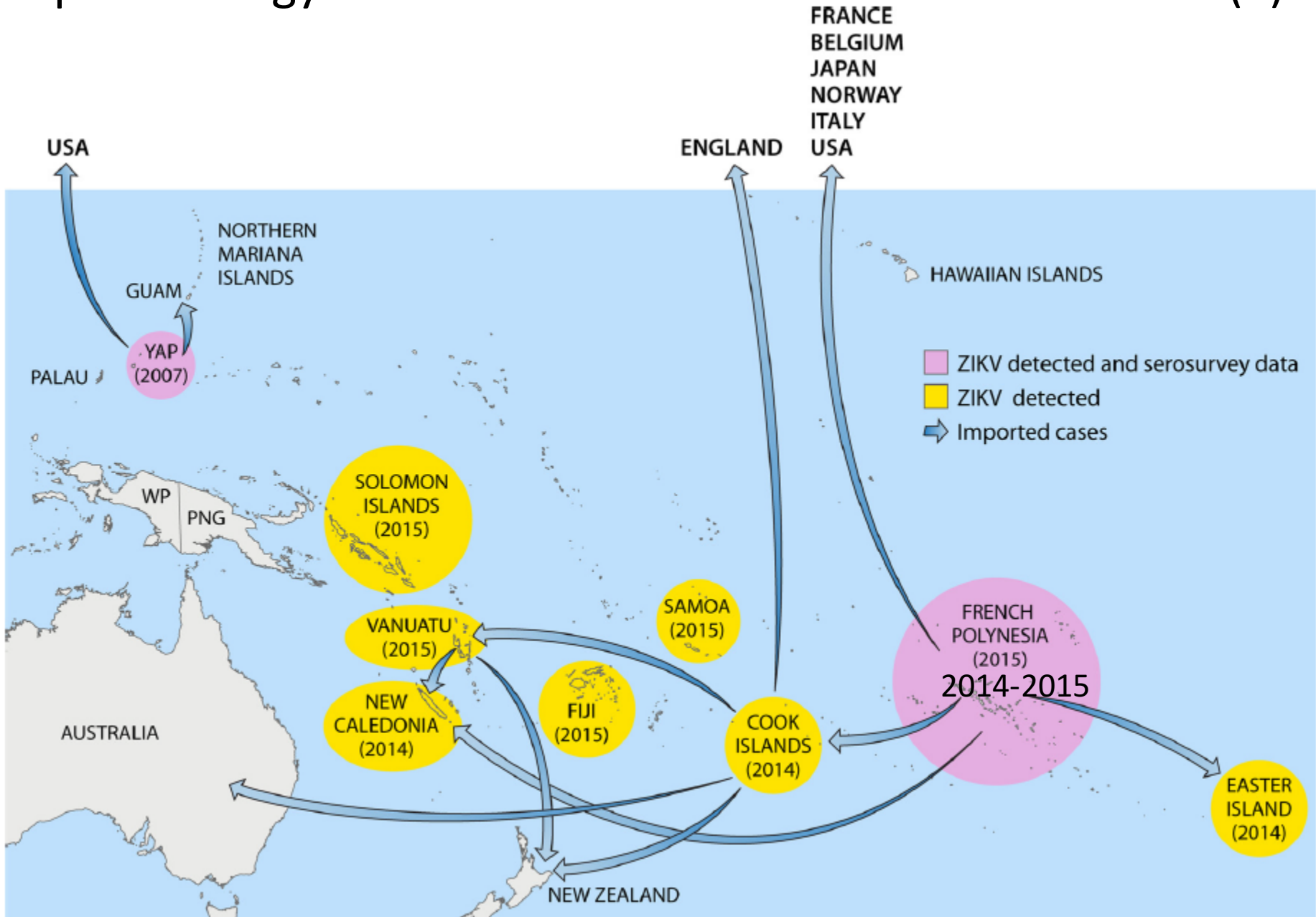
# Zika virus infection from Oct 2013 ~ (1)

- Oct 2013-April 2014: **French Polynesia**
  - the second outbreak >400 laboratory-confirmed cases, **66-86%** general population (270,000) was infected.
  - Increased GBS cases and retrospectively observed increased microcephaly (> x40) : seven cases during four months period Mar 1- Jul 10 2014, (Chauchemez et al; *Lancet* 2016)

## Zika virus infection from Oct 2013 ~ (2)

- New Caledonia
  - Outbreak- Jan 2014 to Aug 2014
  - 1400 confirmed cases of which 35 imported cases. The outbreak peaked in April 2014.
  - Virus is still circulating in 2015
- Cook Island: 932 suspected and 50 confirmed cases
- Other Polynesia islands and Easter Island

# Epidemiology with Zika virus infection from Oct 2013 ~ (3)

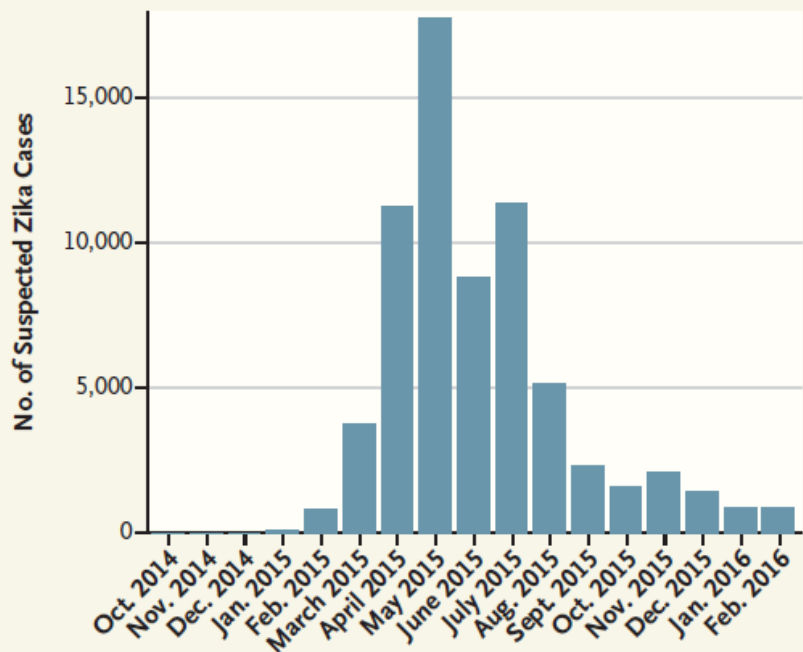




# Zika virus infection in Brazil

- First case was confirmed from Bahia (Northeastern state) in March 2015
- May 2015, the first autochthonous Zika fever was confirmed in a patient from Bahía
- December 2015, 18/26 states in Brazil have confirmed autochthonous virus transmission in the northern, northeastern, southeastern, central, western, and southern regions.
- Huge outbreak (millions of patients) still ongoing (May 2016)
- 1384 cases of confirmed microcephaly or CNS malformation
- 7,534 suspected cases of microcephaly and other congenital malformation of the central nervous system (CNS) have been reported as per Brazil's Surveillance and Response Protocol.

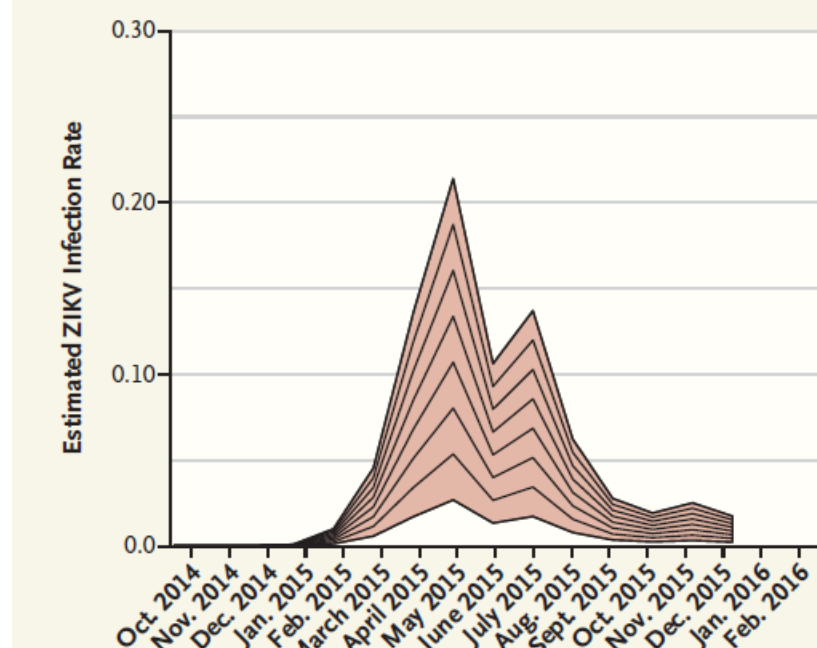
### A Suspected Zika Cases



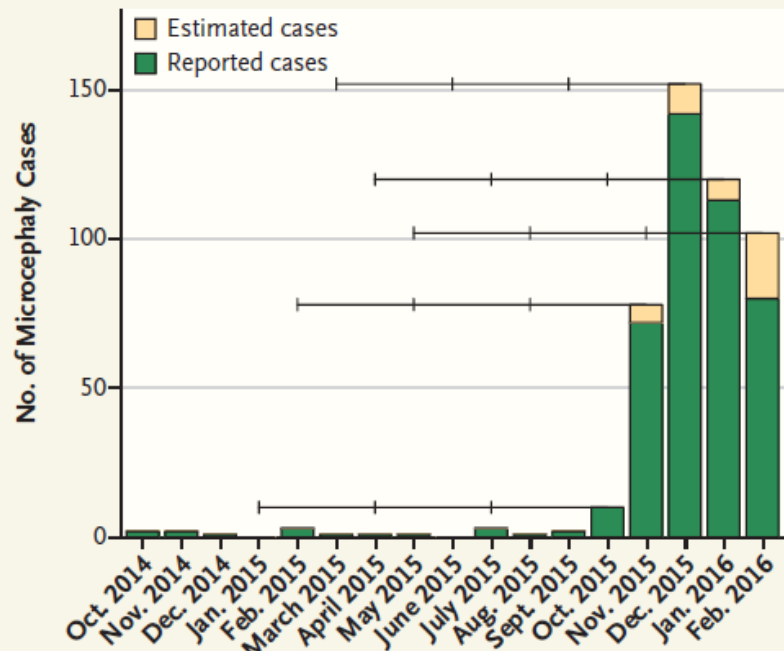
## Risk of Microcephaly in Zika virus infection

### Analysis of data from Bahia, Brazil

### C Estimated ZIKV Infection Rate

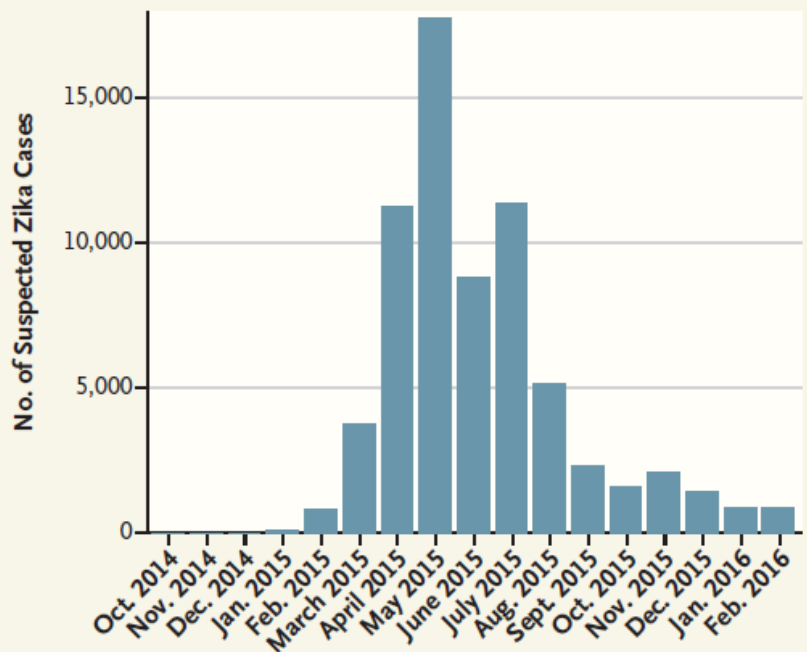


### E Microcephaly Cases



Overall ZIKV infection rate	Estimated microcephaly risk (%)							
	Baseline		With 1 <sup>st</sup> trimester ZIKV infection		With 2 <sup>nd</sup> trimester ZIKV infection		With 3 <sup>rd</sup> trimester ZIKV infection	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
10%	0.023	(0.02, 0.029)	13.2	(12.0, 14.4)	0.055	(0.001, 0.2)	0.063	(0.002, 0.222)
20%	0.022	(0.02, 0.029)	6.69	(6.07, 7.35)	0.028	(0.001, 0.101)	0.033	(0.001, 0.115)
30%	0.023	(0.02, 0.029)	4.52	(4.10, 4.96)	0.018	(0, 0.066)	0.023	(0.001, 0.081)
40%	0.022	(0.02, 0.029)	3.44	(3.12, 3.77)	0.014	(0, 0.05)	0.018	(0, 0.065)
50%	0.022	(0.02, 0.029)	2.79	(2.53, 3.06)	0.011	(0, 0.039)	0.015	(0, 0.054)
60%	0.023	(0.02, 0.029)	2.36	(2.15, 2.59)	0.009	(0, 0.033)	0.013	(0, 0.048)
70%	0.023	(0.02, 0.029)	2.05	(1.86, 2.25)	0.008	(0, 0.028)	0.012	(0, 0.043)
80%	0.023	(0.02, 0.029)	1.83	(1.65, 2.00)	0.007	(0, 0.025)	0.011	(0, 0.04)

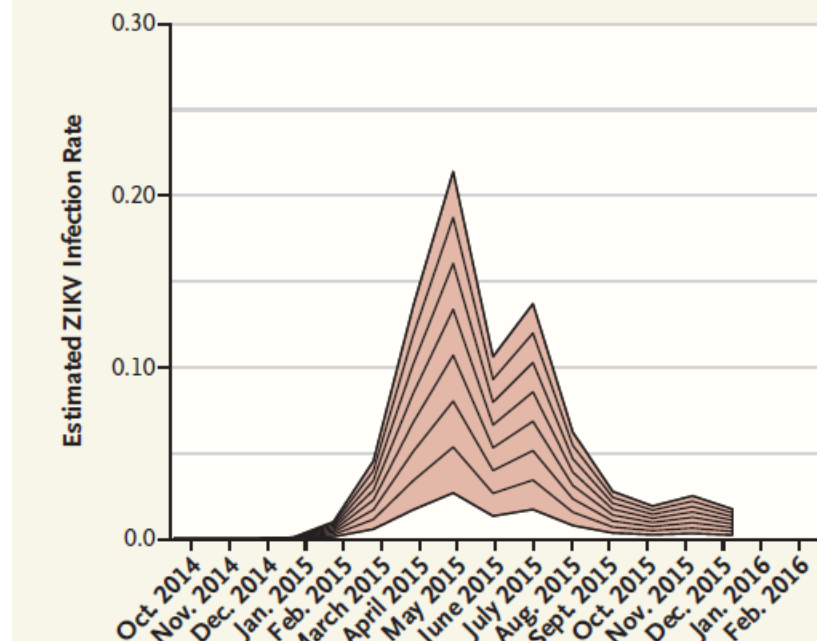
### A Suspected Zika Cases



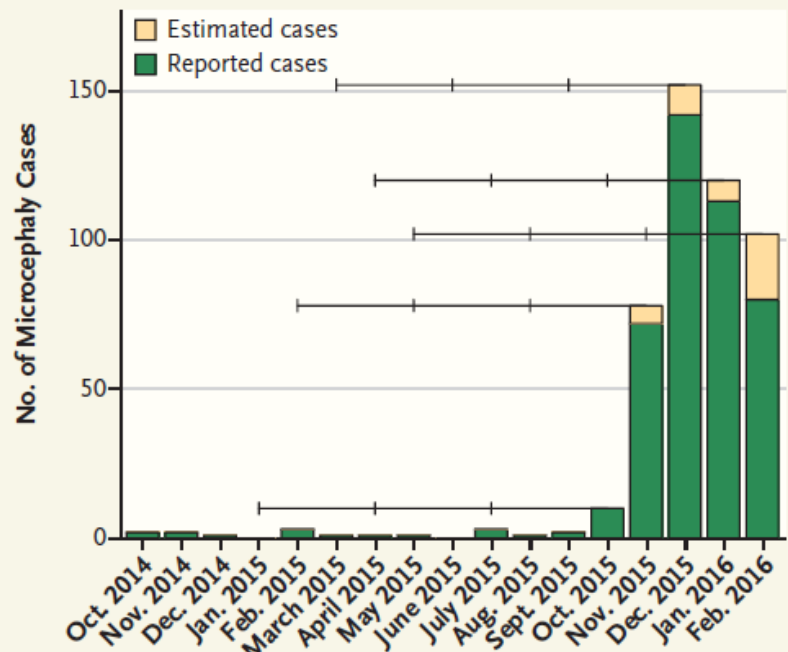
## Risk of Microcephaly in Zika virus infection

### Analysis of data from Bahia, Brazil

### C Estimated ZIKV Infection Rate

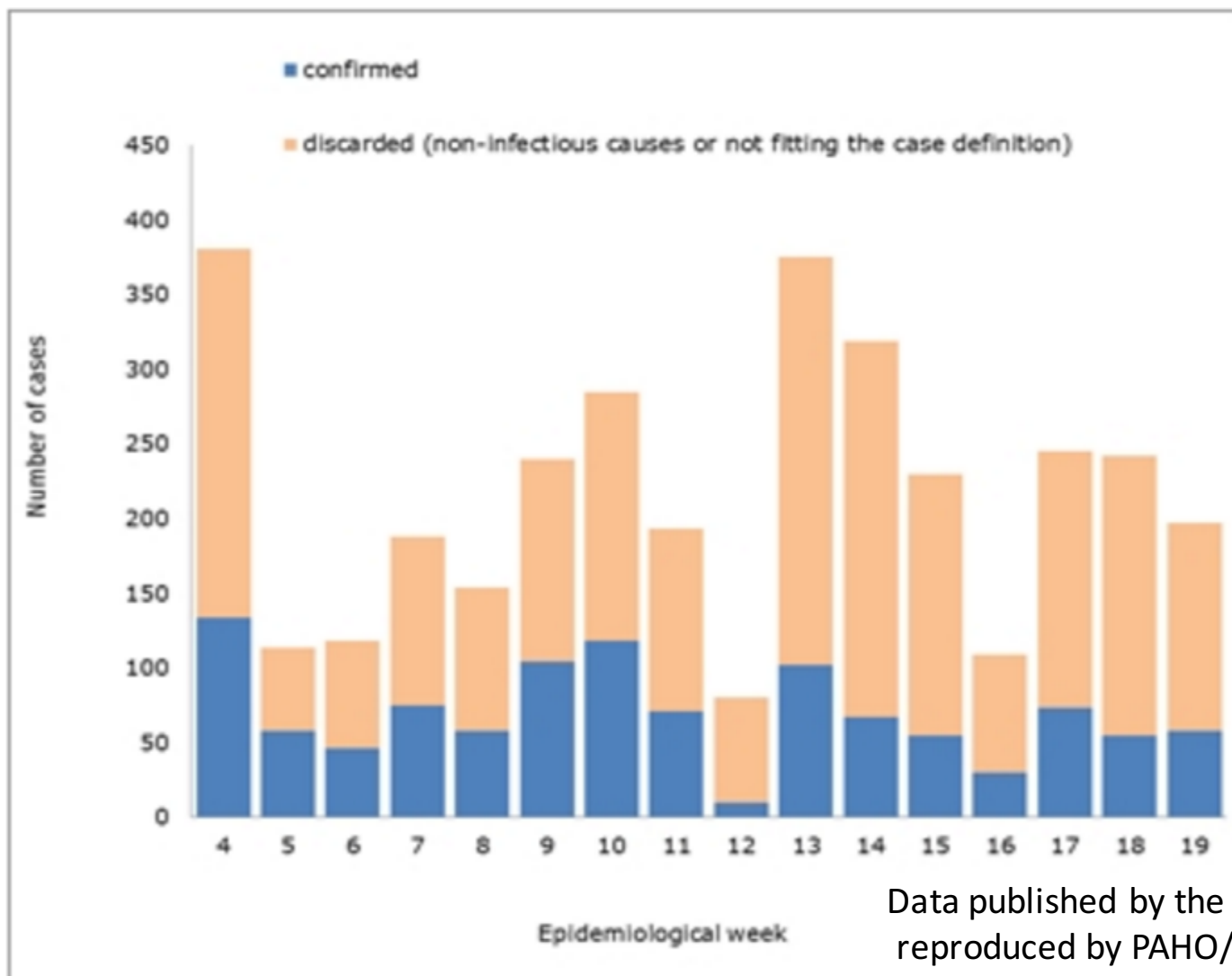


### E Microcephaly Cases



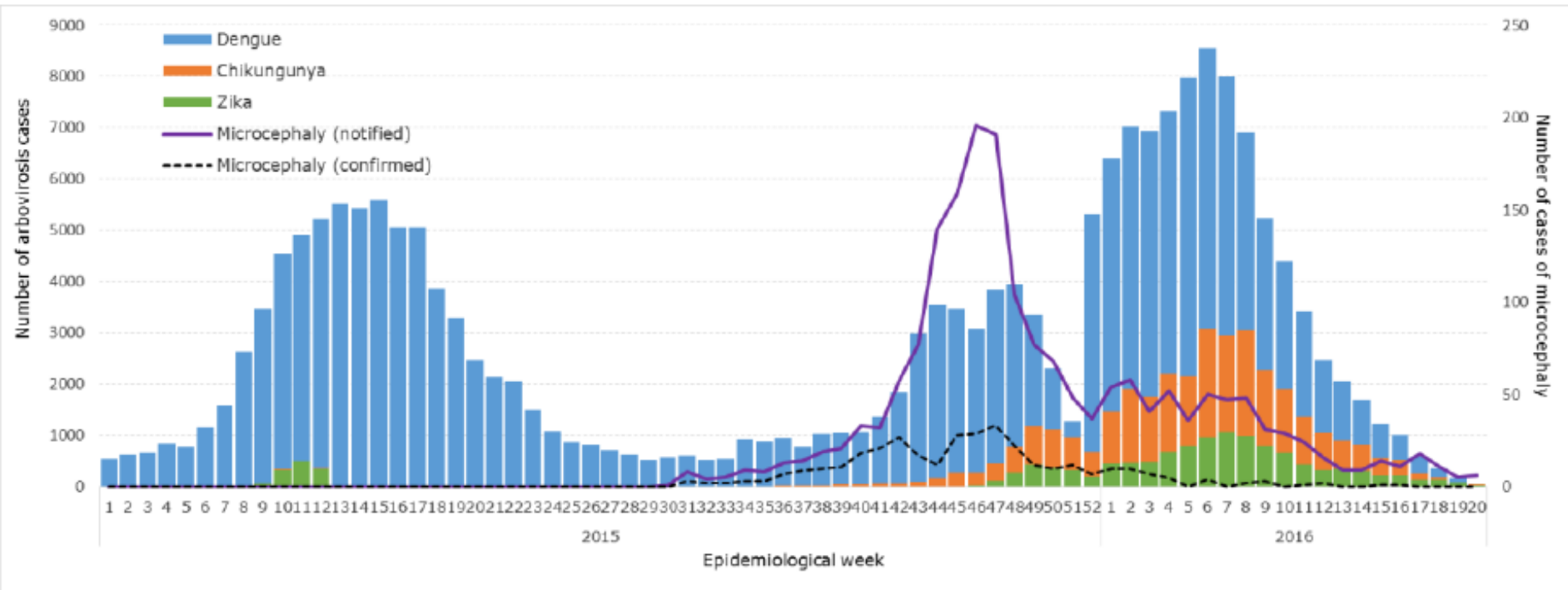
Overall ZIKV infection rate	Estimated microcephaly risk (%)							
	Baseline		With 1 <sup>st</sup> trimester ZIKV infection		With 2 <sup>nd</sup> trimester ZIKV infection		With 3 <sup>rd</sup> trimester ZIKV infection	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
10%	0.023	(0.02, 0.029)	13.2	(12.0, 14.4)	0.055	(0.001, 0.2)	0.063	(0.002, 0.222)
20%	0.022	(0.02, 0.029)	6.69	(6.07, 7.35)	0.028	(0.001, 0.101)	0.033	(0.001, 0.115)
30%	0.023	(0.02, 0.029)	4.52	(4.10, 4.96)	0.018	(0, 0.066)	0.023	(0.001, 0.081)
40%	0.022	(0.02, 0.029)	3.44	(3.12, 3.77)	0.014	(0, 0.05)	0.018	(0, 0.065)
50%	0.022	(0.02, 0.029)	2.79	(2.53, 3.06)	0.011	(0, 0.039)	0.015	(0, 0.054)
60%	0.023	(0.02, 0.029)	2.36	(2.15, 2.59)	0.009	(0, 0.033)	0.013	(0, 0.048)
70%	0.023	(0.02, 0.029)	2.05	(1.86, 2.25)	0.008	(0, 0.028)	0.012	(0, 0.043)
80%	0.023	(0.02, 0.029)	1.83	(1.65, 2.00)	0.007	(0, 0.025)	0.011	(0, 0.04)

# Number of investigated cases of microcephaly and other congenital malformation of the CNS by epidemiological week, Brazil, EW 3 – EW 19 of 2016.



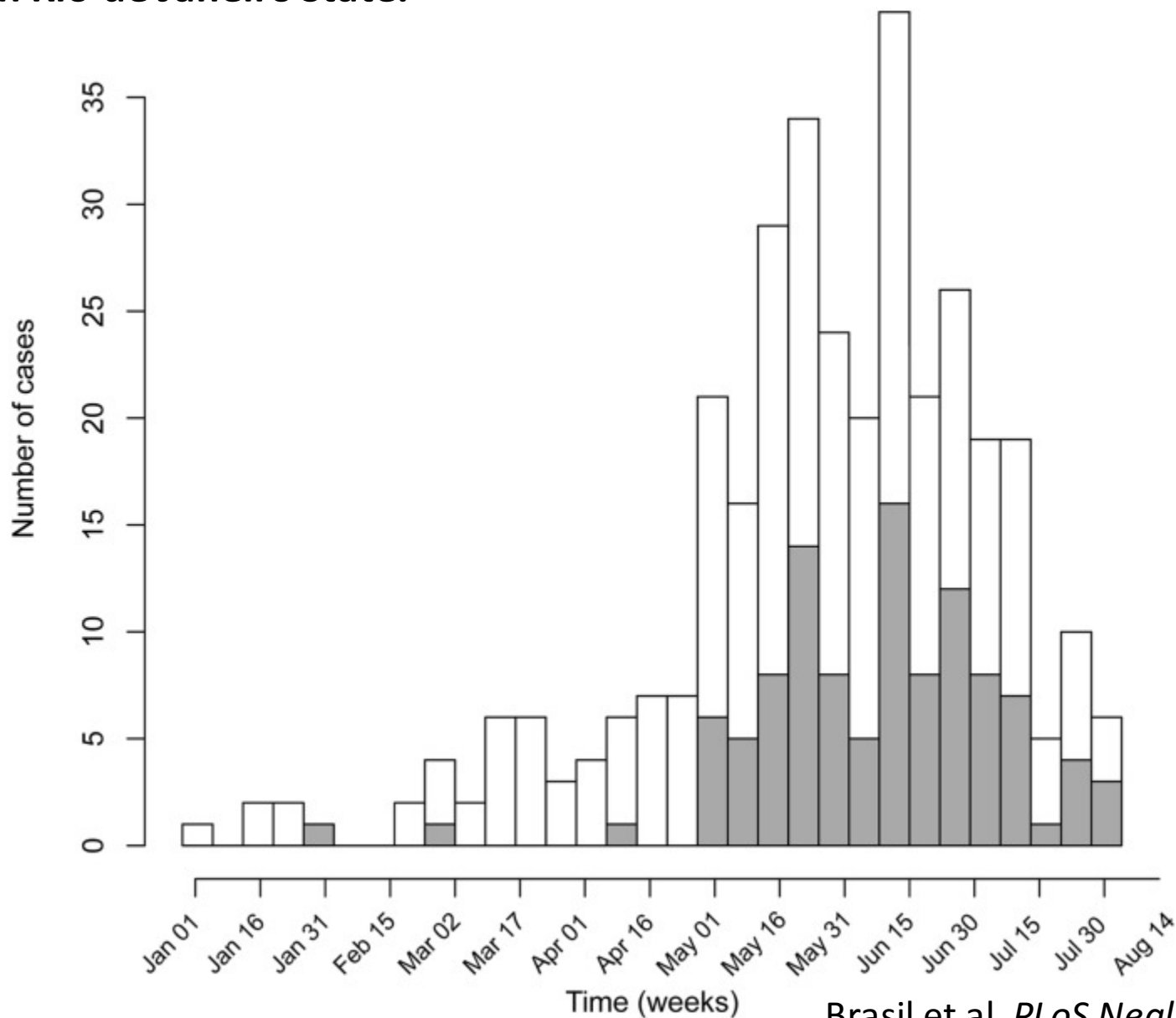
Data published by the Brazil MOH and reproduced by PAHO/WHO

# Cases of dengue, chikungunya, Zika virus, and microcephaly in the state of Pernambuco, Brazil, reported in EW. 2015-2016

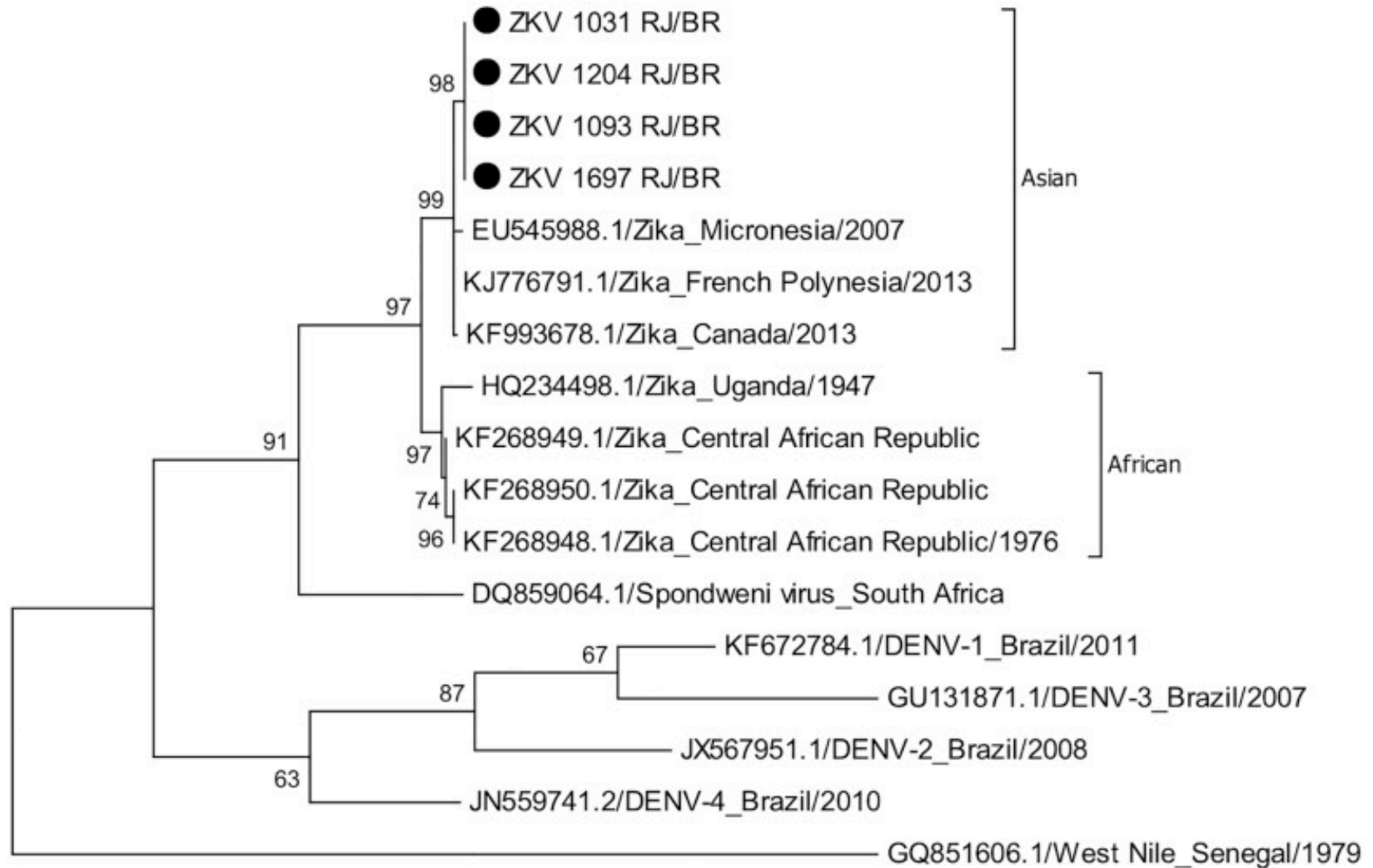


Data published by the Pernambuco State Secretary of Health

**Time series for number of cases confirmed (gray background) and not confirmed (white background) for ZIKV between January 1, 2015 and July 31, 2015 in Rio de Janeiro State.**

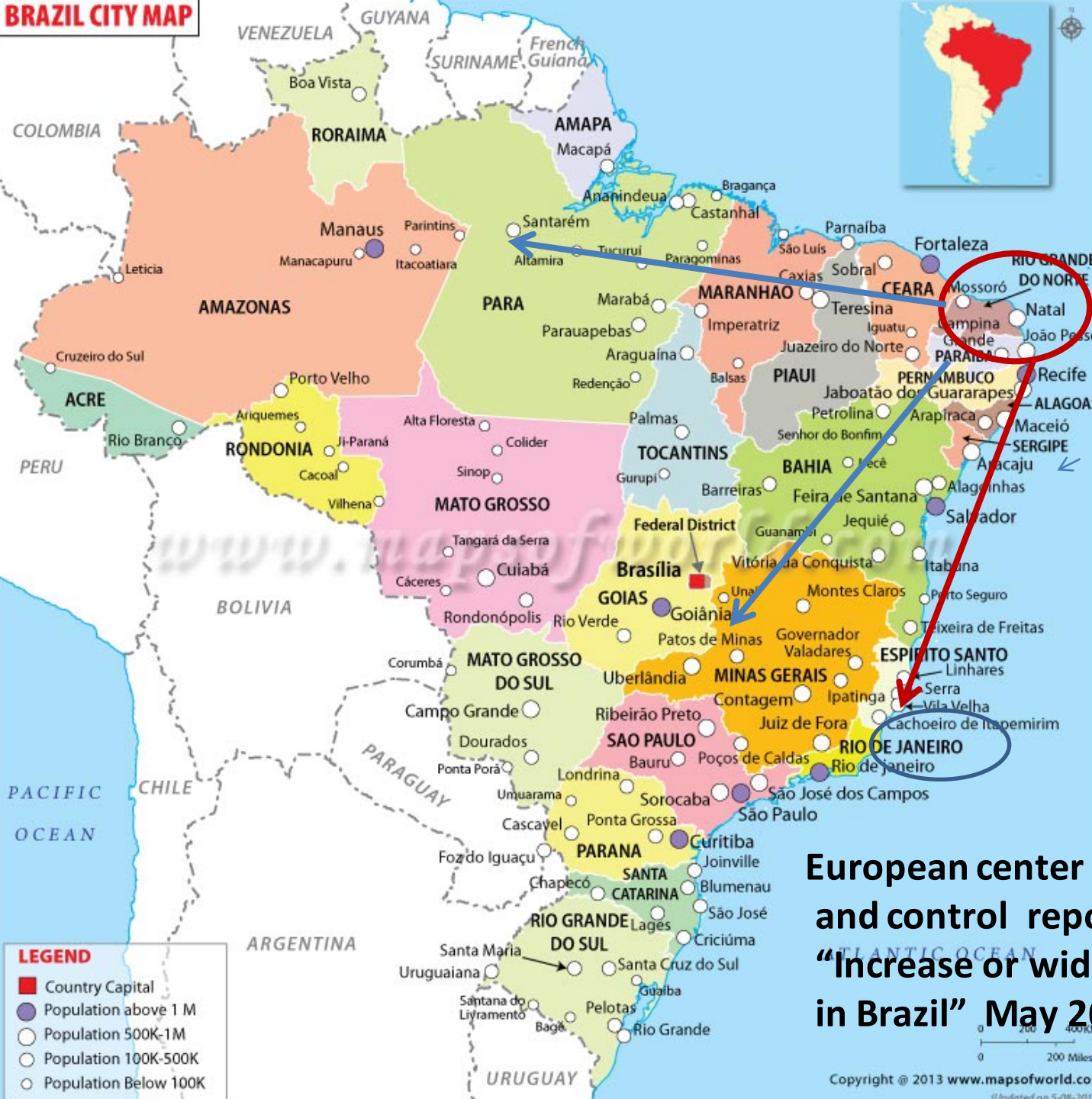


# Phylogenetic analysis based on partial E gene nucleic acid sequences (327bp) of Zika virus isolated in Rio de Janeiro





# BRAZIL CITY MAP



European center of disease prevention and control reported  
“Increase or wide spread transmission in Brazil” May 26<sup>th</sup> 2016

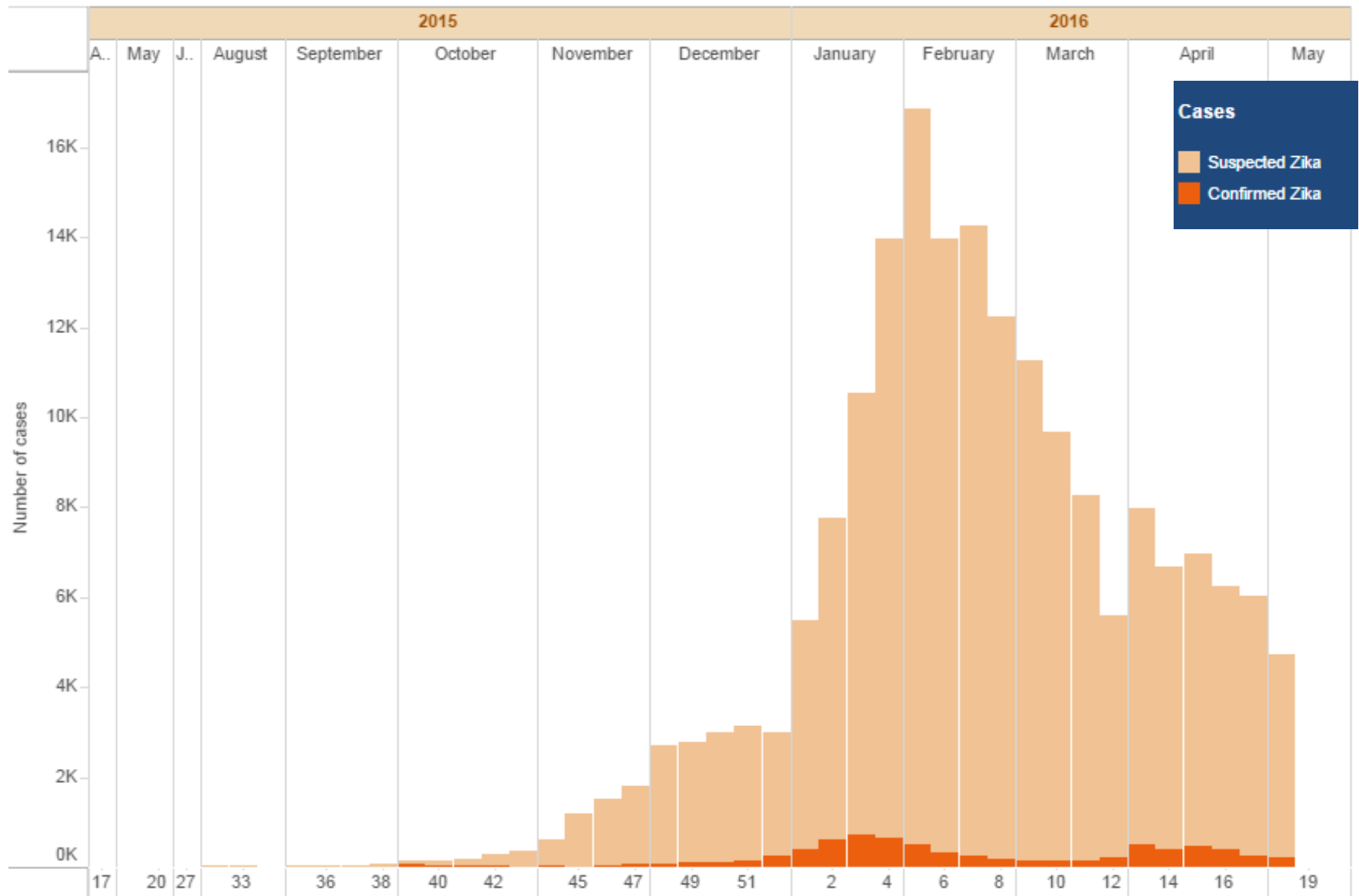


# Zika virus infection 2015~ (3)

- Feb 2015: Solomon Islands
- April 2015: Papua New Guinea
- July 2015: Samoa, Fiji
- Oct 2015: El Salvador, Guatemala, Mexico, Surina, Paraguay, Venezuela, **Columbia, Cabo Verde** (Africa strain)
- 2016: Maldives, Micronesia, Vietnam, Cuba, Philipines, Laos, New Caledonia

## Suspected and confirmed Zika cases reported by countries and territories in the Americas, 2015-2016

New cases by Epidemiological Week. Updated as of 19 May 2016



# US States as of May 25, 2016

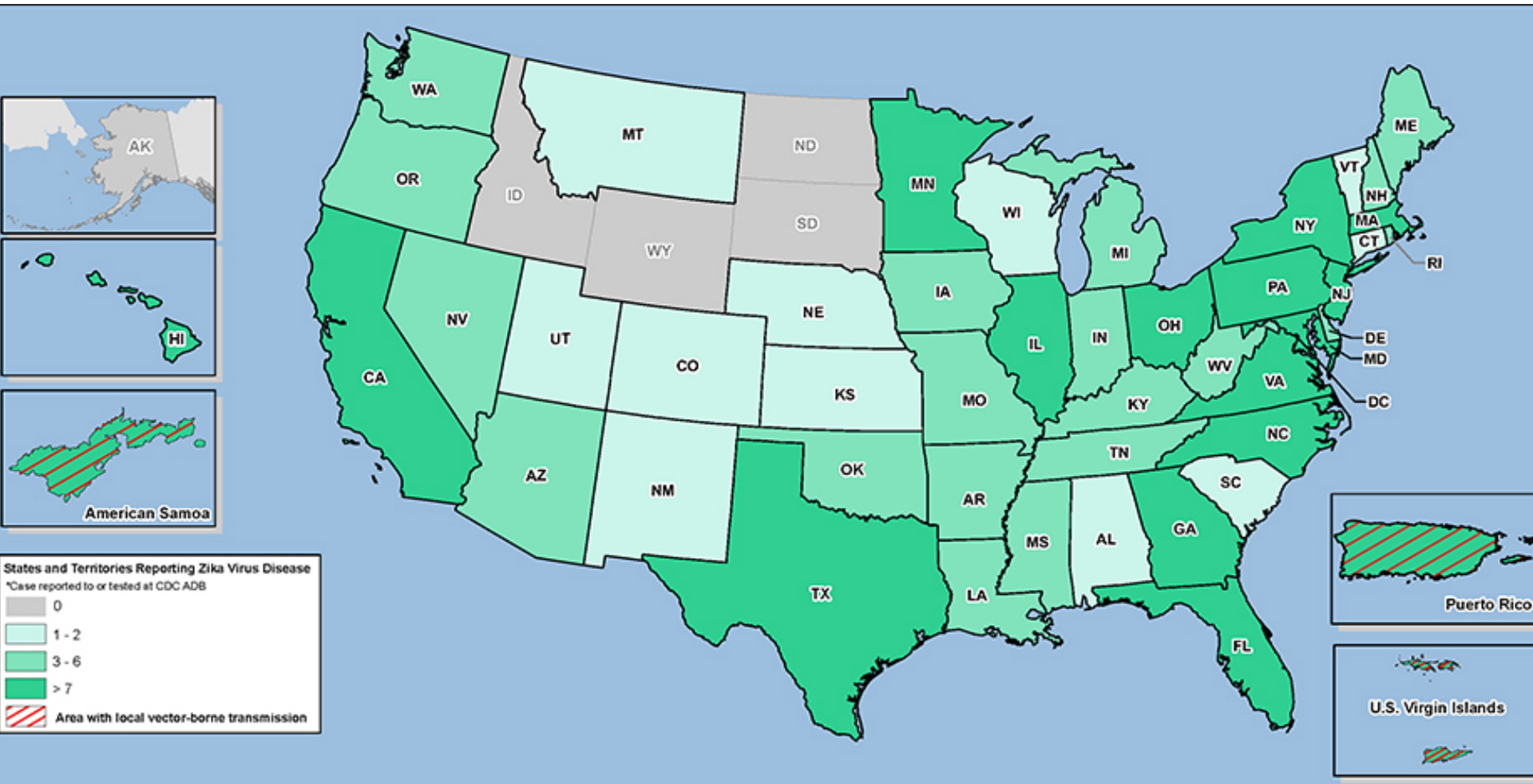
## Main Land

- Travel-associated cases reported: 591
- Locally acquired vector-borne cases reported: 0
  - Total: 591
  - Sexually transmitted: 11
  - Guillain-Barré syndrome: 1

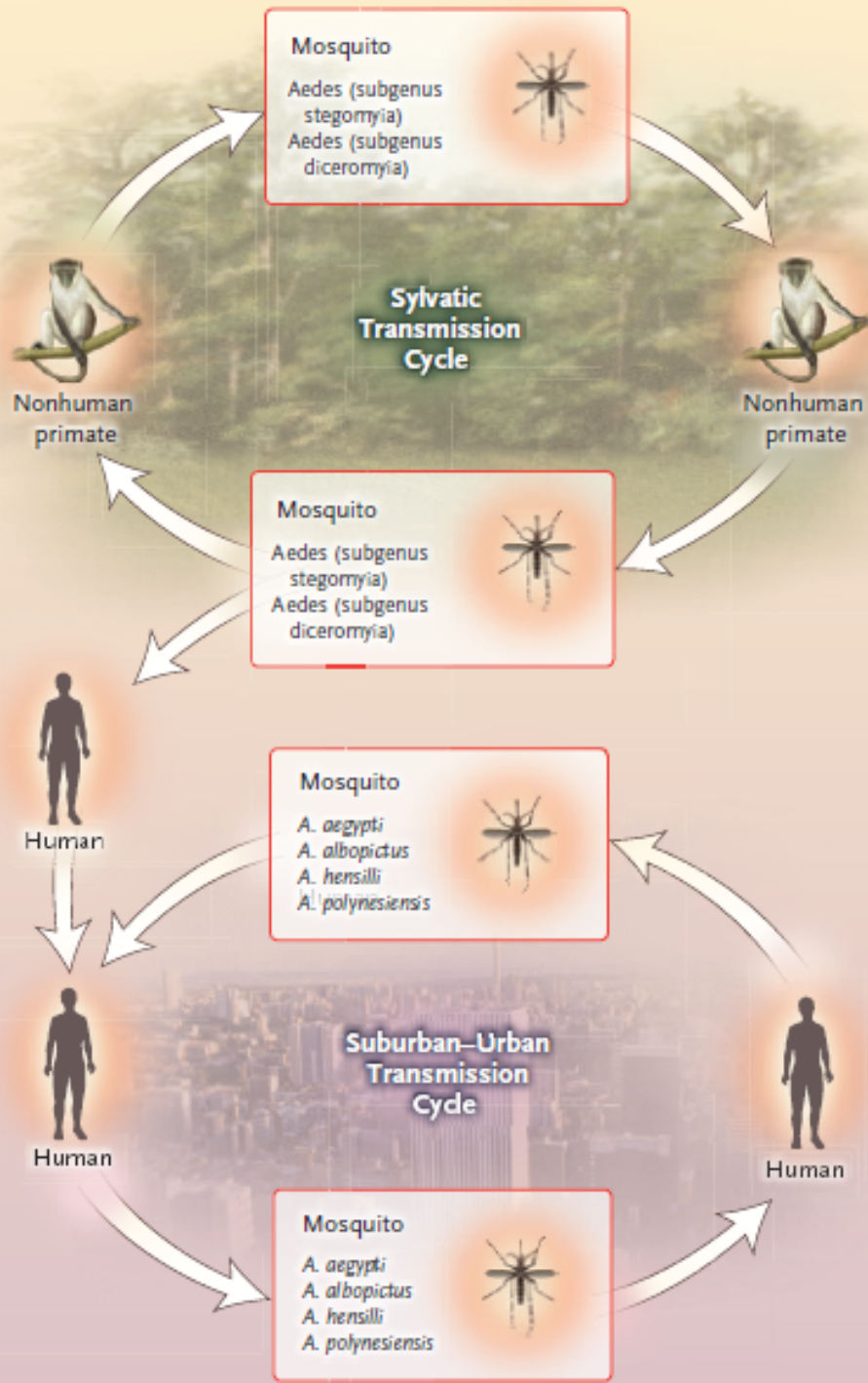
## US Territories

- Travel-associated cases reported: 4
- Locally acquired cases reported: 935
  - Total: 939
  - Guillain-Barré syndrome: 5

Except ID, WY, ND, SD, all 46 states have travel associated Zika virus infection patients



NY (127) > FL (121) > CA (44) > TX (36) > PA (19) > MN, MD (17) > IL, MA (16) > VA (15) > NJ (14)



**Animal reservoir:** Nonhuman primates in Africa and Brazil\*

**Vectors:** *Aedes spp.*

*Aedes africanus* (1960' in Africa)

*A. hensilli* (Yap Island)

*A. Aegypti and polynesiensis* (Polynesia)

*A. aegypti* (Brazil)

*A. albopictus* (Mexico)

← ***A. aegypti***

**Higher vectorial capacity:  
It bites primarily on humans,  
Multiple bites in a single blood meal,  
Almost imperceptible bite  
lives in close association  
with human habitation.**

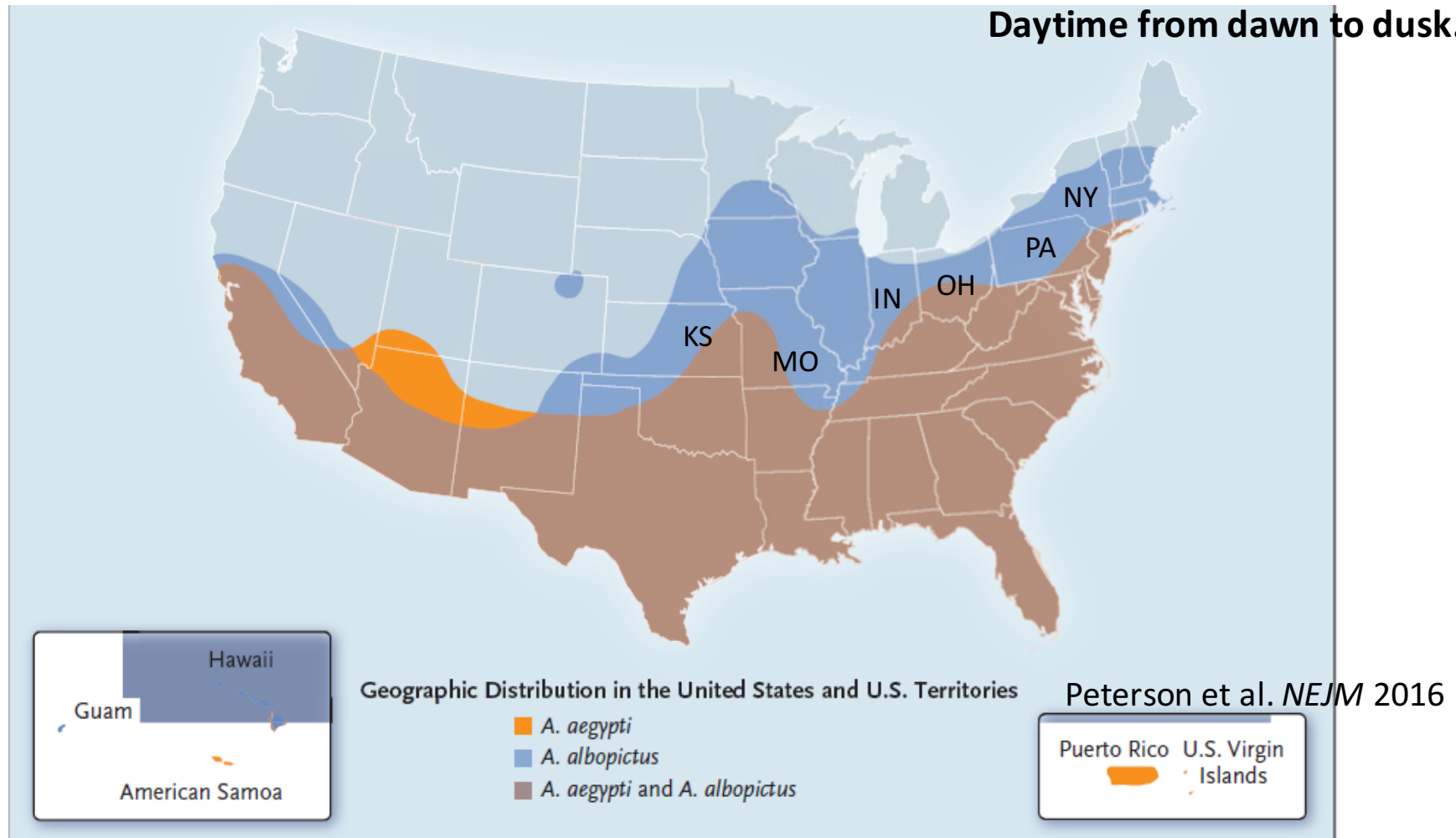


*A. albopictus*





*A. aegypti* and *A. albopictus* are widely distributed throughout the tropical and subtropical world. *A. albopictus* can exist in more temperate areas than *A. aegypti*, thus extending the potential range where outbreaks may occur.



**Figure 3.** Approximate Ranges of *A. aegypti* and *A. albopictus* in the United States (as of March 2016).

These mosquitoes may not be present in all areas, and vector density may vary considerably within these ranges.

# Transmission between humans

## Zika virus exists in body fluids

- **Blood**: infection through transfusion, trans placental infection
- Urine: most reliable sample for virus identification
- **Semen**: hematospermia, sexual transmission (before and after the symptom start); up to 62 days after the onset of symptoms; 6 months condom use is recommended after travel to ZIKV area)
- Saliva: more frequent than blood in Yap island investigation.
- Milk:



# Clinical manifestations

Asymptomatic infections: 80%

Incubation period

- 3.5-10 days

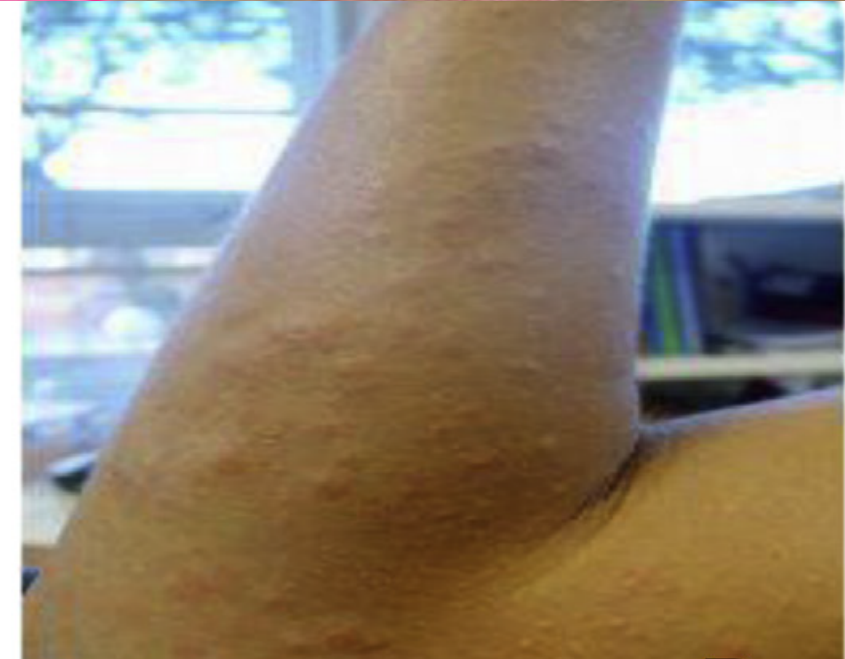
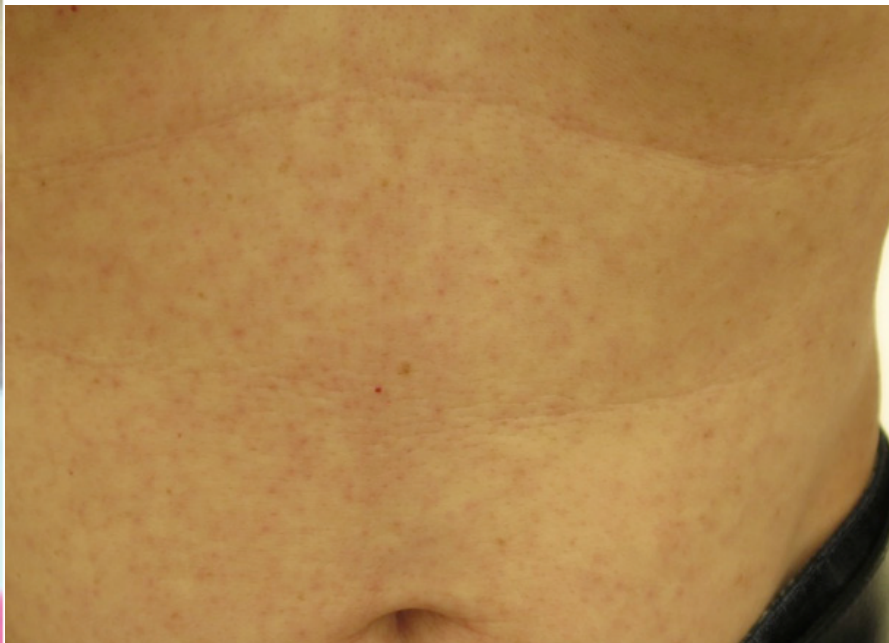
Mild febrile illness with rash, conjunctivitis and arthralgia about 1 week

Viremia (-10D to +11D)

- Usually after symptoms start
- Before symptoms start: 26% of virus positive blood donors had the symptoms after 3 to 10 days

# Common Symptoms (denguelike illness)

- Macular or papular rash with itchiness (90%)
- Fatigue/lethargy/asthenia
- Fever (65%)
- Arthritis or arthralgia (65%)
- Nonpurulent conjunctivitis (55%)
- Myalgia (48%), Headache (45%), retro-orbital pain (39%)
- Vomiting (10%), Edema (19%)
- Generalized lymphadenopathy, swelling of the hands and ankles and subcutaneous bleeding, hematospermia, transient dull and metallic hearing, transient hearing loss.



Brasil et al. *NEJM* 2016

Soni *APJR* 2016

Farahnik et al *J Am Acad Dermatol* 2016



30/11/2015 10:55

Brasil et al. *NEJM* 2016

Soni *APJR* 2016

Farahnik et al *J Am Acad Dermatol* 2016

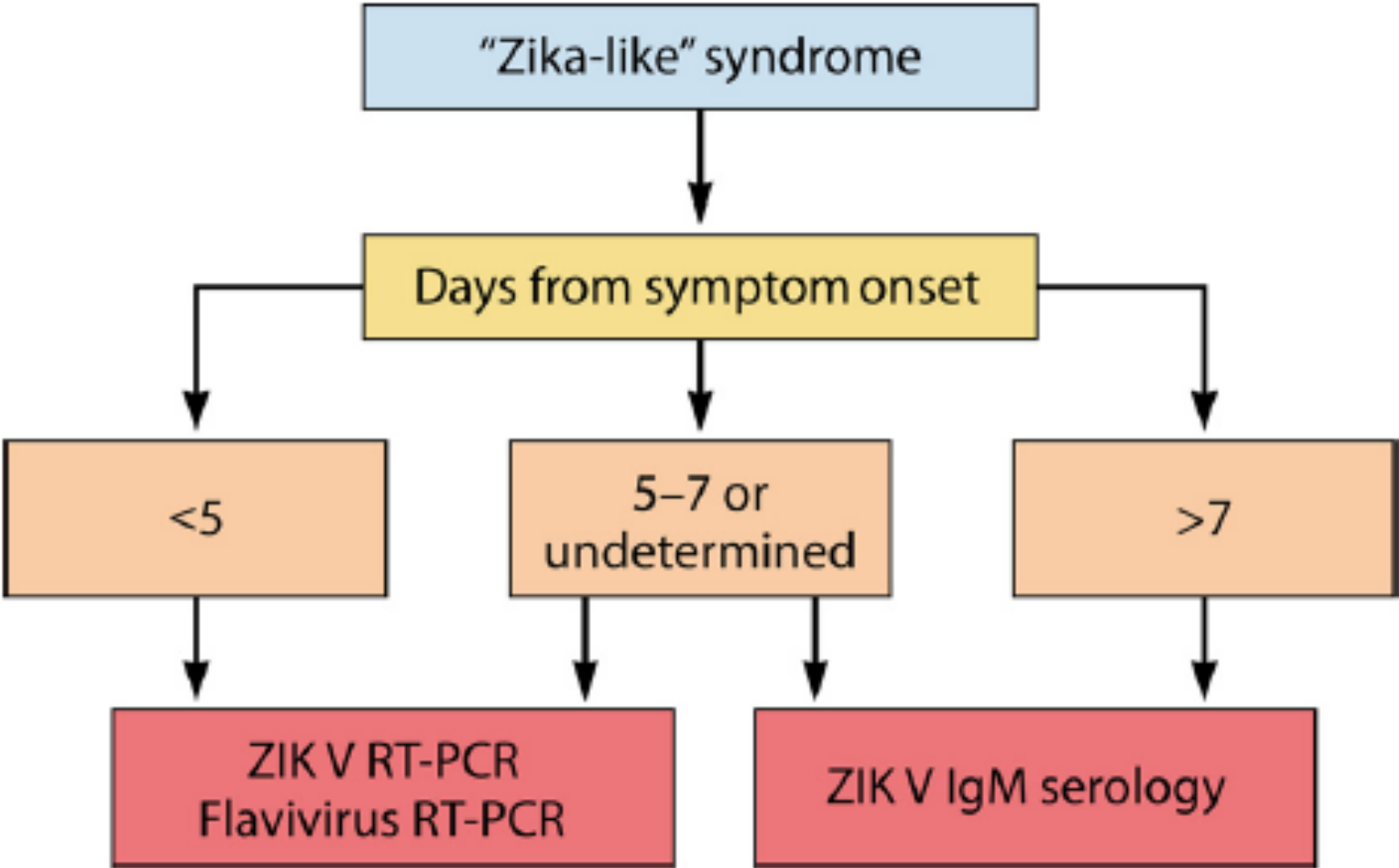
## Detection of ZIKV in different body fluids.

- Patients presenting in the acute phase of infection with a “dengue- or chikungunya-like syndrome” or with “fever and rash” and found to be negative by specific DENV NS1 antigen and CHIKV RT-PCR assays should be tested with a specific ZIKV RT-PCR assay.
- RT-PCR in serum (-10 to 11), saliva, urine (after acute phase), semen, breast milk

# Serological diagnosis

- ZIKV serology is usually performed by ELISA and then should be confirmed with PRNT.
- Cross reactivity among other *Flaviviruses*





# Neurologic complications of adults (1)

## Guillain-Barre Syndrome

French Polynesia (2013):

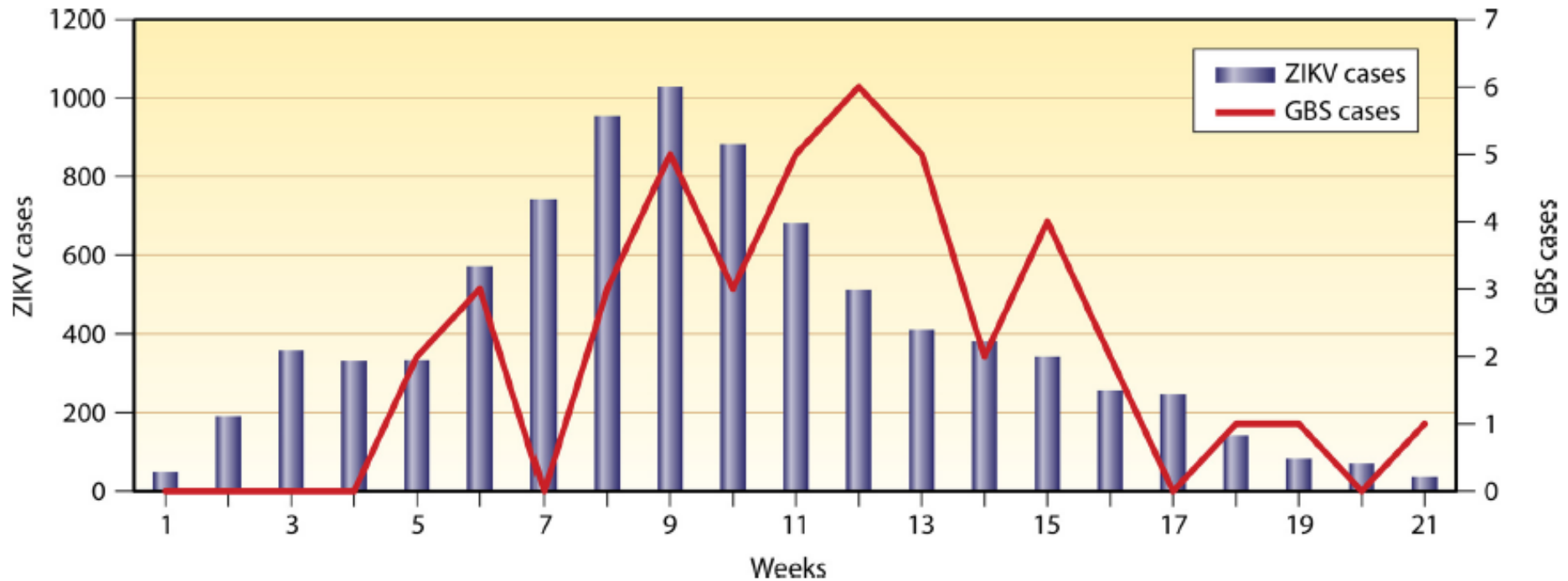
42 cases of GBS (20 fold higher) were reported (previous annual GBS cases were 3 to 10).

All GBS patients developed neurological symptoms following a “Zika-like syndrome” episode.

Brazil, El Salvador, Venezuela (2015-2016)



# Temporal association between cases of Zika fever and GBS during the French Polynesian outbreak in 2013.



# Neurologic complications of adults (2)

## Zika virus infection associated case reports

- Acute meningoencephalitis (case reports)
  - 81 yr old man returning from 4 week cruise in polynesia with fever, coma, left hemiparesis, positive MRI finding with Zika virus RT PCR and culture positive CSF (Carteaux et al *NEJM* 2016)
- Hypertensive iridocyclitis
  - One week after the systemic manifestations of zika virus infection
  - bilateral ocular discomfort for near tasks, blurry vision, and mild redness.
  - Best-corrected visual acuity: 20/40; moderate ciliary injection, mild anterior chamber reaction (1+ cells) on slit lamp exam and miosis in both eyes.
  - Intraocular pressure : 40 and 28 (nl: 12-22) mmHg in right and left eyes, respectively.(Fontes. *Arq. Bras. Oftalmol* 2016)

# Microcephaly (1)

- Increased microcephaly cases reported in Pernambuco State, northeastern Brazil september 2015.
- A relationship between ZIKV and microcephaly was first suspected in Brazil in late October 2015.
- 20-fold annual increase of microcephaly cases (prevalence of 99.7 per 100 000 livebirths)
- ZIKV has been isolated from the amniotic fluid of women who are pregnant with infants who have confirmed microcephaly and from the brain of a fetus with central nervous system (CNS) abnormalities.

## Microcephaly (2)

- Brain size and weight  $\leq 2$  SD
- Widely open sylvian fissures, small cerebellum and brain stem, agyria, hydrocephalus of the lateral ventricles.
- Numerous variable-sized calcifications in the cortex and subcortical white matter in the frontal, parietal, and occipital lobes.
- 10 of 29 infants with microcephaly (34.5%) had severe ocular abnormalities (focal pigment mottling of the retina and chorioretinal atrophy, optic nerve abnormalities, bilateral iris coloboma and lens subluxation)
- Severe seizure, developmental delay and hearing and vision loss.

Risk of Microcephaly indwell mainly when a pregnant woman is infected during her first trimester.

The risk is from 1.83% to 13.2%

Overall ZIKV infection rate	Estimated microcephaly risk (%)							
	Baseline		With 1 <sup>st</sup> trimester ZIKV infection		With 2 <sup>nd</sup> trimester ZIKV infection		With 3 <sup>rd</sup> trimester ZIKV infection	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
10%	0.023	(0.02, 0.029)	13.2	(12.0, 14.4)	0.055	(0.001, 0.2)	0.063	(0.002, 0.222)
20%	0.022	(0.02, 0.029)	6.69	(6.07, 7.35)	0.028	(0.001, 0.101)	0.033	(0.001, 0.115)
30%	0.023	(0.02, 0.029)	4.52	(4.10, 4.96)	0.018	(0, 0.066)	0.023	(0.001, 0.081)
40%	0.022	(0.02, 0.029)	3.44	(3.12, 3.77)	0.014	(0, 0.05)	0.018	(0, 0.065)
50%	0.022	(0.02, 0.029)	2.79	(2.53, 3.06)	0.011	(0, 0.039)	0.015	(0, 0.054)
60%	0.023	(0.02, 0.029)	2.36	(2.15, 2.59)	0.009	(0, 0.033)	0.013	(0, 0.048)
70%	0.023	(0.02, 0.029)	2.05	(1.86, 2.25)	0.008	(0, 0.028)	0.012	(0, 0.043)
80%	0.023	(0.02, 0.029)	1.83	(1.65, 2.00)	0.007	(0, 0.025)	0.011	(0, 0.04)

## Other complications from intrauterine infections

A cohort study of pregnant women with rash in Rio de Janeiro showed 29% (12/42) of the pregnant women who had been Zika virus positive and took fetal USGs had USG abnormalities of fetus.

- Fetal deaths after 30 weeks of gestation: 2 (4.76%)
- intrauterine growth restriction: 5 fetuses (12%)
- Abnormal arterial flow in the cerebral or umbilical arteries: 4 (9.5%)
- Oligohydramnios and anhydramnios: 2 (4.76%)

# Prevention (CDC)

- No vaccine exists to prevent Zika virus disease.
- Prevent Zika by avoiding mosquito bites.
- Mosquitoes that spread Zika virus bite mostly during the daytime.
- Mosquitoes that spread Zika virus also spread dengue and chikungunya viruses.
- [Prevent sexual transmission of Zika by using condoms or not having sex](#)

# Steps to prevent mosquito bites

Wear **long-sleeved shirts and long pants**.

Stay in places with **air conditioning** and window and door **screens** to keep mosquitoes outside.

Sleep under a **mosquito bed net** if you are overseas or outside and are not able to protect yourself from mosquito bites.

Use **Environmental Protection Agency (EPA)-registered insect repellents** with one of the following active ingredients: **DEET**, picaridin, IR3535, oil of lemon eucalyptus, or para-menthane-diol. Choosing an EPA-registered repellent ensures the EPA has evaluated the product for effectiveness. When used as directed, EPA-registered insect repellents are proven safe and effective, even for pregnant and breast-feeding women.

Always follow the product label instructions.

Reapply insect repellent as directed.

Do not spray repellent on the skin under clothing.

If you are also using sunscreen, apply sunscreen before applying insect repellent.



## **To protect your child from mosquito bites:**

Do not use insect repellent on babies younger than 2 months old.

Do not use products containing oil of lemon eucalyptus or para-menthane-diol on children younger than 3 years old.

Dress your child in clothing that covers arms and legs.

Cover crib, stroller, and baby carrier with mosquito netting.

Do not apply insect repellent onto a child's hands, eyes, mouth, and cut or irritated skin.

Adults: Spray insect repellent onto your hands and then apply to a child's face.

## **Treat clothing and gear with permethrin or purchase permethrin-treated items.**

Treated clothing remains protective after multiple washings. See product information to learn how long the protection will last.

If treating items yourself, follow the product instructions carefully.

Do NOT use permethrin products directly on skin. They are intended to treat clothing.

Even if they do not feel sick, travelers returning to the United States from an area with Zika should take steps to prevent mosquito bites for 3 weeks so they do not spread Zika to mosquitoes that could spread the virus to other people.

## Here's what you can do to control mosquitoes outside your home

Prevention  
CDC protocol

### **Install or repair and use window and door screens.**

Do not leave doors propped open.

**Once a week**, empty and scrub, turn over, cover, or throw out any items that hold water like tires, buckets, planters, toys, pools, birdbaths, flowerpot saucers, or trash containers. Mosquitoes lay eggs near water.

Tightly cover water storage containers (buckets, cisterns, rain barrels) so that mosquitoes cannot get inside to lay eggs.

For containers without lids, use wire mesh with holes smaller than an adult mosquito.

Use larvicides to treat large containers of water that will not be used for drinking and cannot be covered or dumped out.

**Use an outdoor flying insect spray** where mosquitoes rest. Mosquitoes rest in dark, humid areas like under patio furniture, or under the carport or garage. When using insecticides, always follow label instructions.

**If you have a septic tank**, repair cracks or gaps. Cover open vent or plumbing pipes. Use wire mesh with holes smaller than an adult mosquito.

## Here's what you can do to control mosquitoes inside your home

**Keep windows and doors shut** and use air conditioning

**Keep mosquitoes from laying eggs inside your home. Once a week,** empty and scrub, turn over, cover, or throw out any items that hold water like vases and flowerpot saucers.

**Kill mosquitoes inside your home.**

Use an indoor flying insect fogger\* or indoor insect spray\* to kill mosquitoes and treat areas where they rest (dark, humid places like under the sink, in closets, under furniture, or in the laundry room). These products work immediately, but may need to be reapplied. Always follow label directions.

Use an indoor fogger\* or indoor insect spray\* to reach and treat areas where mosquitos rest inside the home.