THE COLORADO CHILDREN'S IMMUNIZATION COALITION AND THE CENTER FOR GLOBAL HEALTH PRESENT:

COLORADO CHILDREN'S IMMUNIZATION COALITION

Center for Global Health
colorado school of public health

Vector-Borne Disease and Related Vaccine Developments:

Zika, Dengue & Chikungunya

Presented by Edwin J. Asturias, MD, and J. David Beckham, MD

WEDNESDAY, JUNE 22, 2016

12 – 1:30 P.M.

CHILDREN'S HOSPITAL COLORADO

MT. OXFORD

CELEBRATING 25 YEARS
Keeping Colorado Kids Healthy

OUR MISSION

Founded in 1991, the Colorado Children's Immunization Coalition (CCIC) is a statewide 501(c)3 nonprofit that strategically mobilizes diverse partners and families to advance children's health through immunizations.

COLORADO CHILDREN'S IMMUNIZATION COALITION

Arbovirus Essentials: Biology, Transmission, and Clinical Features

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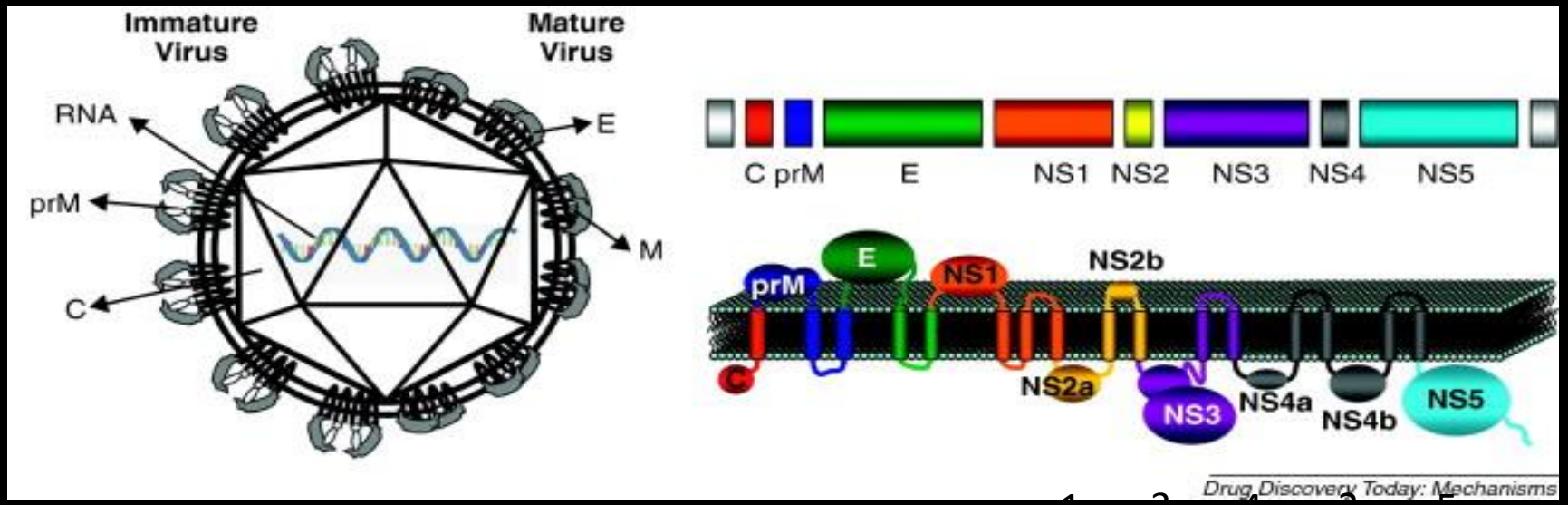
Associate Professor
Department of Medicine
Division of Infectious Diseases

Summary

- Arbovirus virology
- Epidemiology/Transmission
- Clinical Features

Arboviruses

- Arthropod-Borne Viruses
  - Flaviviruses =West Nile virus, Zika Virus, Dengue
  - Alphaviruses = Chikungunya, RRV, VEEV
  - Bunyaviridae = Rift Valley Fever virus
  - Reovirus = Colorado Tick Fever virus


Immature Virus
Mature Virus
RNA
prM
C
E
M
C prM
E
NS1
NS2
NS3
NS4
NS5
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NS1
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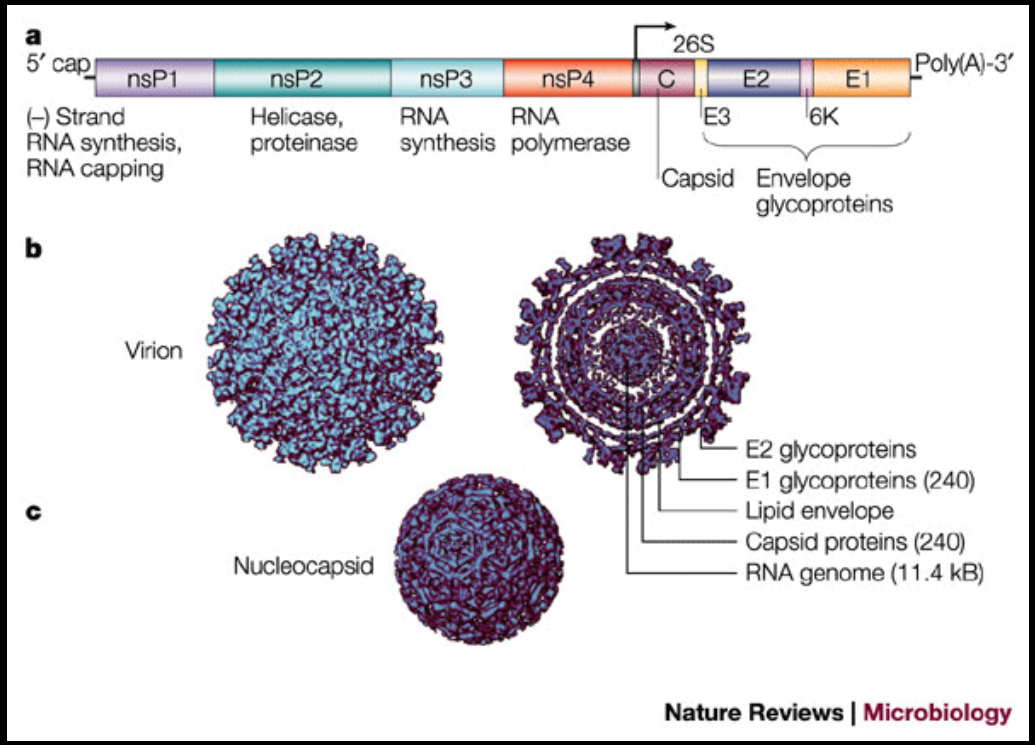
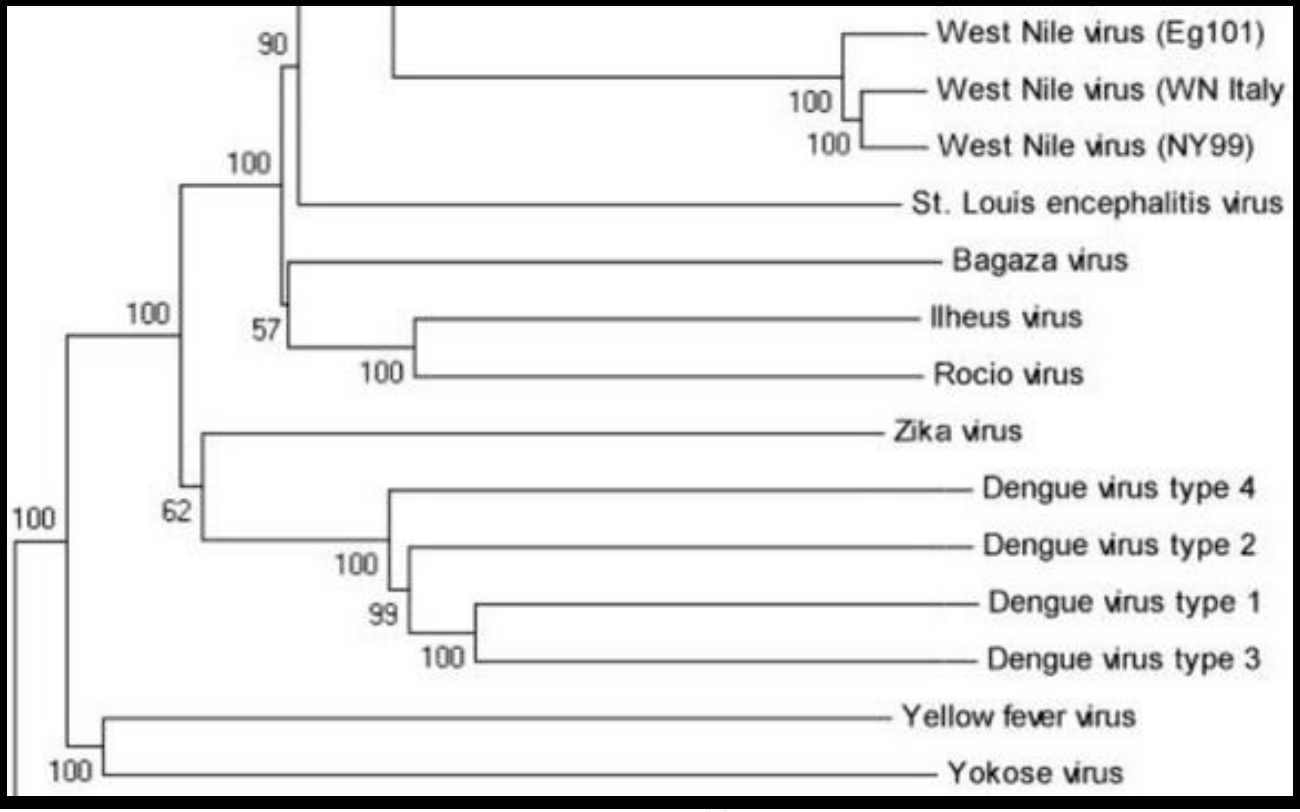
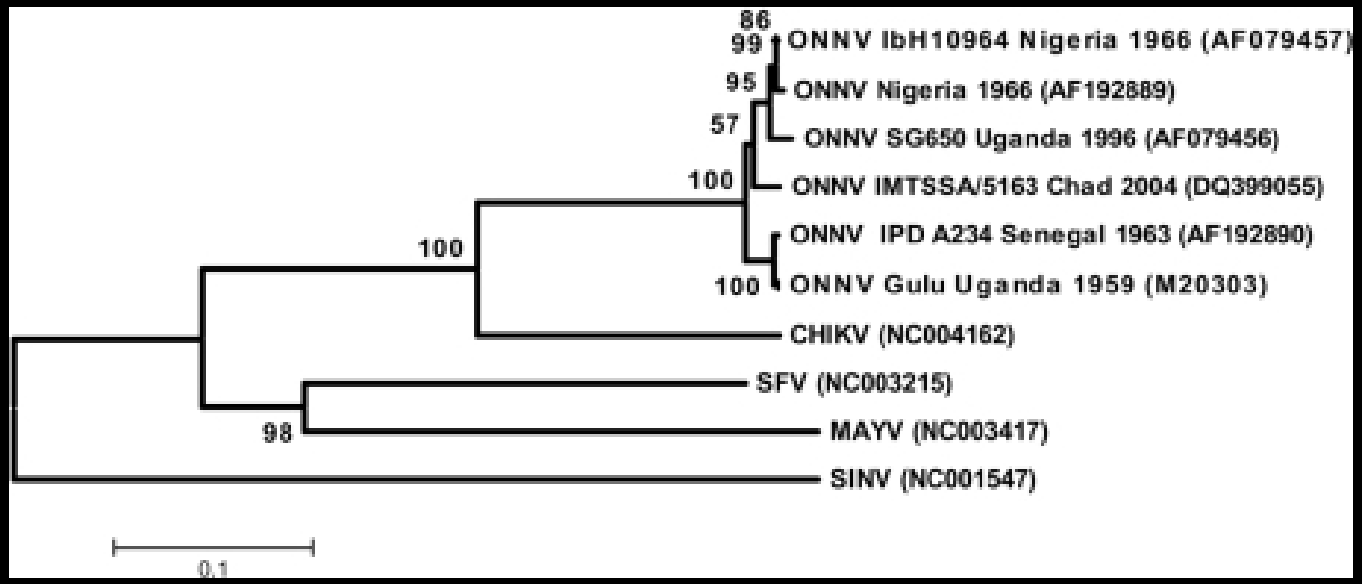
NS4b
NS5
Drug Discovery Today: Mechanisms


a
5′ cap
nsP1
nsP2
nsP3
nsP4
C
E2
E1
Poly(A)-3′
26S
(–) Strand RNA synthesis, RNA capping
Helicase, proteinase
RNA synthesis
RNA polymerase
E3
6K
Capsid
Envelope glycoproteins
b
Virion
c
Nucleocapsid
E2 glycoproteins
E1 glycoproteins (240)
Lipid envelope
Capsid proteins (240)
RNA genome (11.4 kB)
Nature Reviews | Microbiology



Family *Flaviviridae* contains over 70 viruses!!

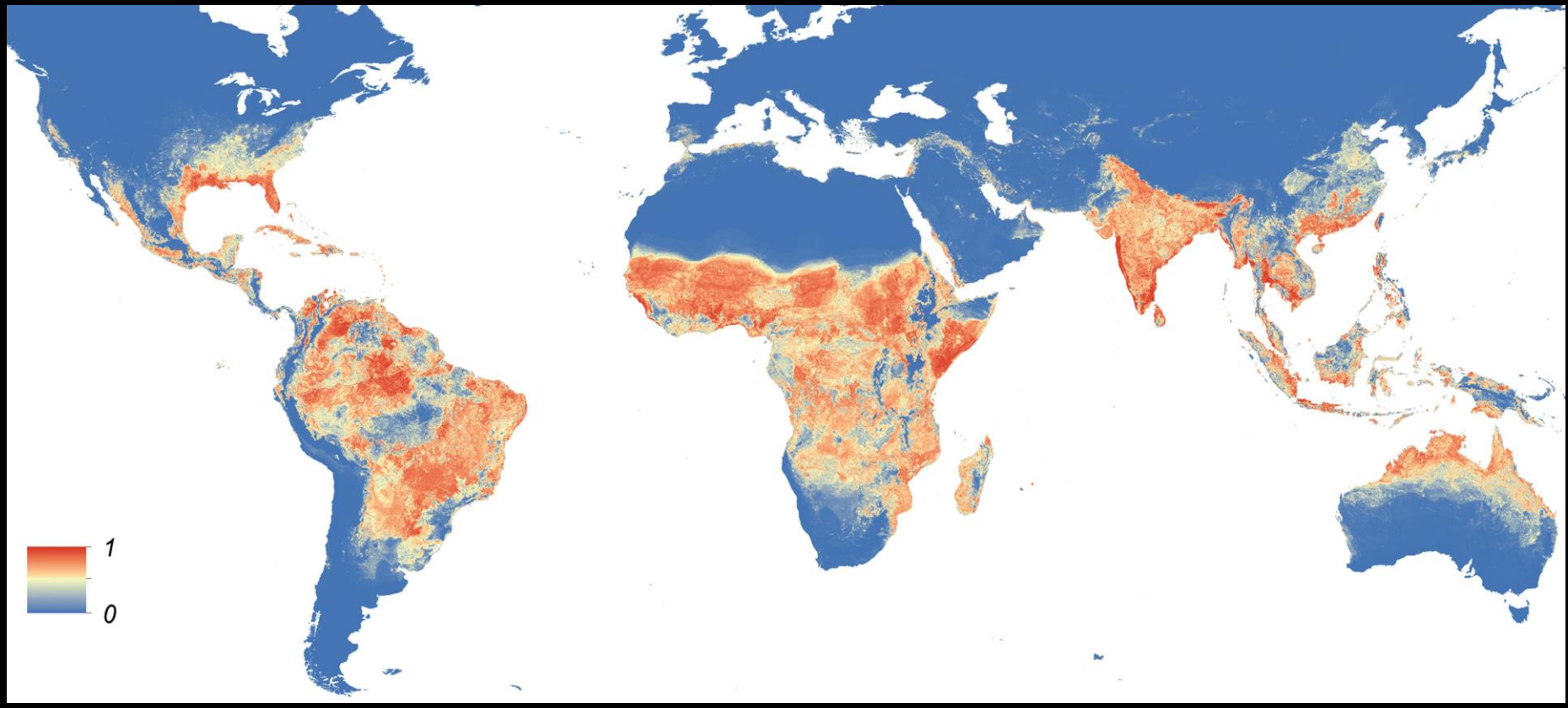


Mosquito Transmission by *Aedes* spp.

- Most common method of Dengue/CHIK/Zika virus transmission
- Primarily *Aedes aegypti*; secondarily *Aedes albopictus*
- "Domesticated" mosquitoes; evolved to live near humans

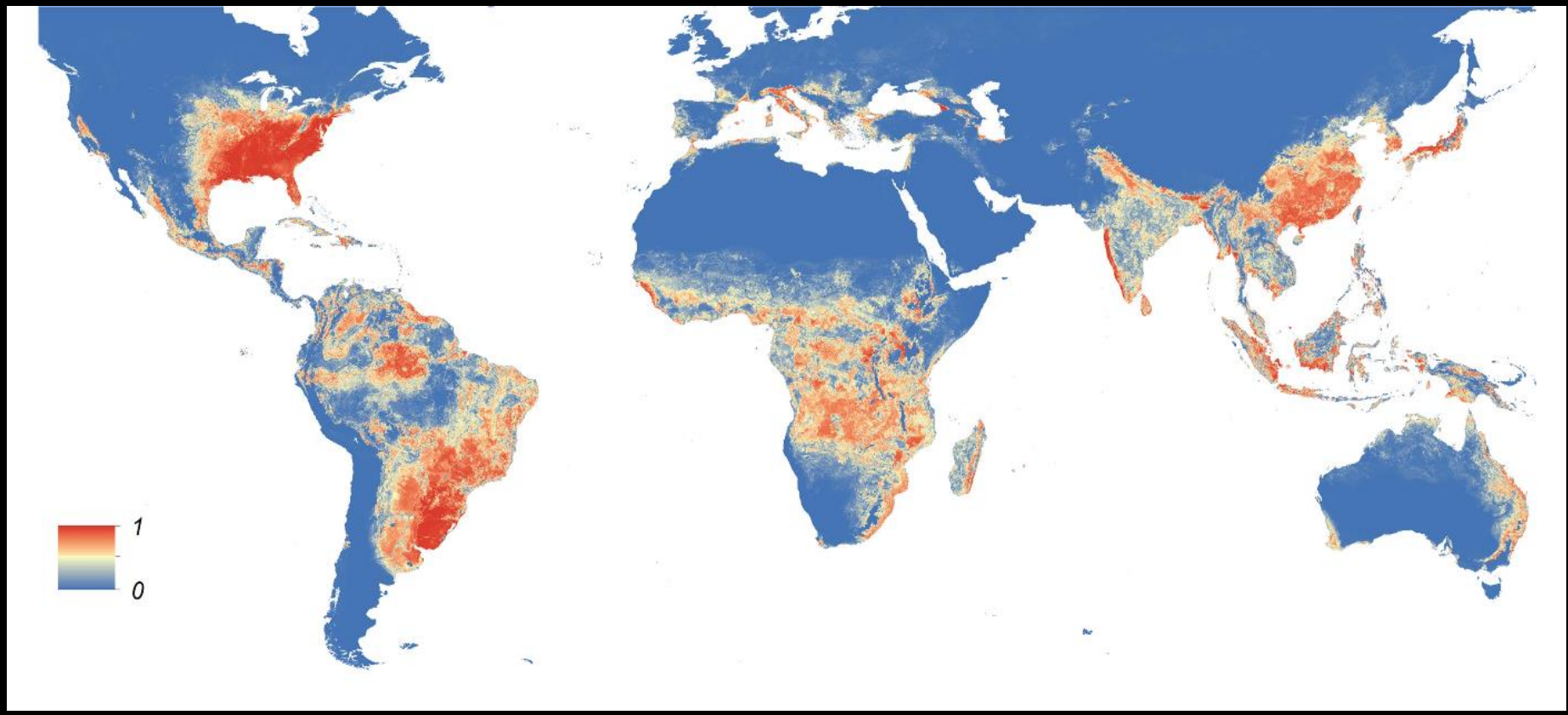
- Photos of Aedes aegypti and Aedes albopictus courtesy of http://www.cdc.gov/chikungunya/resources/vector-control.html

Aedes aegypti Predicted Geographic Range



- Probability map of *Aedes aeqypti* courtesy of Kraemer M. et al. The global distribution of the arbovirus vectors Aedes aegypti and Ae. albopictus . eLife. 4, e08347 (2015).

Aedes albopictus Predicted Geographic Range



- Probability map of *Aedes albopictus* courtesy of Kraemer M. et al. The global distribution of the arbovirus vectors Aedes aegypti and Ae. albopictus . eLife. 4, e08347 (2015).

Aedes spp. Geographic Range in the United States

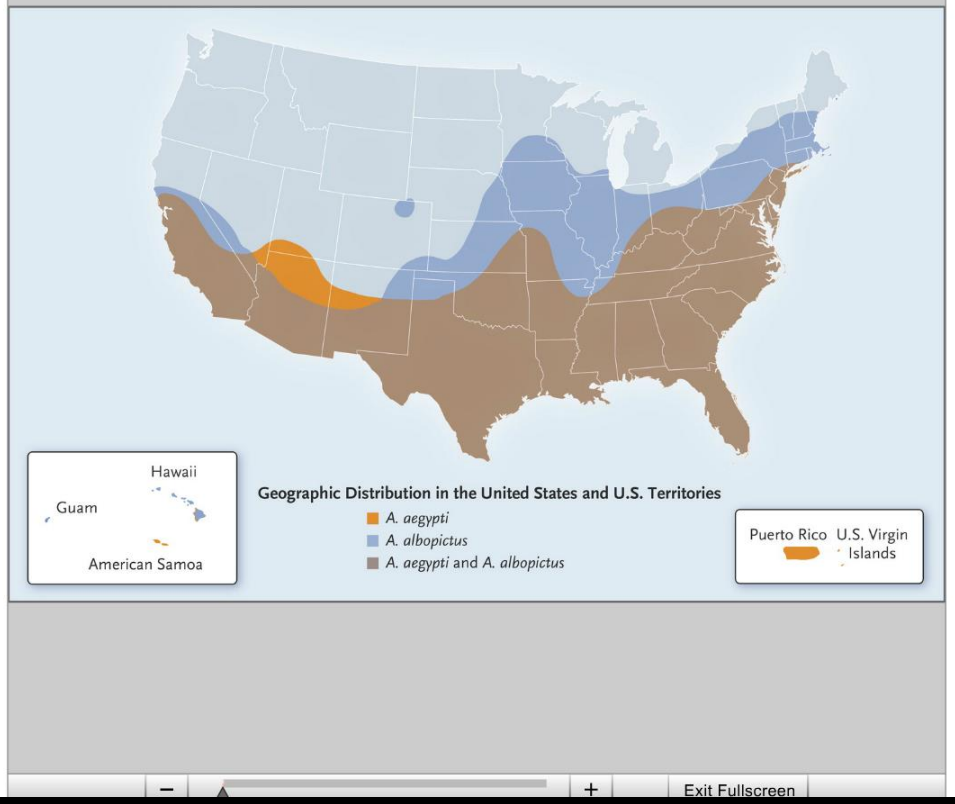


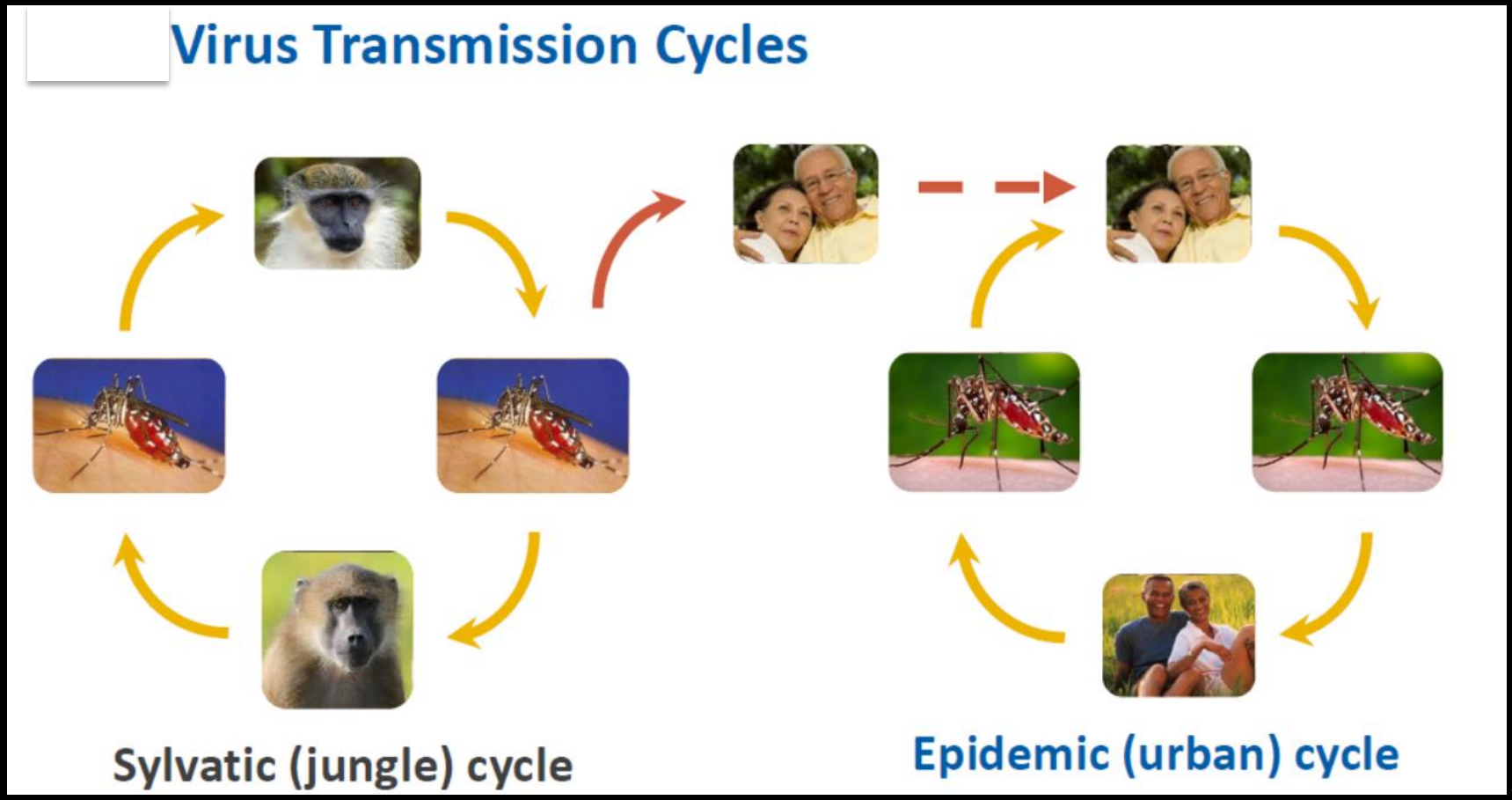
Figure 3. Approximate Ranges of *A. aegypti* and *A. albopictus* in the United States (as of March 2016).

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

- Map of approximate ranges of Aedes spp. of mosquitoes in the United States as of March 2016 courtesy of Petersen, et al. Zika Virus. NEJM March 2016.

Rhesus Macaque

Dengue/CHIK/Zika Virus-Mosquito Transmission Cycles



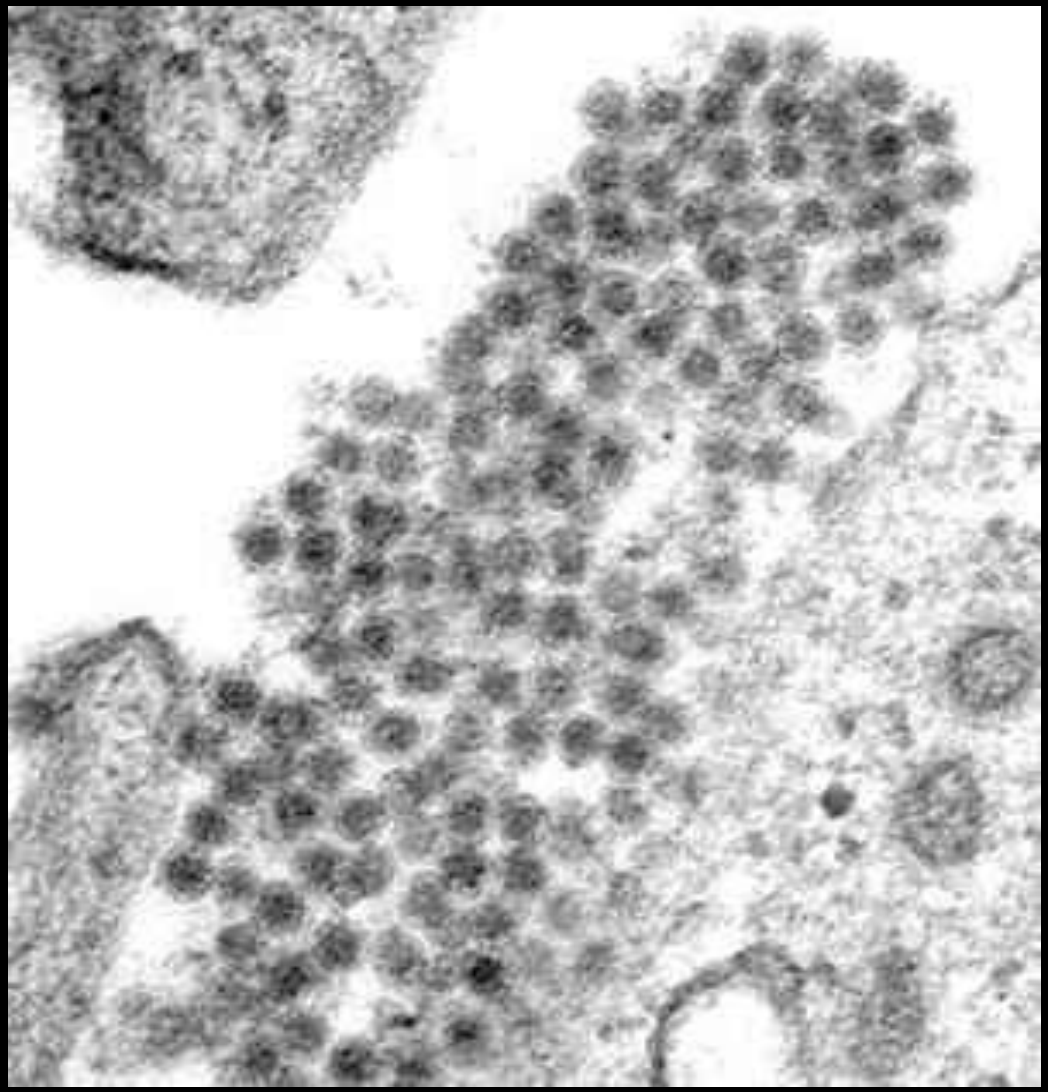
Clinical Features

Dengue

CHIK

ZIKA

Dengue



Dengue

- 50-100million infections per year and up to 500,000 hospital admissions/year
- Transmitted by the *Aedes aegypti*. Other Aedes sp. can transmit as well. Amplifying host-humans.
- 4 serotypes occur in epidemics throughout the tropics and continue to spread with recent infections in Hawaii*, Texas and Florida.

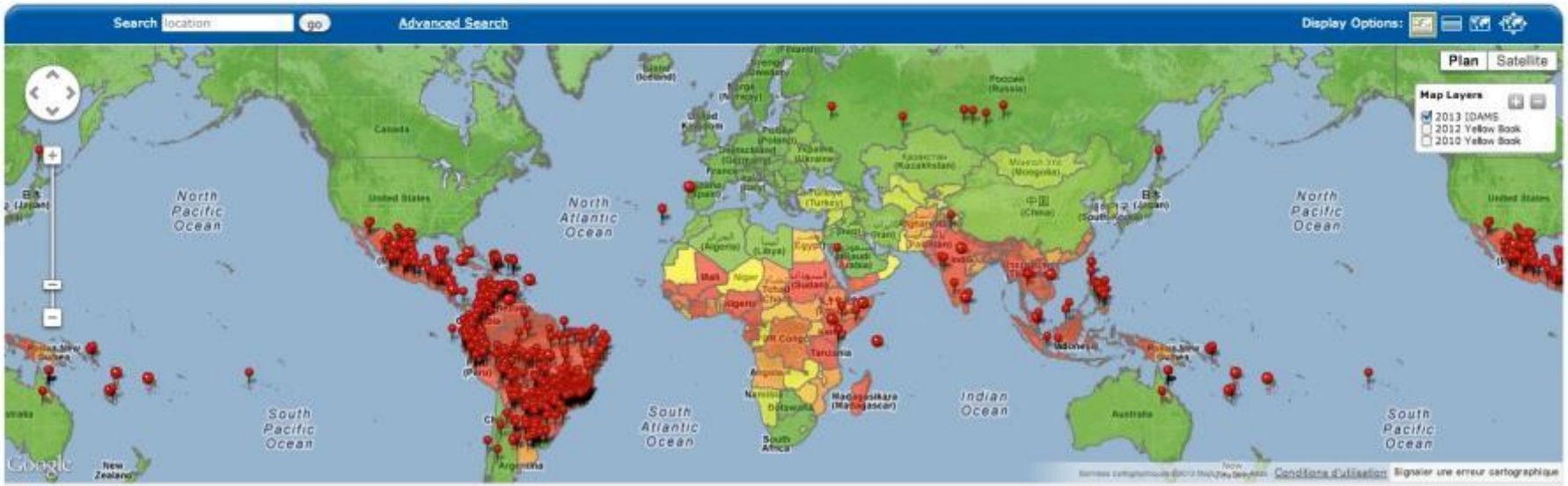
*EID 2005; 11:742

DengueMap

A CDC-HealthMap Collaboration

Visit the CDC Dengue Page

HealthMap
Global health, local information



HealthMap Reports: Recent reports of local and regional dengue or imported cases of dengue from official, newspaper, and other media sources. View source »

Country Level Local or Province Level

IDAMS Global Consensus Map: These risk areas are defined based on consensus between a variety of data sources including: national surveillance systems, published literature, questionnaires and formal and informal news reports. View source »

Absent Unlikely Uncertain Likely Present

CDC Yellow Book Map: These risk areas are endemic regions assessed using data from Ministries of Health, international health organizations, journals, and knowledgeable experts. View source »

Endemic Area

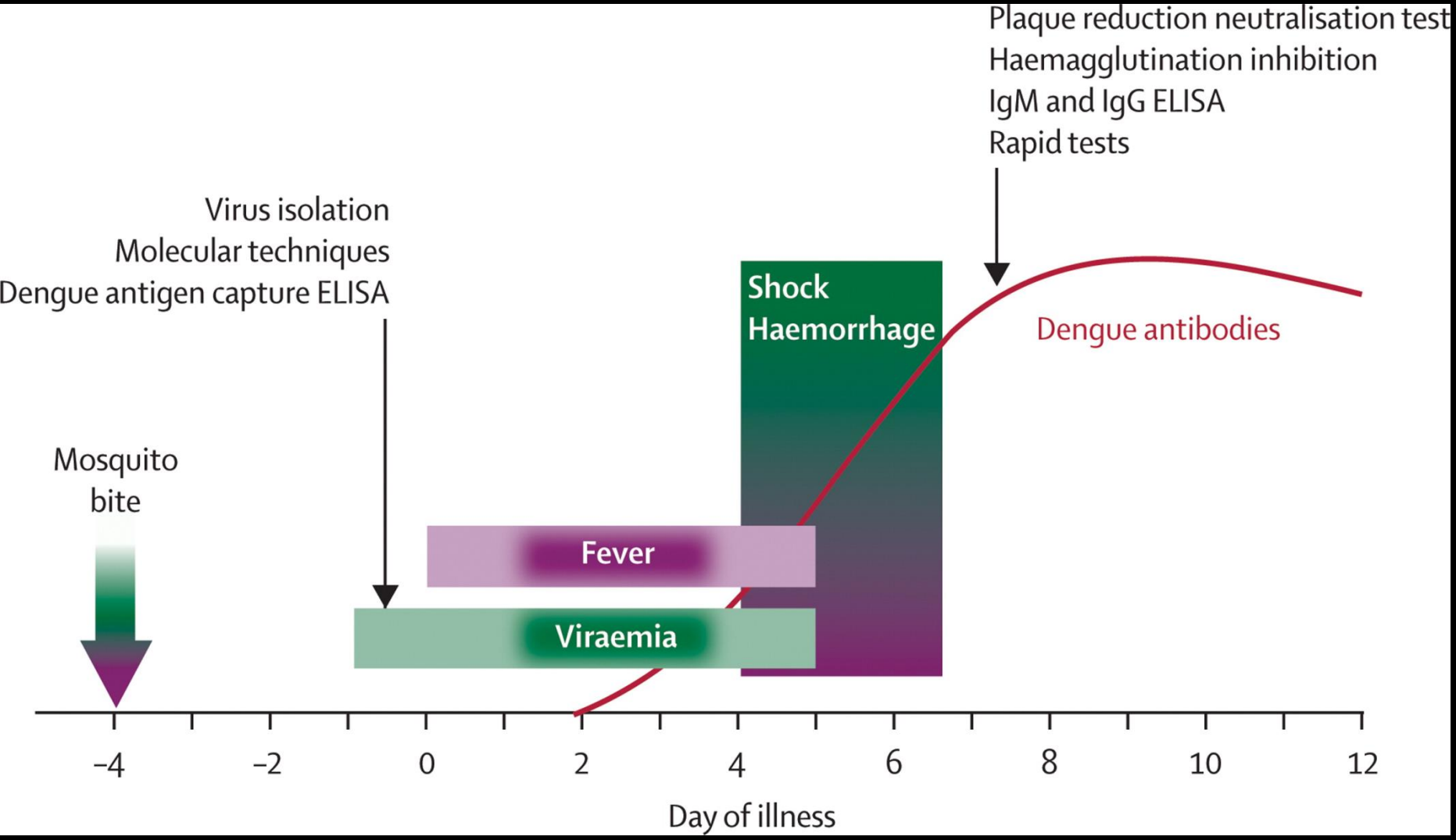
Clinical and Laboratory Presentation

- Dengue Fever:
  - Fever, maculopapular rash, flu-like symptoms, headache, bone/joint pain, retro-orbital pain, petiechial hemorrhaging.
- Dengue Hemorrhagic Fever 4 Diagnostic Criteria:
  - 1) Fever, 2)hemorrhagic episodes with + tourniquet test, petechiae, ecchymoses, purpura, mucosal bleeding, 3) excessive capillary permeability, 4)thrombocytopenia

Dengue Diagnosis

- Epidemiologic exposure
- Clinical symptoms
- Virus Isolation on C6/36 cells
- Antigen Detection: ELISA NS1
- Serology: Elisa Kits: Sensitivity 21-99% and Specficity 77-99%. (Hunsperger et al. EID 2009)
  - MAC-ELISA (IgM antibody Capture) sensi98%/specif98%.
- CDC RT-PCR assay for patients with symptoms (viremia). Sens(89-99%), Spec(91-100%)

Diagnosis of Dengue



Dengue Clinical Spectrum

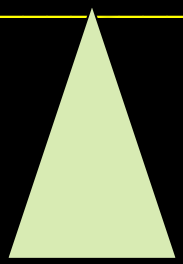
Dengue Fever

- Fever, HA, myalgias (severe)
- Rash
- Pharyngeal injection, URI symptoms
- Hepatitis, encephalopathy or –encephalitis,
- Thrombocytopenia, leukopenia

DHF/DSS

Dengue Hemorrhagic fever/ dengue shock syndrome

- Fever lysis followed by:
  - Abdominal pain, leukopenia, elev AST
  - Vasculopathy resulting in shock signs/sx
  - Bleeding, pleural effusions, ARDS
  - Tourniquet test- low sensitivity



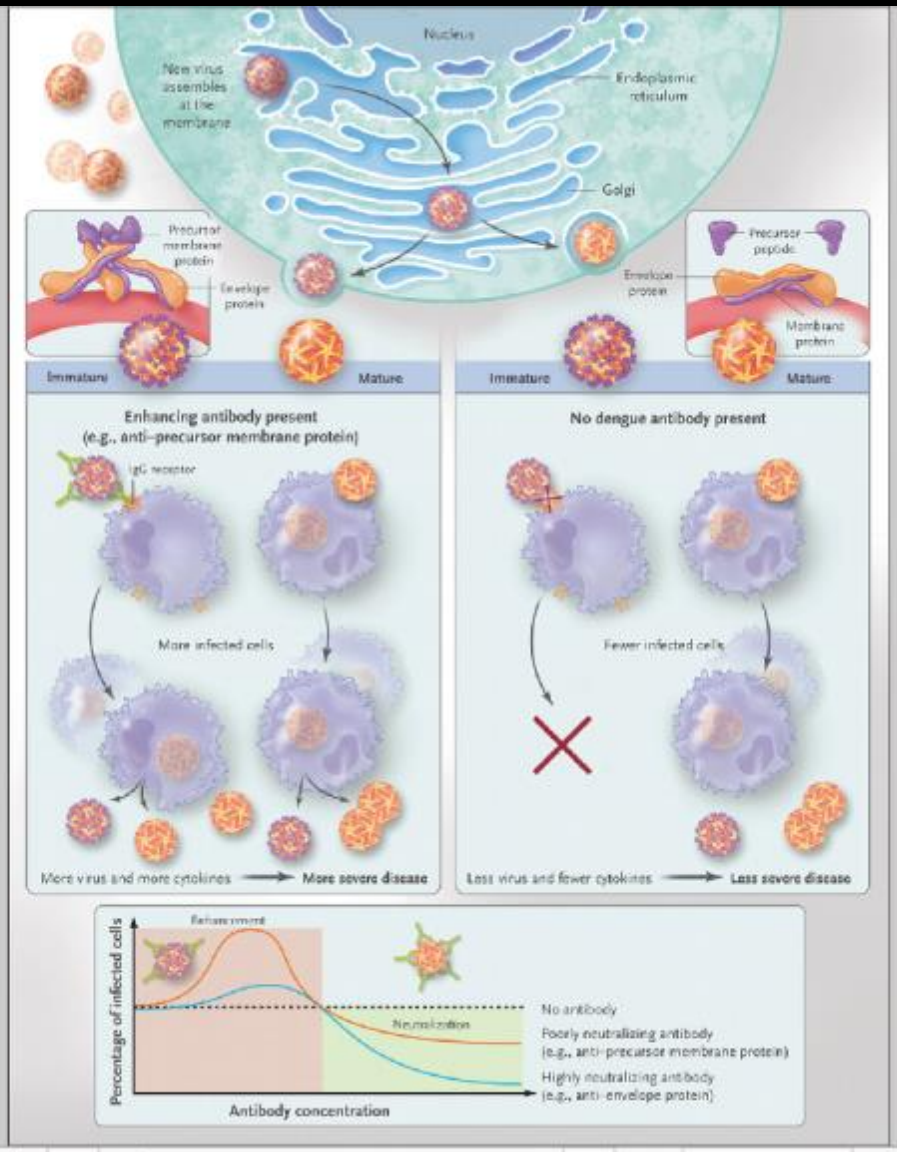


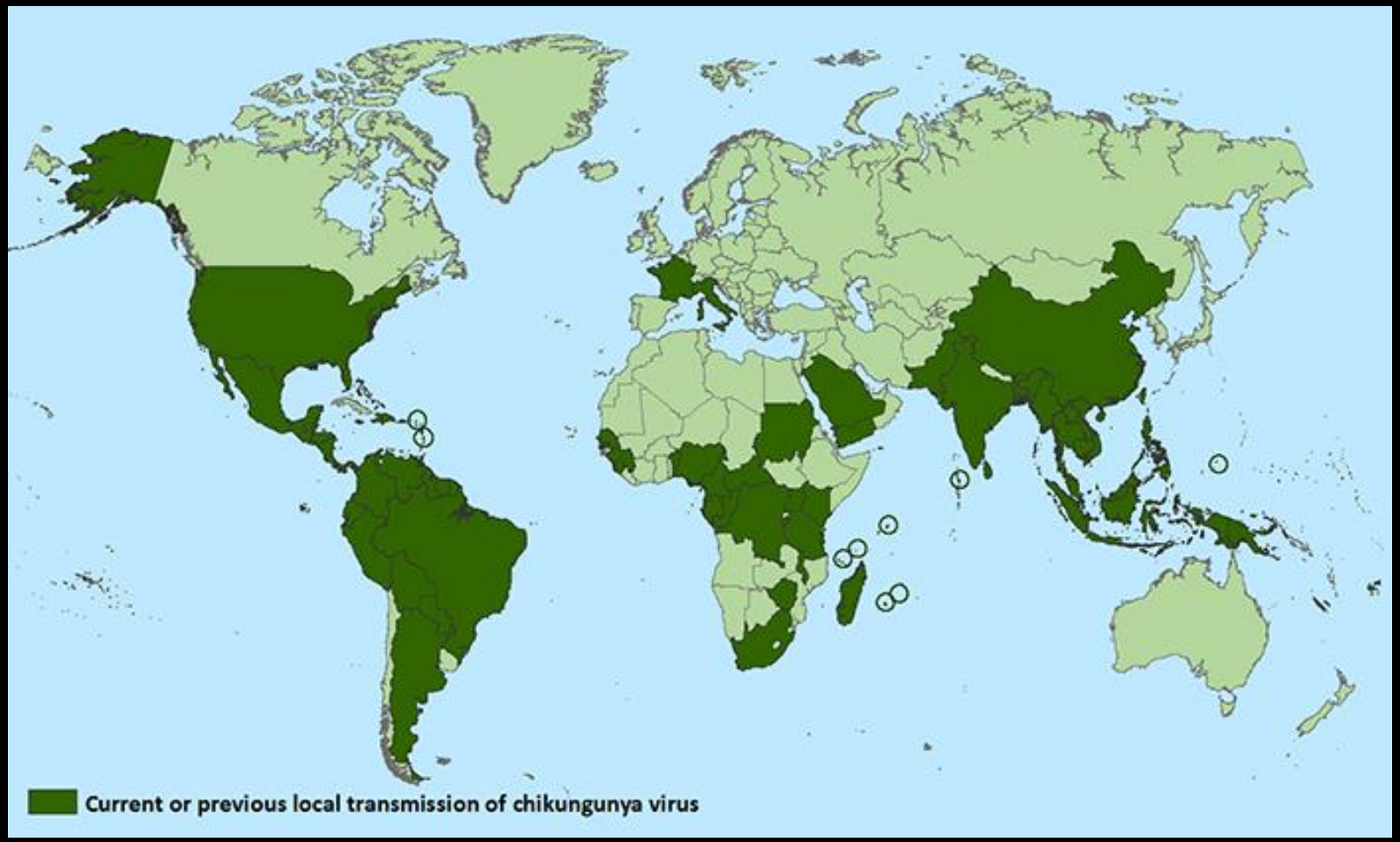
Figure 1 Antibody-Dependent Enhancement of Dengue Infection.

Dejnirattisai et al.1 analyzed a panel of monoclonal antibodies from human B cells isolated from patients after secondary dengue infection. Although the majority of monoclonal antibodies against anti–envelope protein neutralized dengue virus effectively, the majority of monoclonal antibodies against anti–precursor membrane protein failed to do so. The precursor membrane antigen is abundant on immature and noninfectious virions, but the precursor membrane protein density decreases as the virion matures and becomes infectious. Mature virus can always — unless neutralized — infect mononuclear cells through clathrin-mediated endocytosis. However, in the presence of non-neutralizing anti–precursor membrane protein antibodies, even immature and otherwise noninfectious virus can enter IgG receptor–bearing cells and replicate efficiently, leading to more infected cells that then produce more virus and more cytokines, potentially contributing to more severe disease. Although monoclonal antibodies against both envelope protein and precursor membrane protein, and even polyclonal convalescent serum, can enhance infection at low concentrations, the anti–precursor membrane protein response might be

Management of Dengue

- Blood transfusion- only if bleeding. No evidence for prophylactic platelet transfusions.
- Shock is due to venous pooling (inc Diastolic pressure) and narrow pulse pressure.
  - Ringer's lactate (NEJM 2005. 353: 877)
  - Severe shock: 6% hydroxyethyl starch
- Coagulopathy: pathophysiology not understood and neither is the treatment.

Chikungunya



Courtesy http://www.cdc.gov/chikungunya/geo/

Chikungunya

- Attack Rate ~80%
- Disease tends to occur in clusters or outbreaks.
- Symptoms begin 3-7 days after mosquito bite
- Symptoms: Fever, headache, muscle pain, rash. Joint swelling, synovitis, & tendonitis are common, can be chronic and debilitating.

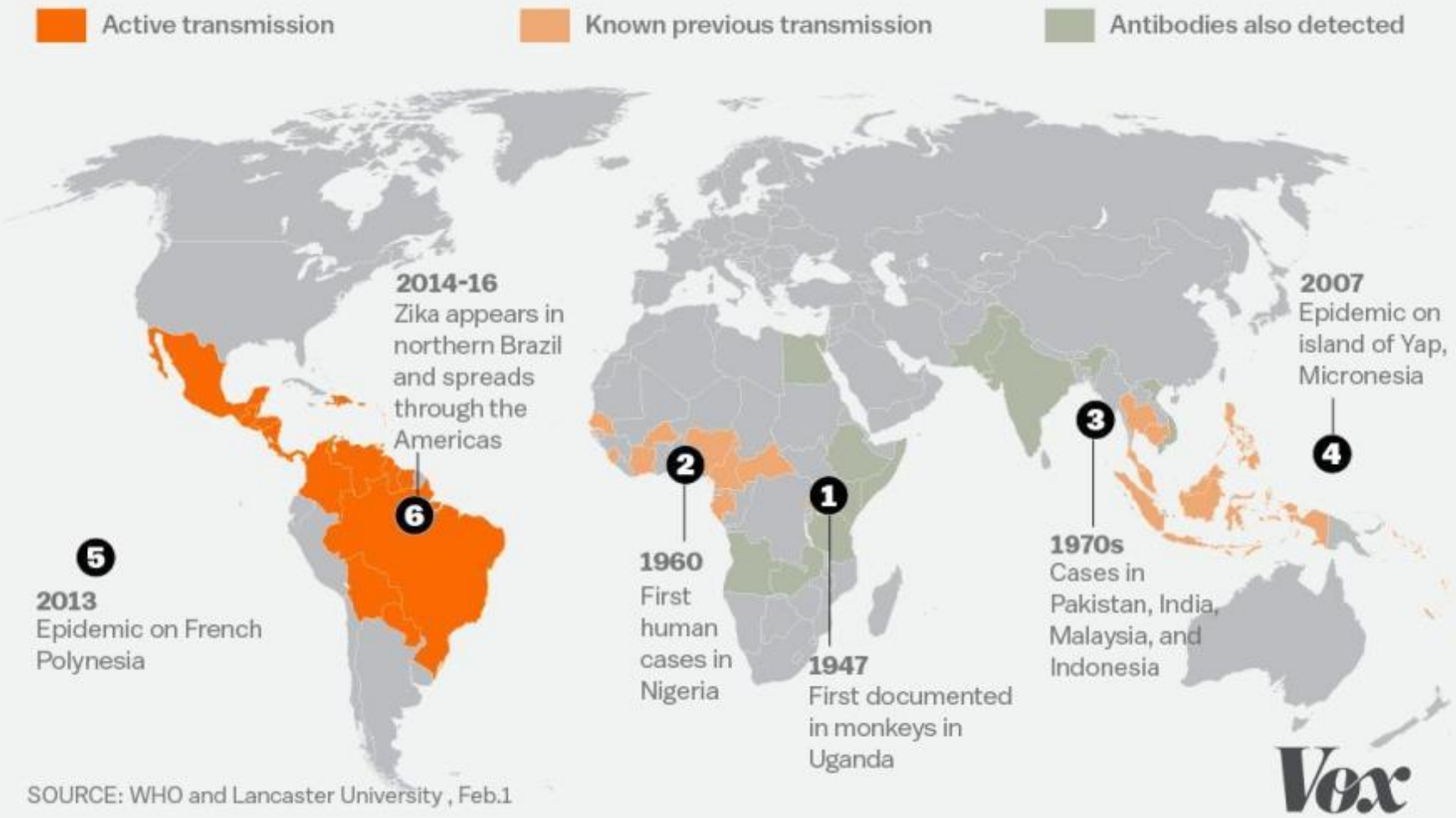
Chikungunya

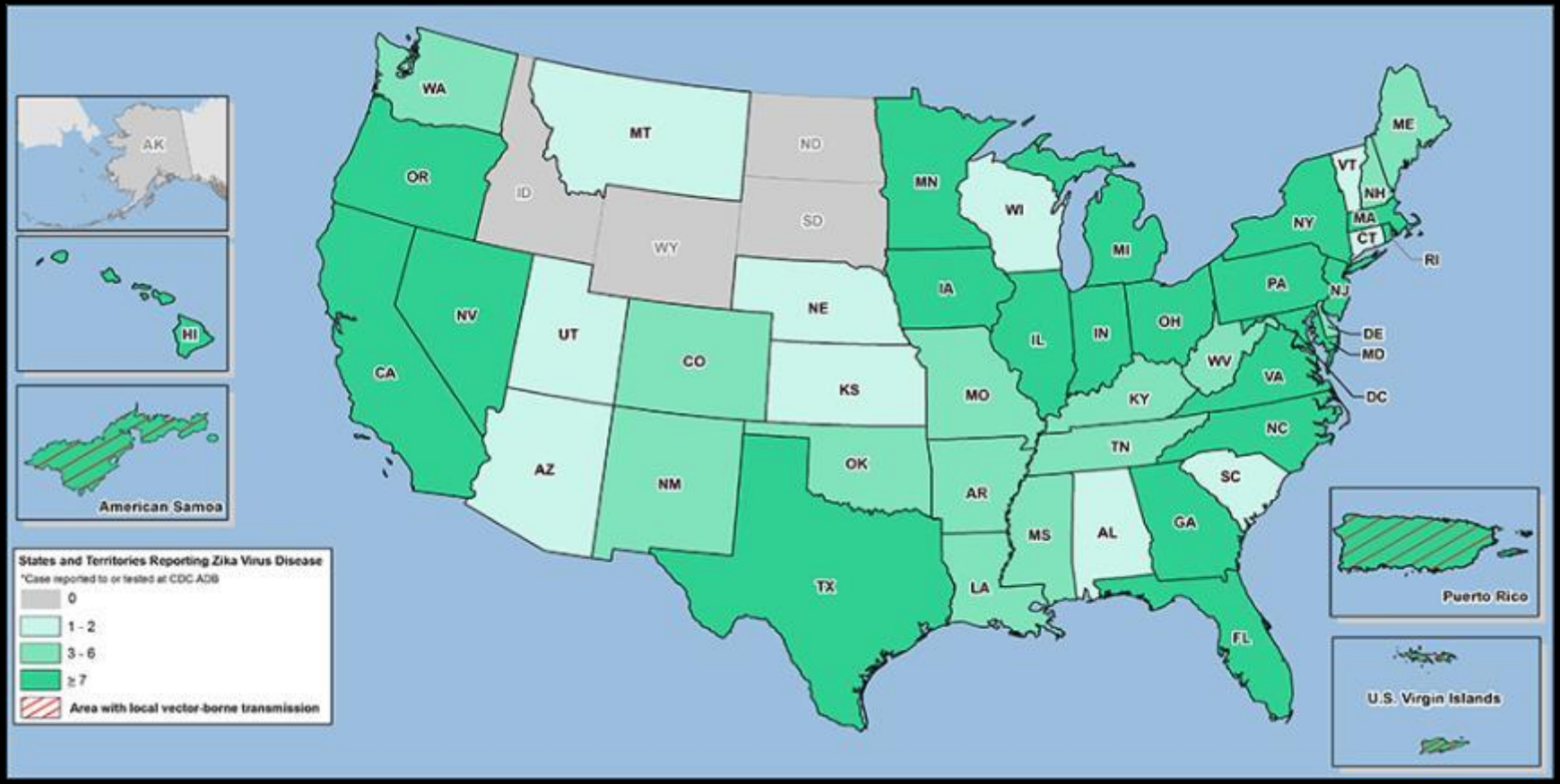
ZIKA Virus


A109
Kampala
Jinja
Eldoret
Kasese
Entebbe
Kisumu
A1
Sudan
Eritrea
Ethiopia
Uganda
Kenya
Nairobi
Tanzania
Dar es Salaam
Kampala - Entebbe Rd
Zika Forest
Kisubi Post Office
University Of Kisubi
St Mary's College Kisubi (SMACK)
Google
Imagery ©2016 DigitalGlobe, Map data ©2016 Google

Zika Forest in Uganda

How the Zika virus spread




AK
HI
American Samoa
States and Territories Reporting Zika Virus Disease
*Case reported to or tested at CDC ADB
0
1 - 2
3 - 6
≥ 7
Area with local vector-borne transmission
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
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NH
MA
CT
RI
NJ
DE
MD
DC
Puerto Rico
U.S. Virgin Islands

Zika virus Disease

- Cases in US (CDC)
- All Cases: US and DC: 756
  - US Territories: 1440
- Pregnant Women:
  - US and DC: 234, US Territories: 189 in pregnant women
- 11 sexually transmitted cases: Male to female
- 3 patient with Guillain-Barre syndrome

Zika clinical features in Adults

- Only ~20% of infected adults develop symptoms
- Fever 101-103F
- Rash
- Conjunctivitis
- Body and joint aches
- Symptoms last about 1 week
- Complications: Guillain-Barre Syndrome, sexual transmission, vertical transmission (Fetal infection)

CDC's Response to **Zika**

PREGNANT and living in an area with Zika?

What we know about Zika

- Zika can be passed from a pregnant woman to her fetus.
- Infection with Zika during pregnancy is linked to birth defects in babies.
- Zika is spread mostly by the bite of an infected *Aedes* species mosquito.
  - These mosquitoes are aggressive daytime biters. They also bite at night.
- There is no vaccine to prevent or medicine to treat Zika.
- Zika can be spread by a man to his sex partners.

What we don't know about Zika

- When during pregnancy Zika might cause harm to the fetus.
- How likely it is that Zika infection will affect your pregnancy.
- If your baby will develop birth defects from the infection.

Symptoms of Zika

Most people with Zika won't even know they have it. The illness is usually mild with symptoms lasting for several days to a week.

The most common symptoms of Zika are

- Fever
- Rash
- Joint Pain
- Red eyes

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

Zika Virus and Microcephaly: Examples

- Photos of microcephalic infants in Brazil courtesy of AP Photo/Felipe Dana and Ueslei Marcelino/Reuters

Zika Virus and Microcephaly: CT Findings

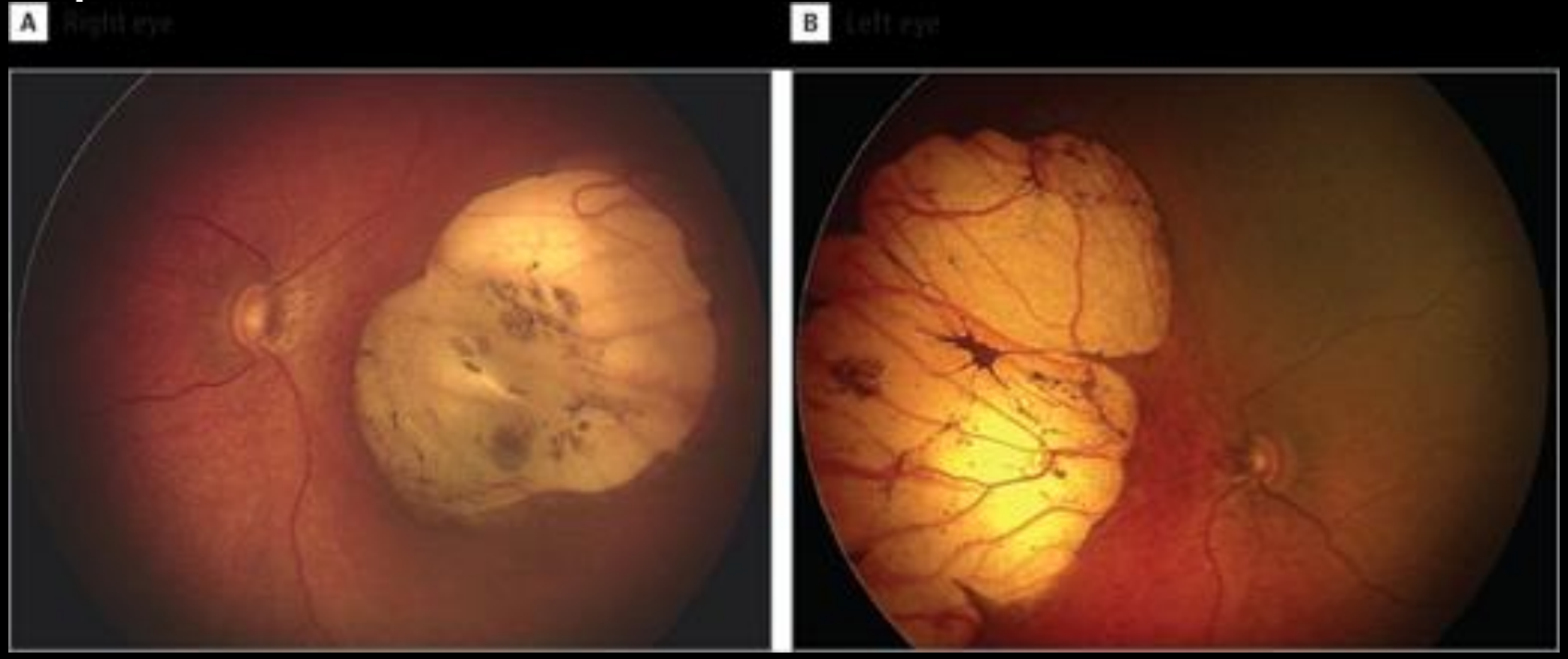
Figure 1. Computed Tomography in Eight Infants with Congenital Microcephaly.

Axial computed tomographic (CT) images of the heads of eight infants who were born with congenital microcephaly associated with intrauterine ZIKV infection show calcifications in bandlike distributions (Panels A, B, and D) with isolated configurations (Panels B, C, E, and G), punctate configurations (Panels B and E), and larger configurations (Panels A, C, D, and G) at the level of the corticomedullary junction (Panels A, B, and D) within the frontal, parietal, and temporal lobes, basal ganglia (Panel C), and upper cervical spinal cord (Panel G, arrow). In addition, there are visible signs of global cortical hypogyration (Panels A through F and H), moderate-to-severe ventriculomegaly (Panels A and C through F), severe global cerebellar hypoplasia (Panel F), abnormal hypodensity of the supratentorial white matter (Panels A, B, D, and H), and encephalomalacic changes after ischemic stroke in the vascular territory of the left middle cerebral artery (Panel H, arrows).

- Photos show CT images of microcephalic infants.
- Hazin AN, et al. Computed Tomographic Findings in Microcephaly Associated with Zika Virus. NEJM 2016.

Zika Virus and Ophthalmologic Birth Defects

- Case series of infants born to mothers with presumed Zika virus infection



- de Paula Freitas B, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol. 2016 Feb 9. Photos show evidence of chorioretinal atrophy, pigment mottling, and an optic nerve defect.

Zika Virus and Guillain-Barré Syndrome (GBS)

- Anecdotal increase in GBS incidence in French Polynesia, Brazil, Colombia, and El Salvador during outbreaks
- Case-control series from French Polynesia showed 100% cases with Zika virus neutralizing antibodies versus 56% controls (odds ratio = 34)
- Study results based on antibody testing
- Predominantly acute axonal motor neuropathy (AMAN)

- Cao-Lormeau V-M, Blake A, Mons S, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case control study. Lancet 2016.

Clinical features of Zika compared to Chikungunya and Dengue

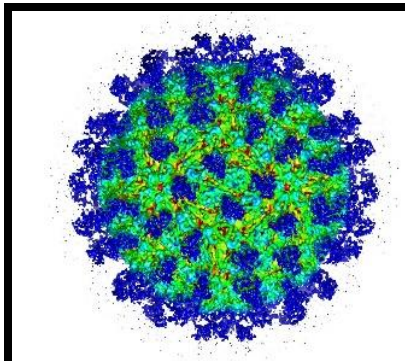
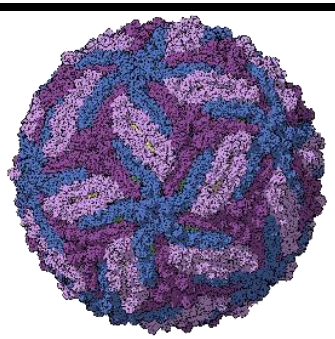
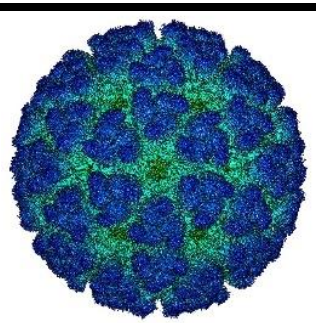
	Dengue	Chikungunya	Zika
Fever (>39C)	++	+++	+
Rash	+	++	+++
Arthritis	-	+	-
Arthralgia	+/-	+++	++
Headache	++	++	+
Conjunctivitis	-	-	++
Myalgia	++	+	+
Hemorrhage	++	+/-	-
Shock	+	-	-

Dengue, Zika and Chikungunya: challenges and opportunities for their prevention

Edwin J. Asturias | Associate Director
Center for Global Health
Associate Professor of Pediatrics and Epidemiology

Dengue Vaccine Expert Group – WHO, Geneva, June 2016

Biological and epidemiological characteristics of DEN, ZIK and CHIK viruses

			
Virus	**Dengue**	**Zika**	**Chikungunya**
Family	**Flavivirus**	**Flavivirus**	**Alpha**
Serotypes	**1-4**	**1**	**1**
Transmission	**Aedes spp.**	**Aedes spp./Sexual**	**Aedes spp.**
Common Presentation	**Acute Febrile Illness**	**Acute Febrile Illness**	**Acute Febrile Illness**
Current Epidemiology	**Endemic/epidemic**	**Epidemic**	**Epidemic**
Protection	**Antibodies/CMI**	**Antibodies?**	**Antibodies**

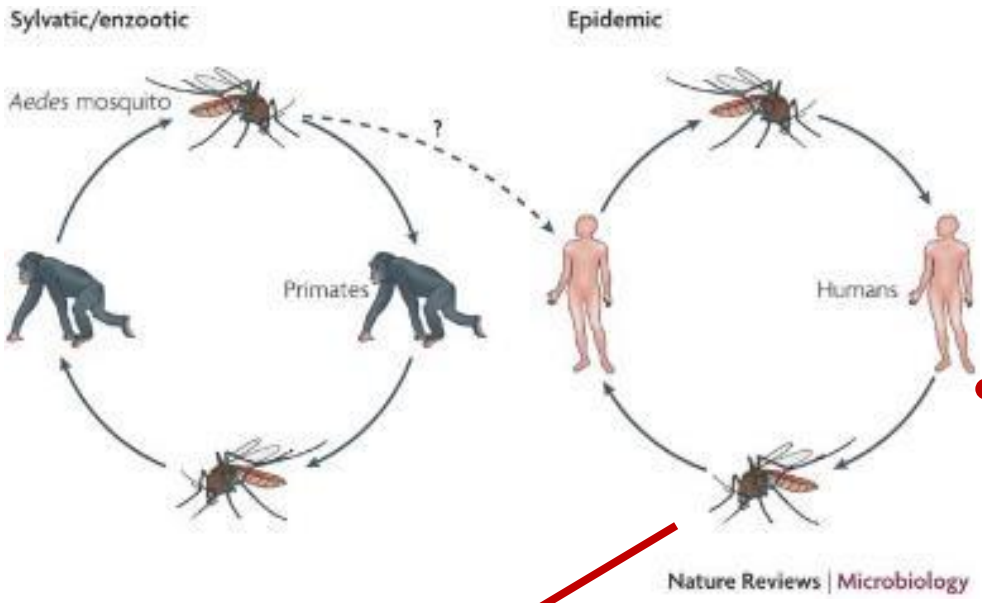
Dengue Burden

Estimated burden of dengue, by continent, 2010

Continent	Dengue	Inapparent infections
	Millions (credible interval)	Millions (credible interval)
Africa	15.7 (10.5-22.5)	48.4 (39.3-65.2)
Asia	66.8 (47.0-94.4)	204.4 (151.8-273.0)
Americas	13.3 (9.5-18.5)	40.5 (30.5-53.3)
Oceana	0.18 (0.11-0.28)	0.55 (0.35-0.82)
Global	*96 (67.1-135.6)*	*293.9 (217.0-392.3)*

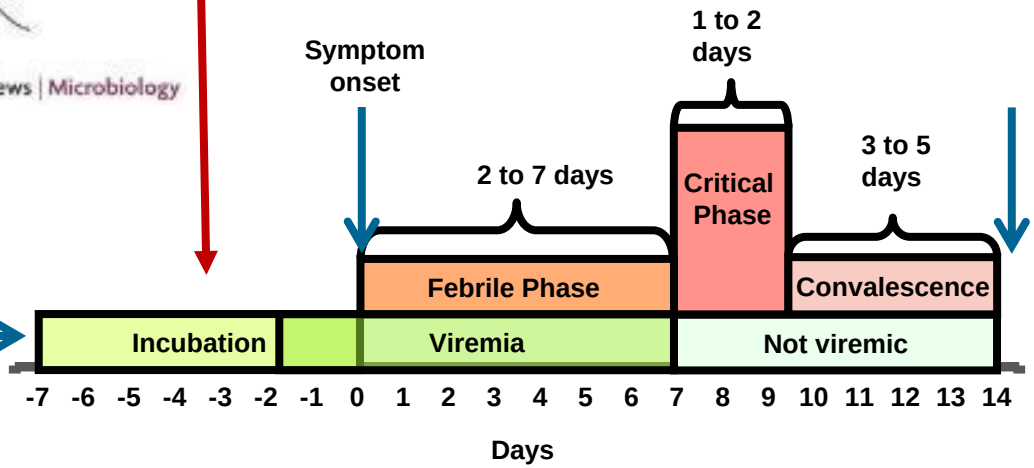
Bhatt, S et al Nature 2013; 496: 504-507

Dengue transmission cycle

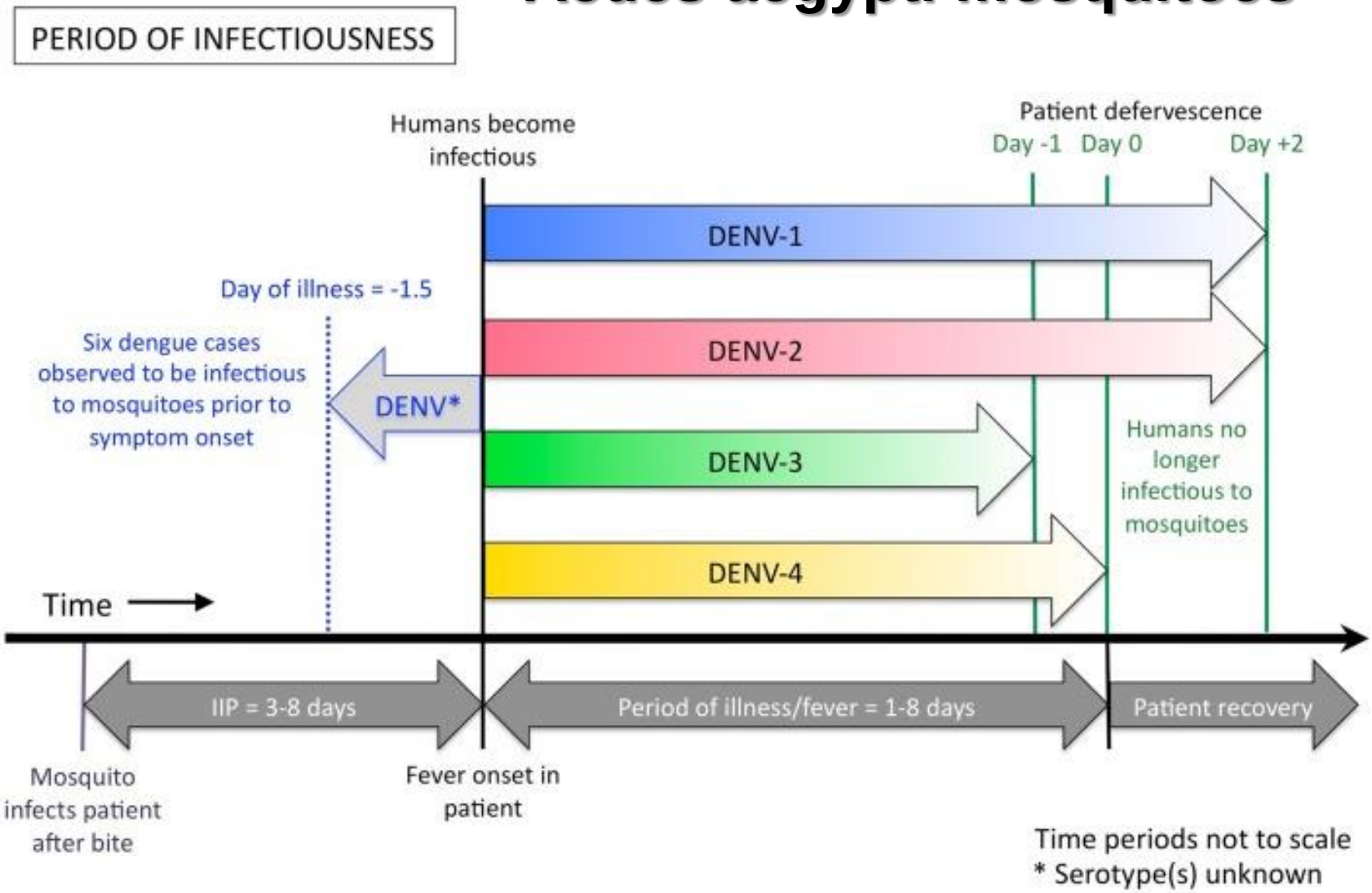


Intrinsic incubation period
3–10 days

Extrinsic incubation period
5–33 days at 25° C
2–15 days at 30° C

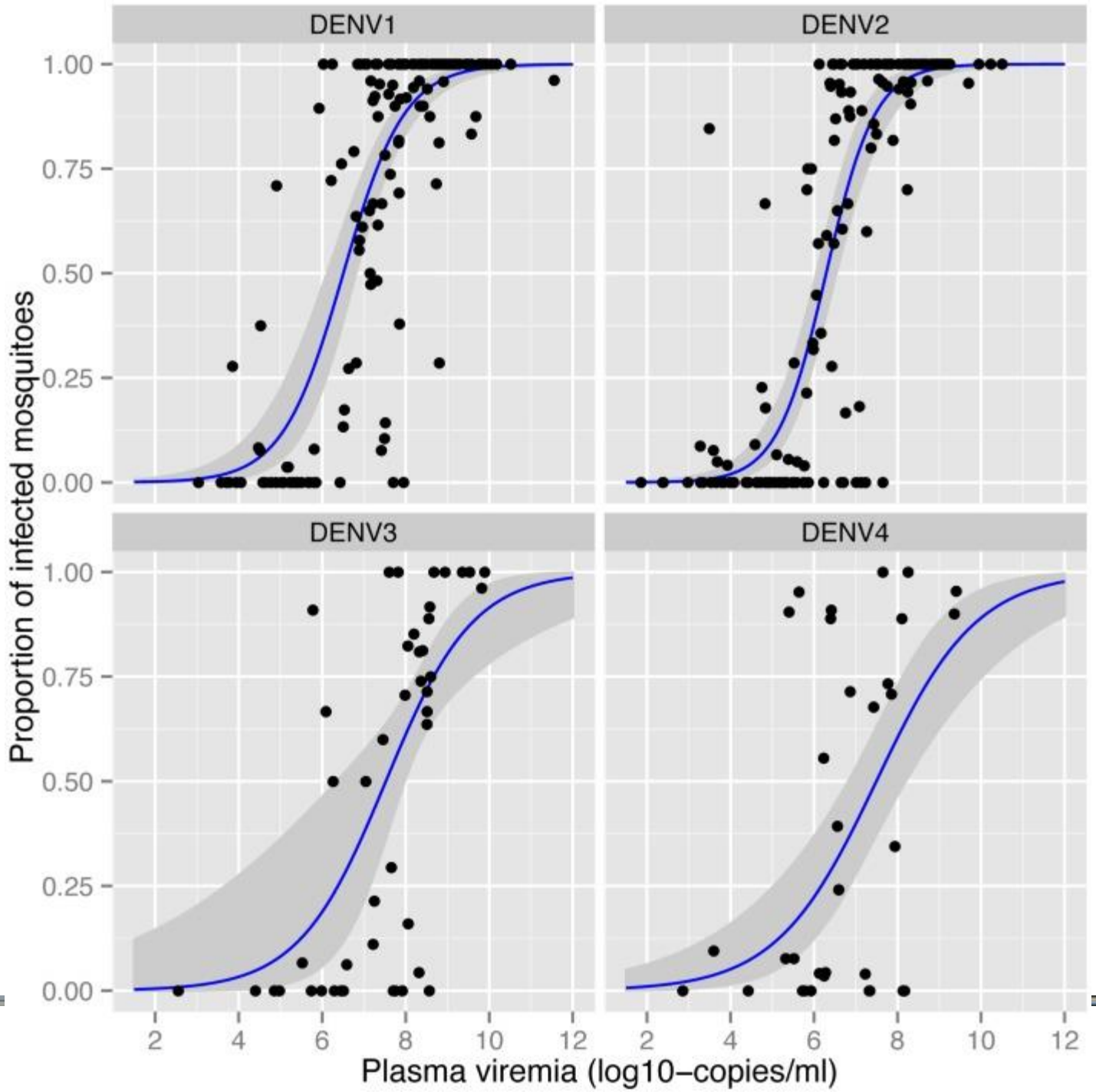


Duration of human DENV infectiousness to Aedes aegypti mosquitoes



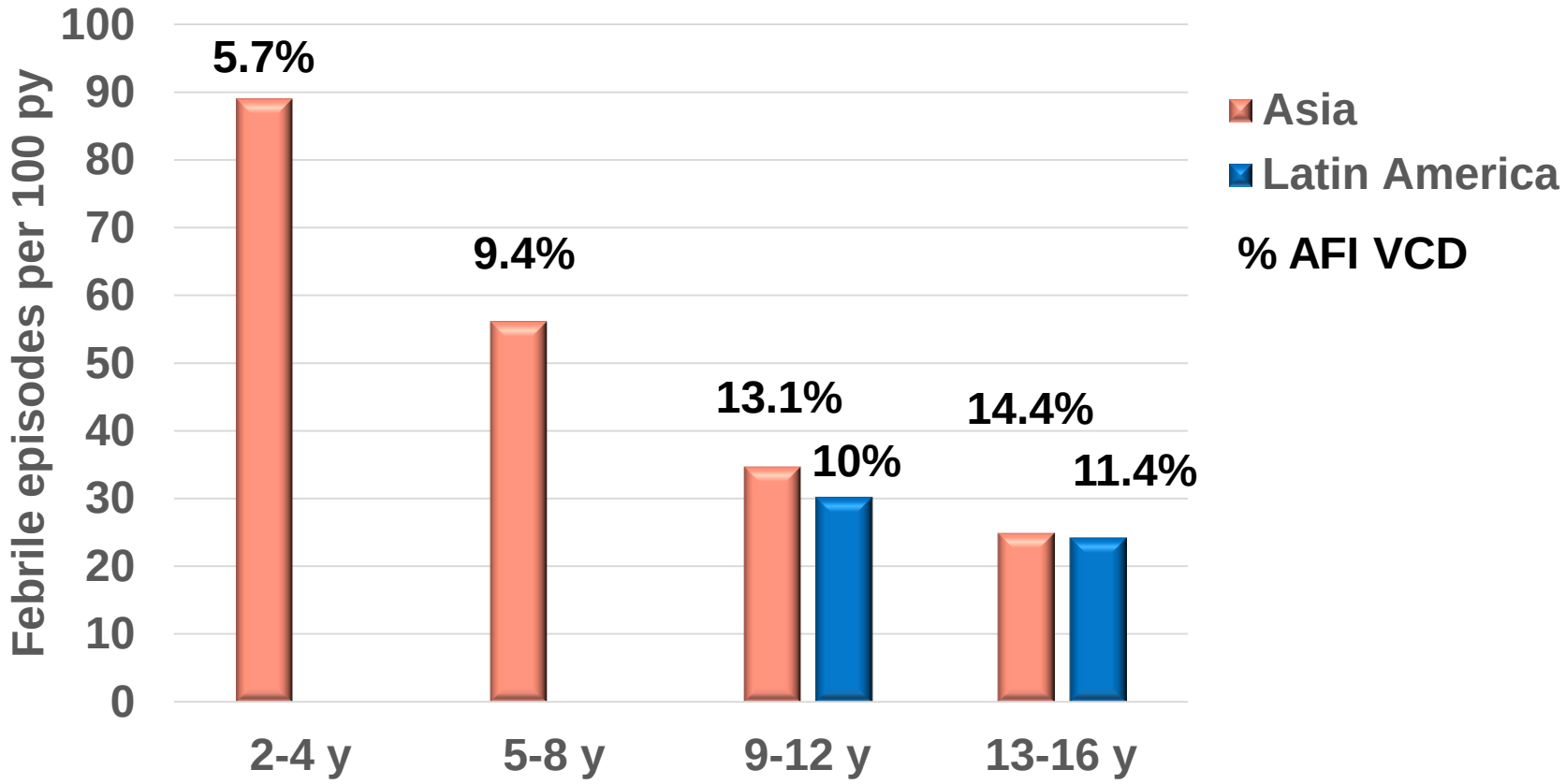
Front Immunol. 2014; 5: 290.

Effect of plasma viremia on mosquito infection



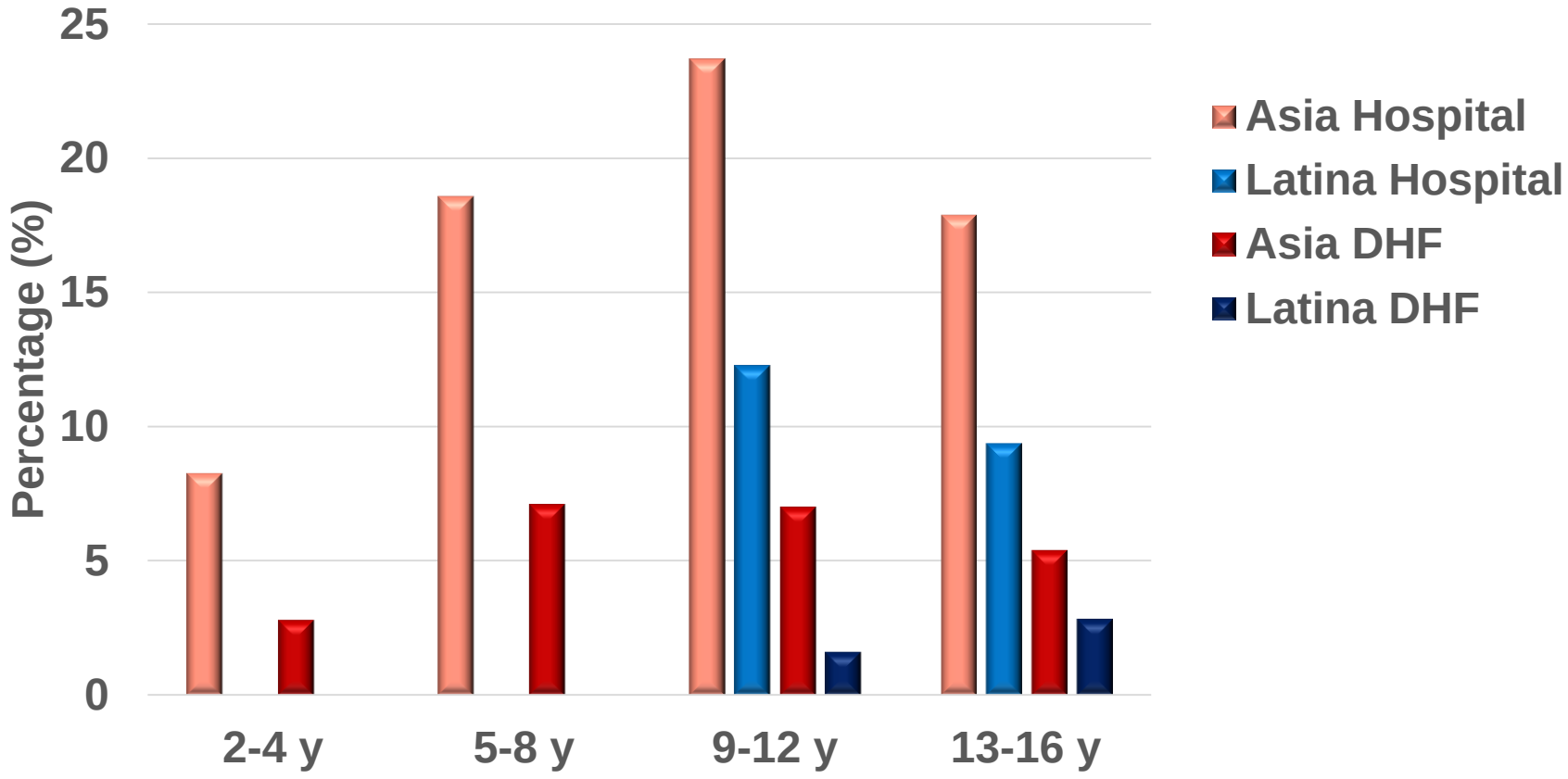
Front Immunol. 2014; 5: 290.

Incidence of febrile episodes and virologically-confirmed dengue episodes in the Asian and Latin American cohorts



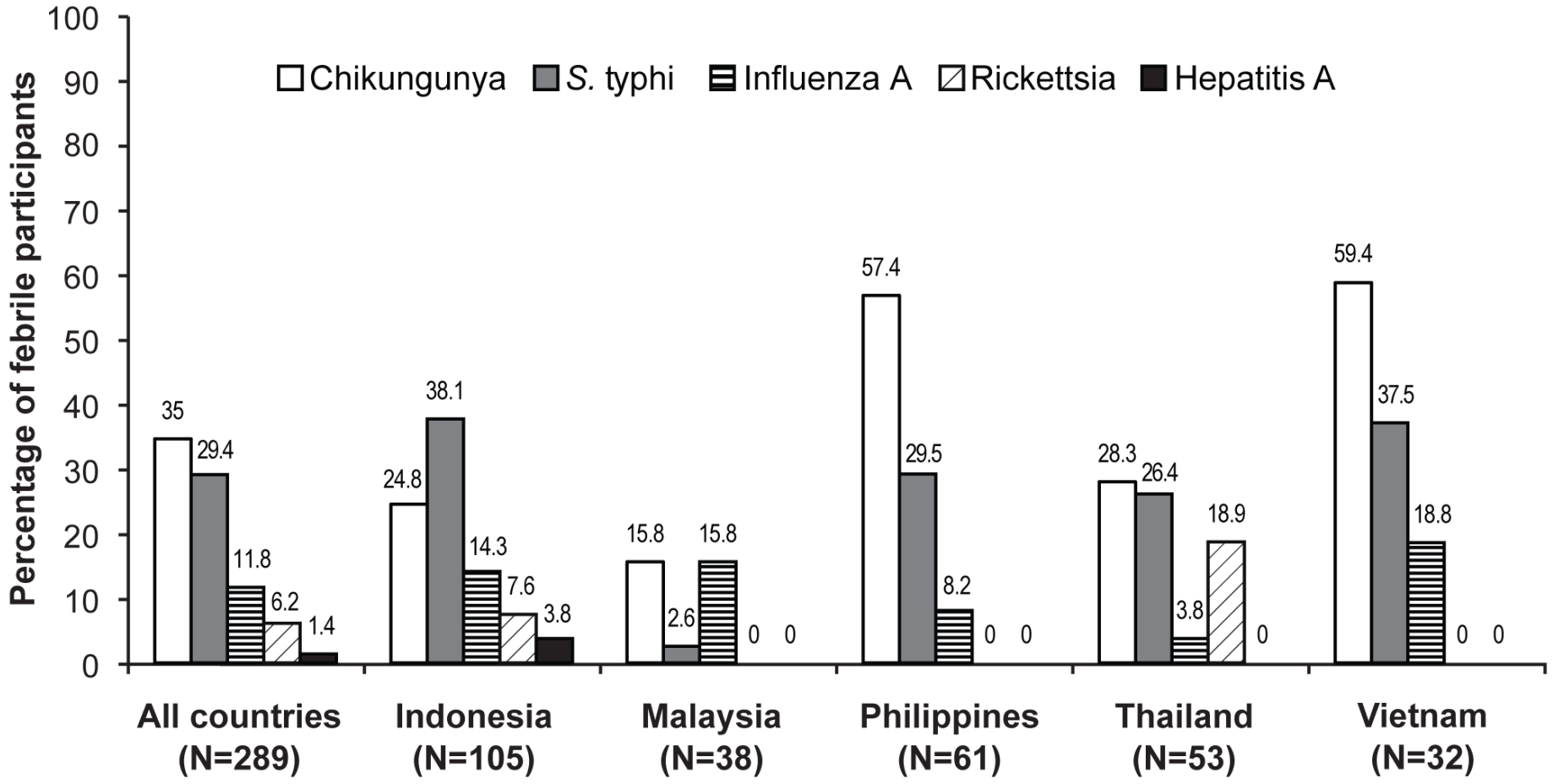
L'Azou M. N Engl J Med 2016;374:1155-66.

Percentage of VCD requiring hospitalization or DHF in the Asian and Latin American cohorts by age group.



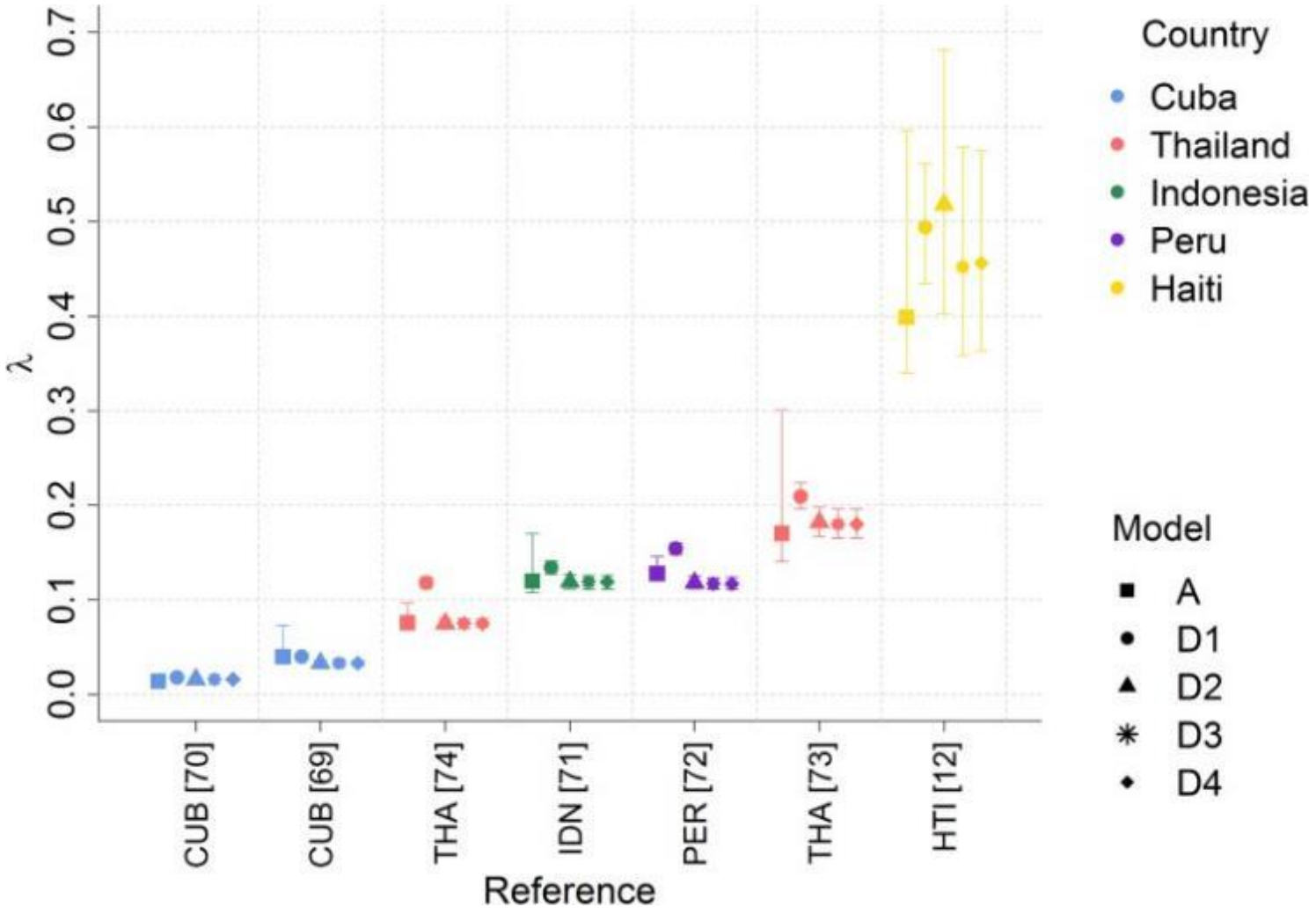
L'Azou M. N Engl J Med 2016;374:1155-66.

Frequency of most commonly detected non-dengue infections in febrile participants in Asia.

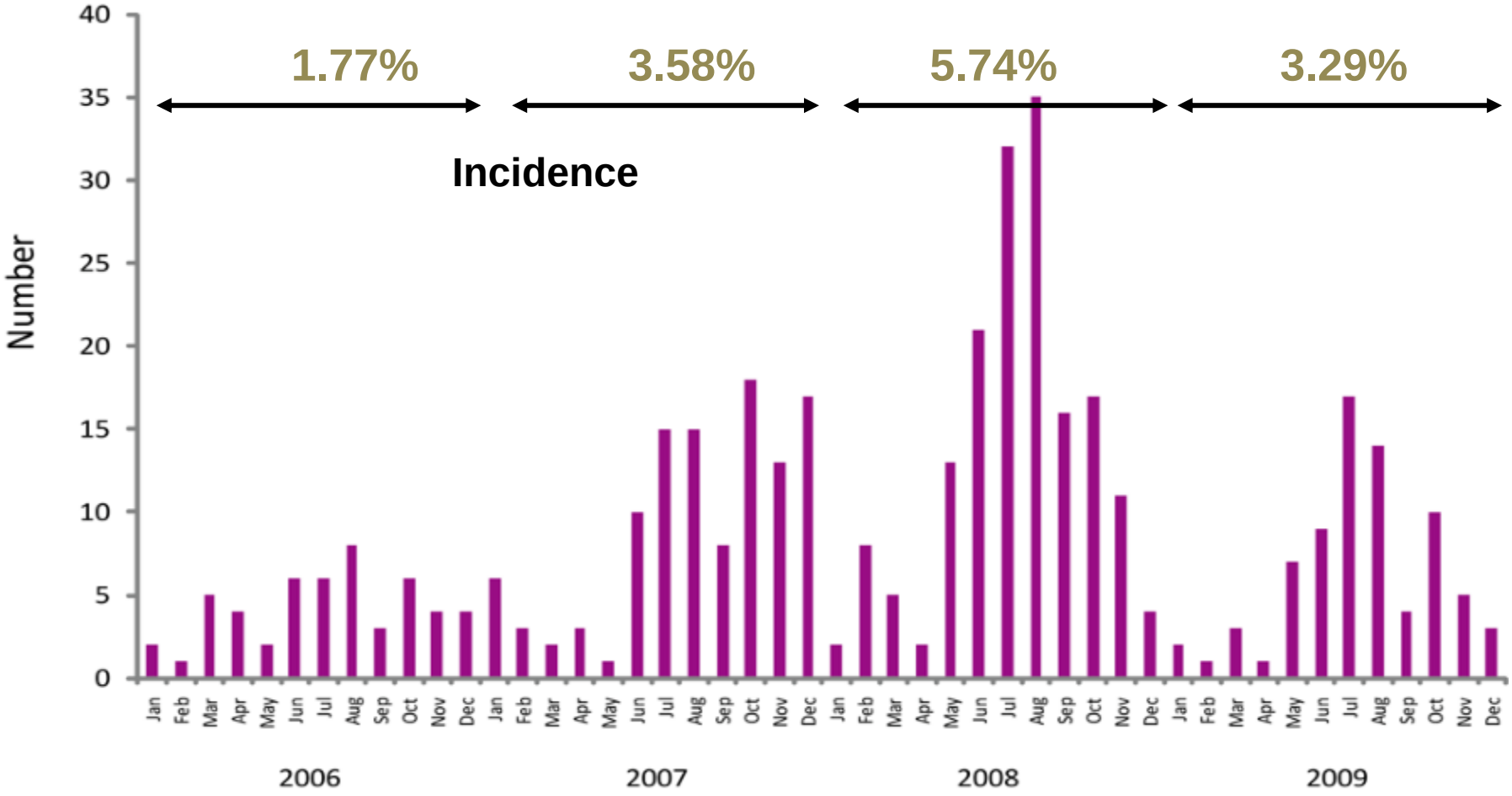


Capeding MR PLoS Negl Trop Dis 7(7): e2331

Total force of infection (λ) estimates (for all 4 serotypes) derived from PRNT datasets

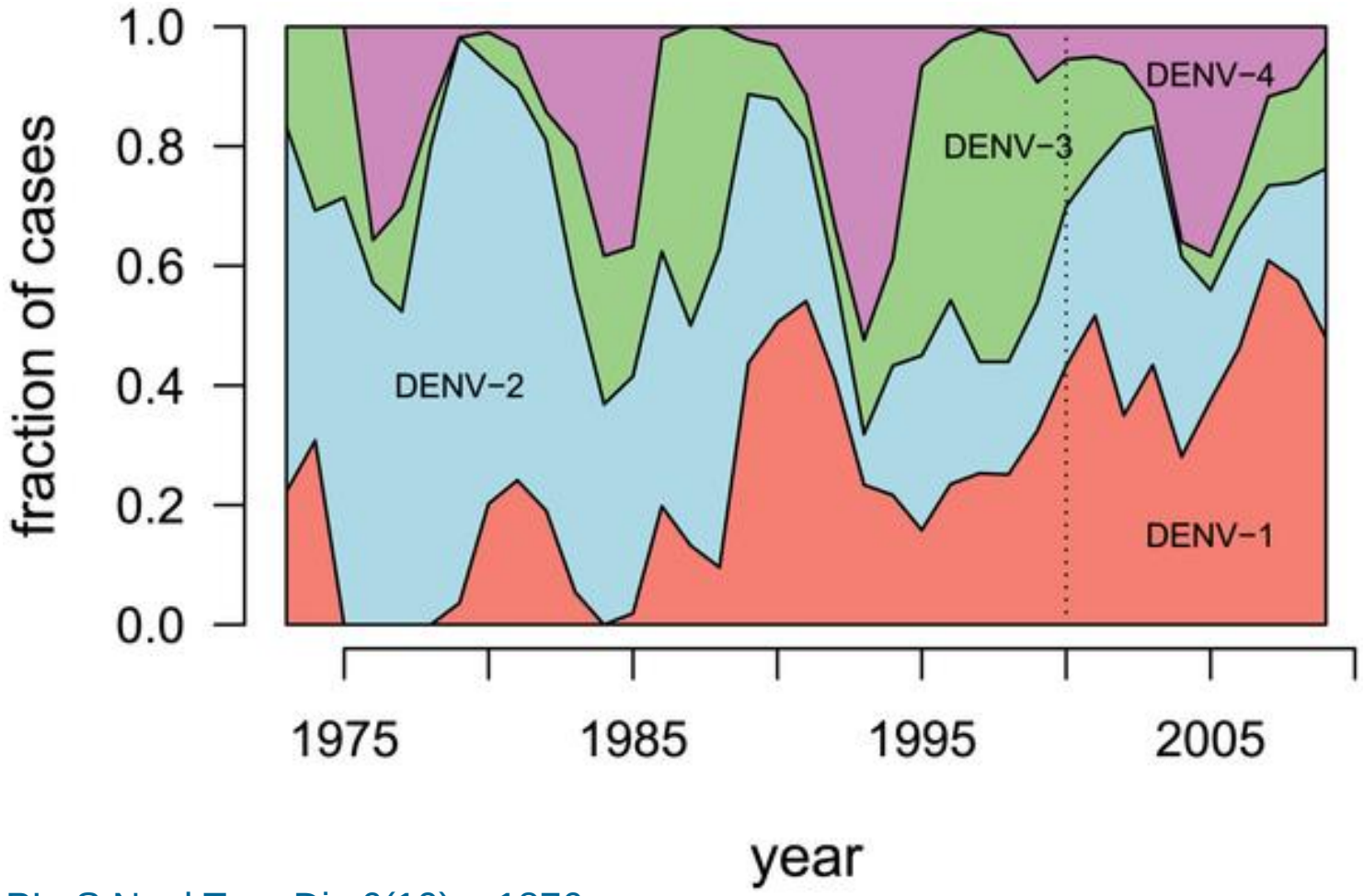


Dengue Cases by Month, Ratchaburi, 2006 - 2009



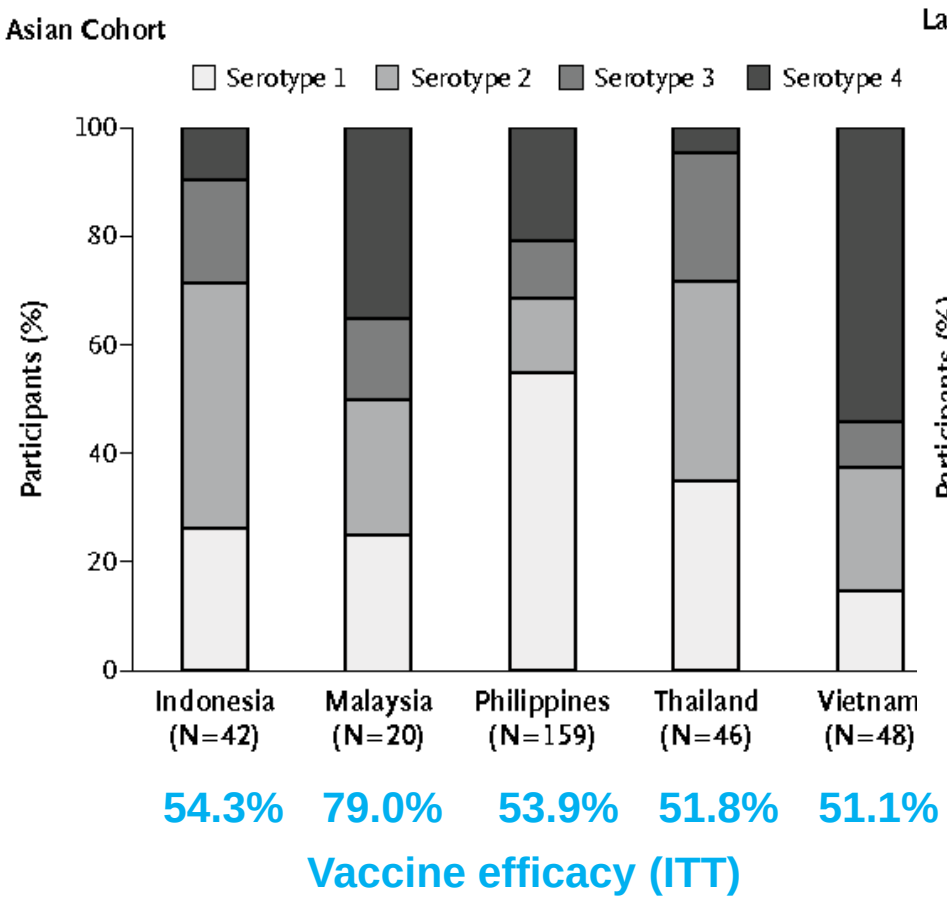
Sabchareon, A et al. PLoS NTD 2012; 6: e1732

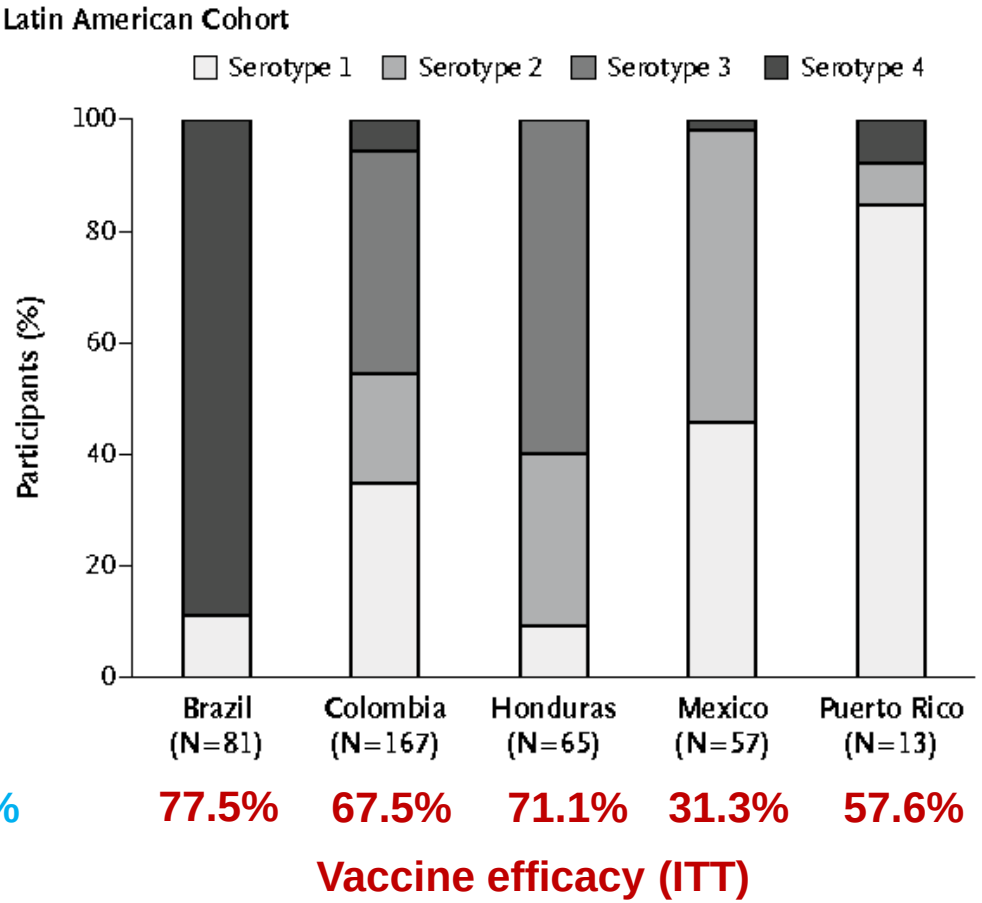
Estimated relative prevalence of the 4 serotypes in Thailand 1975-2009.



Chao DL, PLoS Negl Trop Dis 6(10): e1876.

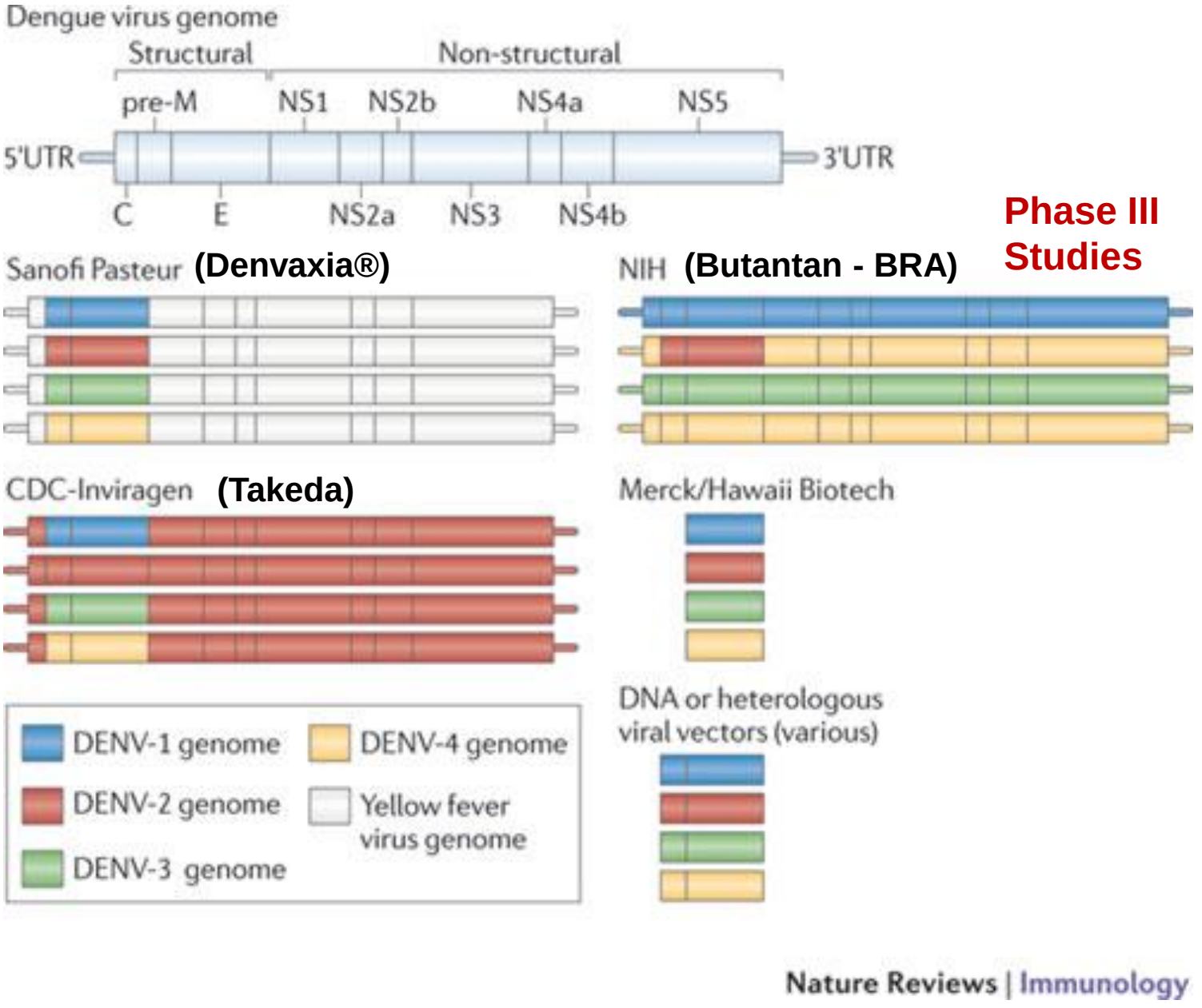
Serotype Distributions in Episodes of VC Dengue, According to Country Subcohort in Asia and Latin America





L'Azou M. N Engl J Med 2016;374:1155-66.

Dengue Vaccines and status



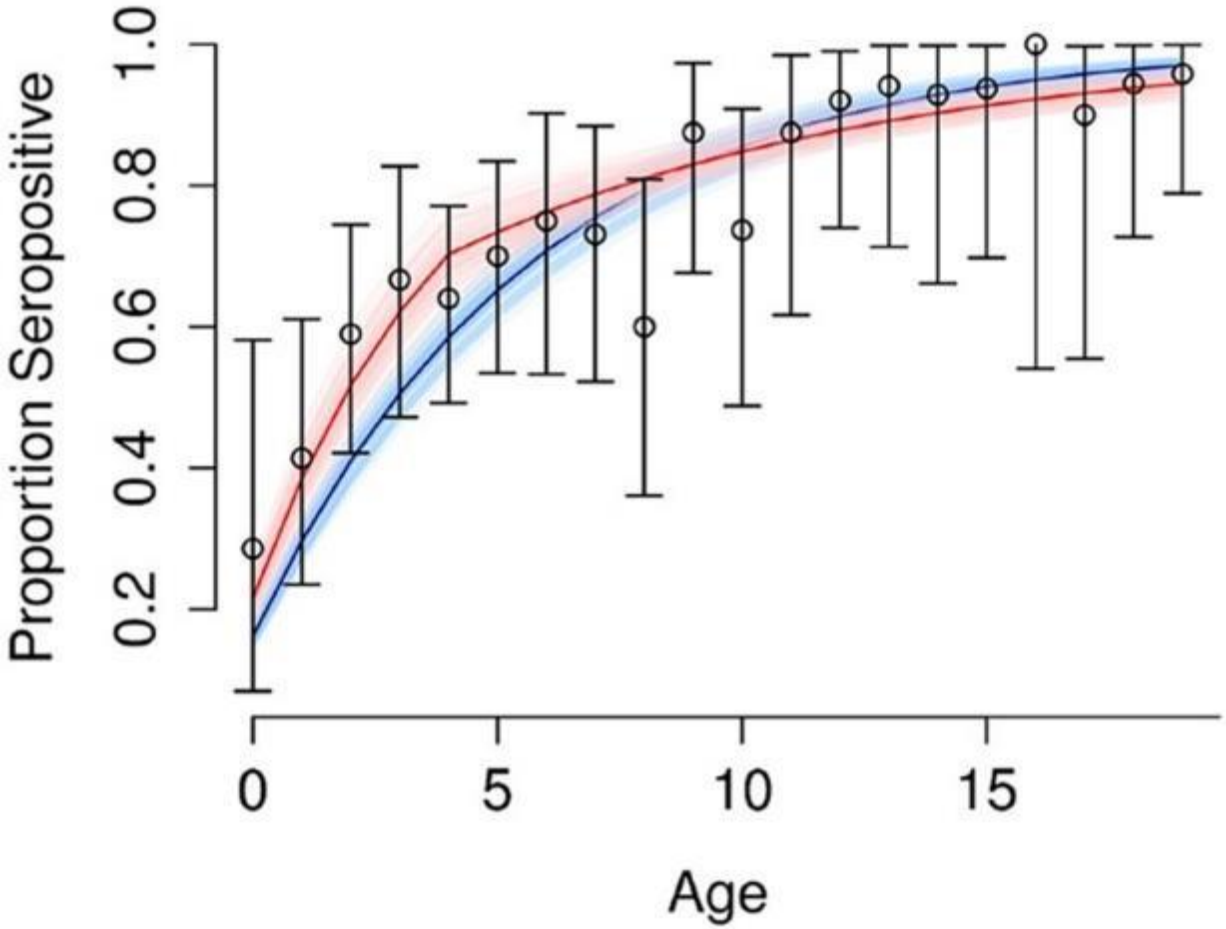
Dengvaxia®: first dengue vaccine

- Live-attenuated chimeric vaccine containing 4 serotypes on a backbone of YF-virus
- 3 dose schedule: 0, 2 and 6 months
- Indicated in children ≥ 9 years of age

WHO SAGE recommendations

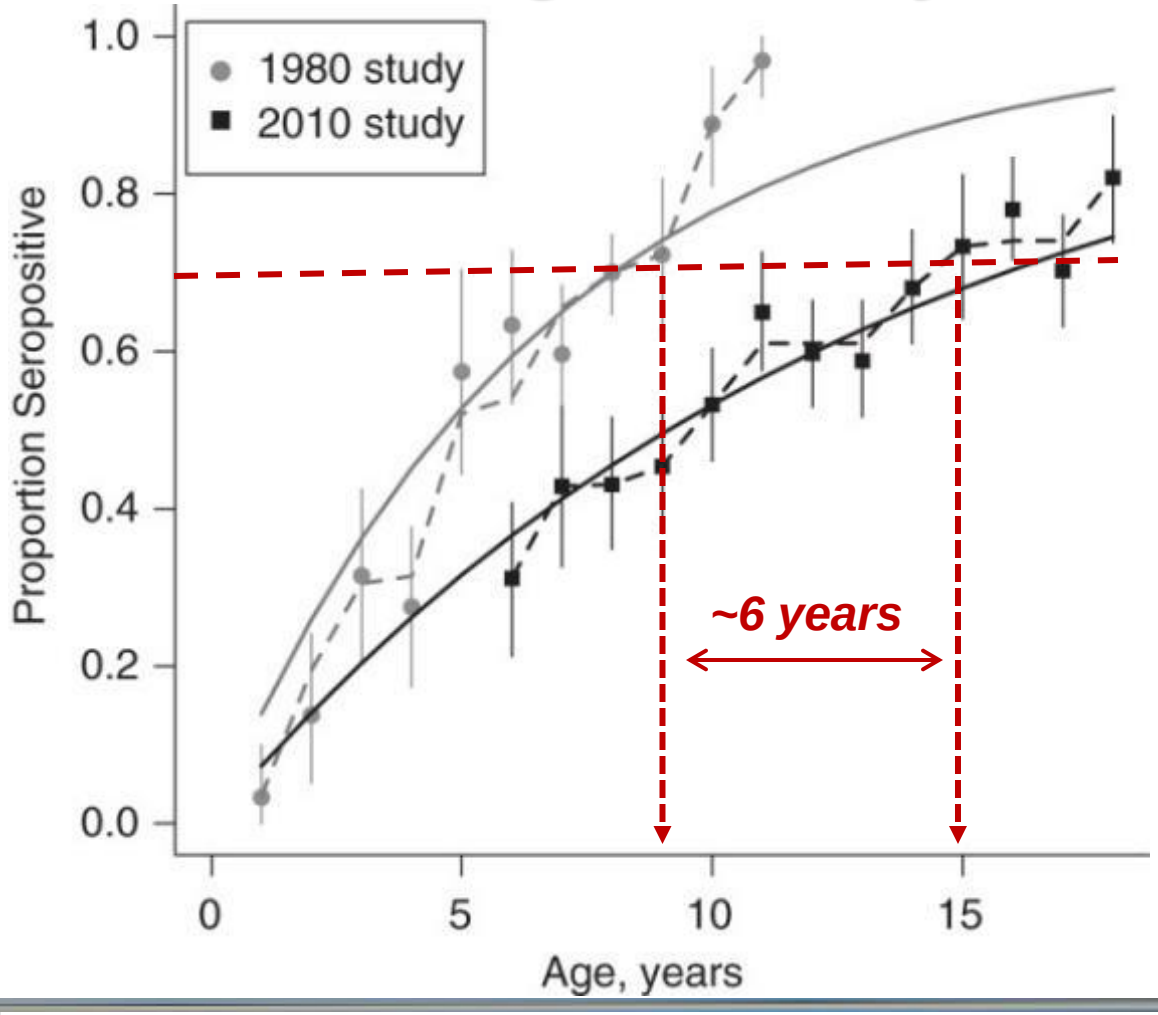
- Indicated if seroprevalence ≥ 70%
- Not recommended if seroprevalence <50%

Proportion of subjects of different ages in the Philippines that were dengue seropositive in 2012



PLoS Negl Trop Dis. 2016 Feb; 10(2): e0004337.

Age-specific dengue seroprevalence in Mueang Rayong district, Thailand, according to the 1980 and 2010 serological survey



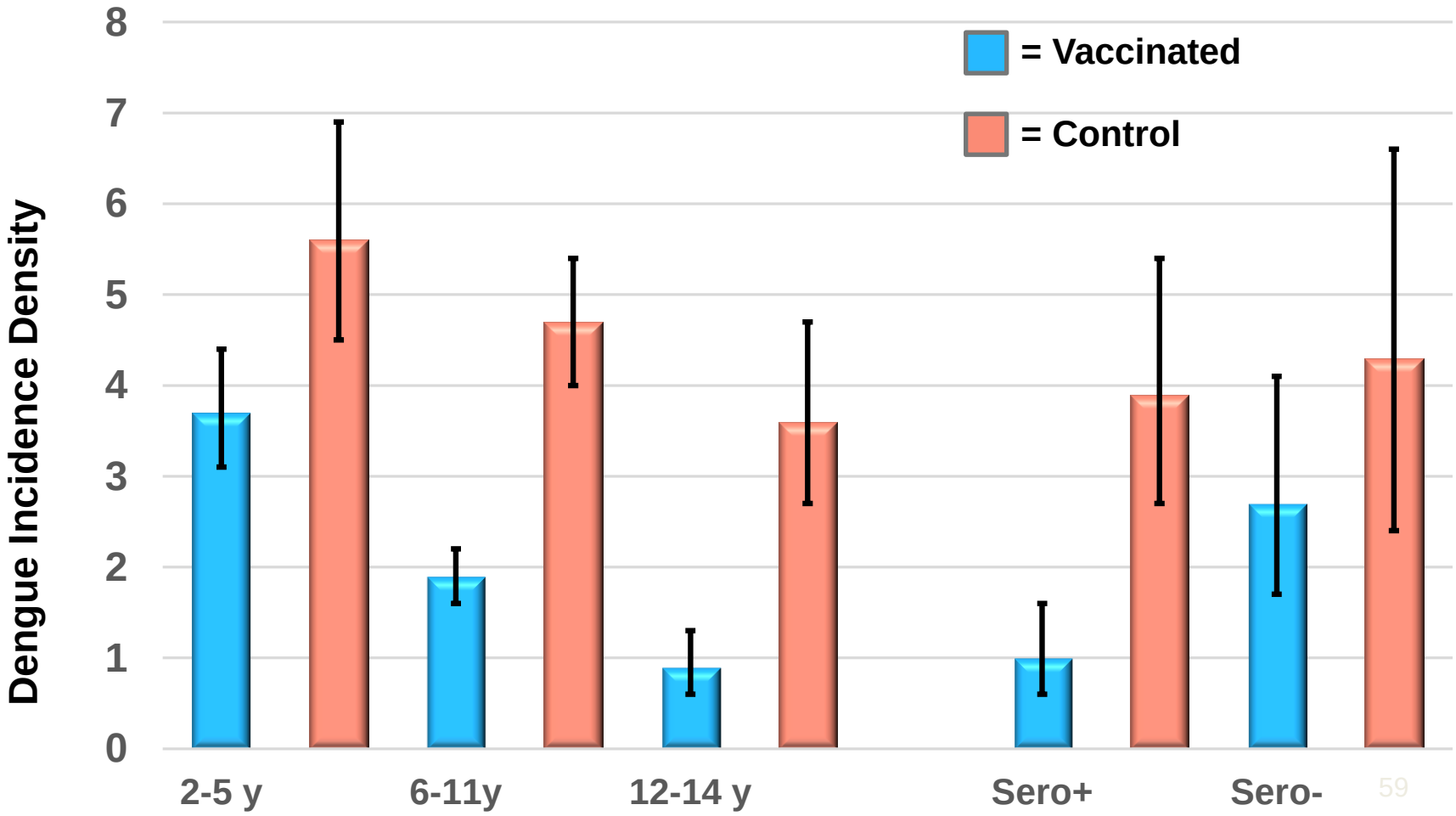
Rodriguez-Barraquer Am J Epidemiol. 2014

Results of Efficacy Trials of Dengvaxia Vaccine (per protocol)

DENV specific	Phase IIB–Thailand N= 4,002		Phase III–Asia N= 10,275		Phase III–Latin America N= 20,869	
	Efficacy	95% CI	Efficacy	95% CI	Efficacy	95% CI
All DENV's	30.2	-13–57	56.5	44–66	60.8	52–68
DENV 1	55.6	22–84	50.0	25–67	50.3	29–65
DENV 2	9.2	-75–51	35.0	-9–61	42.3	14–61
DENV 3	75.3	-38–100	78.4	53–91	74.0	62–82
DENV 4	100	25–100	75.3	55–87	77.7	60–88

Sabchareon, A et al. Lancet 2012; 380:1559-1567
Capeding MR, et al Lancet 2014; 834: 1358-1365
Villar L, et al. NEJM 2015: 372 113-123

Vaccine Efficacy based on Dengue Incidence Density in Asia

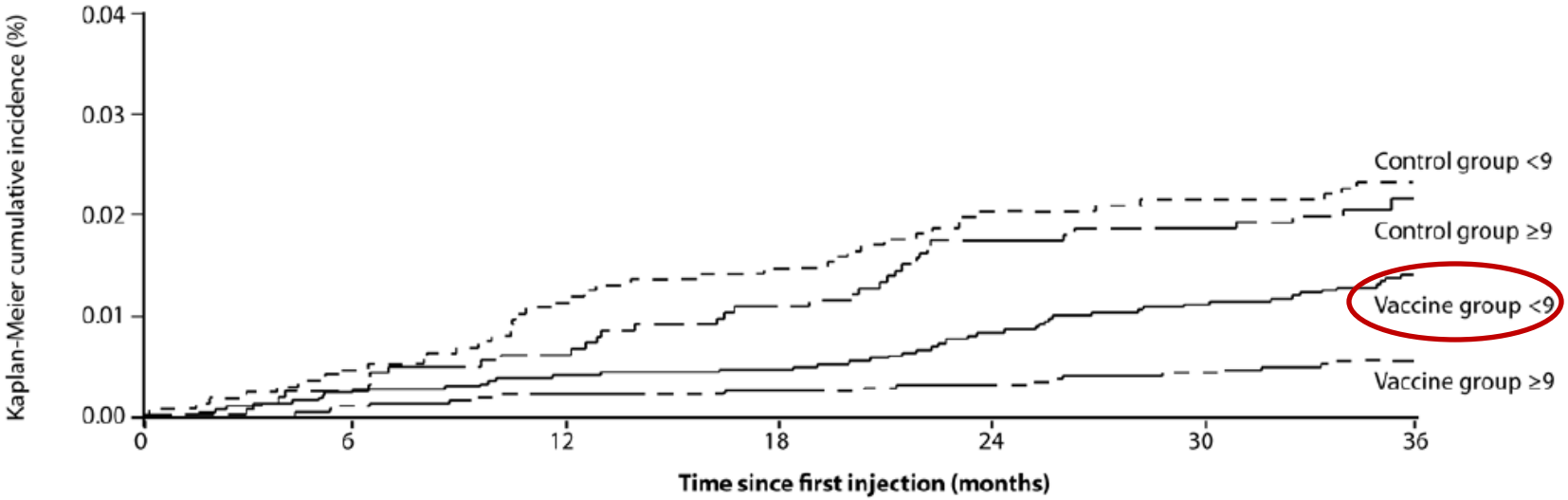


Efficacy Results – Pre-existing Anti-DENV
Sanofi Vaccine (pooled analysis CYD14+15)

- **Yes**
  - ≥ 9 years – 81.9% (CI_{95} 67.2 - 90)
  - <9 years - 44.6% (CI_{95} 32.3 - 87.3)
- **No**
  - ≥ 9 years – 52.5% (CI_{95} 5.9 - 76.1)
  - <9 years - 14.4% (CI_{95} -111 – 63.5)

Hadinegoro SRS, Arredondo-Garcia JL, Capeding MR, et al. N Engl J Med 2015; 373: 1195-206.

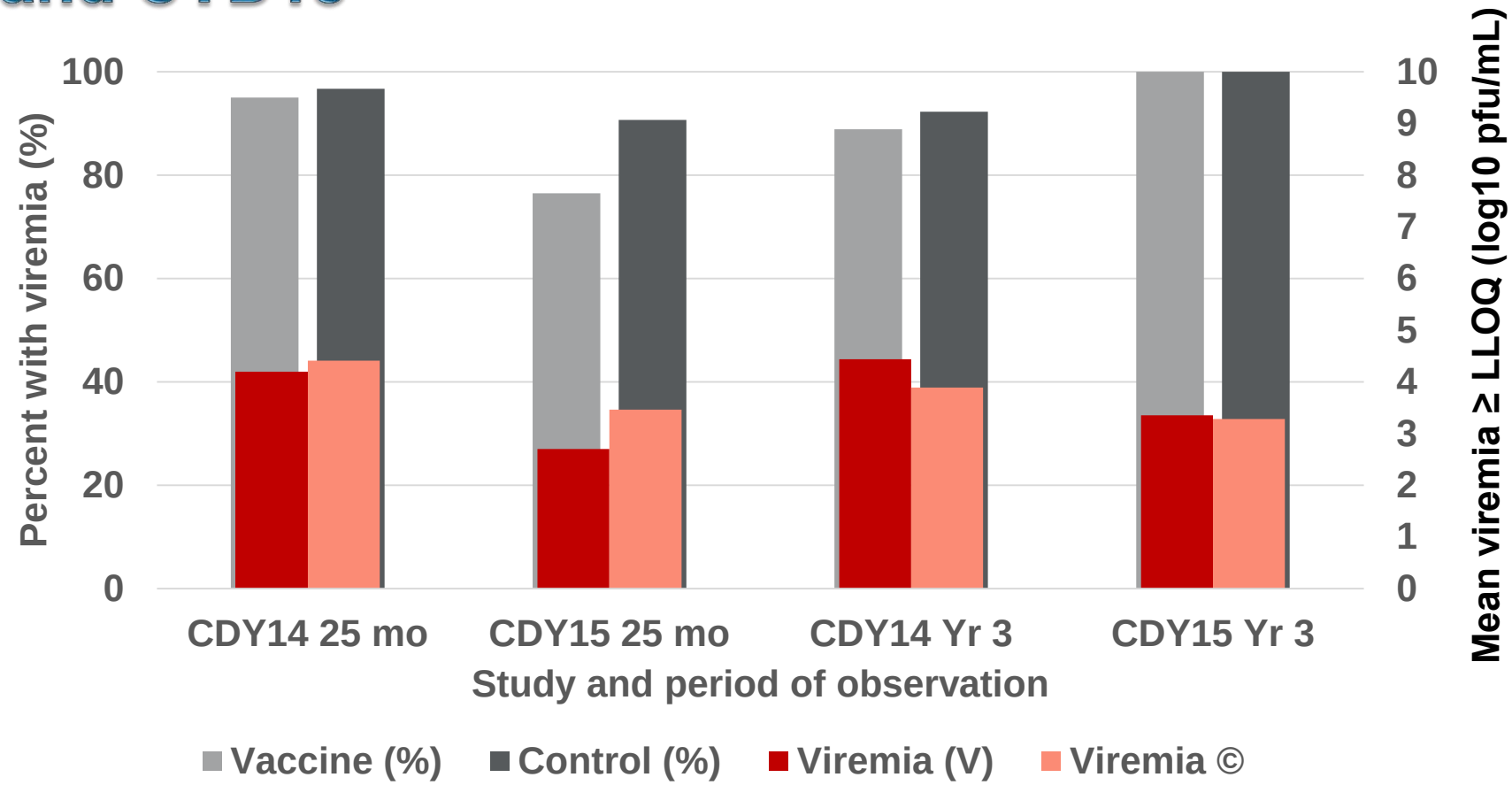
Kaplan-Meier for hospitalized or severe virologically-confirmed dengue in CYD14 by age

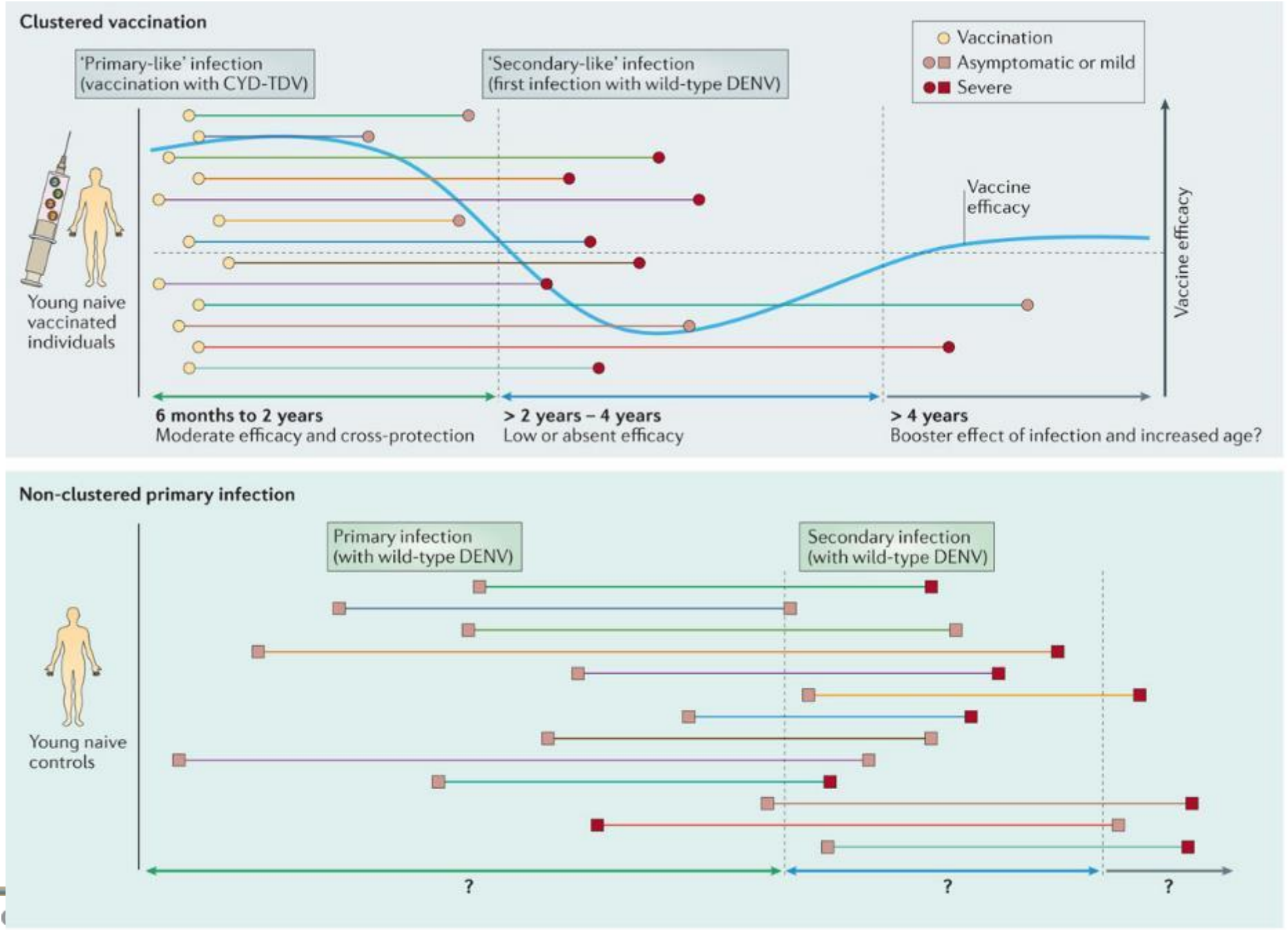


No. at risk:						
<9 years - Vaccine group	3535	3515	3496	3490	3475	3438
<9 years - Control group	1773	1762	1740	1729	1717	1703
≥9 years - Vaccine group	3317	3306	3299	3292	3287	3264
≥9 years - Control group	1660	1656	1646	1635	1622	1608

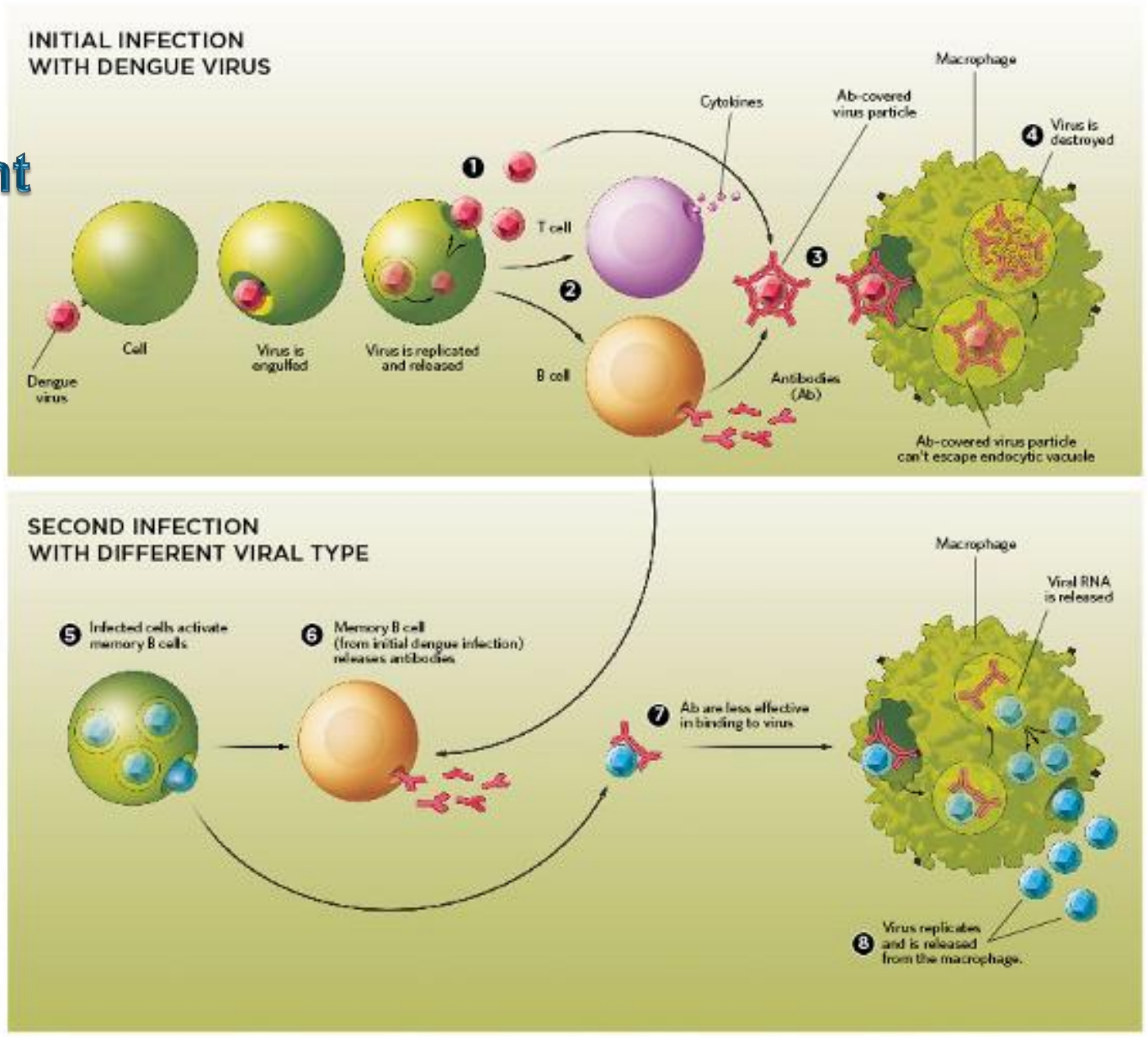
Hadinegoro SRS, Arredondo-Garcia JL, Capeding MR, et al. N Engl J Med 2015; 373: 1195-206.

Non-serotyped dengue viremia in hospitalized VCD of any severity, any serotype from CYD14 and CYD15

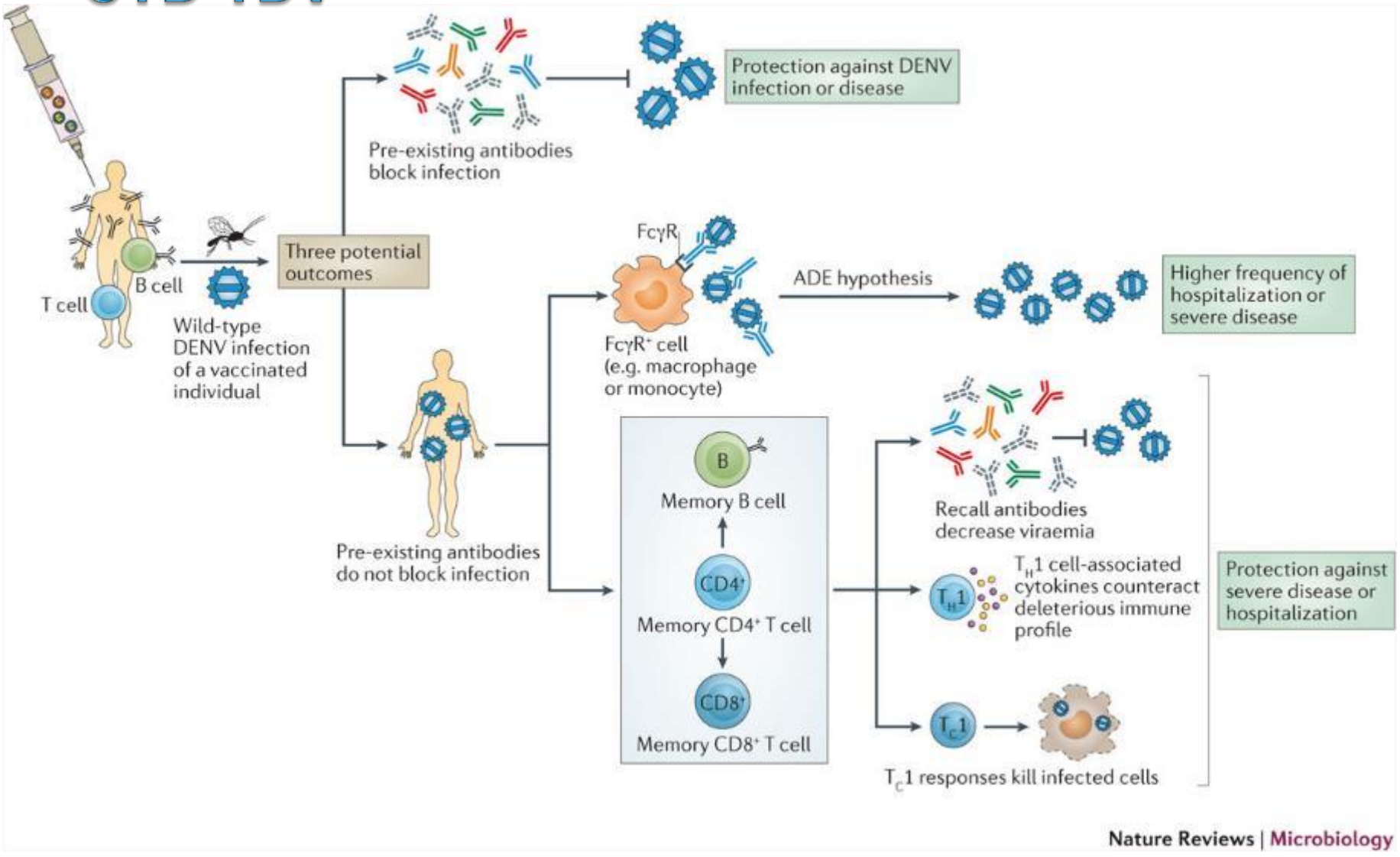



Clustered vaccination
'Primary-like' infection
(vaccination with CYD-TDV)
'Secondary-like' infection
(first infection with wild-type DENV)
Vaccination
Asymptomatic or mild
Severe
Vaccine efficacy
Vaccine efficacy
Young naive
vaccinated
individuals
6 months to 2 years
Moderate efficacy and cross-protection
> 2 years – 4 years
Low or absent efficacy
> 4 years
Booster effect of infection and increased age?
Non-clustered primary infection
Primary infection
(with wild-type DENV)
Secondary infection
(with wild-type DENV)
Young naive
controls
?
?
?

Antibody Disease Enhancement

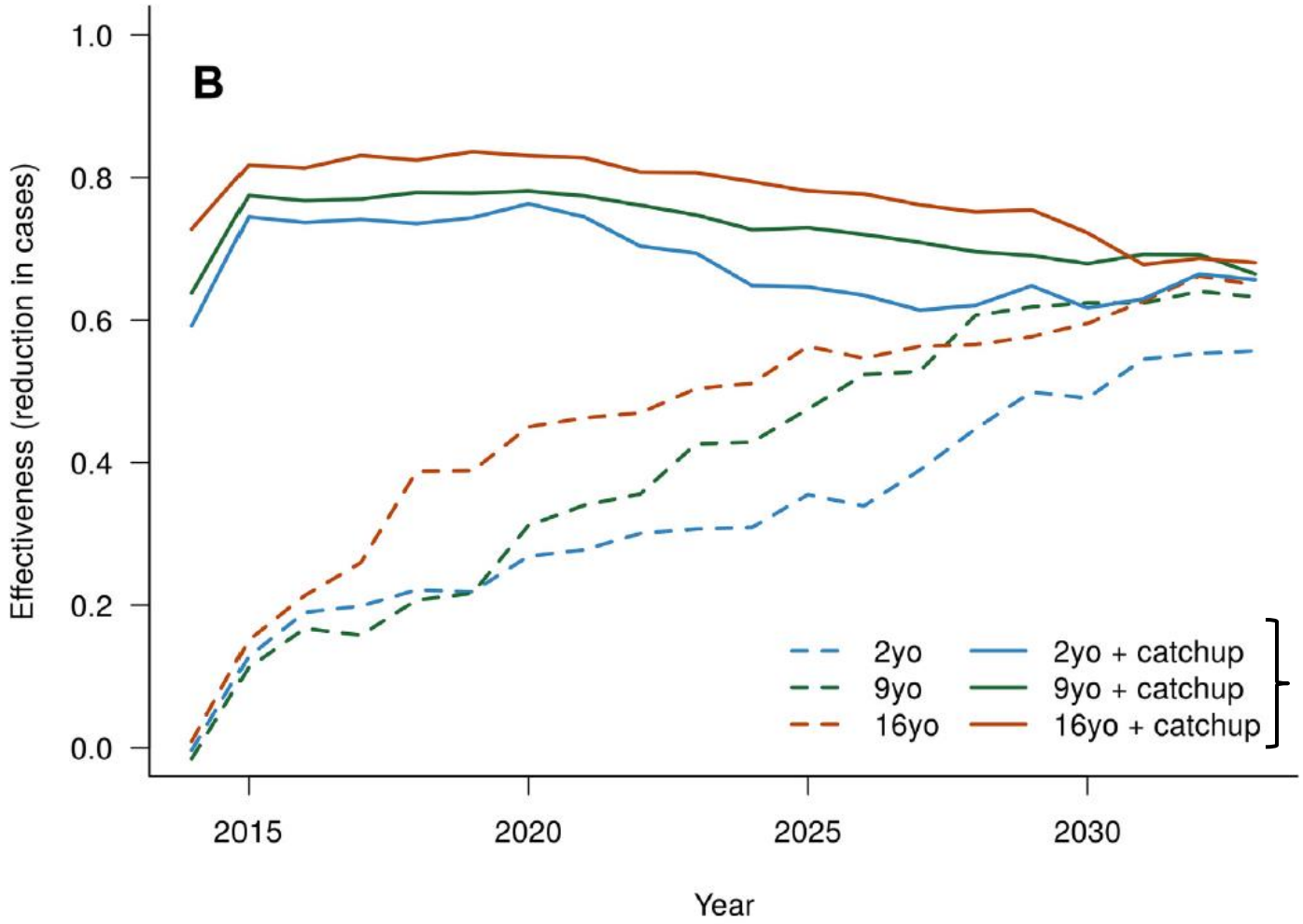


Outcomes in subjects vaccinated with Dengue CYD-TDV



Guy B & Jackson 2016; 14: 45

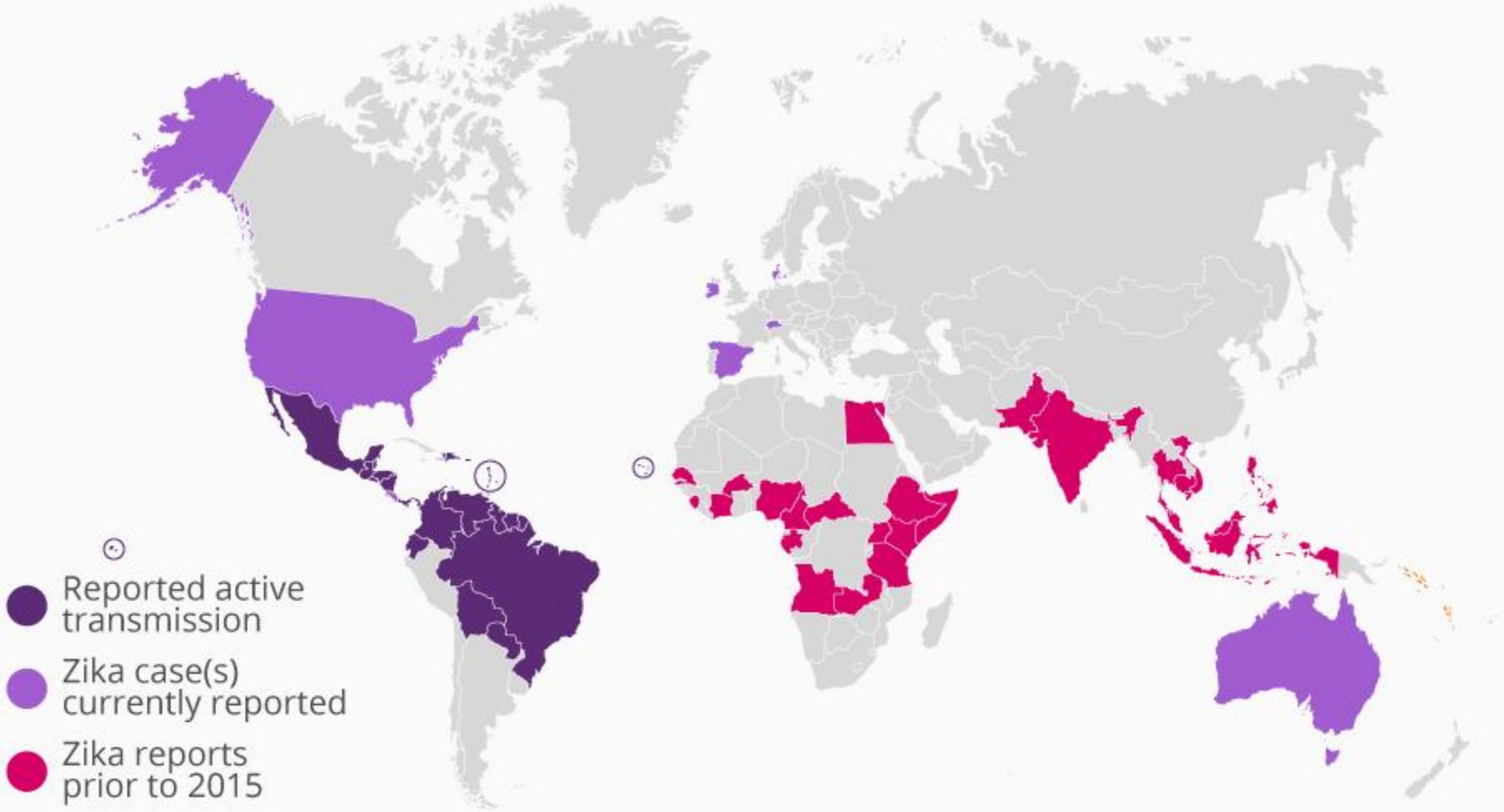
Simulated vaccine effectiveness, relative to the baseline in Yucatan, Mexico (no waning)



Hladish, PLoS Negl Trop Dis. 2016 doi: 10.1371/journal.pntd.0004661

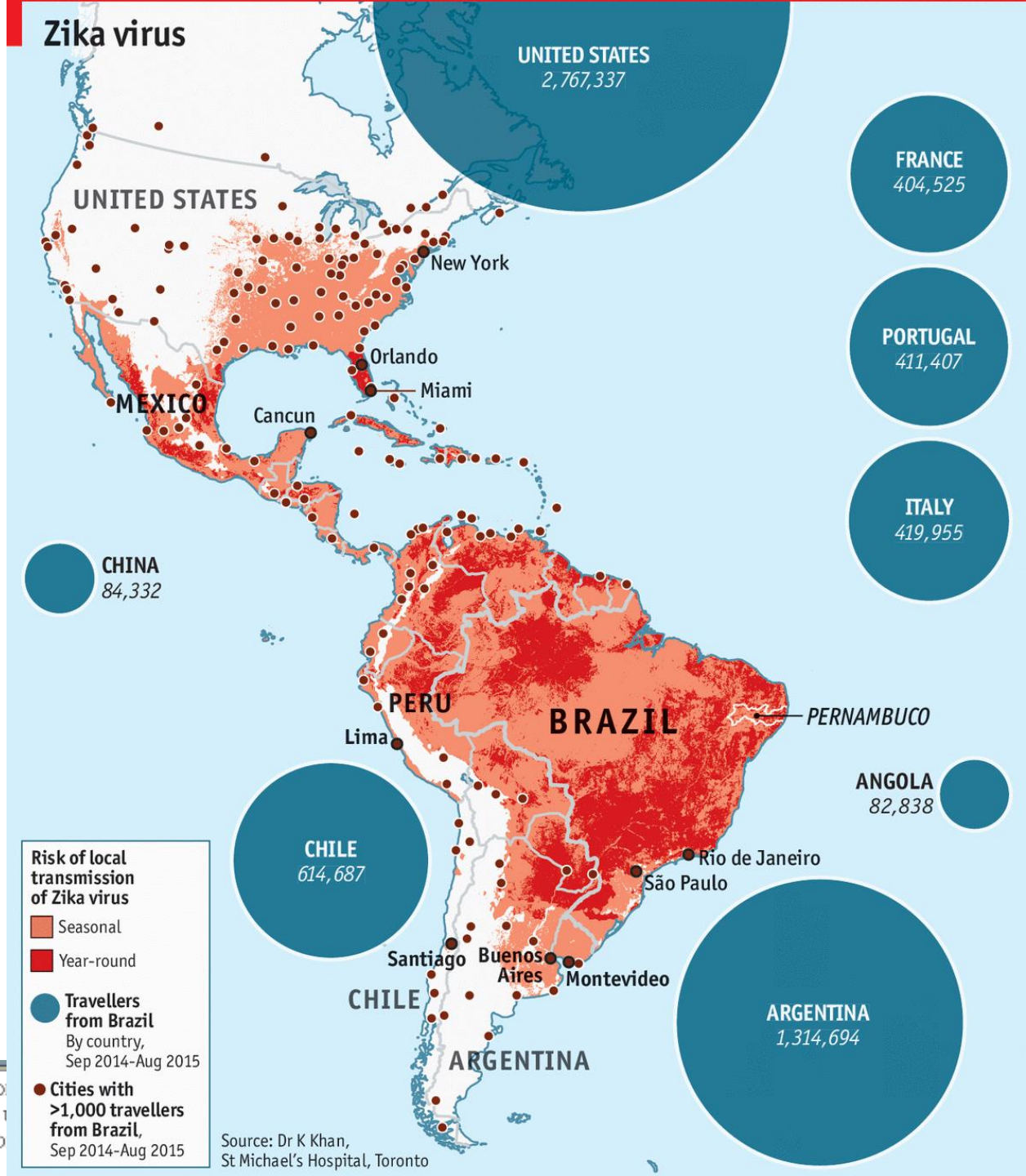
The Spread Of The Zika Virus

Countries and territories with active Zika virus transmission* and reported cases



Source: Centers for Disease Control and Prevention
*As of February 2016

Potential of importation of Zika virus into non-endemic countries



Recommendations for prevention of sexual transmission of Zika virus for couples in which a man has traveled to or resides in area with active Zika virus

- Use condoms consistently and correctly or abstain from sex **for the duration of the pregnancy**

- Confirmed Zika virus infection or clinical illness consider using condoms or abstaining from sex **for at least 6 months** after onset of illness
- Traveled to an active Zika area consider using condoms or abstaining for **at least 8 weeks** after departure
- Reside in a Zika area and no symptoms might consider using condoms or abstaining **while transmission persists**.

MMWR 2016 / 65(12);323–325

How Long to Wait Before Trying to Have a Baby When Living in an Area with Zika Transmission - 2016

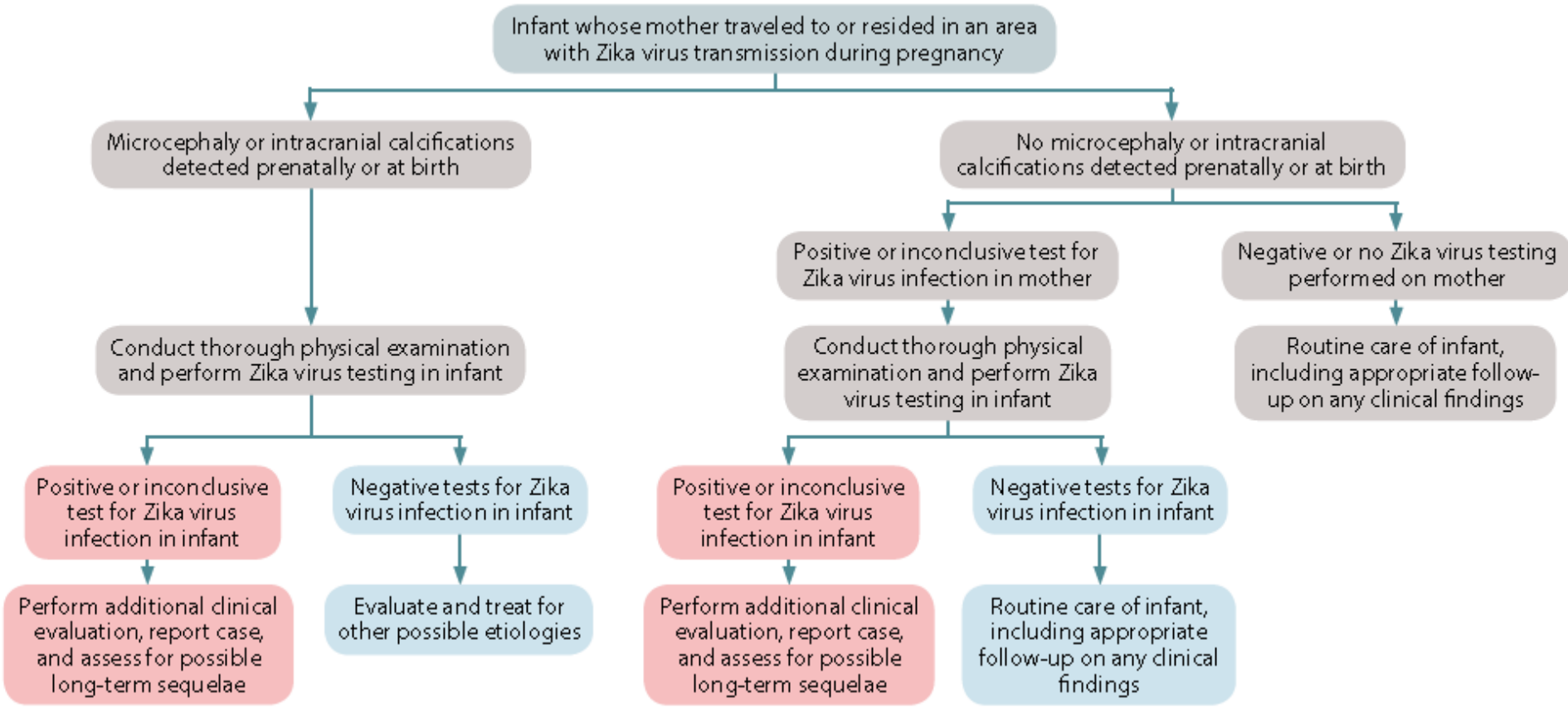
Zika status	Women	Men
Zika symptoms	At least **8 weeks** after symptoms start	At least **6 months** after symptoms start
No Zika symptoms	Talk with doctor or healthcare provider	Talk with doctor or healthcare provider

CDC
Centers for Disease Control and Prevention

Last updated: June 16, 2016

http://wwwnc.cdc.gov/travel/page/us-citizens-living-in-areas-with-zika

Interim guidelines for the evaluation and testing of infants whose mothers traveled to or resided in an area with ongoing Zika virus transmission* during pregnancy†§



Need for a Zika vaccine - 2016

The good

- There are licensed vaccines against other **flaviviruses**
  - **Yellow fever**
  - **JE**
  - **Dengue**
- Expertise on flavivirus research and vaccine development

Challenges

- Many unknowns
  - Animal models, assays
- Safety concerns
  - Possibility of GBS, enhancement and neurovirulence
- Fast moving epidemiology
- Small percentage of symptomatic infections
  - Efficacy endpoints

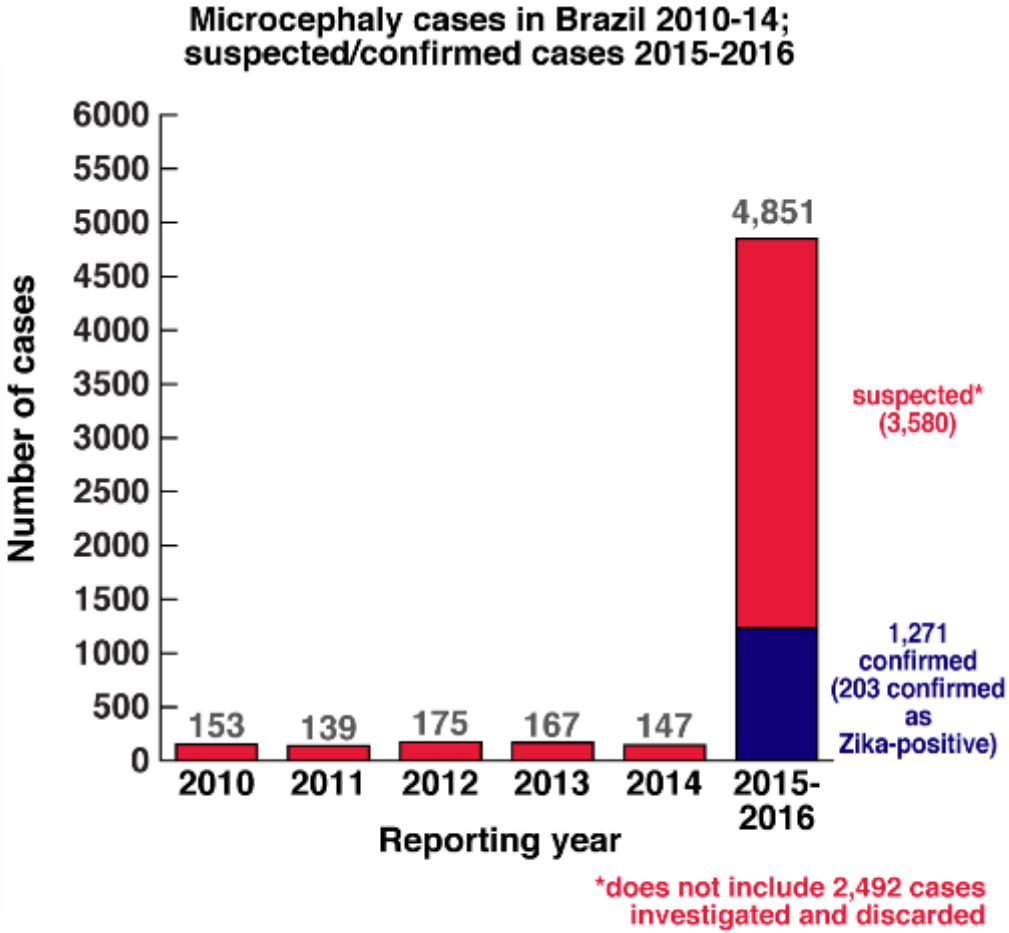
Adapted from C. Cassetti, NIAID

Marked Increase in Microcephaly Cases in Brazil

Associated Press

November 30, 2015

Brazil Links Mosquito-Borne Zika Virus to Microcephaly Birth Defect



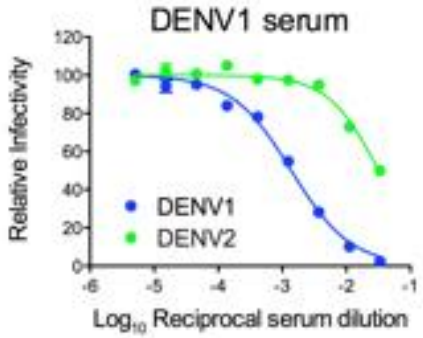
AS Fauci/ NIAID

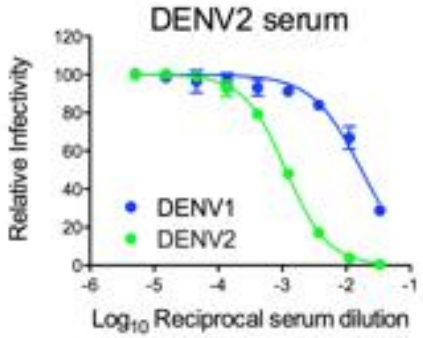
Source: Brazilian MOH; data as of 5/4/2016.

Zika Strain Selection

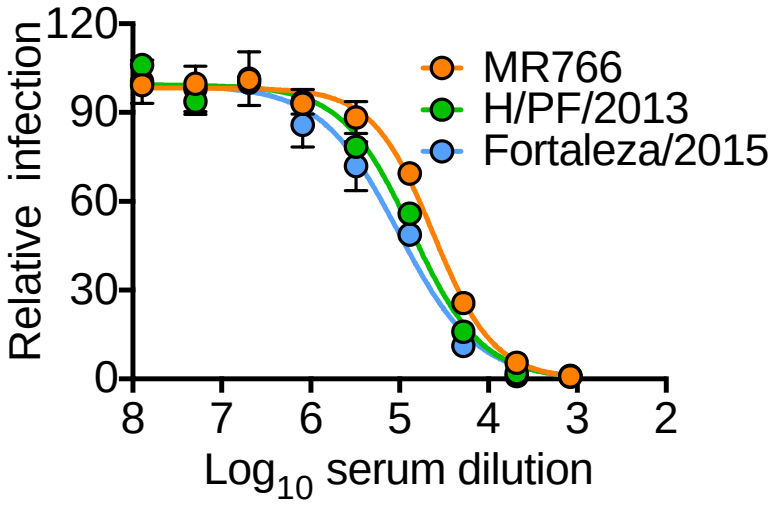
What strain to use? Are there different serotypes?

DENV: multiple serotypes



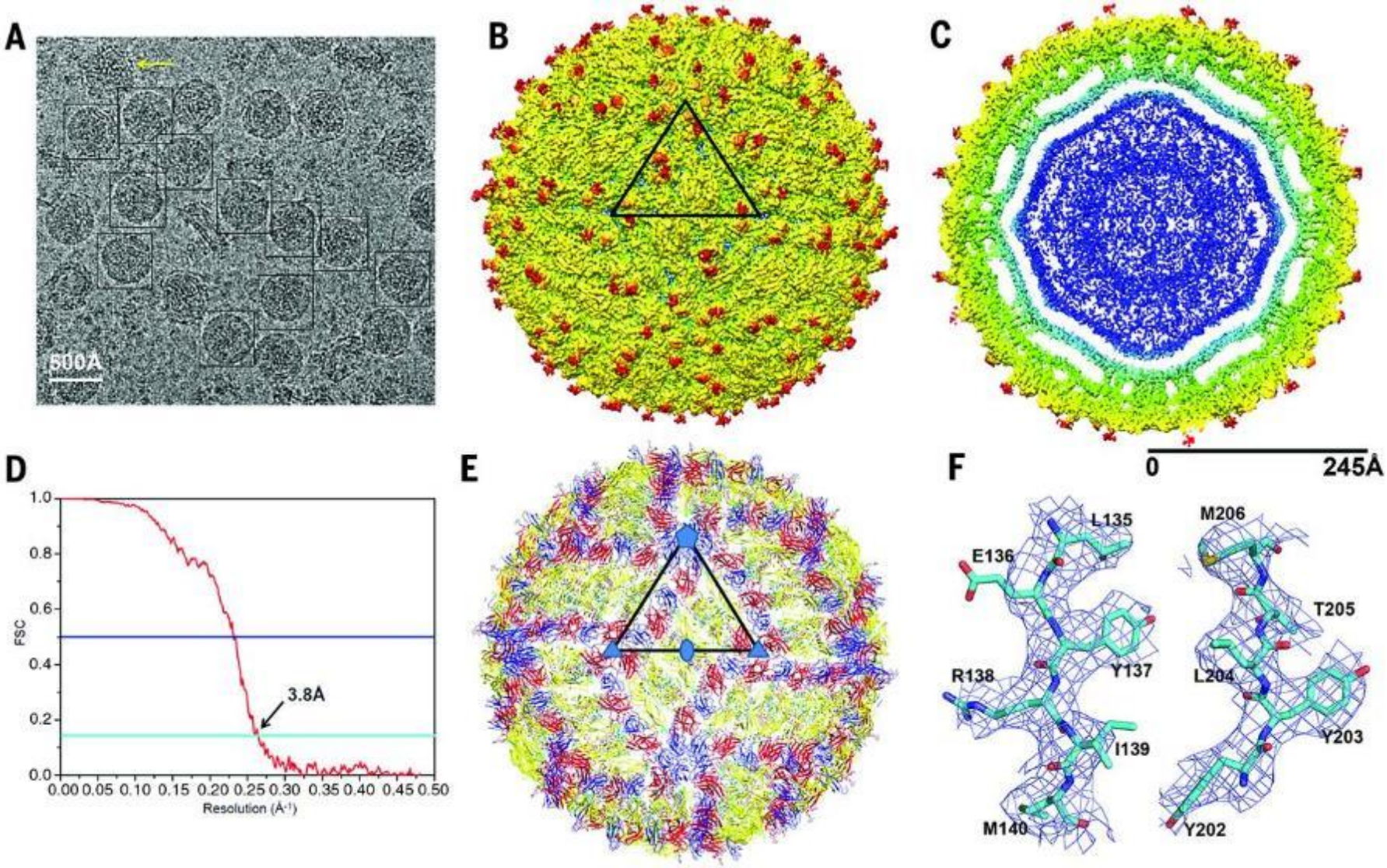


ZIKV: single serotypes



Courtesy of Ted Pierson, NIAID

ZIKV structure and vaccine development



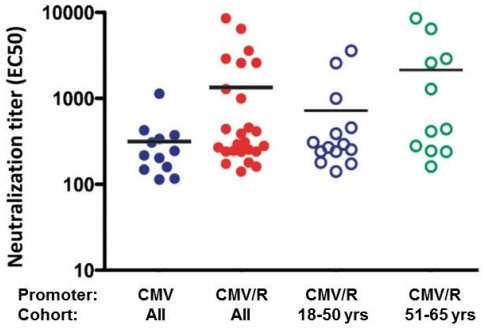
Devika Sirohi et al. Science 2016;science.aaf5316

West Nile Virus VRC DNA Vaccine

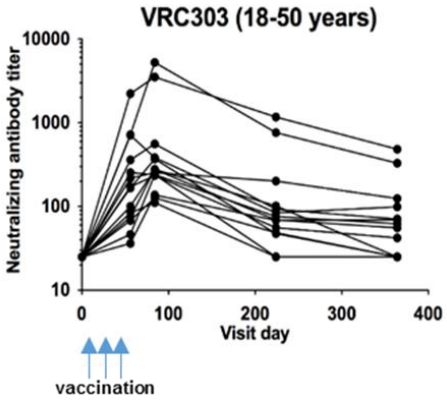
A West Nile Virus DNA Vaccine Utilizing a Modified Promoter Induces Neutralizing Antibody in Younger and Older Healthy Adults in a Phase I Clinical Trial.
Ledgerwood JE, the VRC 303 Study Team, et al.

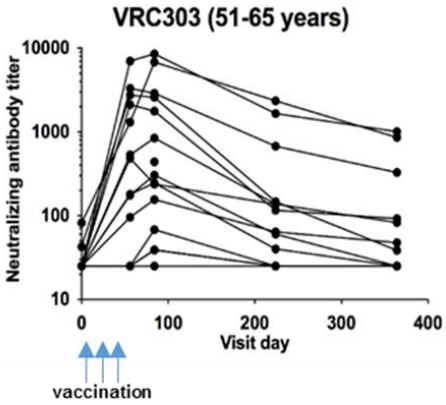
NAb (EC50) by RVP neutralization assay responses

Week 12



Longitudinal





Julie E. Ledgerwood et al. J Infect Dis. 2011;203:1396-1404

Strategy for ZIKV Vaccine Design

- Assume protection is mediated by **neutralizing antibody**
- Develop optimized **Zika prM-E** constructs
- Assume the following with regard to design
  - Antibodies most potent against fully mature particle as the primary form of infectious particle
  - Primary target is in the footprint of the cleaved “pr”
  - Removing fusion peptide will reduce flavivirus cross-reactivity
  - Improving or degrading the cleavage site will affect particle maturity
- Gene-based delivery will result in subviral particle production from transduced cells
- **First trial of ZIKV vaccine scheduled Fall of 2016**

Courtesy of Barney Graham, NIAID

Chikungunya burden map up to 2015

Puerto Rico 2014

Blood donors

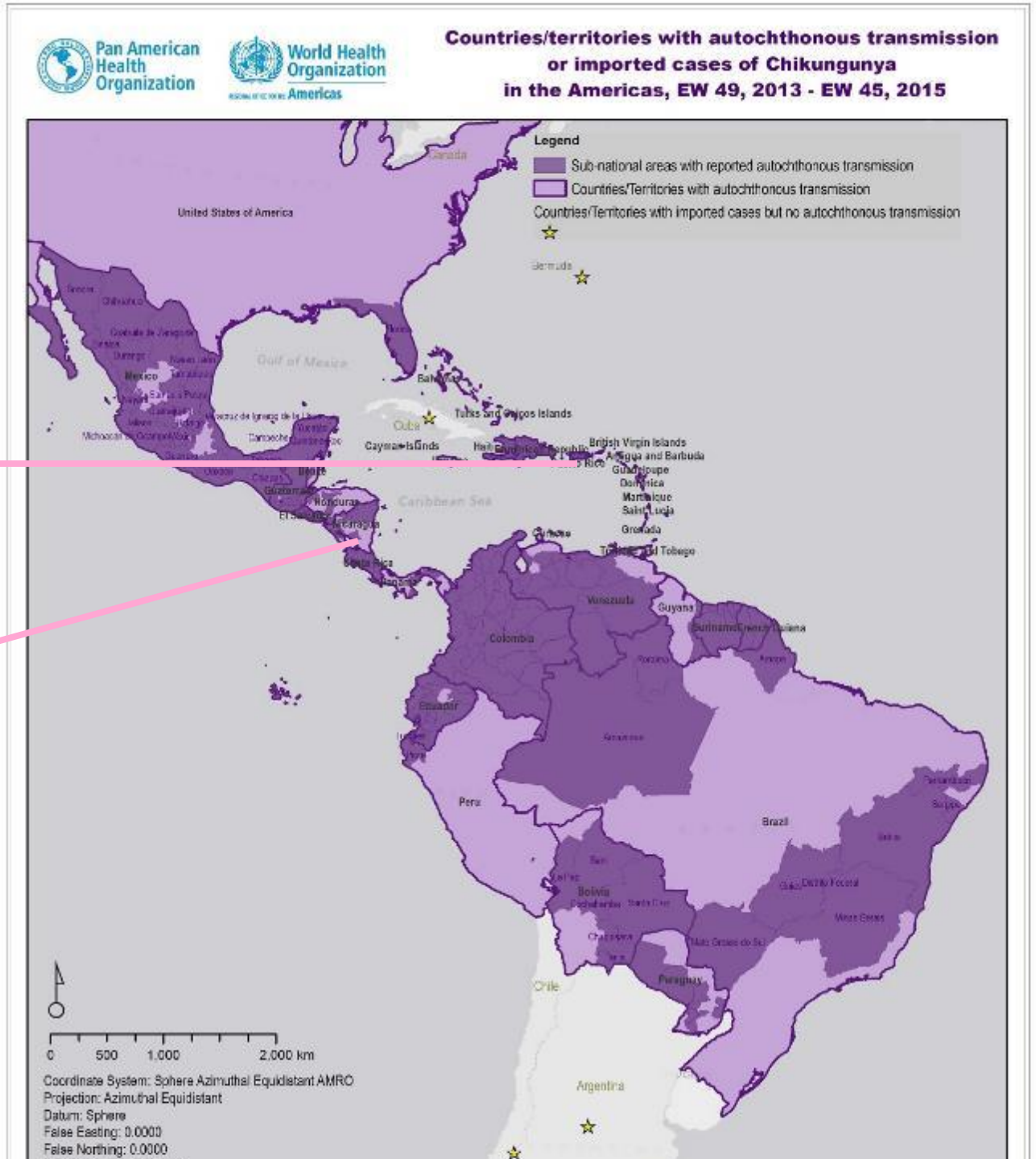
- **25% infected**
- **2.1% (+) CHIK RNA**

Nicaragua 2014-15

13.1% ≥15 years

6.1% 2-14 years

(50-65% inapparent)



Simmons G. Emerg Infect Dis. 2016
Kuang G. PLoS Negl Trop Dis. 2016

Development and research for CHIKV vaccines - 2016

Good news

- CHIK single serotype
- Cross protection x linages
- Formalin-inactivated vaccine USAMRIID 1960 and live-attenuated in 1990 (TSI-GSD-218)
- Macaques as animal model

Issues and Concerns

- Vaccine for outbreak response or travel?
- Inactivated – requires multiple doses
- Phase II/III trials challenging (CHIK epi)
- No minimum correlate of protection established

CHIK virus candidates vaccines - 2016

Candidate	Developer	Type	Preclinical	Phase I	Phase II	Phase III
TSI-GSD-218	USAMRIID Salk Institute	Live Attenuated			X	
VRC-CHKVLP059-00-VP	NIH	VLP			X	
Formalin inactivated (Thailand/1556)	USAMRIID	Inactivated, whole virus		X		
MV-CHIK (Measles virus vector)	Themis Bioscience GmbH/Institut Pasteur	Live, vectored		X	2016	
Formalin inactivated, multiple Indian CHIKV isolates 2006–2010	Bharat Biotech International	Inactivated, whole virus	X			
Formalin inactivated CHIKV181/25	Indian Immunologicals	Inactivated, whole virus	X			
CHIKV-IRES (v1/v2)	Takeda Pharmaceutical + UTMB	Live, attenuated	X			

+ 3 more live-attenuated, 4 live-vectored, 2 DNA, 2 subunits, 1 VLP *in preclinical*

Smalley C. Vaccine 34 (2016) 2976–2981

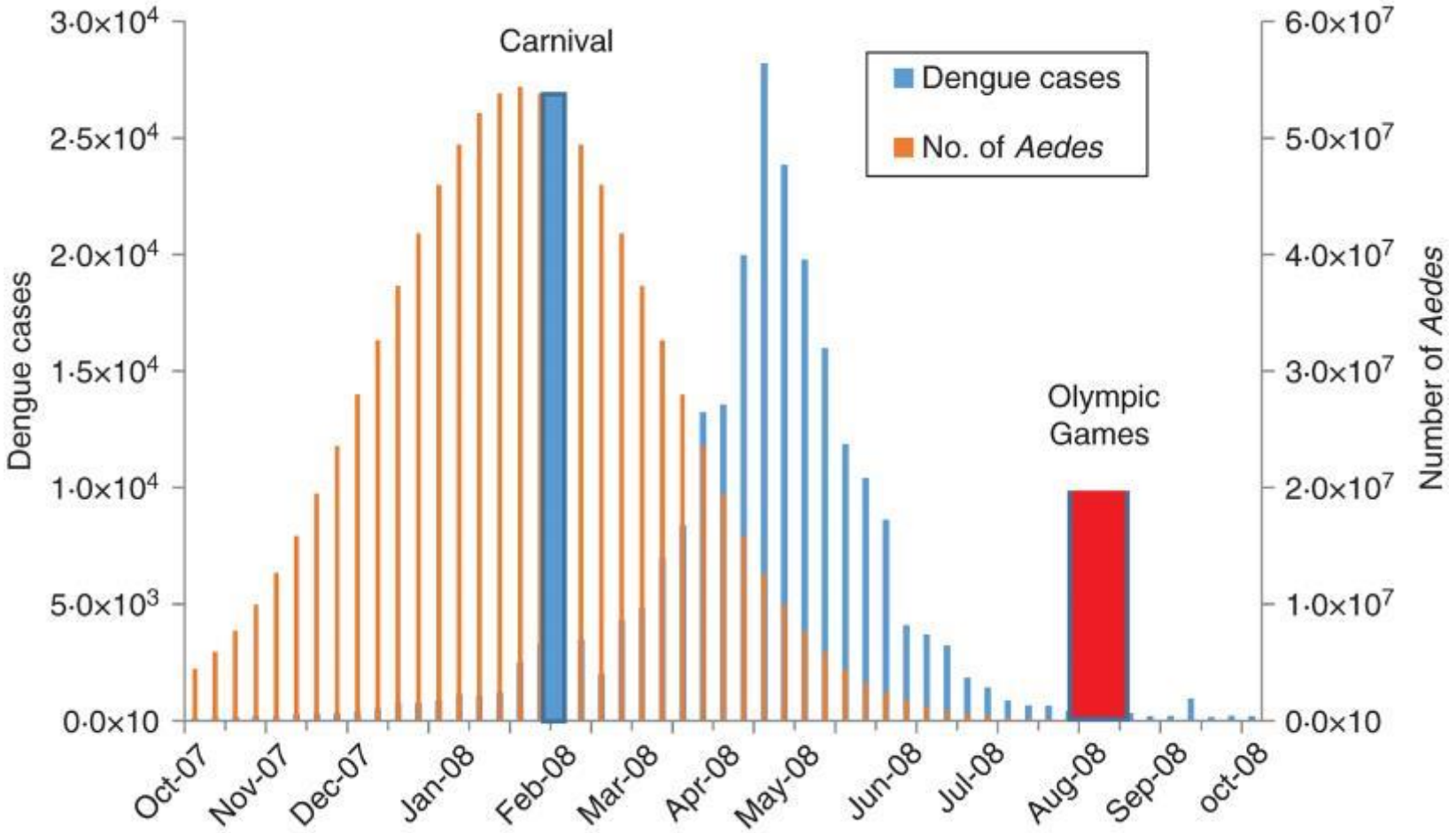
Conclusions

- DENV and ZIKV have complex transmission and epidemiological cycles
- DENV vaccine is now available, although better in **previously infected** individuals and its deployment and impact may prove challenging
- **ZIKV** vaccine development underway, but best platform and strategy needs to be tested
- CHIK control and prevention may be difficult if the outbreak dies out naturally as most of the population becomes infected

Thank you
Obrigado
Gracias

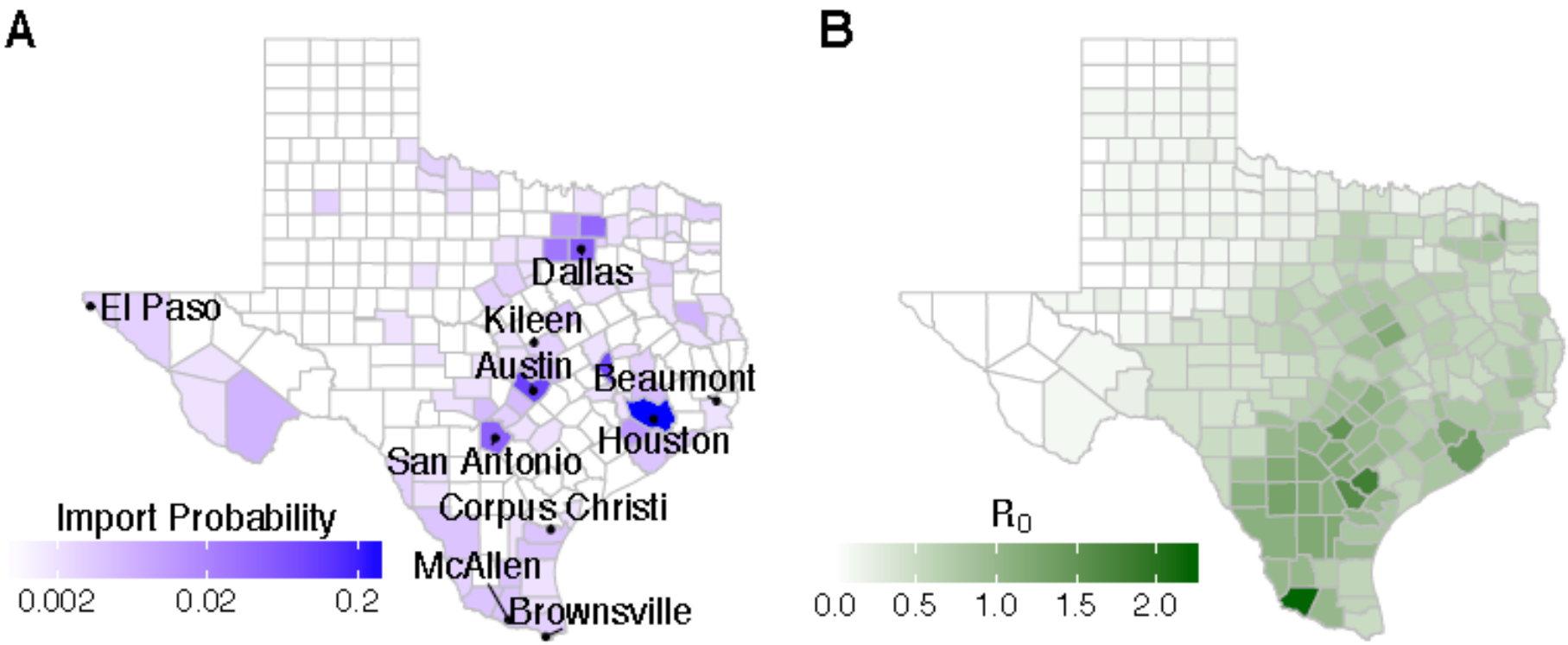
http://media.nbcdfw.com/images

Total number of *Aedes* mosquitoes and dengue cases in Rio distributed along the epidemiological weeks in 2008 – Estimated risk 1.8-3/100,000



Burattini MN. Epidemiol Infect. 2016 Jul;144(9):1904-6.

ZIKV importation and transmission risk across Texas



Castro LA. 2016 http://dx.doi.org/10.1101/056648.