Epidemiology of dengue and considerations on the use of vaccines

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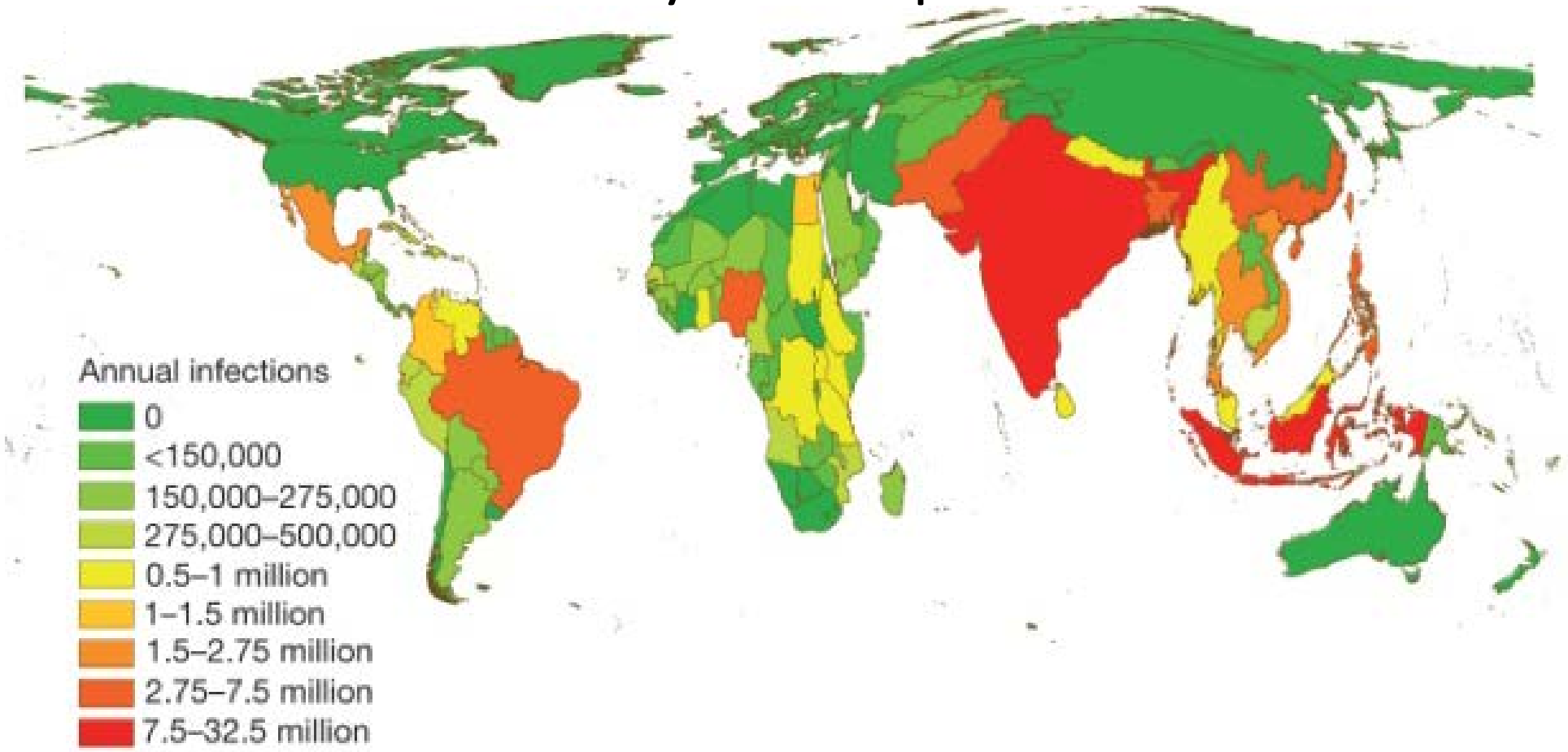
Objectives

- Dengue global epidemiology
- Considerations on Dengvaxia
- Limitations of available tests for past infection
- Dengue epidemiology in US territories

Global Dengue Epidemiology

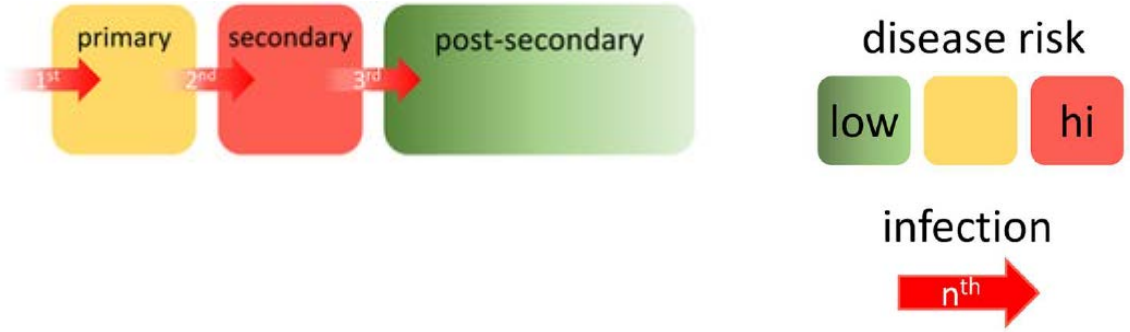
Dengue is the most important virus transmitted by mosquitoes worldwide



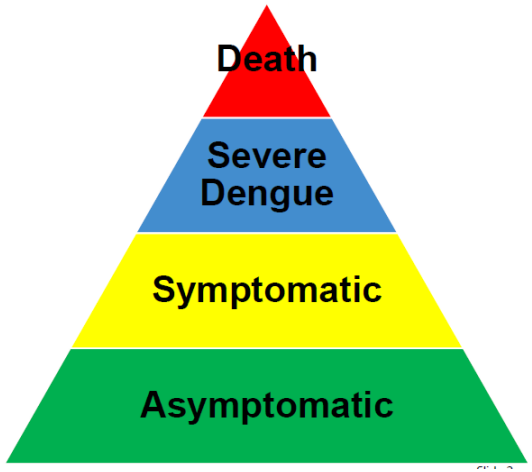
S Bhatt *et al. Nature* **000**, 1-4 (2013) doi:10.1038/nature12060

How dengue virus infections manifest in humans

- Four antigenically distinct sero-types (DENV 1-4)

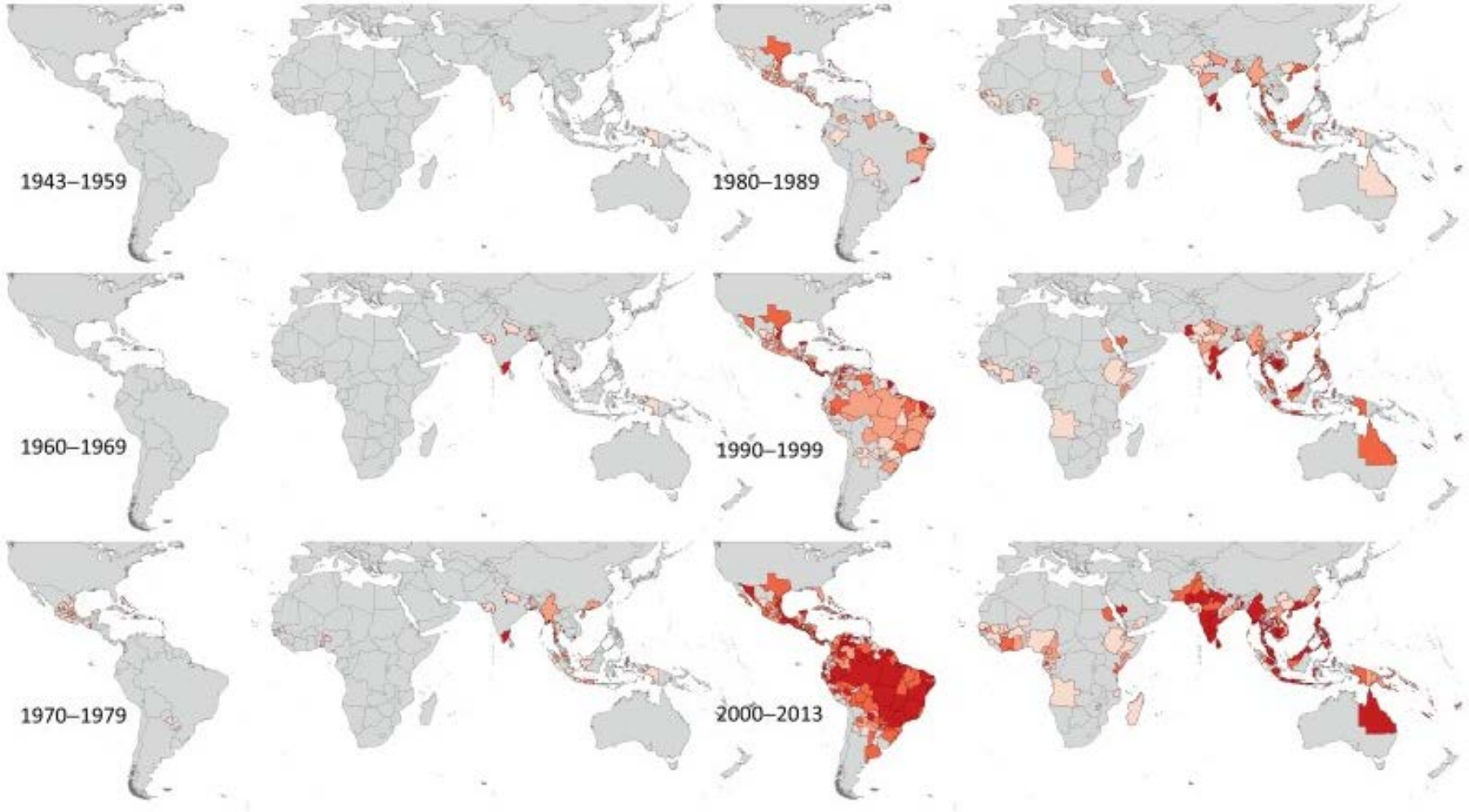


- Clinical spectrum
  - 25-35% symptomatic
  - 10-20% hospitalizations of symptomatic
  - Severe dengue in 1-5% of symptomatic



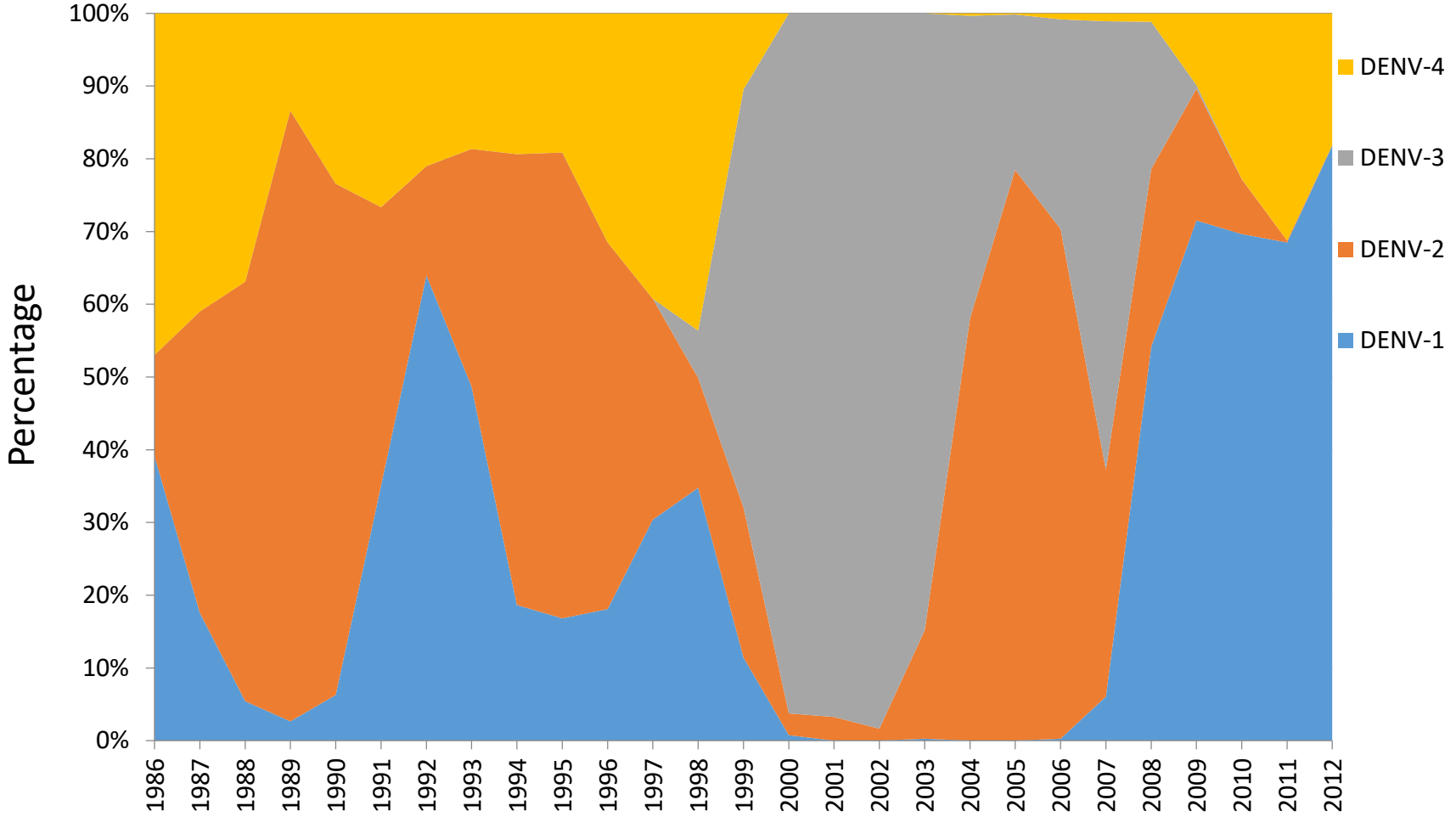
Flasche et al, Plos Med 2016; 13(11):e1002181.
Wilder-Smith A. et al, Lancet 2019;393:350-63.
Salje H. et al, Nature 2018; 557:719-728.

Co-circulation of dengue virus serotypes



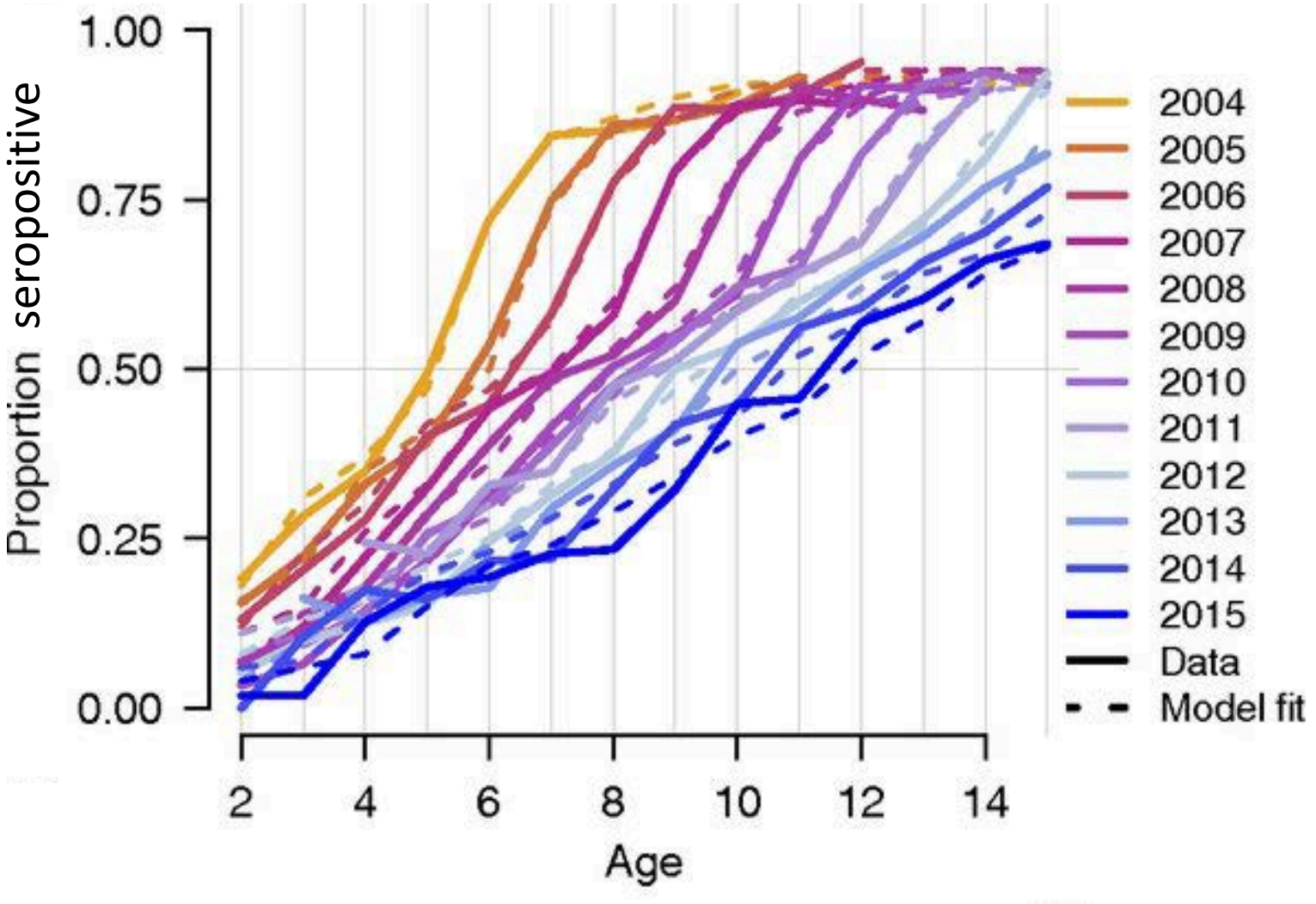
Messina JP et al. Trends in Microbiology 2014:22;3:138-146

Percent of dengue virus isolates by type and year — Puerto Rico, 1986–2012



Data Source: Arbonet, National Arbovirus Surveillance System

Dengue virus transmission intensity is dynamic



Age at DENV infection in the PDCS and PDHS. (A) Age-stratified seroprevalence from 2004 to 2015 in the PDCS (shown as thick lines) and the estimates of seroprevalence based on the model with best performance.

Leah C. Katzelnick et al. PNAS 2018;115:42:10762-10767

PNAS

Risk factors for severe dengue

- Age
- Co-morbidities
- Host genetics
- Virus strain

- Heterotypic secondary infection

Shepard DS et al. Lancet ID 2016; 18(8):935-41.
Wilder-Smith A. et al, Lancet 2019;393:350-63.

Modeled rates of hospitalizations and severe dengue after primary and secondary infections

Dengue virus infections	Symptomatic VCD – 2y	Hospital – 5y	Severe VCD – 5y
1	18.8 (14.8-23.2)	3.1 (1.9, 4.4)	0.3 (0, 0.7)
2	35.1 (31.4-38.7)	10.6 (9.4, 11.8)	2.3 (1.8, 2.9)

Sam Clifford and Stefan Flasche LSHTM, personal communication
Sridhar, NEJM 2018;379:327-40, Flasche et al, Plos Med 2016; 13(11):e1002181.

Dengvaxia

FDA NEWS RELEASE

First FDA-approved vaccine for the prevention dengue disease in endemic regions

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HEALTH NEWS MAY 1, 2019 / 6:50 PM / UPDATED 19 HOURS AGO

Sanofi wins U.S. approval to sell dengue vaccine but with major restrictions

Julie Steenhuysen 3 MIN READ

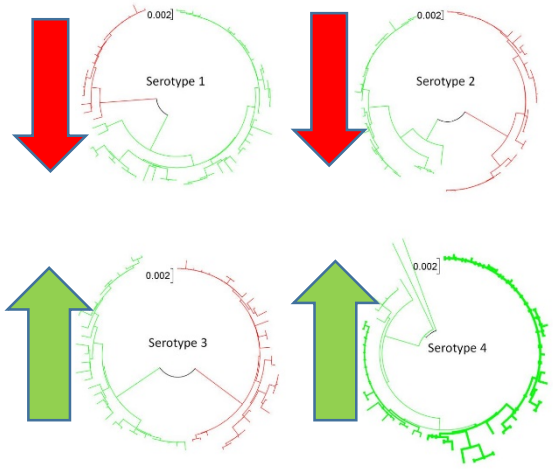
CHICAGO (Reuters) - The U.S. Food and Drug Administration on Wednesday gave Sanofi SA's dengue vaccine Dengvaxia a very narrow approval as the company continues to suffer from evidence that its vaccine, which took 20 years to develop, can cause severe infections in some people.

FDA vaccine indication

Persons 9-16 years of age with laboratory-confirmed previous dengue infection and living in an *endemic areas.*

According to FDA: “Dengue is endemic in the U.S. territories of American Samoa, Guam, Puerto Rico and the U.S. Virgin Islands.”

Vaccine efficacy

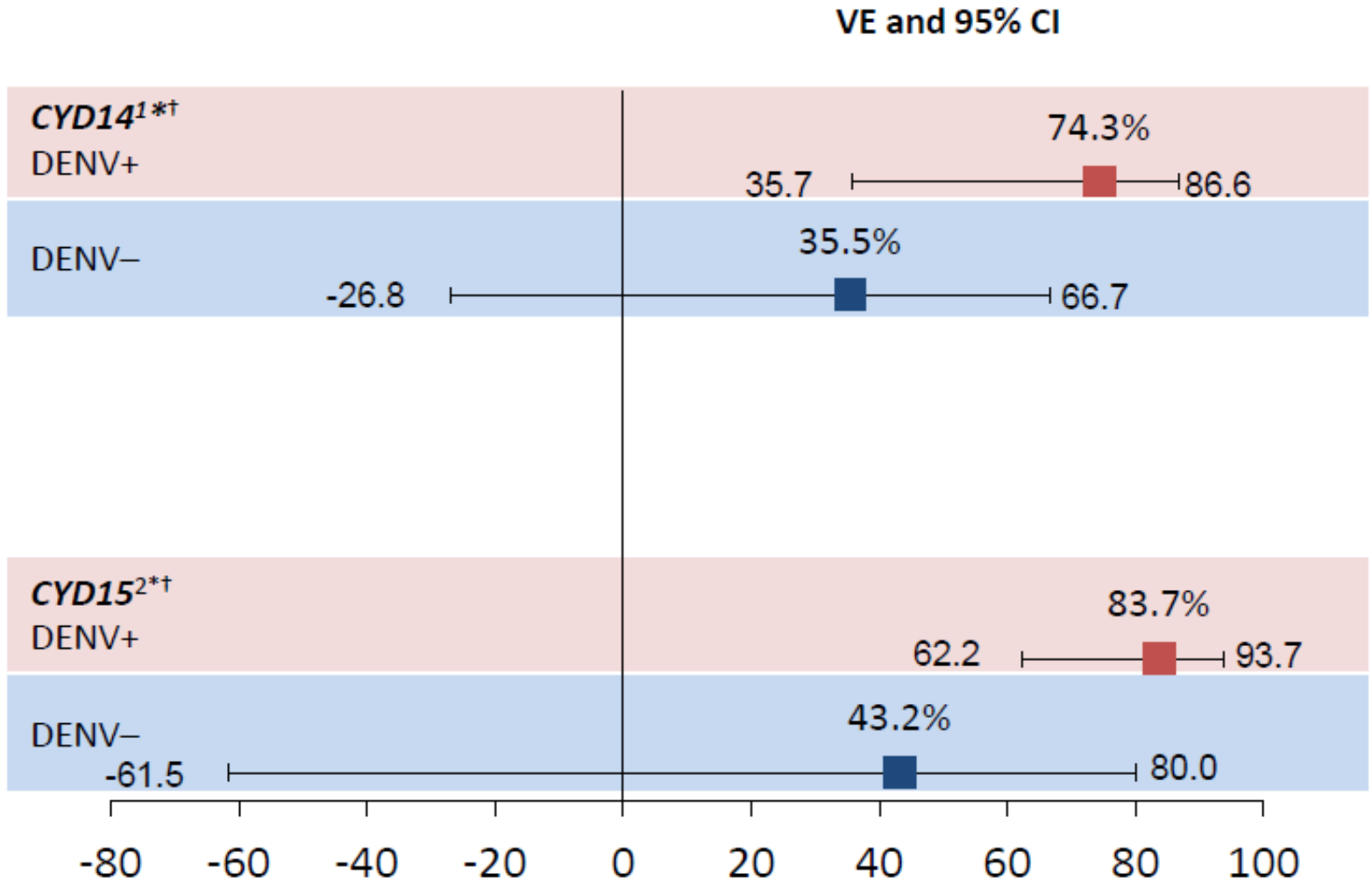


Dengue sero-positive individuals

Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) by baseline serostatus

Capeding. Lancet 2014; 384:1358-65

Villar L. NEJM 2015; 372;2: 113-1264.



Pooled analyses: vaccine efficacy, according to serostatus and age group

Study Population	Cases in Vaccine group (n)	Cases in Placebo group (n)	Pooled (2-16 years)	Pooled (9-16 years)
Seropositive at baseline	26	57	**78.2%** (65.4-86.3)	**81.9%** (67.2-90.0)
Seronegative at baseline	32	27	**38.1%** (-3.4-62.9)	**52.5%** (5.9-76.1)

Hadinegoro SR et al. N Engl J Med 2015;373:1195-1206.

Risk of **hospitalization** comparing vaccinated to controls according to baseline serostatus (2-16y)

Sero-status at dose 1	Relative risk (CYD:Control)	95% confidence interval
Sero-positive	**0.32**	0.23, 0.45
Sero-negative	**1.75**	1.14, 2.70

Follow-up period: 5-6 years post-dose 1

S Sridhar et al. N Engl J Med 2018;379:327-340.

Risk of **severe dengue** comparing vaccinated to controls according to baseline serostatus (2-16y)

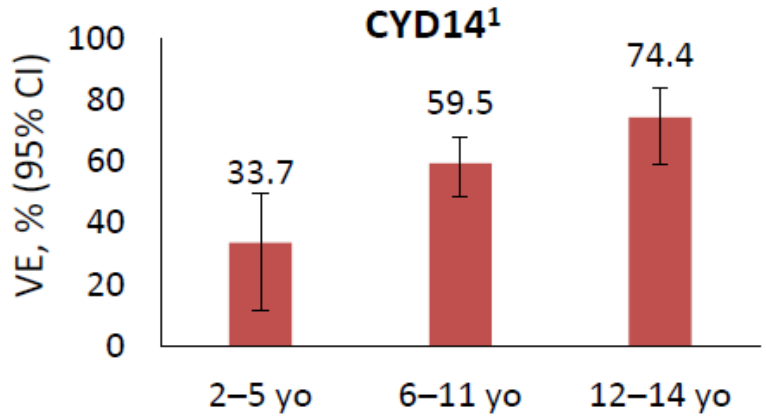
Sero-status at dose 1	Relative risk (CYD:Control)	95% confidence interval
Sero-positive	**0.31**	0.17, 0.58
Sero-negative	**2.87**	1.09, 7.61

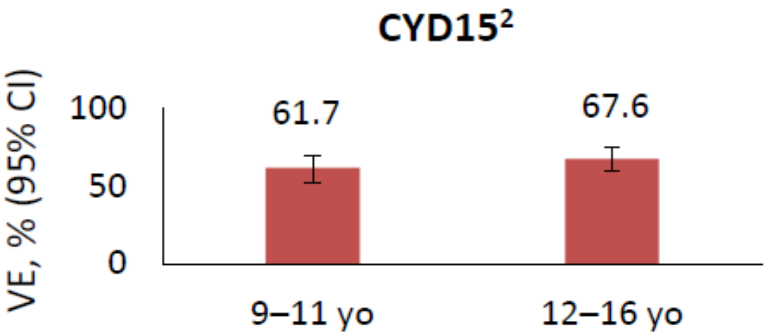
Follow-up period: 5-6 years post-dose 1

S Sridhar et al. N Engl J Med 2018;379:327-340.

Efficacy by age

Vaccine efficacy against virologically confirmed dengue (VCD) up to month 25 by age

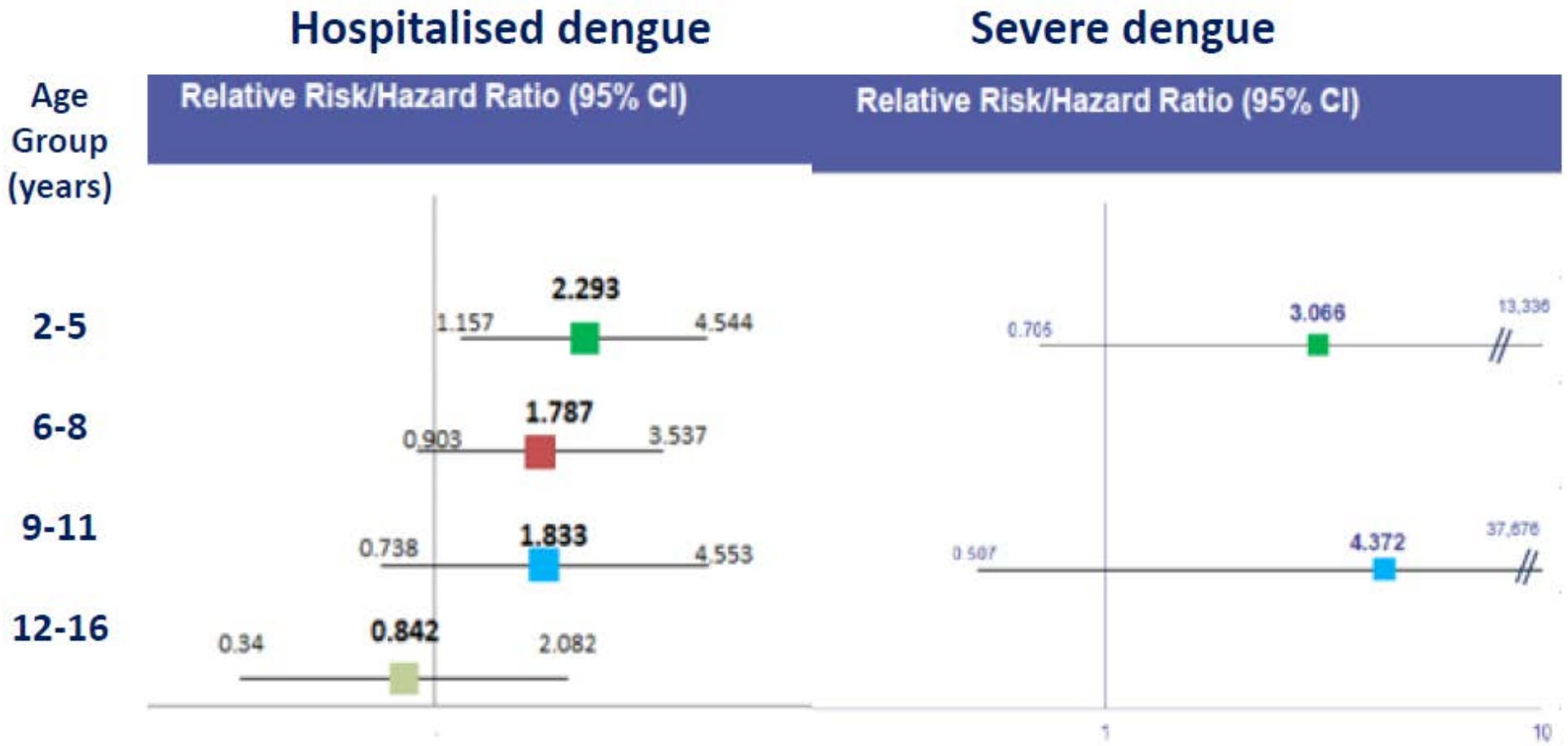




1. Capeding, 2014, Lancet
2. Villar, 2015, N Engl J Med.

*Comparison made on ITT

Risk of hospitalized and severe dengue in sero-negatives comparing vaccinated to controls

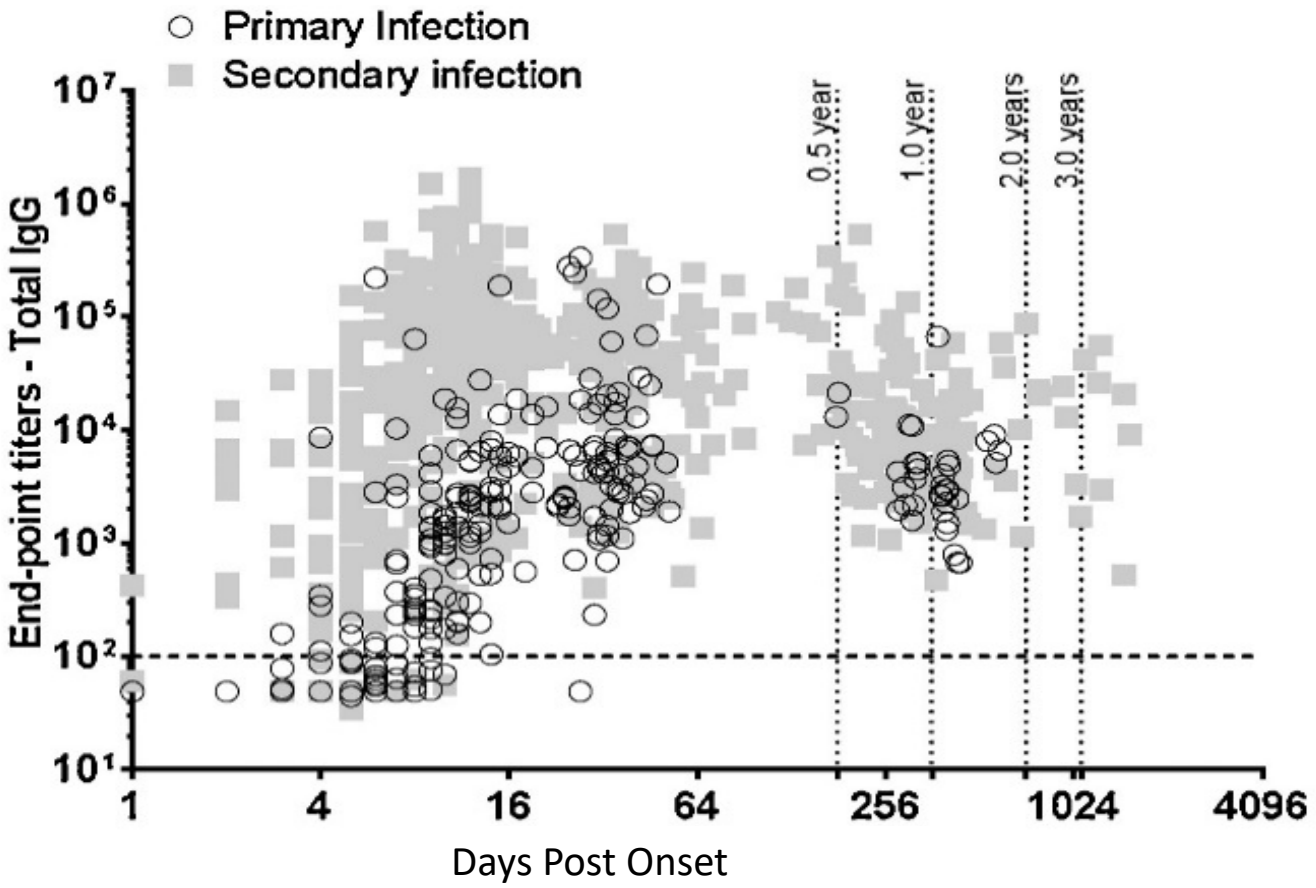


Follow-up period: 5-6 years post-dose 1

From Peter Smith LSHTM and S Sridhar et al. N Engl J Med 2018;379:327-340.

Dengue Laboratory Testing

Detection of IgG antibody after primary and secondary dengue virus infections



Long-term NS1-specific IgG detection

Nascimento et al. Journal of Virological Methods 2018; 257:62-68.

Preliminary landscape analysis of commercial dengue IgG tests

- Several (31) companies have marketed 56 IgG ELISA tests and at least 7 rapid tests
- Performance reported only on 14 tests: 10 ELISAs, 4 RDTs
  - Sensitivity (33-100%)
  - Specificity (92-100%)

Courtesy of Jorge Munoz-Jordan

Dengue IgG tests performance evaluations as reported*

Company and Name of Test	Test Format	Marker	Sensitivity	Specificity	Cross-reactivity Disclaimer
Panbio Dengue IgG Indirect ELISA	ELISA	IgG	33-87	100	
Panbio® Dengue IgG Capture ELISA	ELISA	IgG	96	94	
Euroimmune Anti-Dengue Virus ELISA (IgG)	ELISA	IgG	100	100	yes
Abcam Human Anti-Dengue virus IgG ELISA Kit	ELISA	IgG	90	93	
SD Dengue IgG Capture ELISA	ELISA	IgG	99	99	
Creative Diagnostics Dengue IgG ELISA Kit	ELISA	IgG	90	93	yes
Creative Diagnostics Dengue Virus IgG Human ELISA Kit	ELISA	IgG	90	93	yes
Demeditec Dengue Virus IgG ELISA	ELISA	IgG	100	98	
Abnova Dengue virus IgG ELISA Kit	ELISA	IgG	99	99	
Focus Dengue Virus IgG DxSelect™	ELISA	IgG	96	93	
Bio-Rad RDT Dengue IgA/IgG	Rapid Test	IgA/IgG,NS1	61	92	Yes
CTK OnSite Dengue IgG/IgM Combo Rapid Test	Rapid Test	IgG/IgM	96	97	Yes
Standard Diagnostics Bioline Dengue	Rapid Test	IgG/IgM	95	97	
GenBody Dengue IgG/IgM	Rapid Test	IgG/IgM	99	100	

*Selected tests with reported sensitivity and specificity by manufacturers.

Note: Analysis of other tests still ongoing

Courtesy of Carlos de Leon and Jorge Munoz-Jordan

Limitations on available dengue IgG test evaluations (1)

- Variable (or unavailable) sample sizes
- Specificity measured differently by companies (different panel compositions)
- Limited flavivirus cross-reactivity data (pre-Zika epidemic)
- Calibrated for diagnosis of symptomatic cases (high IgG titers)
- Few assessed independently (performance reported by manufacturers)

Courtesy of Jorge Munoz-Jordan

Limitations on available dengue IgG test evaluations (2)

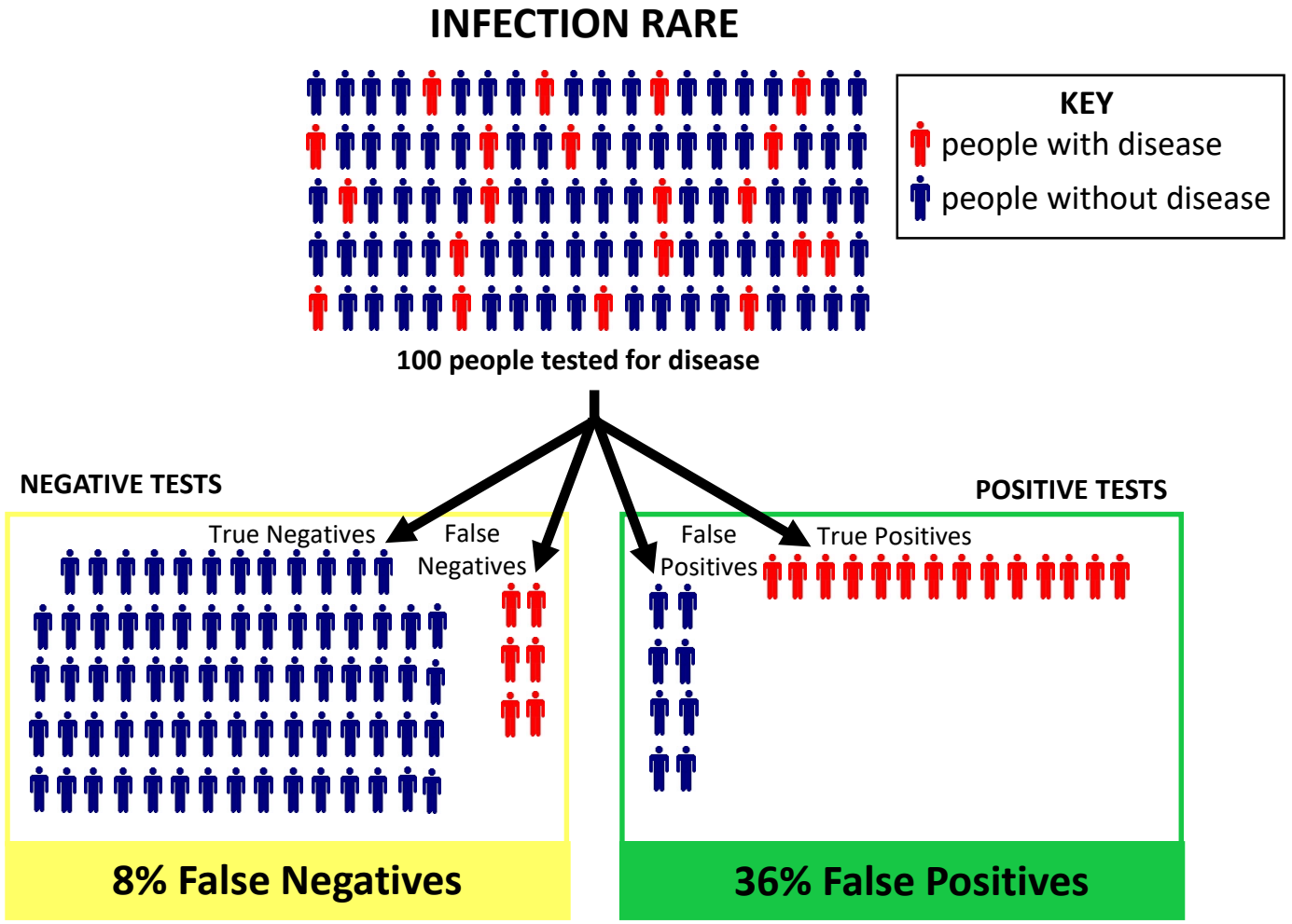
- Commercial IgG tests have not been evaluated for:
  - Long-term detection of confirmed primary and secondary infections
  - Detection of previous infection in asymptomatic persons
  - Differentiating between previous dengue and Zika virus infections

Courtesy of Jorge Munoz-Jordan

Example of prevalence and implications for test performance (1)

Example 1:

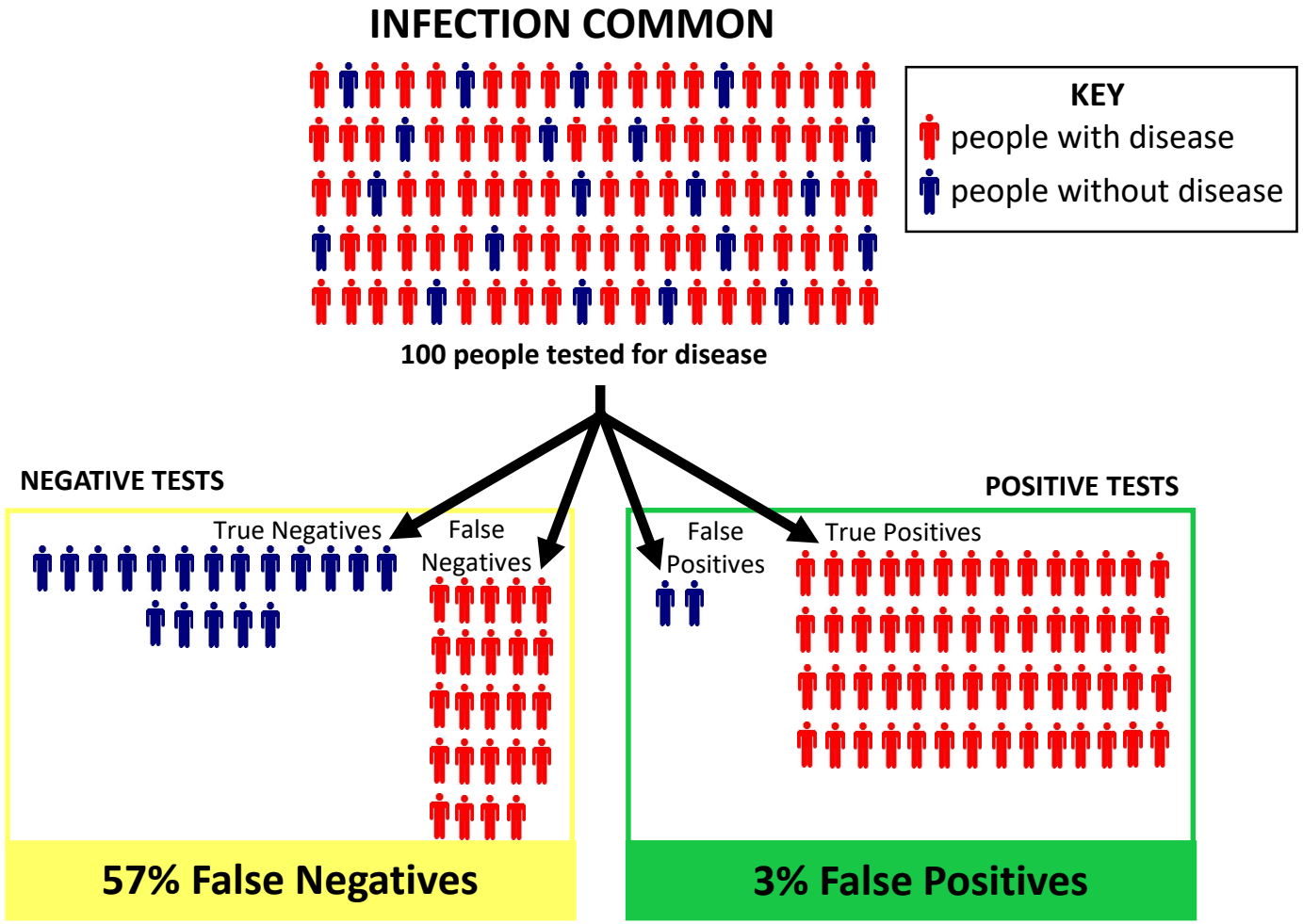
- 20 out of 100 patients in this area previously infected
- Test specificity: 90%
- Test sensitivity: 70%



Example of prevalence and implications for test performance (2)

Example 2:

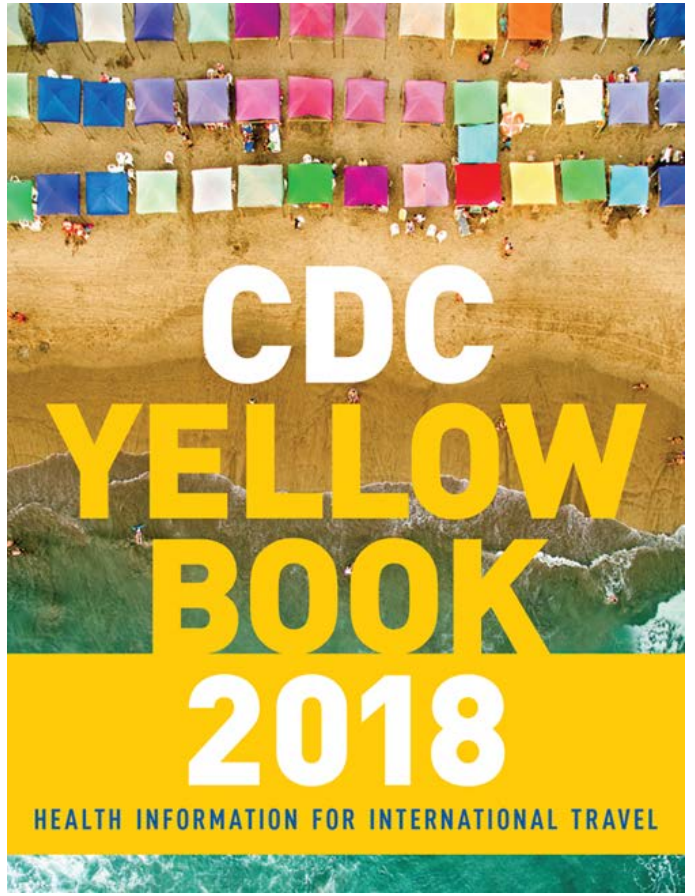
- 80 out of 100 patients in this area previously infected
- Test specificity: 90%
- Test sensitivity: 70%



Dengue Epidemiology in the United States Territories

Yellow Book criteria to assess dengue risk levels

- Frequent/continuous risk: 10 dengue cases in at least three distinct years over the most recent 10-year period.



Jentes et al. Journal of Travel Medicine 2016; 23, 6, 1-5.

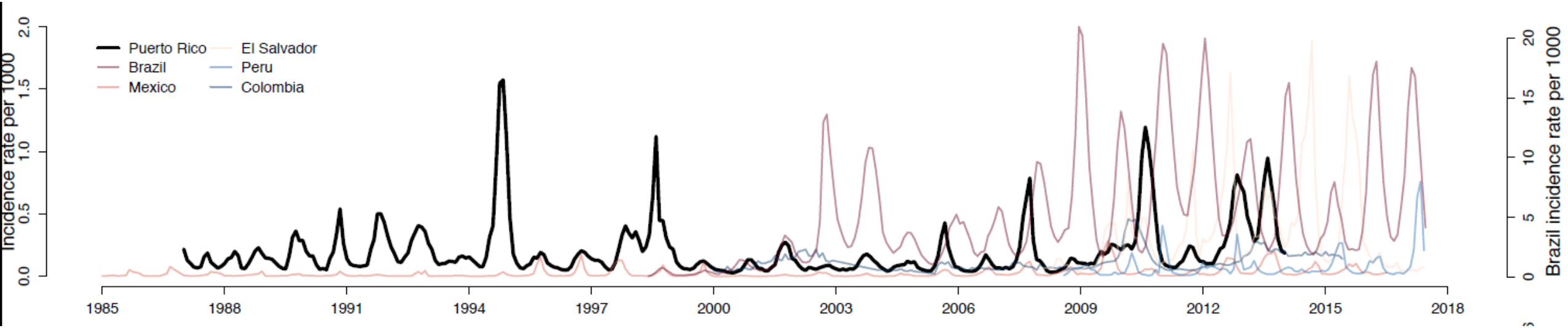
Level of risk based on Yellow Book criteria

Country/Area	Level of risk
US States	Sporadic/uncertain
Territories	
American Samoa	**Frequent/Continuous**
Puerto Rico	**Frequent/Continuous**
US Virgin Islands	**Frequent/Continuous**
Guam	Sporadic/uncertain
Northern Mariana Islands	Sporadic/uncertain
Micronesia	
Federated States of Micronesia	**Frequent/Continuous**
Palau	**Frequent/Continuous**
Marshall Islands	Sporadic/uncertain

Frequent Continuous Risk

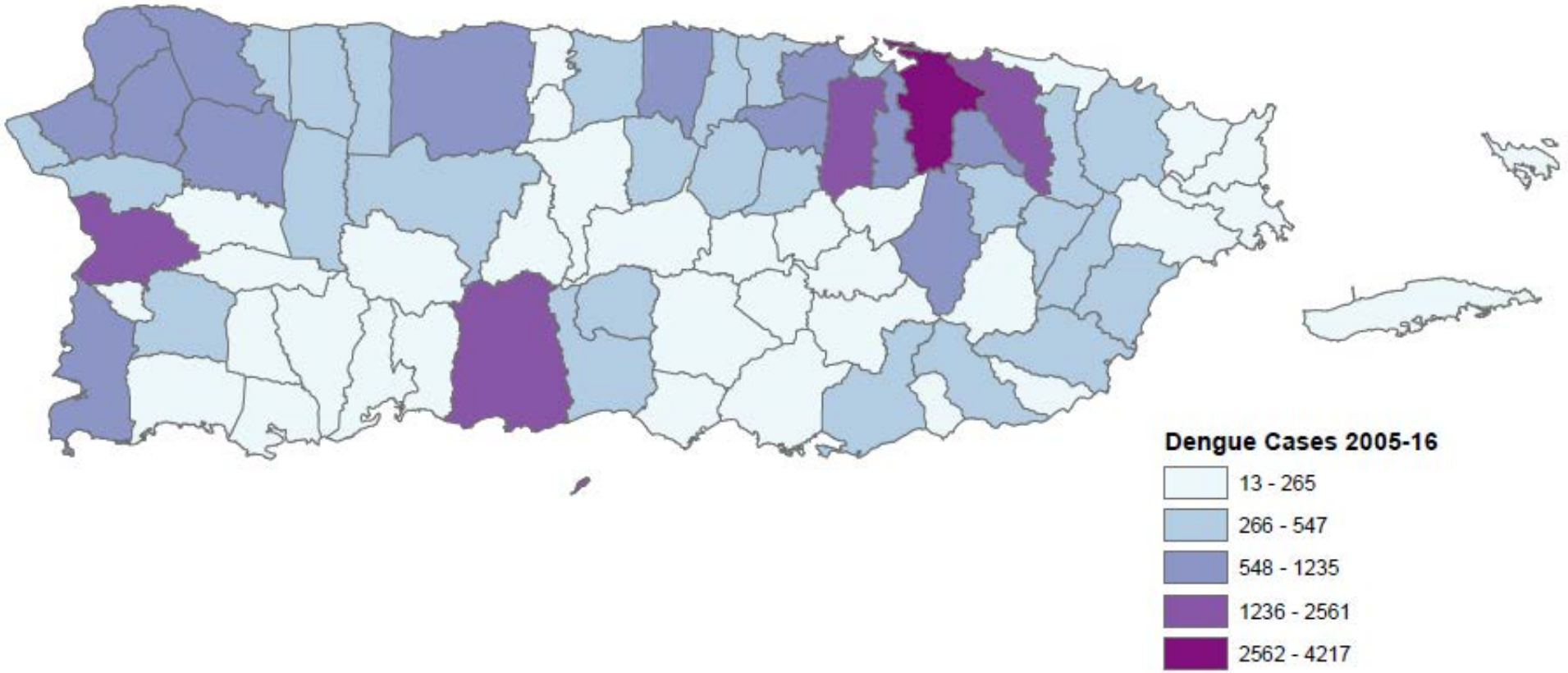
Epidemiology of Dengue in Puerto Rico

Dengue incidence rates per 1000 in Latin America, 1985-2015



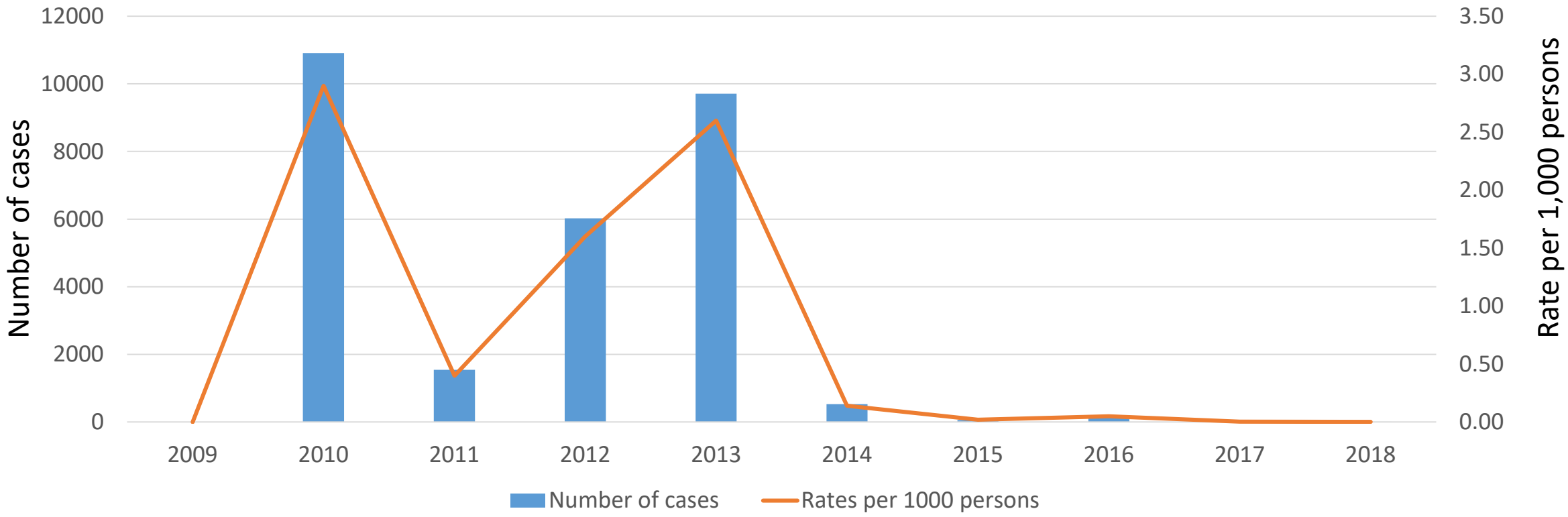
Source: Talia Quandelacy and Mike Johansson, personal communication.
Data from dengue passive surveillance from Ministries of Health and latest population census.

Confirmed and probable dengue cases by municipality of residence, 2005-2016



Data Source: Arbonet, National Arbovirus Surveillance System

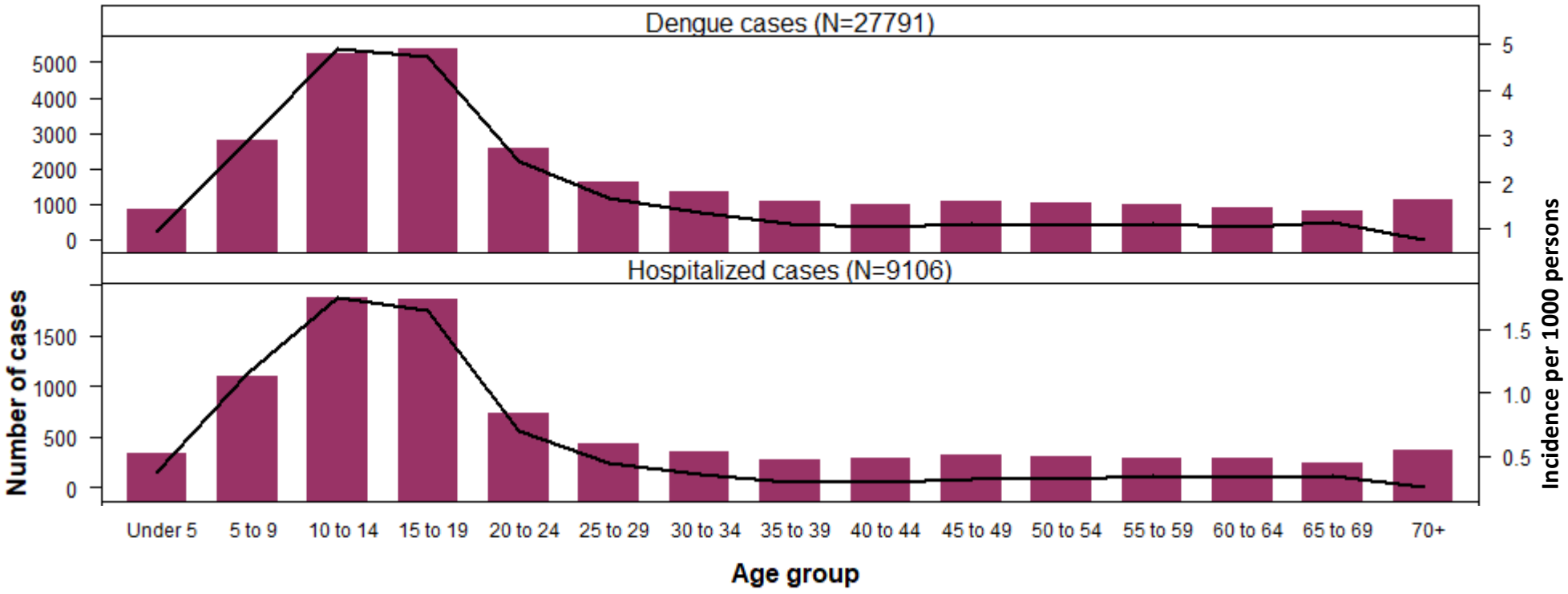
Confirmed/probable* dengue virus cases, Puerto Rico, 2009-2018



*IgM or PCR positive

Data Source: Arbonet, National Arbovirus Surveillance System

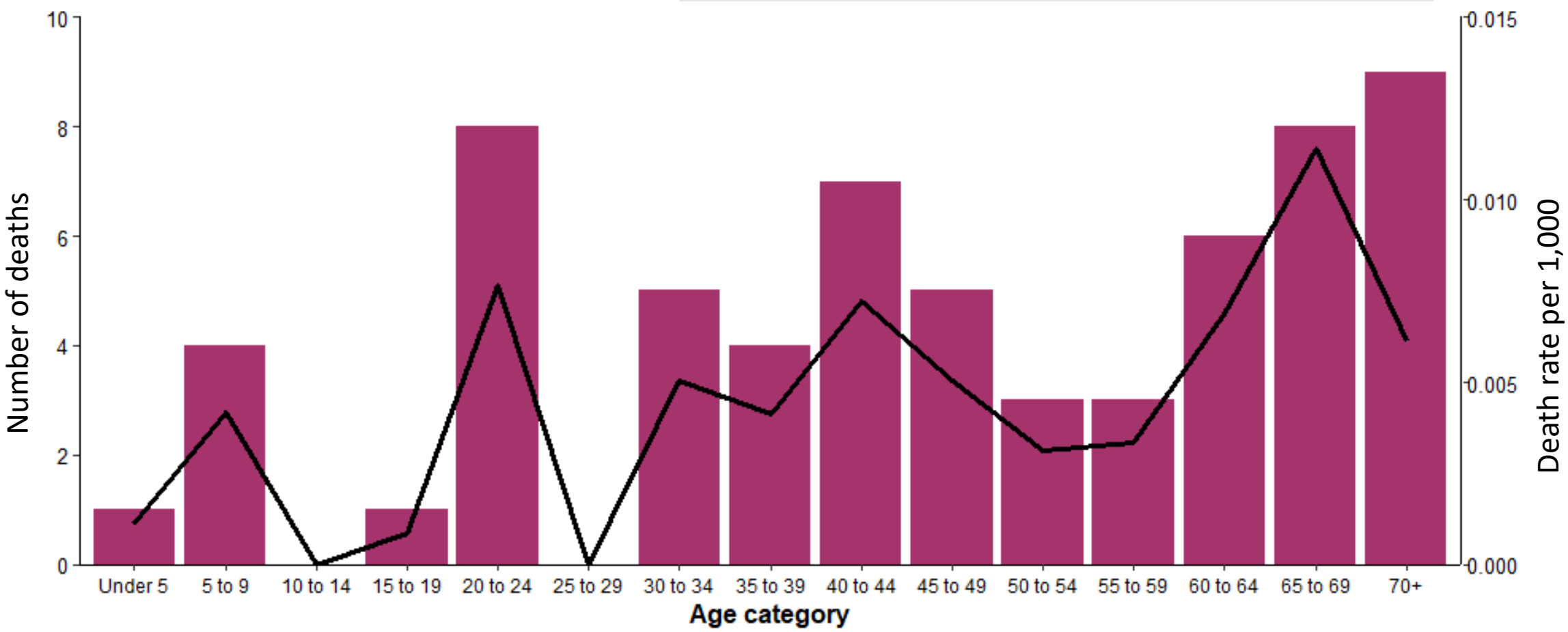
Confirmed/probable* dengue virus cases, hospitalizations and DHF and DSS by age, Puerto Rico, 2010-2013



*IgM or PCR positive

Data Source: Arbonet, National Arbovirus Surveillance System

Fatal dengue cases by age, Puerto Rico (n=64), 2010–2013



Data Source: Arbonet, National Arbovirus Surveillance System

Dengue in US Virgin Islands

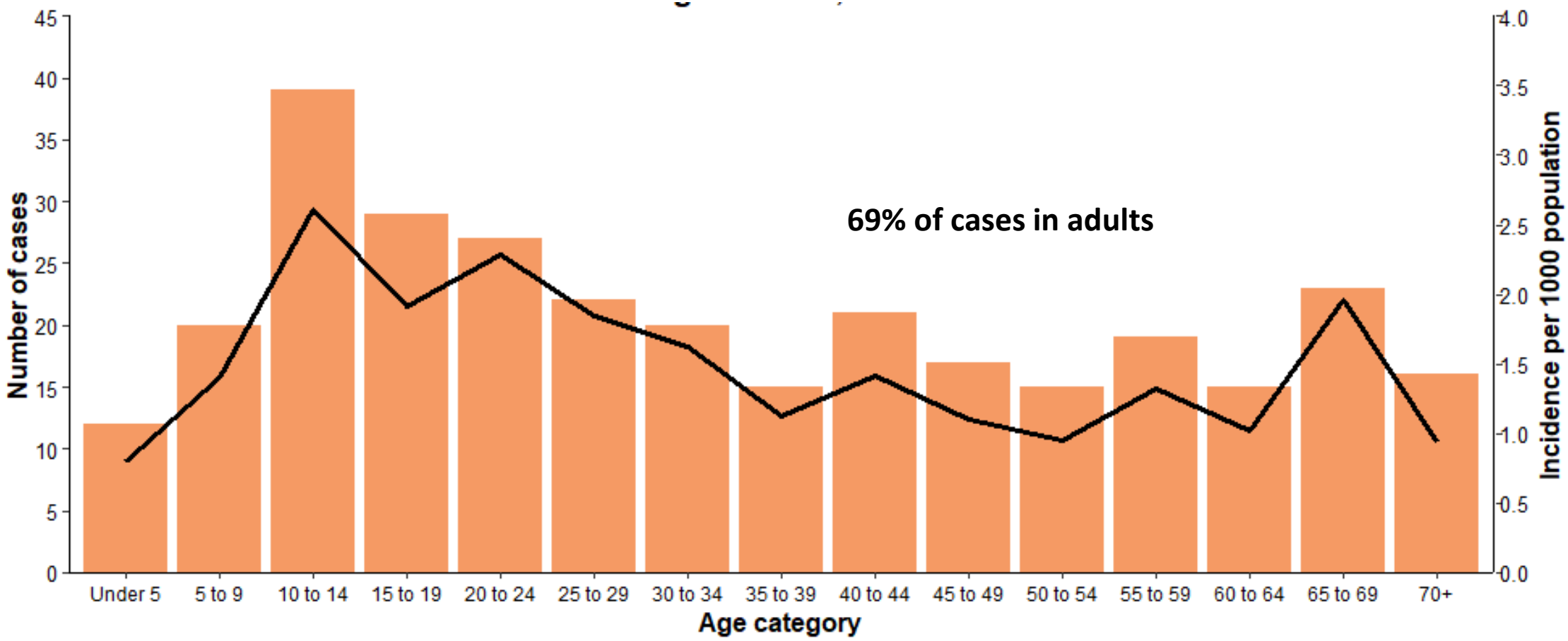
- St. Croix, St. John, St. Thomas and Water Island

- Periodic outbreaks
  - 1986-1987 (DENV-2, -4), St. Johns
  - 1990 (DENV-1, -2, and -4), all islands
  - 2004 (DENV-2), St. Thomas
  - 2005 (DENV-2), St. Croix
  - 2012-2013 (DENV-1, -4), St. Croix

- School survey in 2012
  - ~20% recent infections

Data Source: Arbonet, National Arbovirus Surveillance System
CDC. MMWR 2013;62 (9): 171-172.

Confirmed/probable* dengue cases (n=310), USVI, 2012-2013

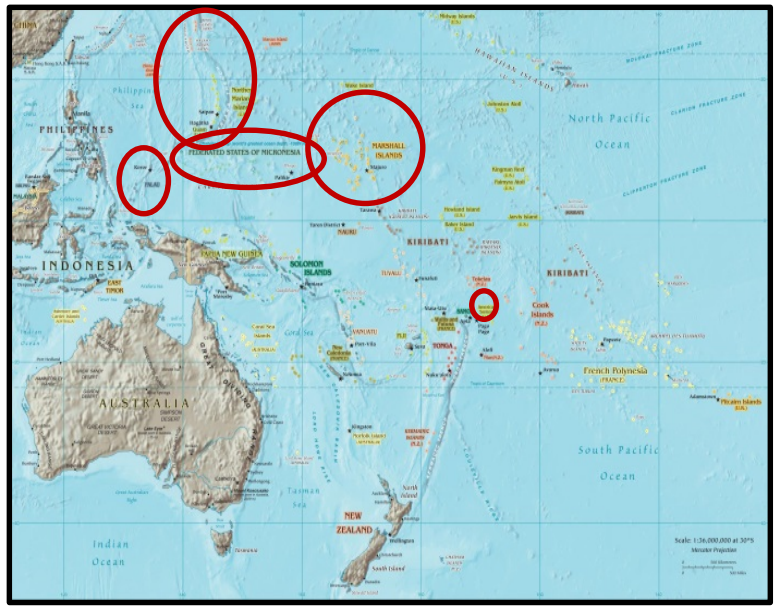


*IgM or PCR positive

Data Source: Arbonet, National Arbovirus Surveillance System

Dengue in the US-affiliated Pacific Islands† and Territories*

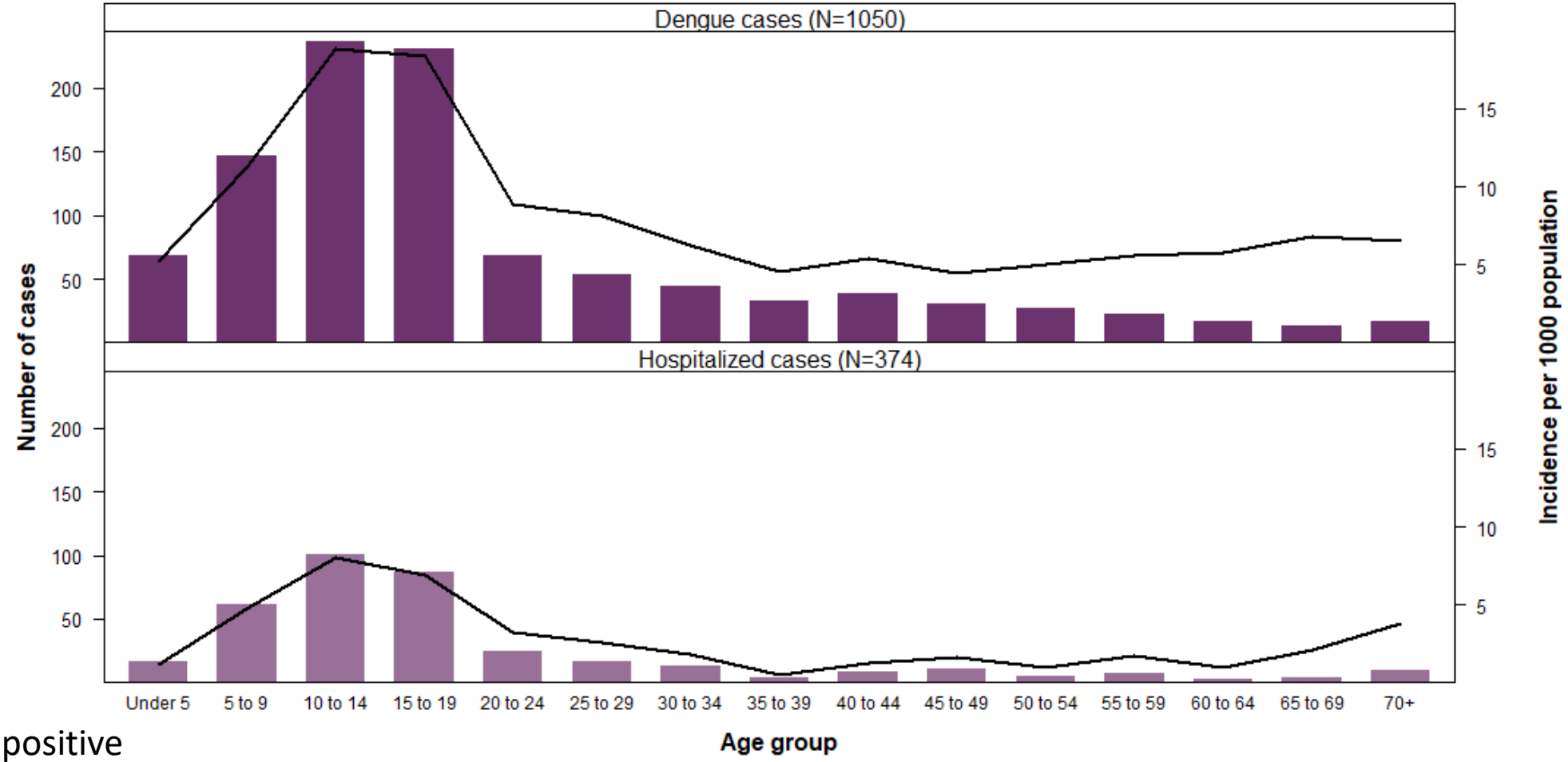
- Periodic outbreaks detected since 1958[1]
  - Unclear which islands, if any, are endemic
- 2010 serosurvey in American Samoa (adults only): 96% IgG seropositive[2]
- 2016-2018 dengue outbreak in American Samoa with over 1000 lab positive cases



†Palau, Republic of the Marshall Islands, Federated States of Micronesia, *American Samoa, Guam, Northern Mariana Islands

[1]Hammon et al., *Am J Trop Med Hyg*, 1958.
[2]Lau, EID, 2013.
[3]Cotter et al. MMWR 2018:67(47);1319–13222.

Confirmed/probable* dengue cases and hospitalizations by age, American Samoa, 2017-2018



*IgM or PCR positive

Data Source: Arbonet, National Arbovirus Surveillance System

Summary

- Dengvaxia approved by FDA for use among children 9-16 years, with laboratory-confirmed previous dengue infection who live in endemic areas
- No IgG tests currently licensed in the US; performance evaluations done before Zika.
- US territories with frequent or continuous risk include Puerto Rico, USVI, American Samoa.
- Cases and incidence rates in PR, USVI and AS highest in 10-19 age group but many cases occur in adults.

Acknowledgements

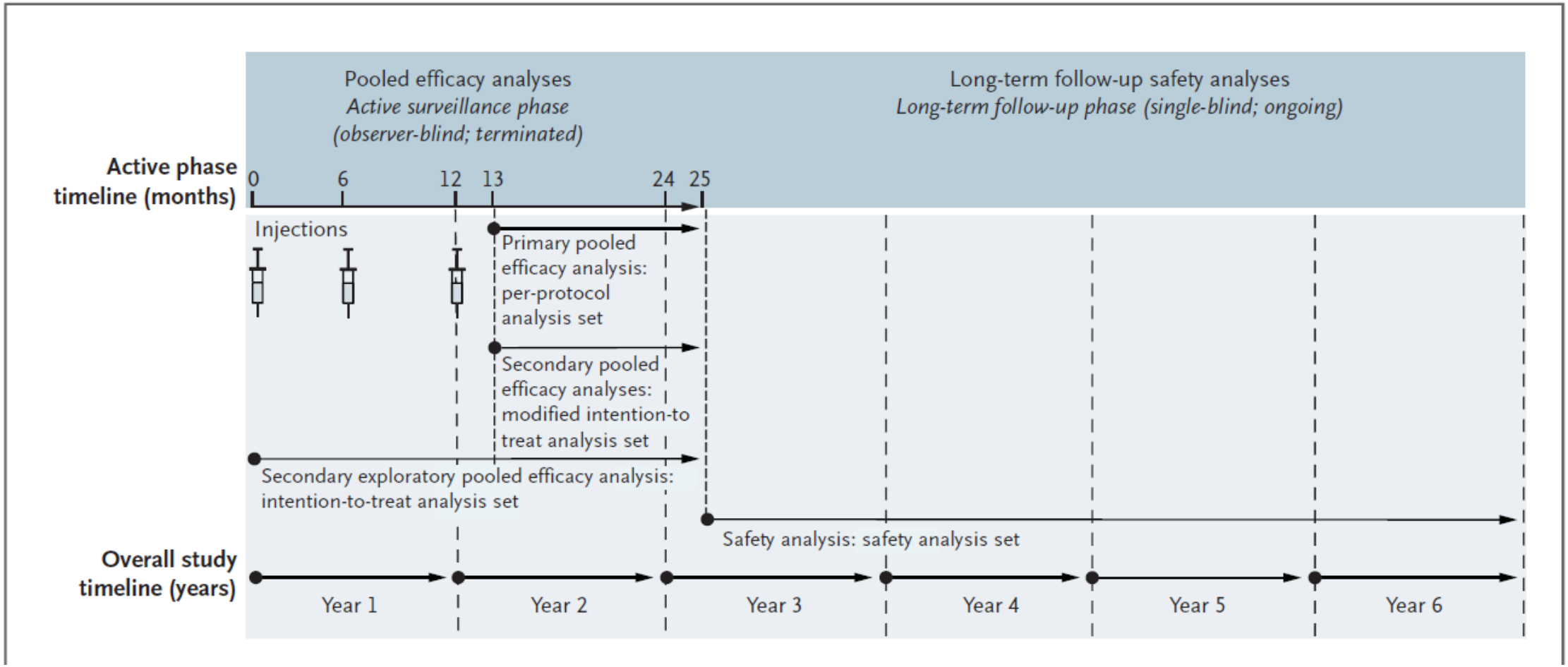
CDC Dengue Branch

- Steve Waterman
- Laura Adams
- Dania Rodriguez
- Michael Johansson
- Tyler Sharp
- Jorge Munoz

Puerto Rico Department of Health

Thank you!

Surveillance phase and long term follow-up phase



Seroprevalence by age, Patillas, Puerto Rico, 2007

TABLE 1

Prevalence of previous DENV infection among 10- to 18-year-olds at enrollment in Patillas, Puerto Rico in 2007

Population characteristics	IgG anti-DENV* at study enrollment: Yes	No	Total
Mean age in years (SE)†	14.0 (0.13)	13.4 (0.12)	13.7 (0.04)
Age in years, *n* (%)‡			
10–11	52/120 (42.7)	68/120 (57.3)	
12–13	55/120 (45.2)	65/120 (54.8)	
14–15	33/56 (57.7)	23/56 (42.3)	
16–18	30/49 (59.2)	19/49 (40.8)	
Male, *n* (%)§	73/157 (48.9)	84/157 (51.1)	
Total, *n*	170/345¶	175/345	

Calibration weighting was applied to the calculation of all proportions, logistic regression odds ratios (ORs), and *P* values.

*IgG anti-DENV detected by an IgG ELISA.

†Adjusted Wald test, $F(1,0.32) = 6.45$; *P* value = 0.02.

‡Logistic regression (age in years used as a continuous variable), OR = 1.15; *P* value = 0.02. Rao–Scott $F(2.64,84.55) = 1.51$; *P* value = 0.22.

§Rao–Scott $F(1,32.0) = 0.11$; *P* value = 0.74.

¶In total, 49.8% of total participants (95% CI = 43.6–56.0%).

Argüello DF et al. Incidence of dengue virus infection in school-aged children in Puerto Rico: a prospective seroepidemiologic study. Am J Trop Med Hyg. 2015 Mar;92(3):486-91. doi: 10.4269/ajtmh.14-0231. Epub 2015 Feb 2.

Higher risk of severe dengue after secondary infections in a specific antibody titer range

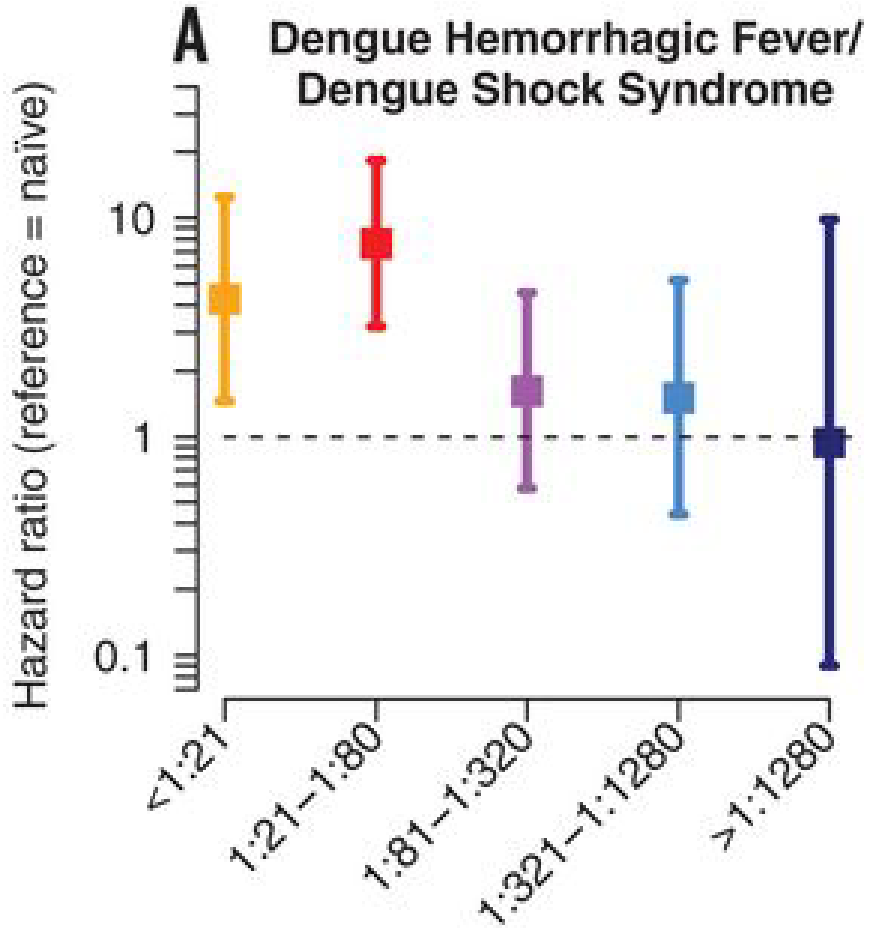


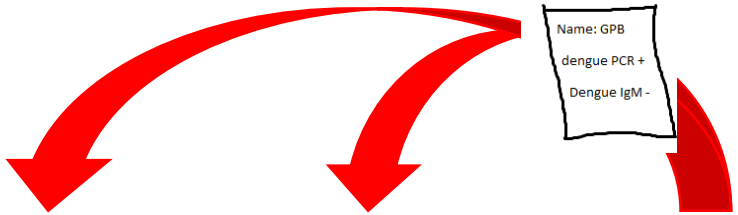
Fig. 1 Longitudinal analyses of the hazard of severe dengue disease or any dengue case by preexisting DENV-Ab titer for the full pediatric dengue cohort.

Published by AAAS

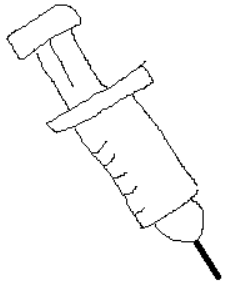
Leah C. Katzelnick et al. Science 2017;358:929-932

Science
AAAS

Dengue test result flow in Puerto Rico



Seek care



If dengue is suspected referred to clinical lab

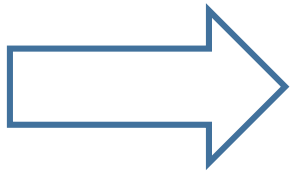
Testing centralized at PRDH, results sent back to provider

All historical results in surveillance database at PRDH

Immunization registry in Puerto Rico

220 VFC* providers
60% of vaccines

300 private providers
40% of vaccines



Immunization registry for children and adults
70% coverage of private providers
100% coverage of VFC

*Vaccines for children program

Personal communication, Angel Rivera and Iris Cardona, PRDH