Dengue virus, epidemiology and vaccines

Gabriela Paz-Bailey, MD, PhD, MSc

Chief Dengue Branch, Division of Vector Borne Diseases, Centers for Disease Control and Prevention

Disclaimer

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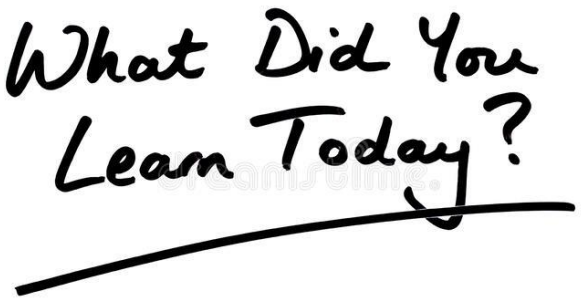
Outline

- Routes of transmission
- Clinical spectrum
- Global burden
- Epidemiology in the United States
- Dengue vaccines

Summary

- Dengue viruses are transmitted by mosquitoes, most common arbovirus globally.
- The second dengue infection with a heterologous virus has the highest risk of severe disease.
- Dengue is **endemic** in **six** US territories and freely associated states.
- Dengvaxia vaccine approved for children 9-16 years who had dengue before and may increase risk of severe disease if administered to seronegatives.
- A second dengue vaccine, TAK-003, is currently under review at FDA and ACIP.
- A third dengue vaccine, TV003, is in phase 3 trials.

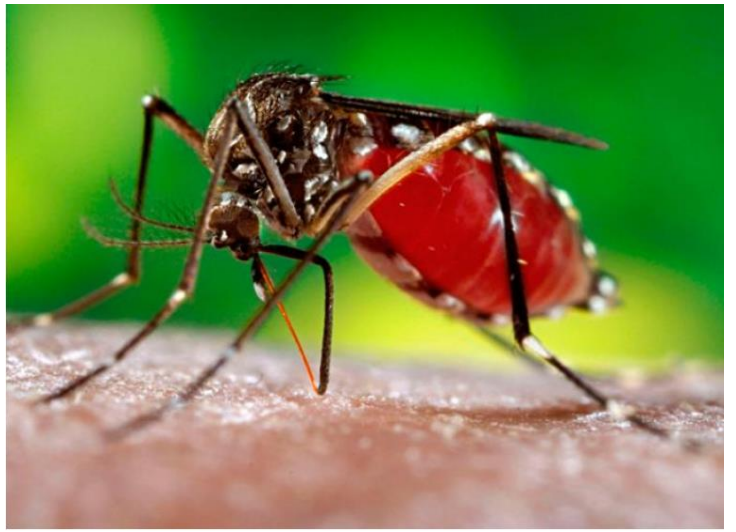


Dengue virus (DENV)

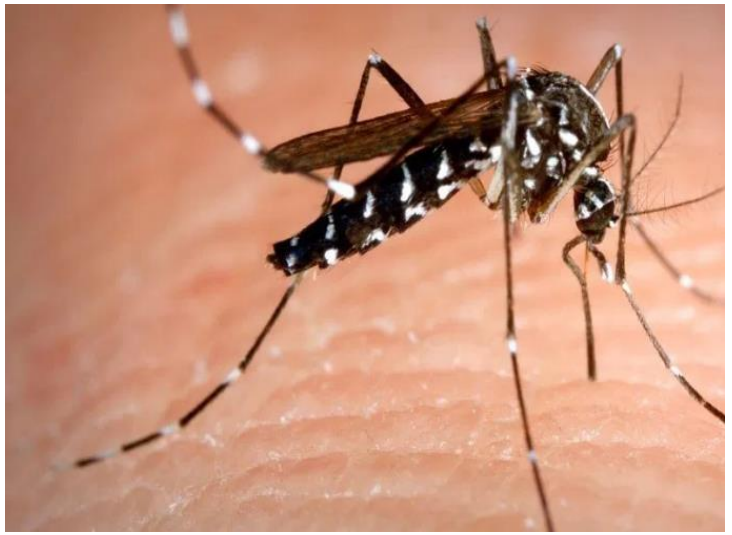
- DENV-1, 2, 3, 4
  - Lifelong DENV type-specific immunity
  - Short-term cross-immunity (~1–3 years)

DENV transmission

- Vector-borne
  - Saliva of infected *Aedes spp* mosquito
- Other modes
  - Vertical from mother to baby
  - Blood transfusion or organ transplantation
  - Needle stick, mucocutaneous, or hospital/laboratory accident
  - Breast milk



Aedes aegypti

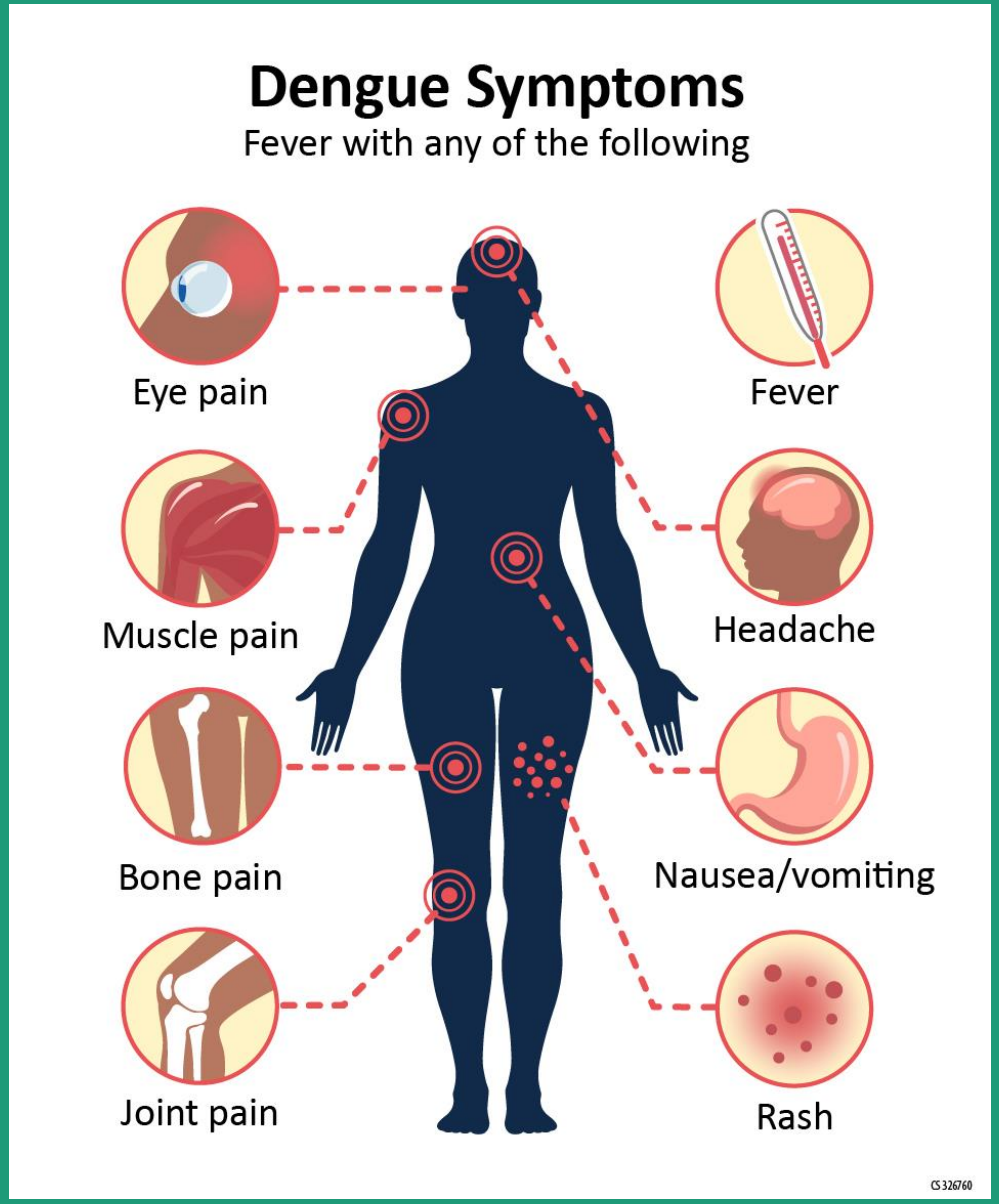


Aedes albopictus

DENGUE CLINICAL SPECTRUM

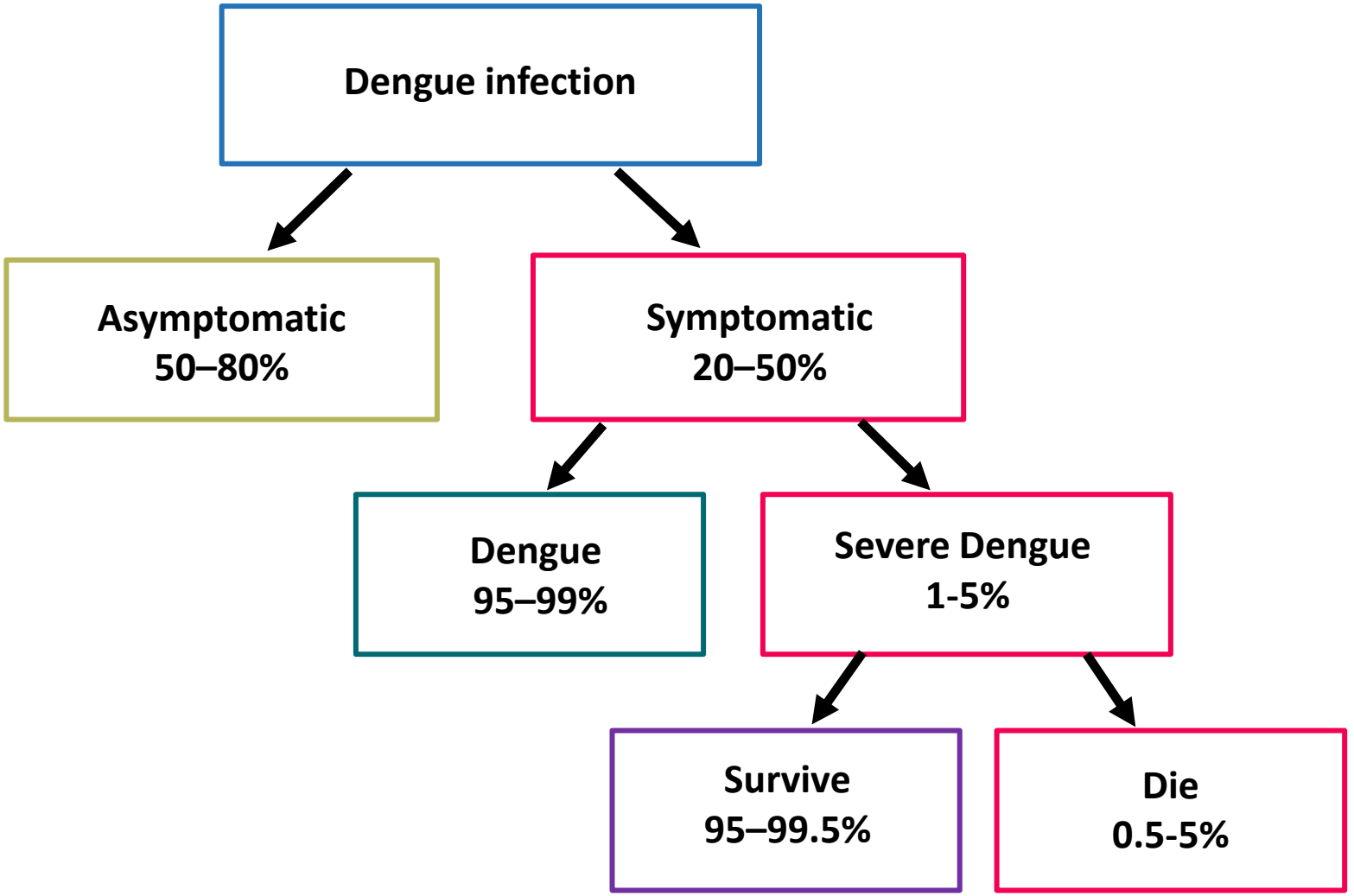
Dengue clinical manifestations

- ~1 in 4 DENV infections are symptomatic
- Often a mild, undifferentiated febrile illness.
- Mortality ranges from <1% if treated appropriately to 15% if untreated



Dengue Outcomes

Most dengue infections are asymptomatic or mild, but dengue can be severe and fatal.



Wilder-Smith A. et al, Lancet 2019;393:350-63.

1997 WHO dengue classification

- Dengue Hemorrhagic Fever (DHF) defined as:
  - Fever (2 to 7 days)
  - Hemorrhagic manifestations
  - Thrombocytopenia (≤100,000 cells per mm^3)
  - Plasma leakage

- Dengue shock syndrome (DSS) defined as DHF + circulatory failure:
  - Rapid, weak pulse + narrow pulse pressure, OR
  - Hypotension + cold, clammy skin + restlessness

Dengue hemorrhagic fever: diagnosis, treatment, prevention and control. 2nd edition. Geneva; World Health Organization. 1997.

Current WHO dengue classification

Dengue

Probable Dengue
Live in/travel to endemic area.

Fever and 2 of the following criteria:

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

Laboratory-confirmed dengue
Molecular techniques/ IgM or IgG seroconversion

Dengue with warning signs

Presence of warning signs:

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation (ascites, pleural effusion)
- Mucosal bleeding
- Lethargy, restlessness
- Postural hypotension
- Liver enlargement >2 cm
- Progressive increase in hematrocrit

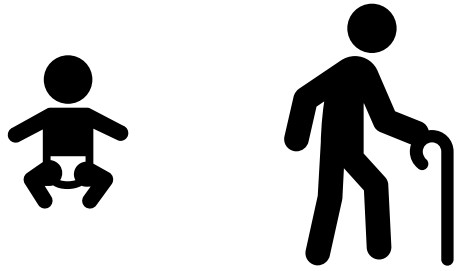
Severe dengue

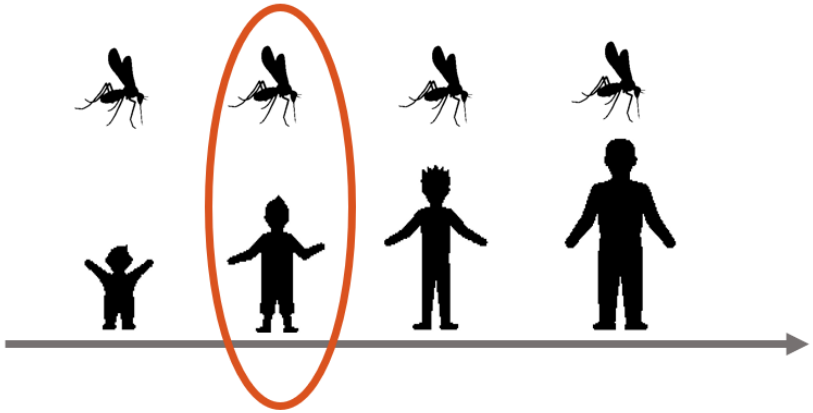
One of the following manifestations:

- Shock or respiratory distress due to severe plasma leakage
- Severe bleeding: based on evaluation by attending physician
- Severe organ involvement (such as liver or heart)

Dengue: guidelines for patient care in the Region of the Americas. Washington, D.C. : PAHO, 2016

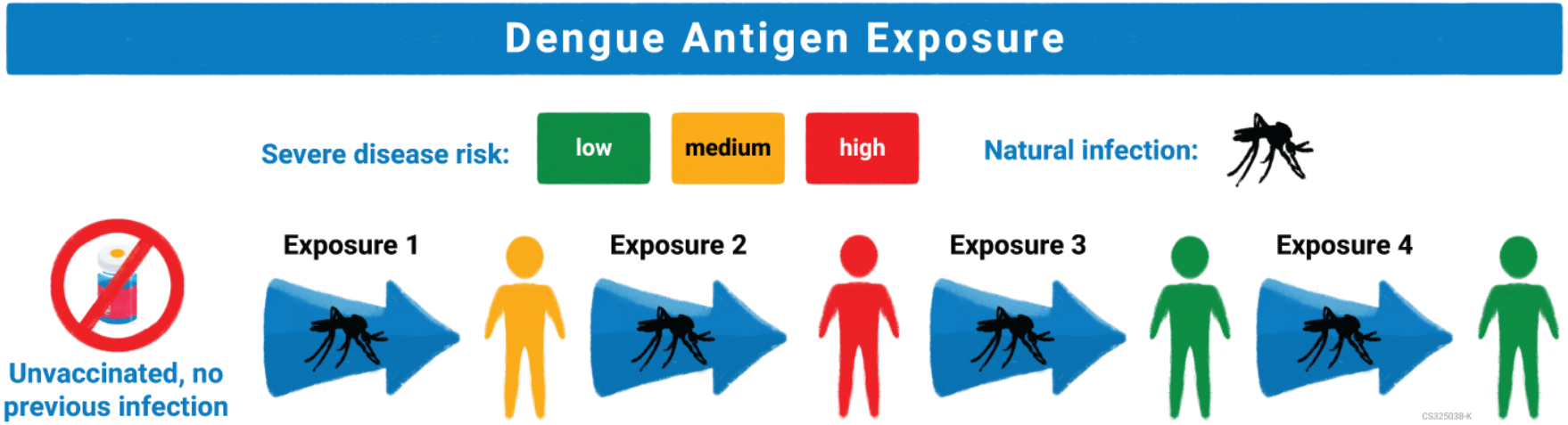
Risk factors for severe dengue





- **Age**
  - Infants born to seropositive mothers
  - Elderly
- **Number of dengue infections**
  - 2nd >> 1st, 3rd, 4th infection
- **Comorbidities**
  - Asthma, diabetes, obesity, hypertension, sickle cell disease, kidney disease, hypertension, or on anticoagulant therapy

Severe dengue and multiple DENV infections



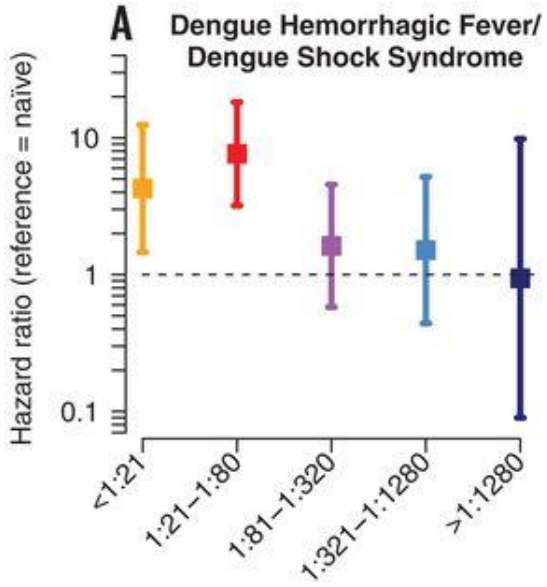
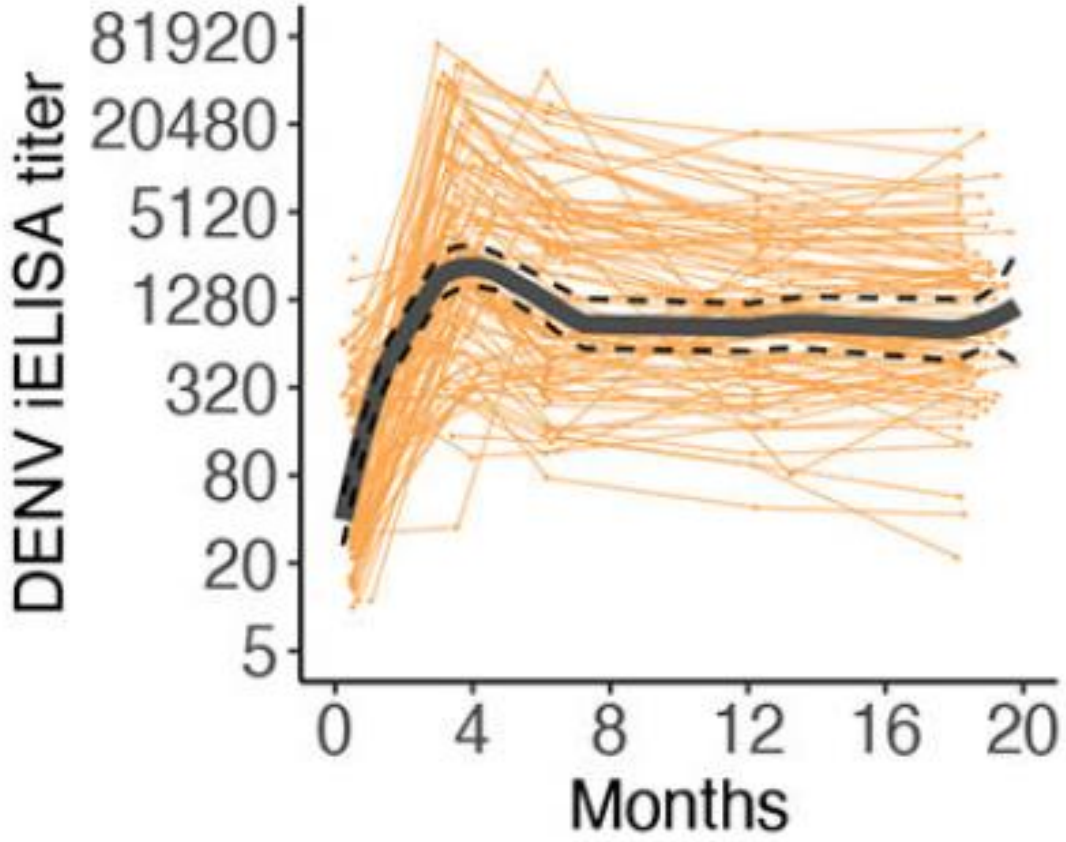


Fig. 1 Longitudinal analyses of the hazard of severe dengue disease or any dengue case by preexisting DENV-Ab titer for the full pediatric dengue cohort. Leah C. Katzelnick et al. Science 2017;358:929-932

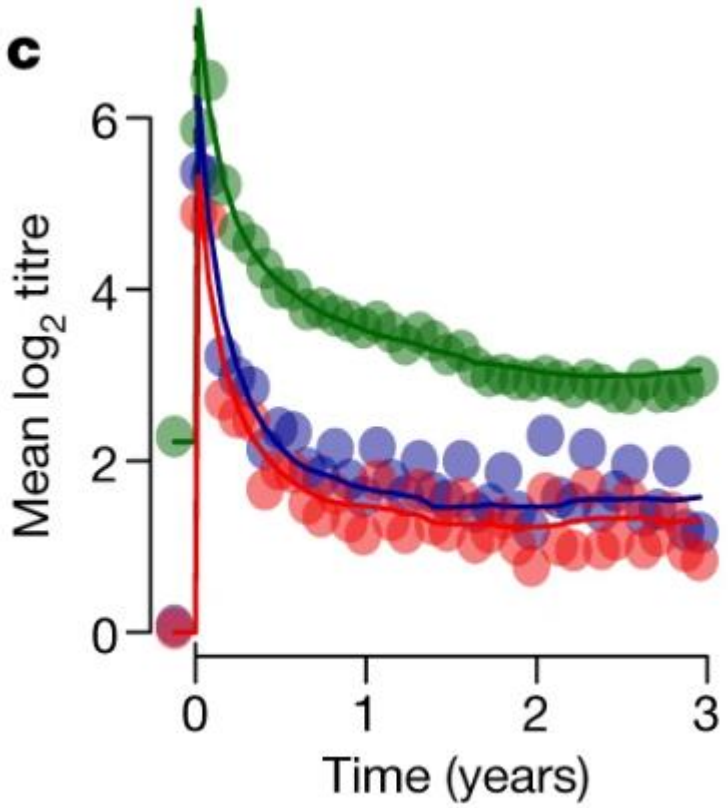
Science
AAAS

Antibody titers reach a setpoint by about 1 year after primary DENV infection and persist long term



DENV antibody titers after primary infection reach stable setpoints after 8 months.

Individual trajectories of DENV iELISA titers in children after primary DENV infection hospital based study in Nicaragua. Katzelnich et al. Sci Transl Med, 2022.



DENV titers stabilize on year after infection to a setpoint.

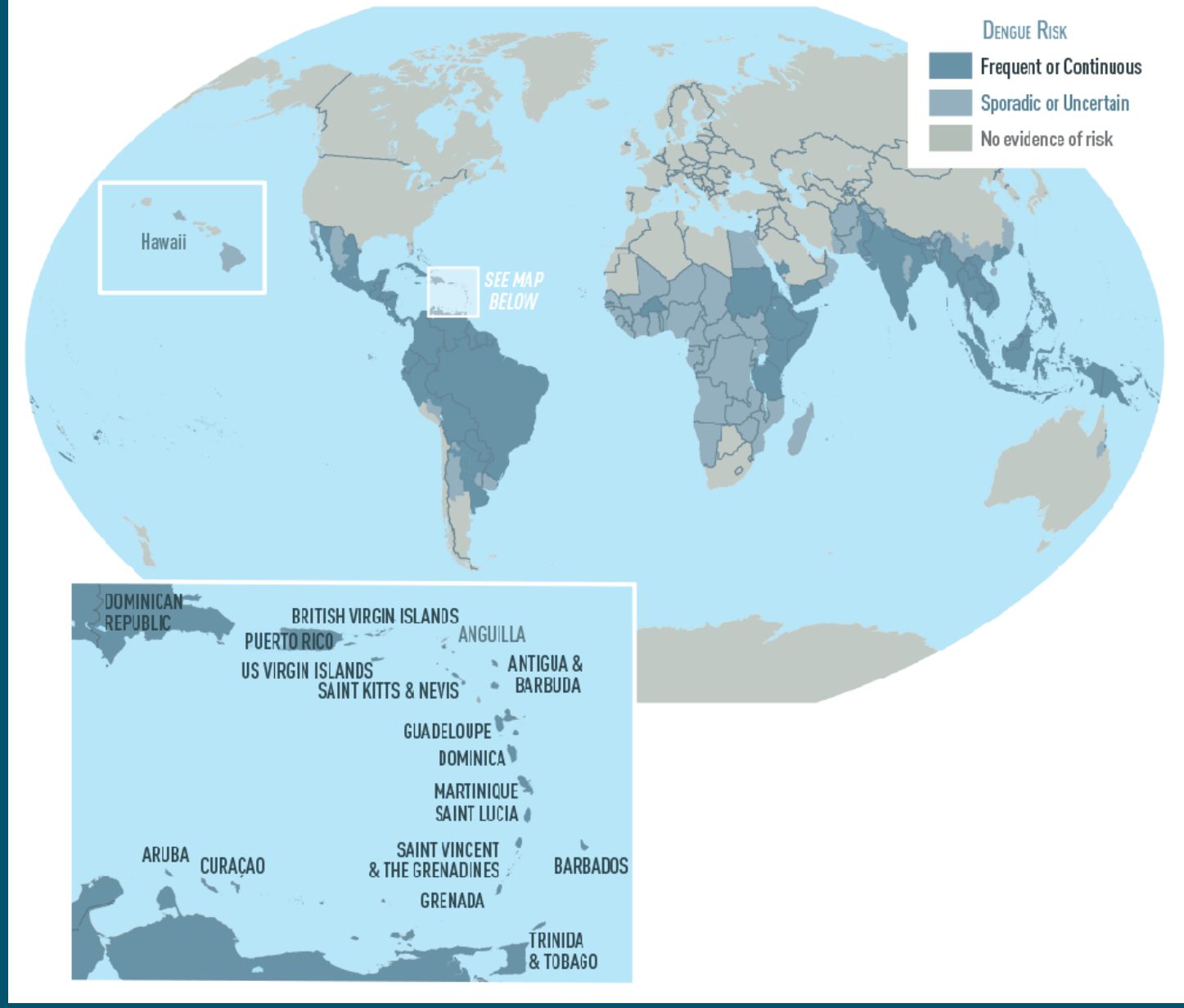
Primary infections (infecting serotype in blue, non-infecting serotypes in red) and subsequent infections (green). School based cohort study in Thailand with haemagglutination inhibition test. Salje et al. Nature 2018.

Dengue hemorrhagic fever and dengue shock syndrome by immune status and serotype, Nicaragua 2005-2022

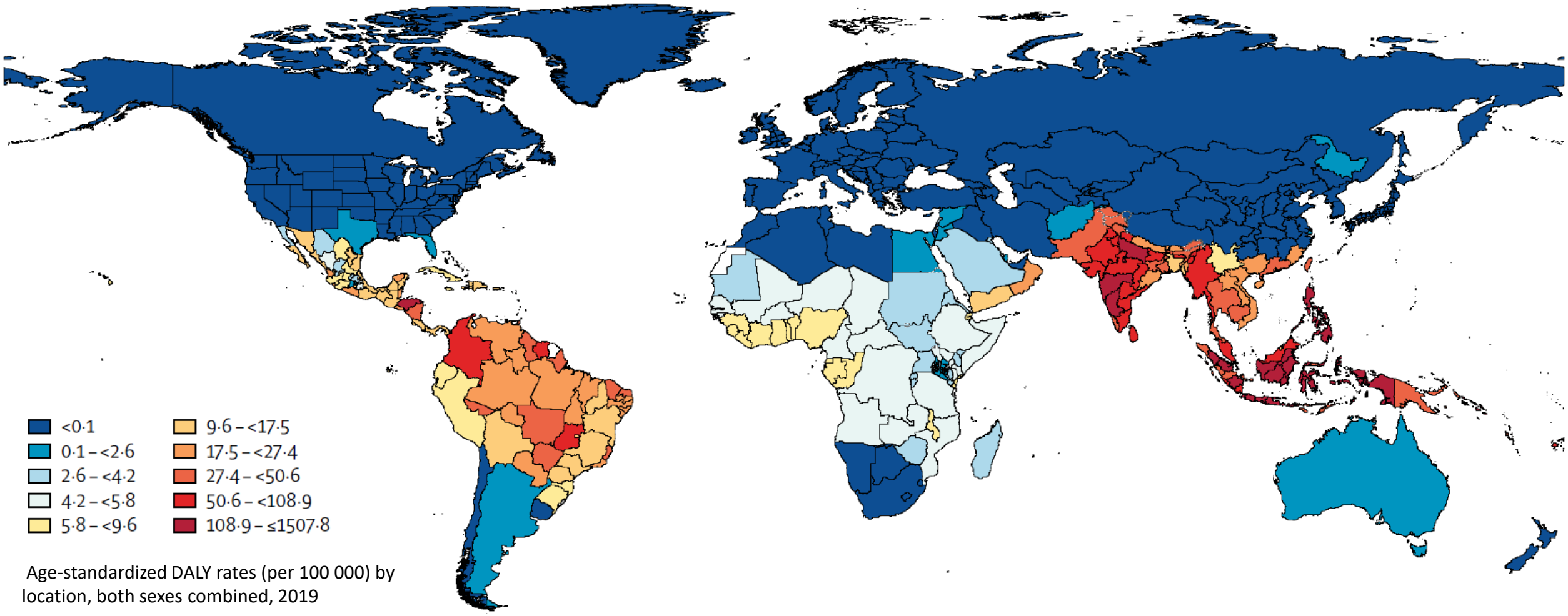
Serotypes	DHF/DSS n	%	Total N
DENV1 primary	14	10.4	134
DENV1 secondary	22	17.2	128
DENV2 primary	11	18.0	61
DENV2 secondary	167	34.9	478
DENV3 primary	40	16.9	237
DENV3 secondary	63	30.1	209
DENV4 primary	0	0.0	1
DENV4 secondary	2	9.5	21

From Dr. Eva Harris, University of California Berkley and Dr. Angel Balmaseda, Ministry of Health, Nicaragua. Unpublished data, not to distribute. Patients recruited at tertiary care hospital. WHO 1997 definition.

Dengue Global Burden



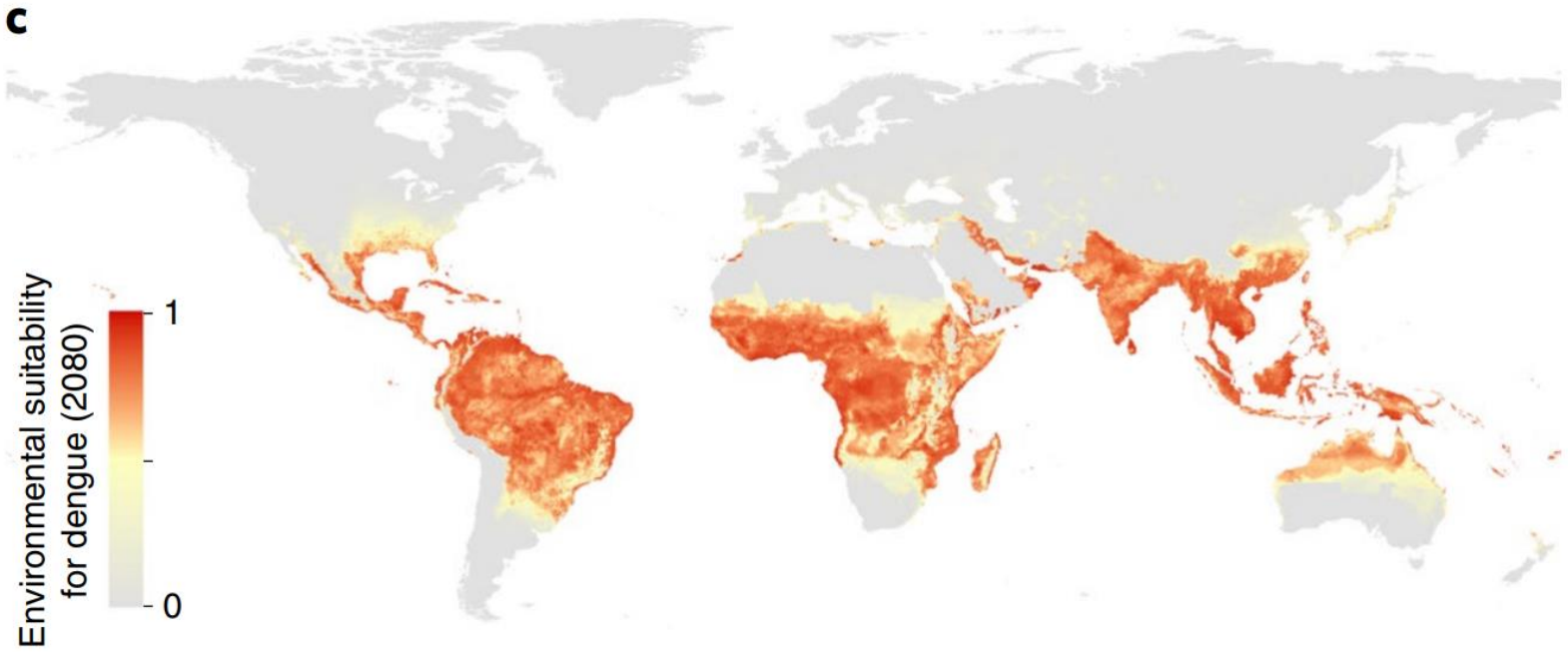
Dengue is the most common arboviral disease and causes **significant disability and death**



Age-standardized DALY rates (per 100 000) by location, both sexes combined, 2019

Dengue — Level 3 cause | Institute for Health Metrics and Evaluation (healthdata.org)

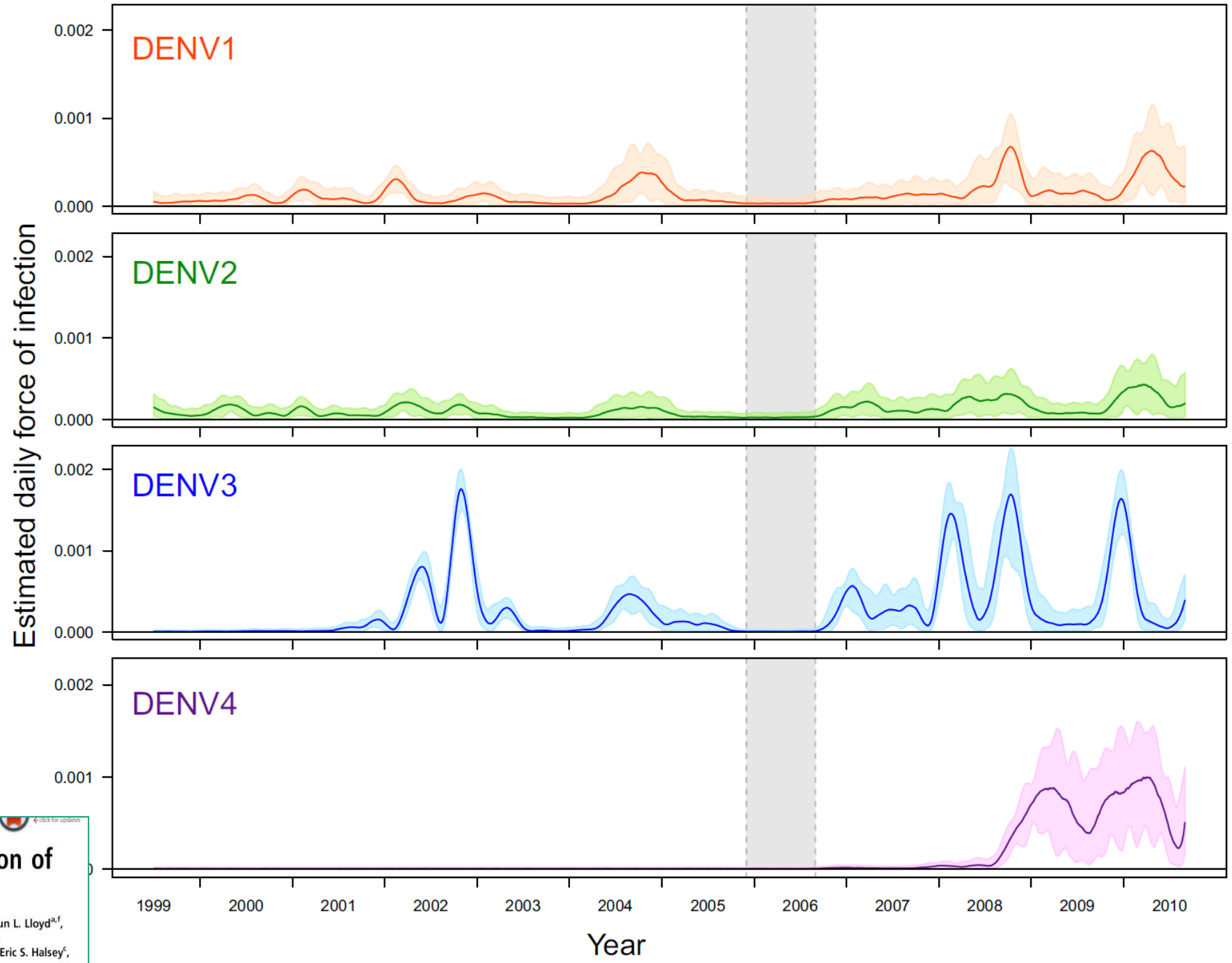
Dengue incidence is **likely to increase** as the climate warms.



A total of 6.1 (95%CI 4.7–6.9) billion people will be at risk for dengue by 2080, an increase of 2.25 billion compared to 2015.

The current and future global distribution and population at risk of dengue (nature.com)

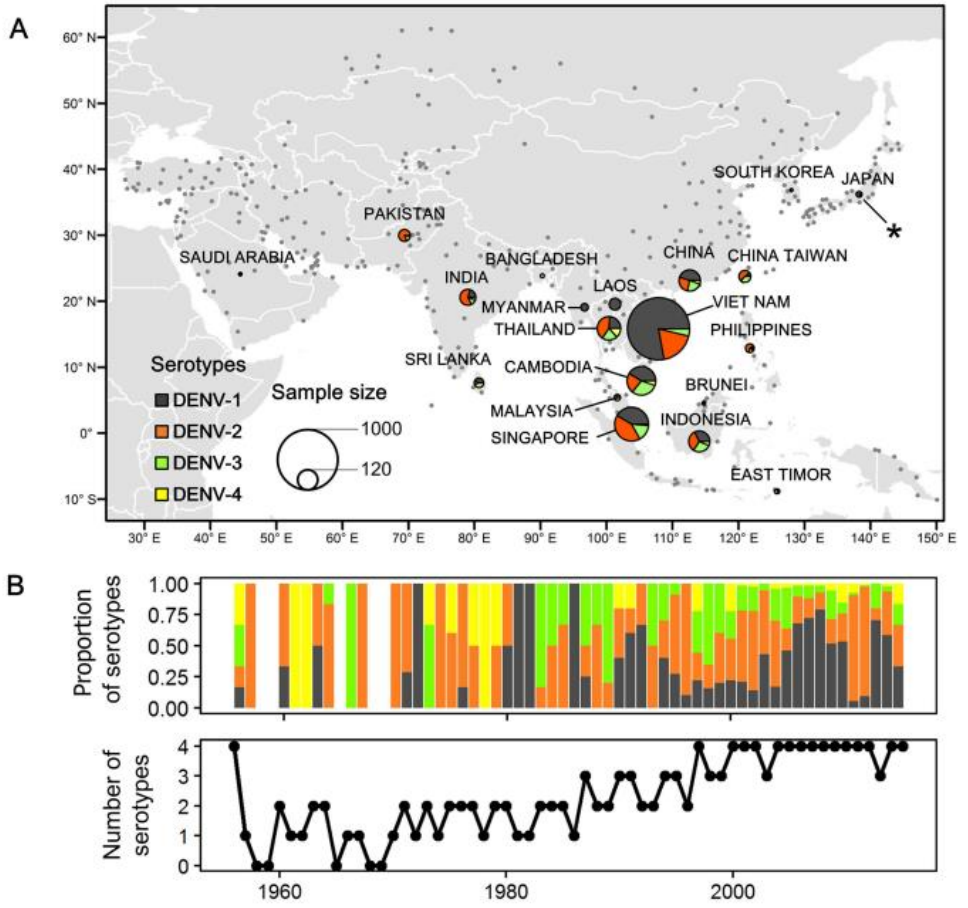
Iquitos Peru: overlap of different serotypes but most of the contribution to the force of Infection was DENV3



Time-varying, serotype-specific force of infection of dengue virus

Robert C. Reiner, Jr.[a,b,1], Steven T. Stoddard[a,b], Brett M. Forshey[c], Aaron A. King[a,d], Alicia M. Ellis[a,e], Alun L. Lloyd[a,f], Kanya C. Long[b,g], Claudio Rocha[c], Stalin Vilcarromero[c], Helvio Astete[c], Isabel Bazan[c], Audrey Lenhart[h,i], Gonzalo M. Vazquez-Prokopec[a,j], Valerie A. Paz-Soldan[k], Philip J. McCall[h], Uriel Kitron[a,j], John P. Elder[l], Eric S. Halsey[c], Amy C. Morrison[b,c], Tadeusz J. Kochel[c], and Thomas W. Scott[a,b]

Co-circulation of dengue virus serotypes in Asia

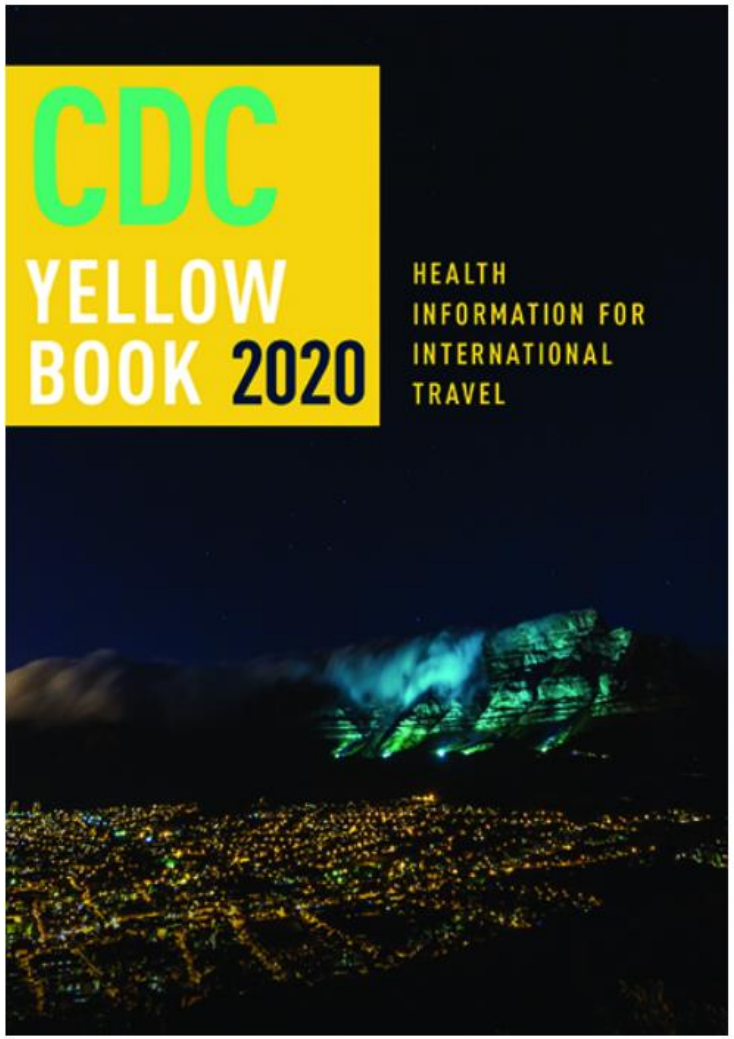


A. Locations of available viral sequences. B. Proportion of sequences from each serotype and number of serotypes isolated per year. Tian et al. Plos NTD 2017.

Dengue Epidemiology in the United States

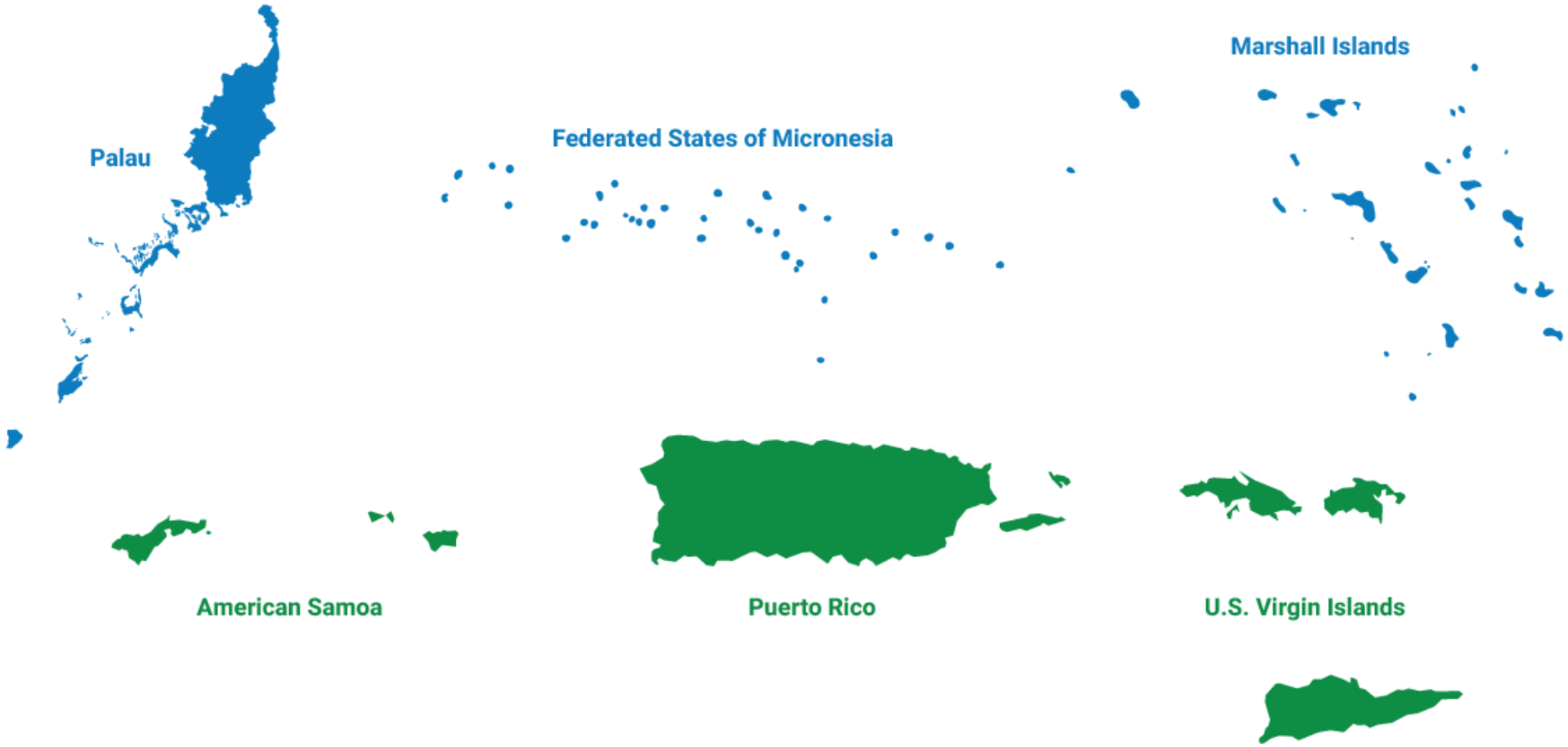
Yellow Book criteria to assess dengue risk levels

- **Frequent/continuous risk (endemic):**
  - 10 dengue cases in at least three distinct years over the most recent 10-year period.
- **Sporadic/uncertain risk:**
  - At least one reported, locally acquired case in the previous 10 years.
- **No evidence of risk:** no reports of DENV transmission.

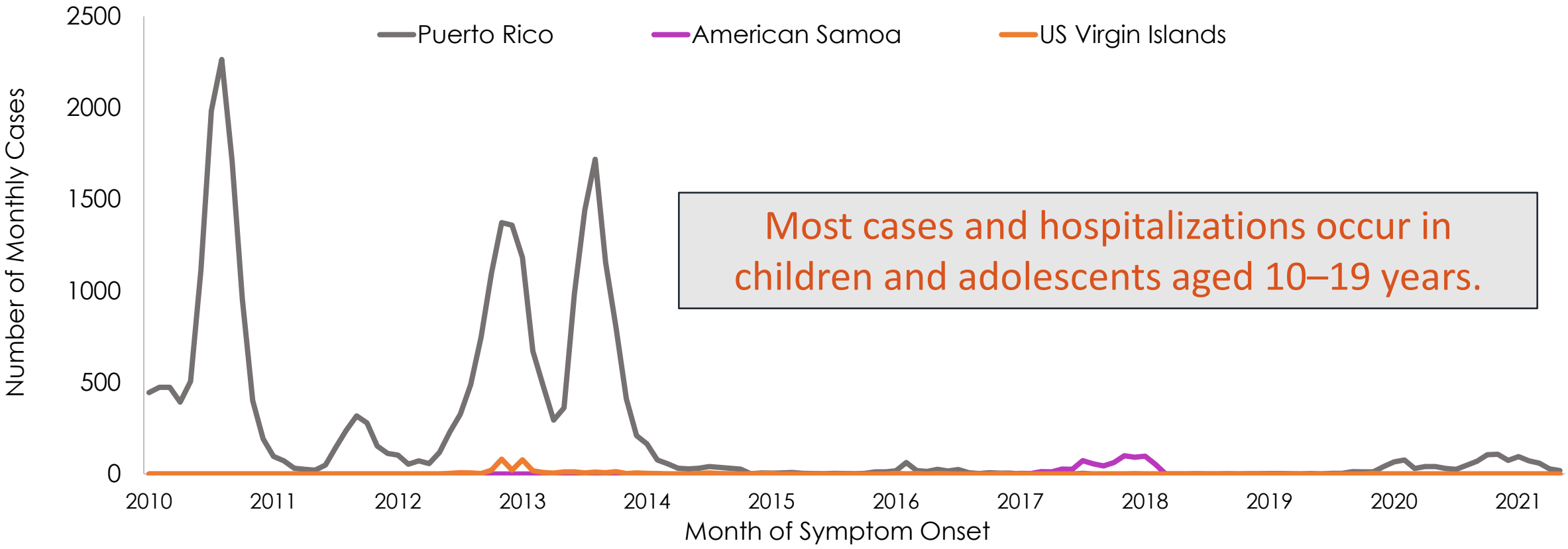


Jentes et al. Journal of Travel Medicine 2016; 23, 6, 1-5.

Dengue is endemic in **six** U.S. territories and freely associated states



Large, cyclical epidemics of dengue occur every 3–7 years in endemic areas of the U.S.



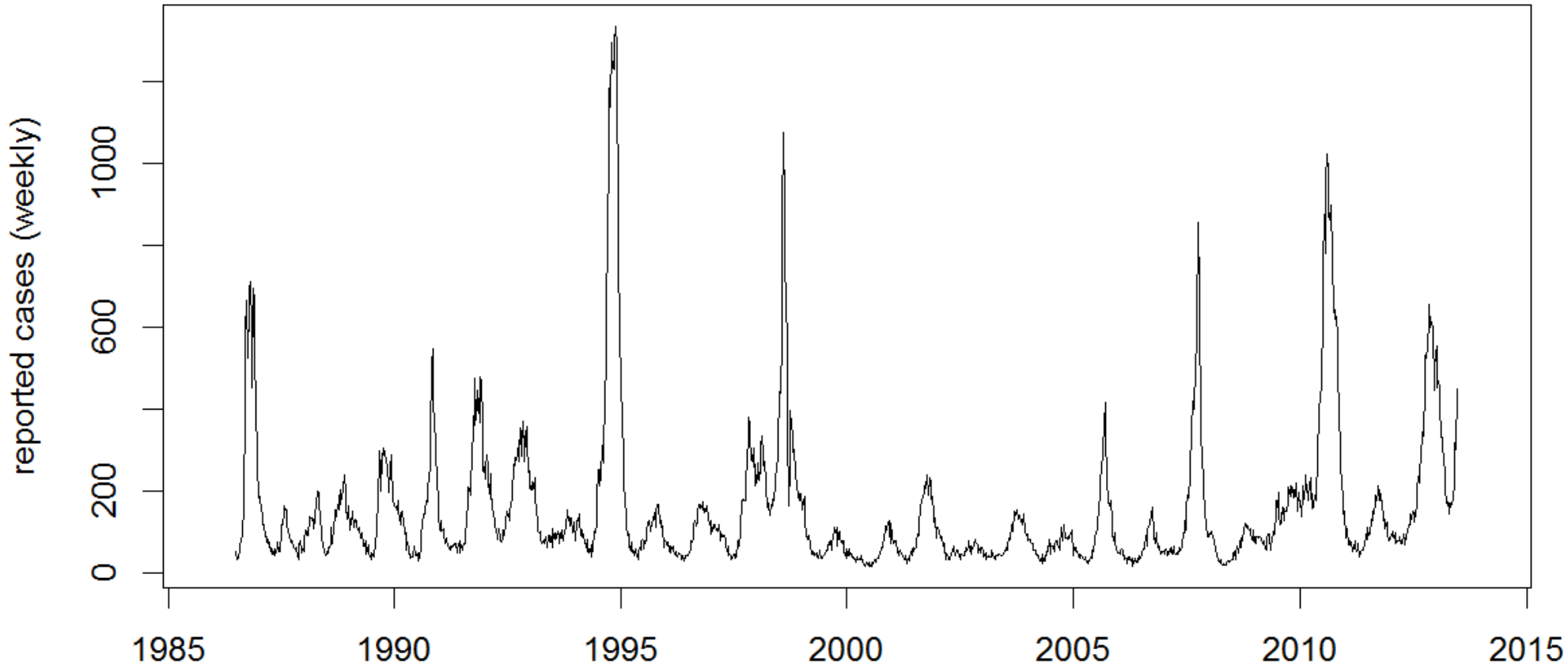
Paz-Bailey G. Dengue vaccine draft recommendations using the evidence to recommendation framework. Advisory Committee on Immunization Practices (ACIP); 2021 June 24, 2021; Atlanta, GA.

Dengue in Puerto Rico

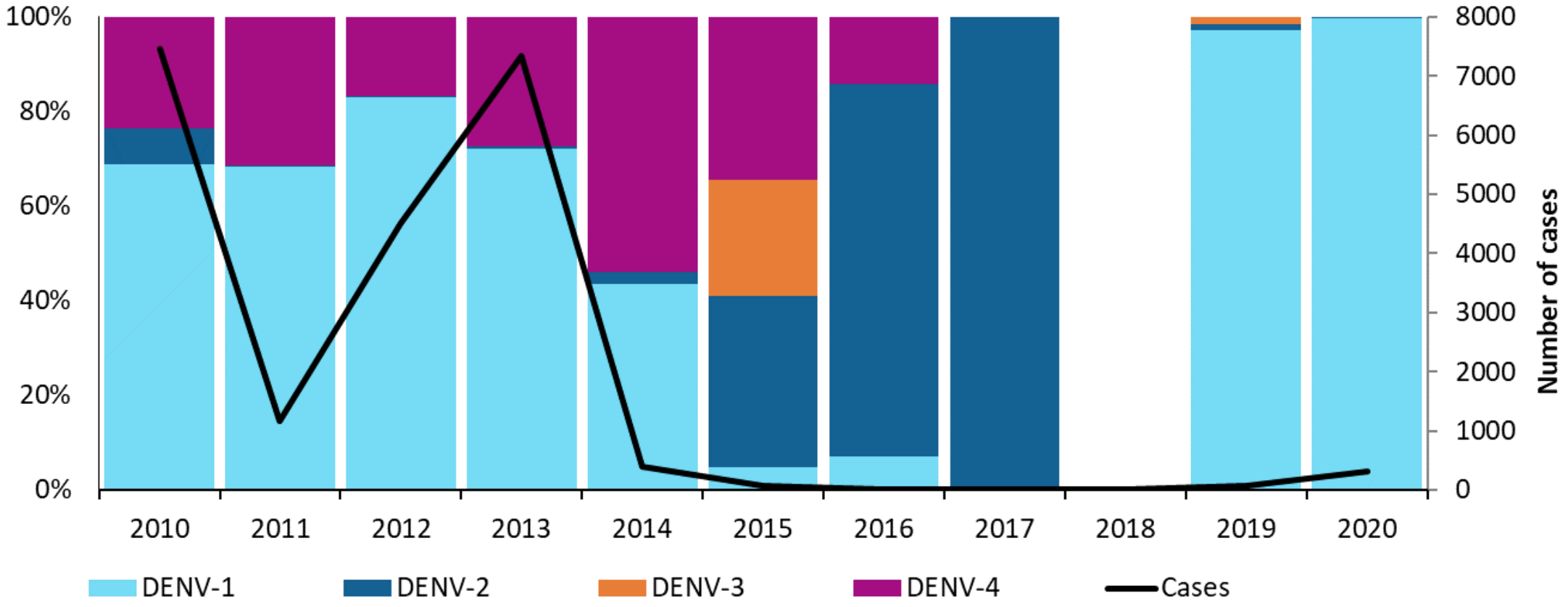
- **>95%** of dengue cases from endemic areas of the United States during 2010–2020 were reported from Puerto Rico (n=29,862)

Source: CDC ArboNET, 2010-2020, unpublished data

Suspected dengue cases, Puerto Rico, 1986-2013



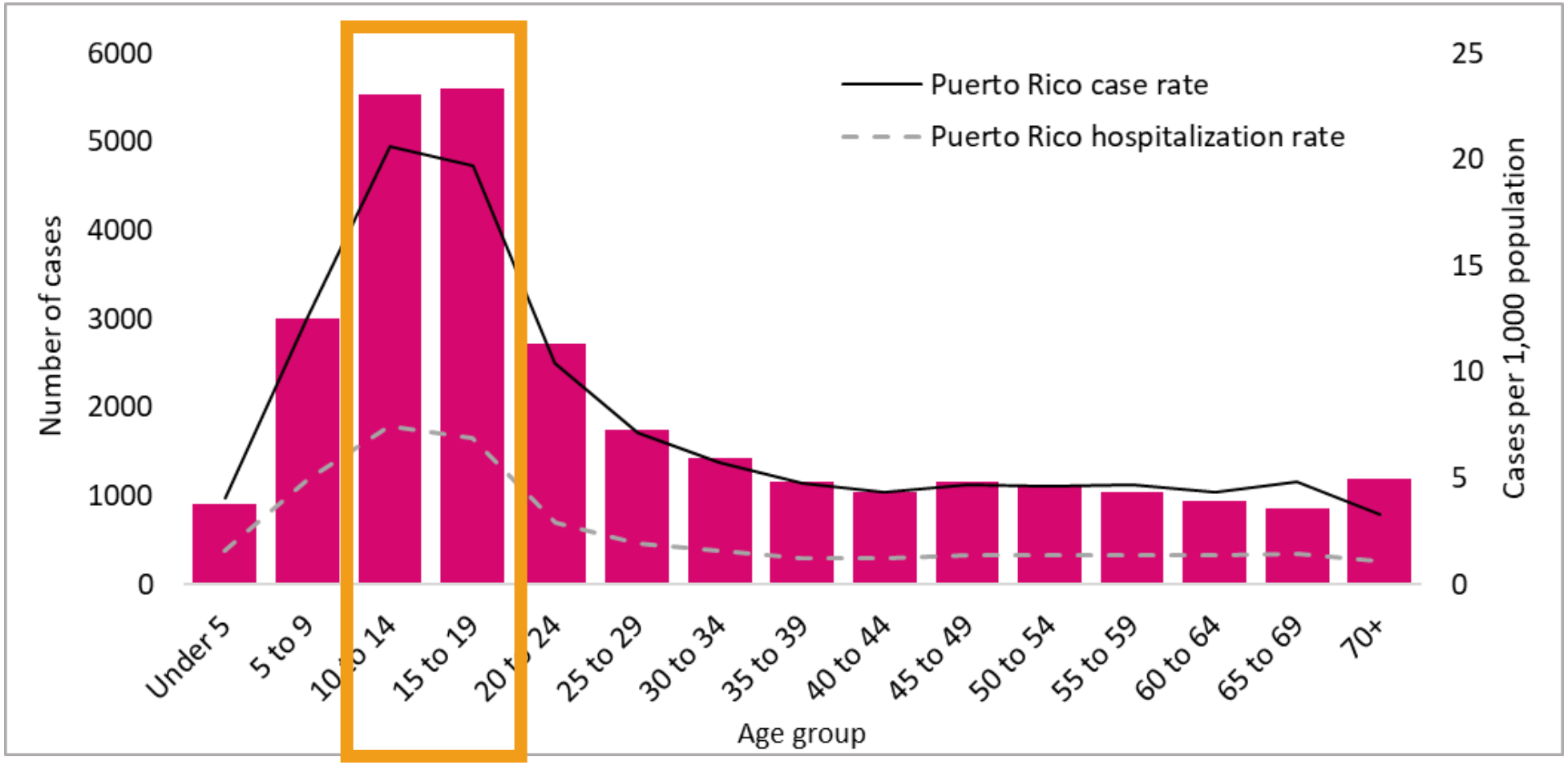
DENV serotypes by year in Puerto Rico, 2010–2020



Source: CDC Dengue Branch laboratory, unpublished data

Dengue cases and hospitalizations by age group in Puerto Rico, 2010–2020

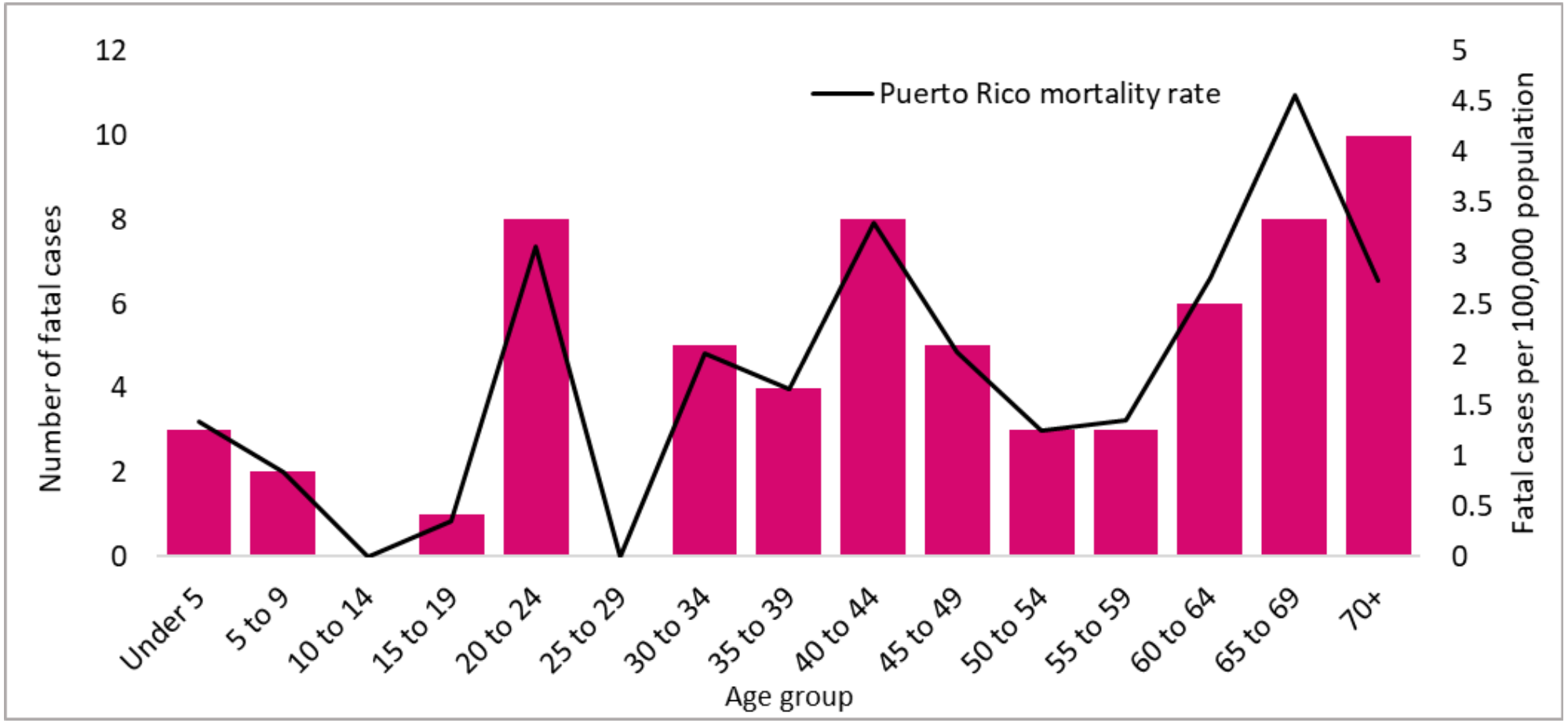
Highest case rates occurred among children 10–19 years old



Source: CDC ArboNET, unpublished

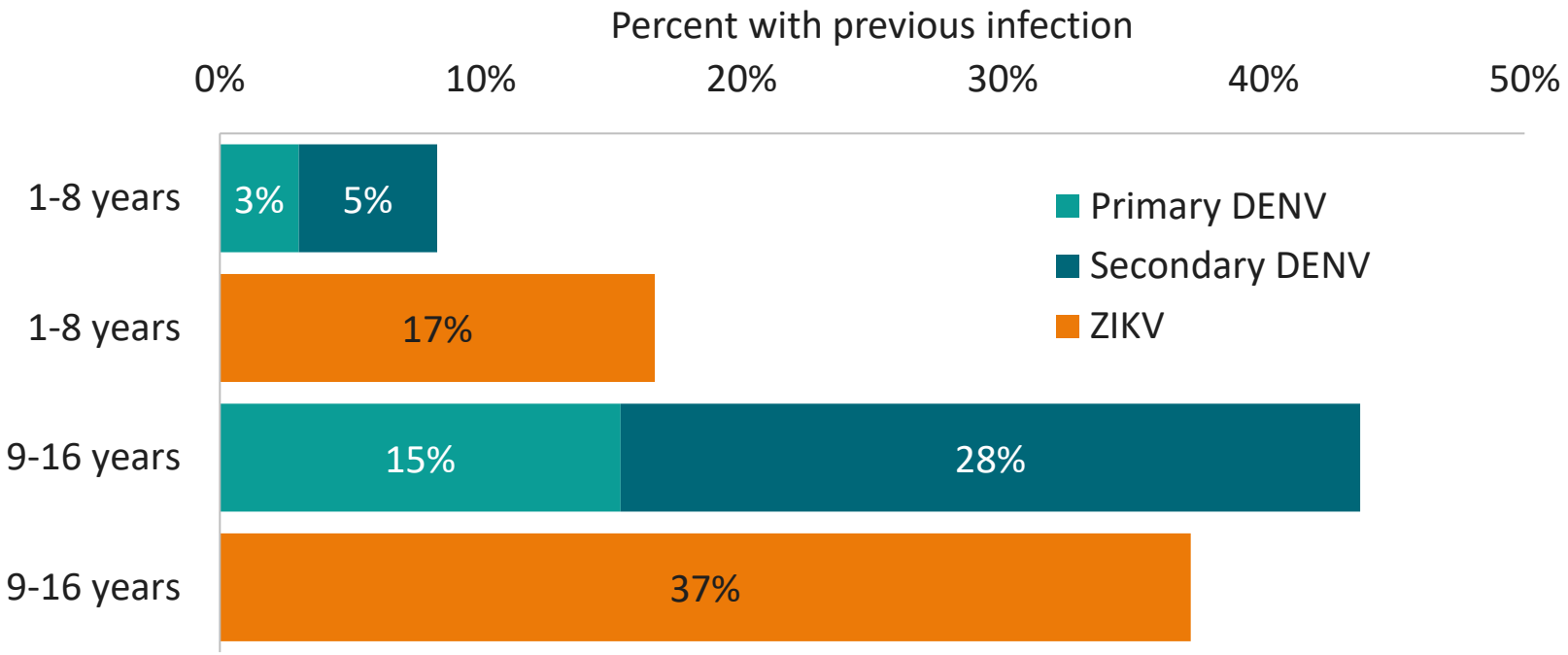
Fatal dengue cases by age group in Puerto Rico, 2010–2020

Higher mortality rates occurred among adults



Source: CDC ArboNET, unpublished

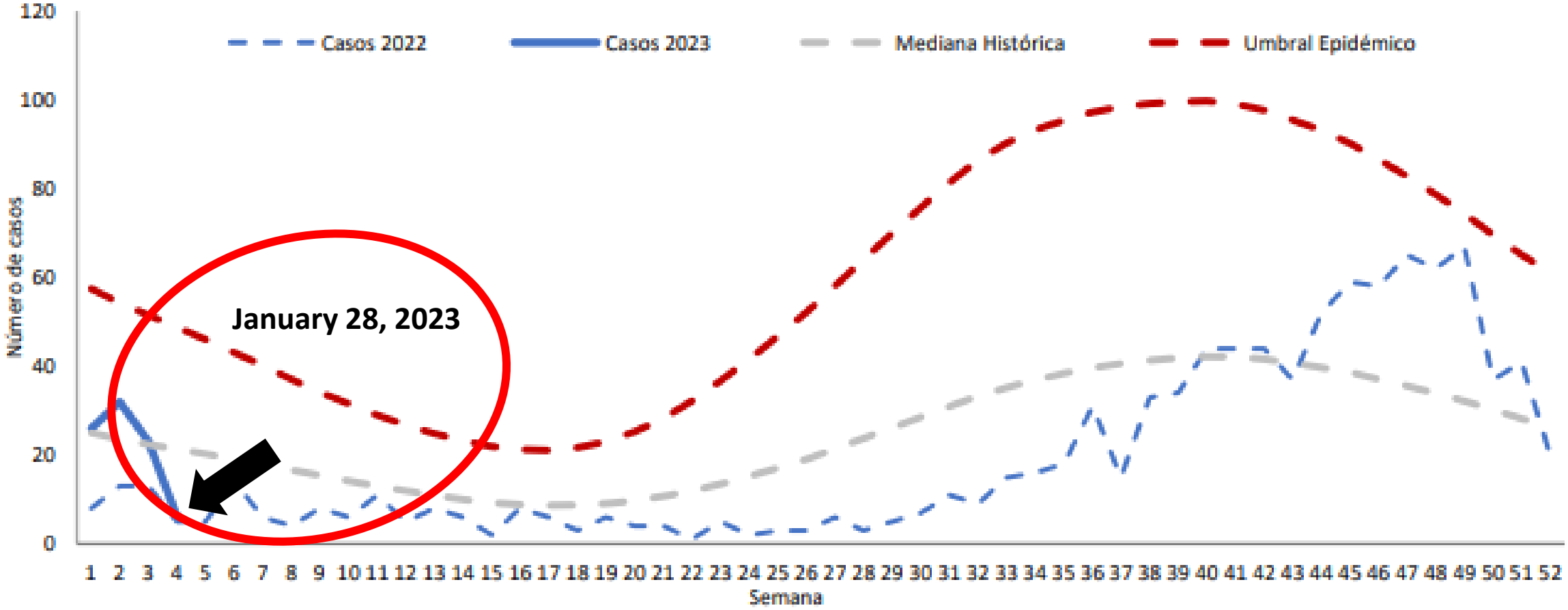
Previous DENV and ZIKV infection status among children 1–8 and 9–16 years old in southern Puerto Rico (n = 718), 2018–2019



8% of children 1–8 and **44%** of children 9–16 years old had evidence of previous DENV infection

Source: Communities Organized to Prevent Arboviruses (COPA) seroprevalence study, 2018–2019; unpublished data

Dengue cases reported in 2022–2023, Puerto Rico (1,155)†



*Información del Informe Semanal de Enfermedades Arbovirales – Semana 4. Departamento de Salud de Puerto Rico. Obtenido el 6 de energo de 2023 en https://www.salud.gov.pr/CMS/DOWNLOAD/7211 .

†1,022 casos confirmados con un resultado RT-PCR positivo y 133 casos probables con un resultado IgM positivo. Hay 94 casos sin información de serotipo.

Dengue in American Samoa

- 2010 serosurvey in American Samoa (adults only): 96% seropositive[1]
- 2016–2018 DENV-2 outbreak in American Samoa with over 1,000 confirmed cases[2]

[1]Duncombe J, Lau C, Weinstein P, Aaskov J, Rourke M, Grant R, Clements A. Seroprevalence of dengue in American Samoa, 2010. EID. 2013 Feb;19(2):324.

[2]Cotter CJ, Tufa AJ, Johnson S, Matai'a M, Sciulli R, Ryff KR, Hancock WT, Whelen C, Sharp TM, Anesi MS. Outbreak of Dengue Virus Type 2—American Samoa, November 2016–October 2018. Morbidity and Mortality Weekly Report. 2018 Nov 11;67(47):1319.

Dengue in US Virgin Islands

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

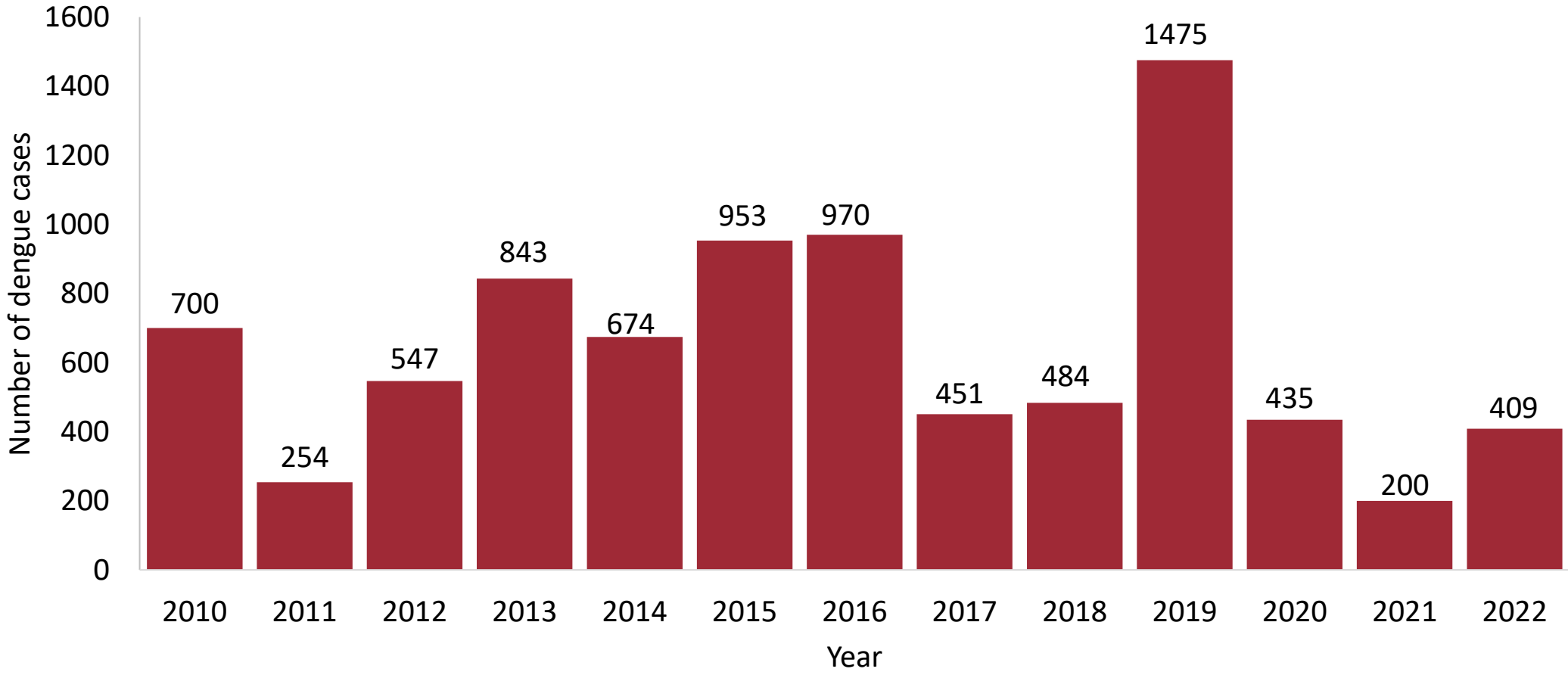
- Periodic outbreaks
  - 1986-1987 (DENV-2, -4), St. John
  - 1990 (DENV-1, -2, and -4), all islands
  - 2004 (DENV-2), St. Thomas
  - 2005 (DENV-2), St. Croix
  - 2012-2013 (DENV-1, -4), St. Croix

- School survey in 2022
  - ~50% seropositive

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

Dengue cases (N = 8,395) reported to ArboNET from US states by **year**, Jan 2010–Sept 2022*

Average 665 cases annually

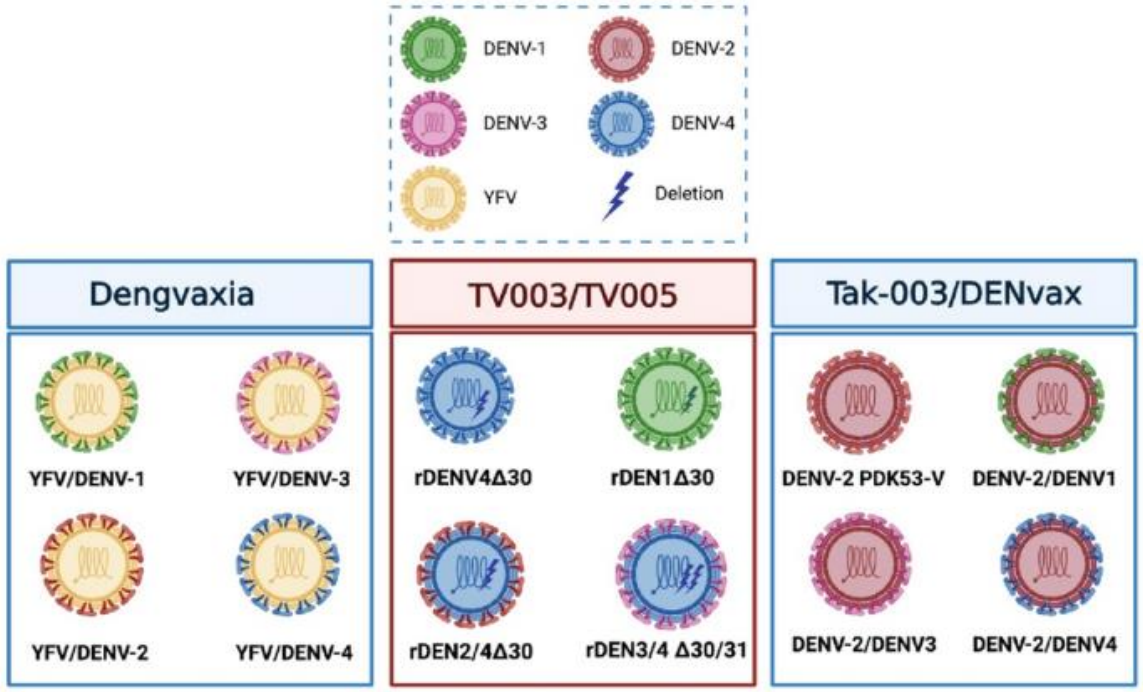


*2021–2022 numbers are preliminary and subject to change.

Dengue Vaccines

Challenges with DENV vaccines

- Need to provide protection against all serotypes.
- If the vaccine is imbalanced there is a risk to enhance disease for serotypes for which the vaccine has no efficacy.
- Evaluation of vaccines is challenging as different serotypes circulate at different times and places.
- Lack of a clear correlate of immune protection limits interpretation of immunobridging data.

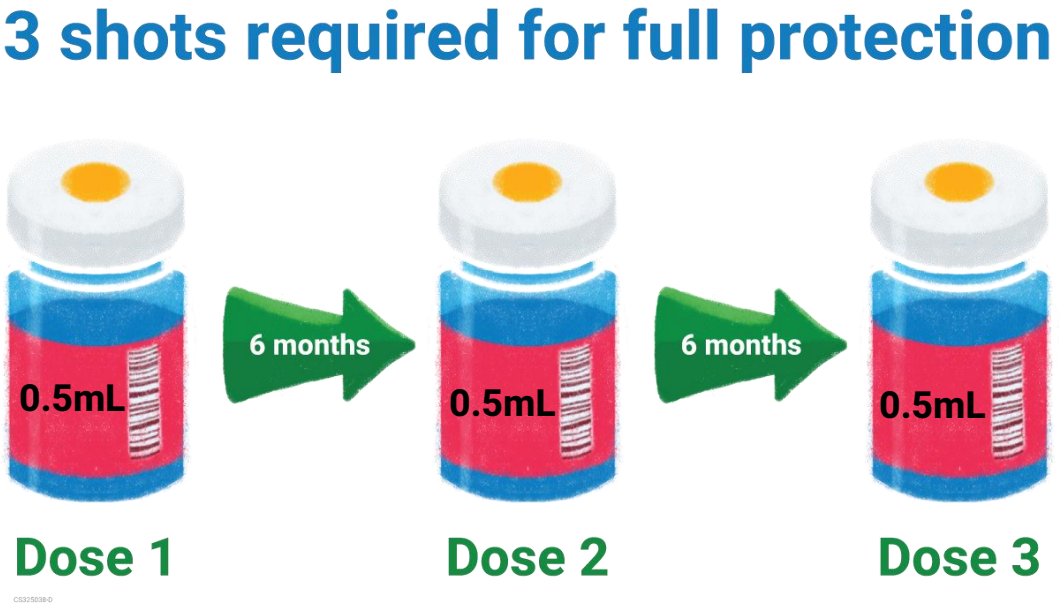


Molecular design of dengue vaccines that have been approved or are in advanced sages of clinical development. Torres Flores et al. BioDrugs, 2022.

ABOUT DENGVAXIA

Dengvaxia™ construct and schedule

- **Construct:** Tetravalent live attenuated vaccine on a yellow fever backbone with four chimeric viruses for each DENV serotype.
- **Schedule:**



For more information, visit:

- https://www.cdc.gov/dengue/vaccine/hcp/schedule-dosing.html
- https://www.cdc.gov/dengue/vaccine/hcp/storage-handling.html

Dengvaxia™ timeline

- 2015
  - Trial results showed increased risk of severe disease among 2–5-year-olds.
- 2016
  - WHO recommends the vaccine among children ≥9 years old in endemic areas.
- 2017
  - Additional testing showed increased risk of severe dengue and hospitalization among vaccinated seronegative children compared to controls.
  - WHO revised their recommendations to vaccinate children with laboratory-confirmed evidence of a past infection.

BENEFITS

Vaccine efficacy

Dengvaxia protects persons aged 9–16 years with **previous DENV infection against dengue, hospitalization, and severe disease.**

Outcome	Efficacy
Symptomatic virologically confirmed dengue*	82% (67-90)
Hospitalization for dengue**	79% (69-86)
Severe dengue**	84% (63-93)

*Followed over 25 months
**Followed over 60 months

Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. New England Journal of Medicine. 2018 2018-07-26;379(4):327-40.
Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. New England Journal of Medicine. 2015 2015-09-24;373(13):1195-206.

Dengvaxia protects persons aged 9–16 years **with previous DENV** infection **against all 4 serotypes.**

Serotype	Efficacy*
DENV-1	67% (46-80)
DENV-2	67% (47-80)
DENV-3	80% (67-88)
DENV-4	89% (80-94)

*Outcome of symptomatic virologically-confirmed disease.

Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. New England Journal of Medicine. 2018 2018-07-26;379(4):327-40.

HARMS

Vaccine safety

Dengvaxia™ and previous dengue infection

Clinical trials found **different outcomes after Dengvaxia™ vaccination** between children with and without previous dengue infection.

- Children **with previous dengue infection** were **protected from hospitalization and severe dengue** if they were vaccinated with Dengvaxia™.
- Children **without previous dengue infection** had a **higher risk hospitalization and severe dengue** if they were vaccinated and then had a DENV infection.

Risk of dengue hospitalization was greater in year 3 after vaccination, seronegative participants ages 9–16y

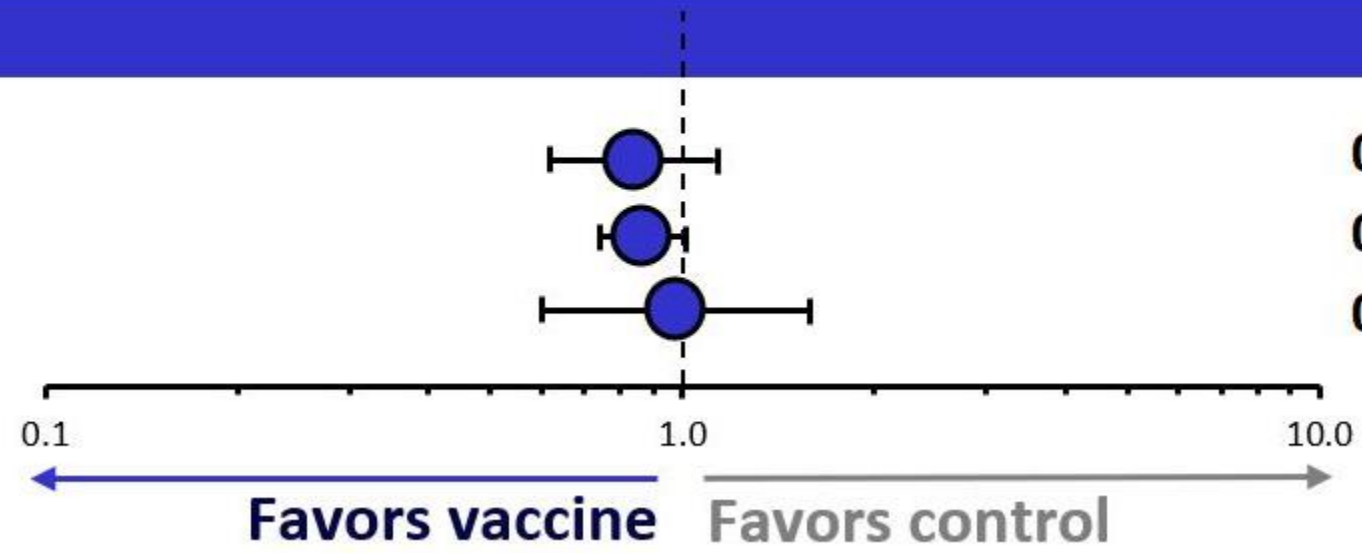
	CYD-TDV n/N	Placebo n/N	Hazard Ratio [95% CI]
Years			
Years 1 and 2	16/382	11/208	**0.85**[0.26 - 2.73]
Year 3	15/382	3/208	**2.64**[0.64 - 10.93]
Year 4	18/382	5/208	**1.68**[0.58 - 4.89]
Year 5 and 6	23/382	12/208	**1.12**[0.48 - 2.09]

Multiple imputation

Sanofi Pasteur, personal communication, March 15, 2021

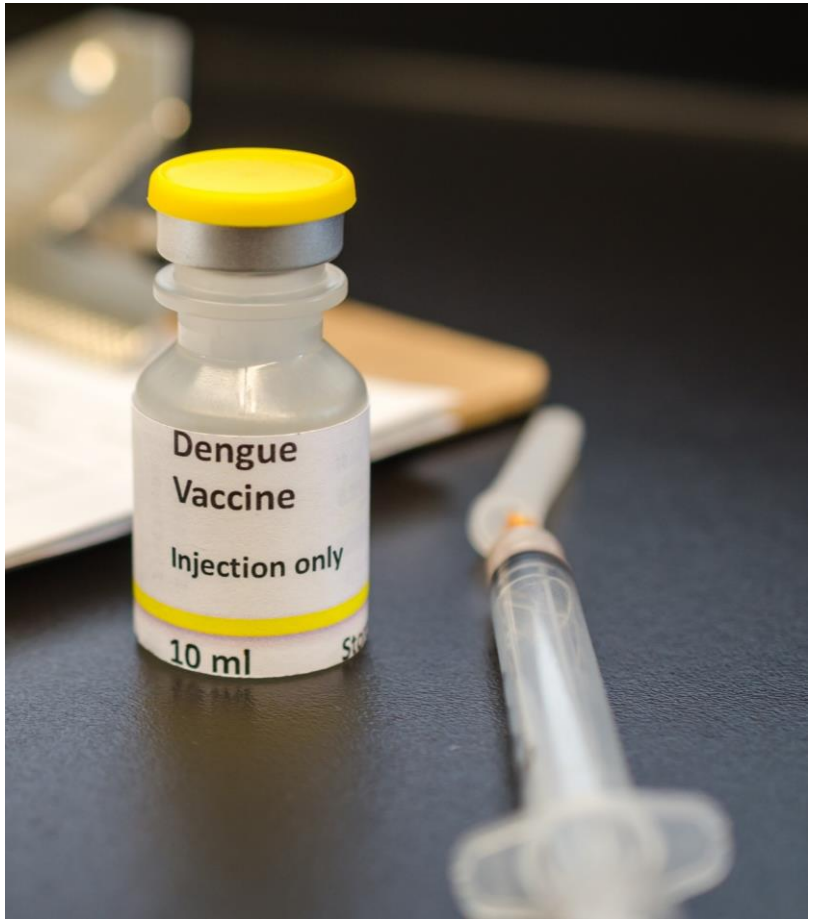
Serious adverse events and deaths among participants 9-16 years, serostatus combined

	Vaccine	Control	Relative Risk [95% CI]
Serostatus combined, 9-16			
SAE 28d	0.6	0.8	**0.84**[0.63 - 1.12]
SAE 6m	2.8	3.2	**0.86**[0.75 - 0.99]
Deaths	0.3	0.3	**0.97**[0.61 - 1.56]



Gustavo Dayan, Sanofi, personal communication.

FDA Licensure (2019) & ACIP Recommendation (2021)



Three doses of Dengvaxia are indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in people 9–16 years old with:

- laboratory confirmation of previous dengue virus infection

AND

- living in endemic areas.

Pre-vaccination testing

- **Approved tests are selected to be highly specific to minimize the risk of a false positive test.**
  - Avoid unintentional vaccination of a child without previous dengue virus infection.

Test Characteristic	Minimum
Sensitivity	≥ 75%
Specificity*	≥ 98%

Tests meeting pre-vaccination screening criteria

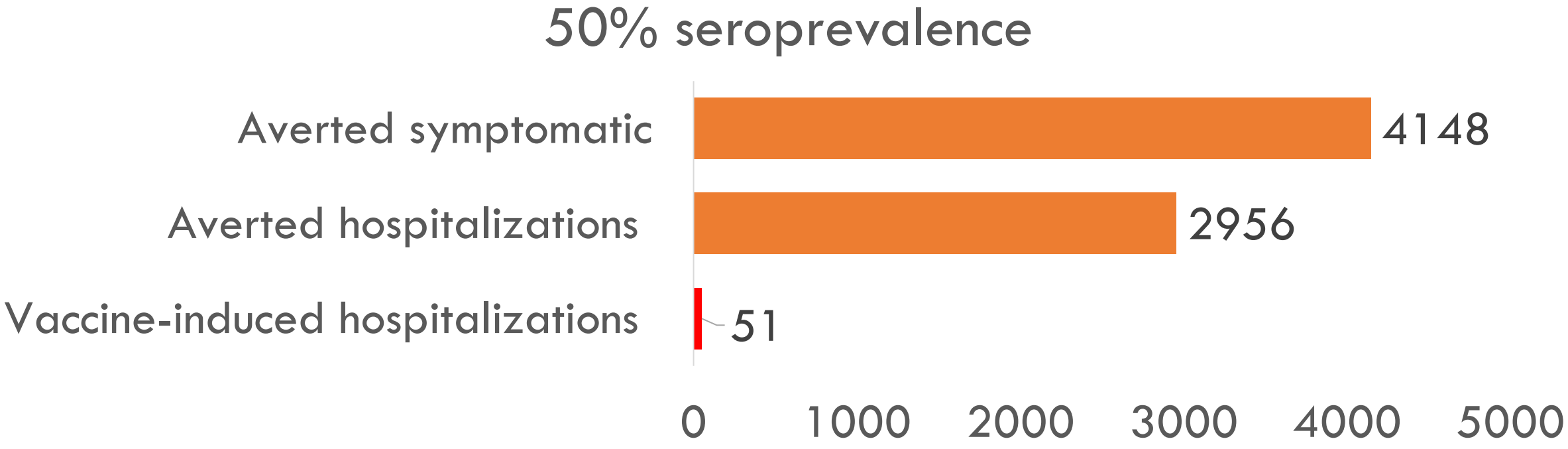
- **Two-test algorithm** with the following:
  - EUROIMMUN Anti-Dengue Virus NS1 Type 1-4 ELISA (IgG)
  - CTK BIOTECH OnSite Dengue IgG Rapid Test

- Positive results required on **both** tests for vaccination with Dengvaxia.

- Other tests meeting performance requirements might become available in the future. For the most up to date information, please visit https://www.cdc.gov/dengue/vaccine/hcp/testing.html

Benefits and harms of vaccination among a 10-year cohort of 9-year-old children 50% seroprevalence

Screening test 75% sensitive and 98% specific



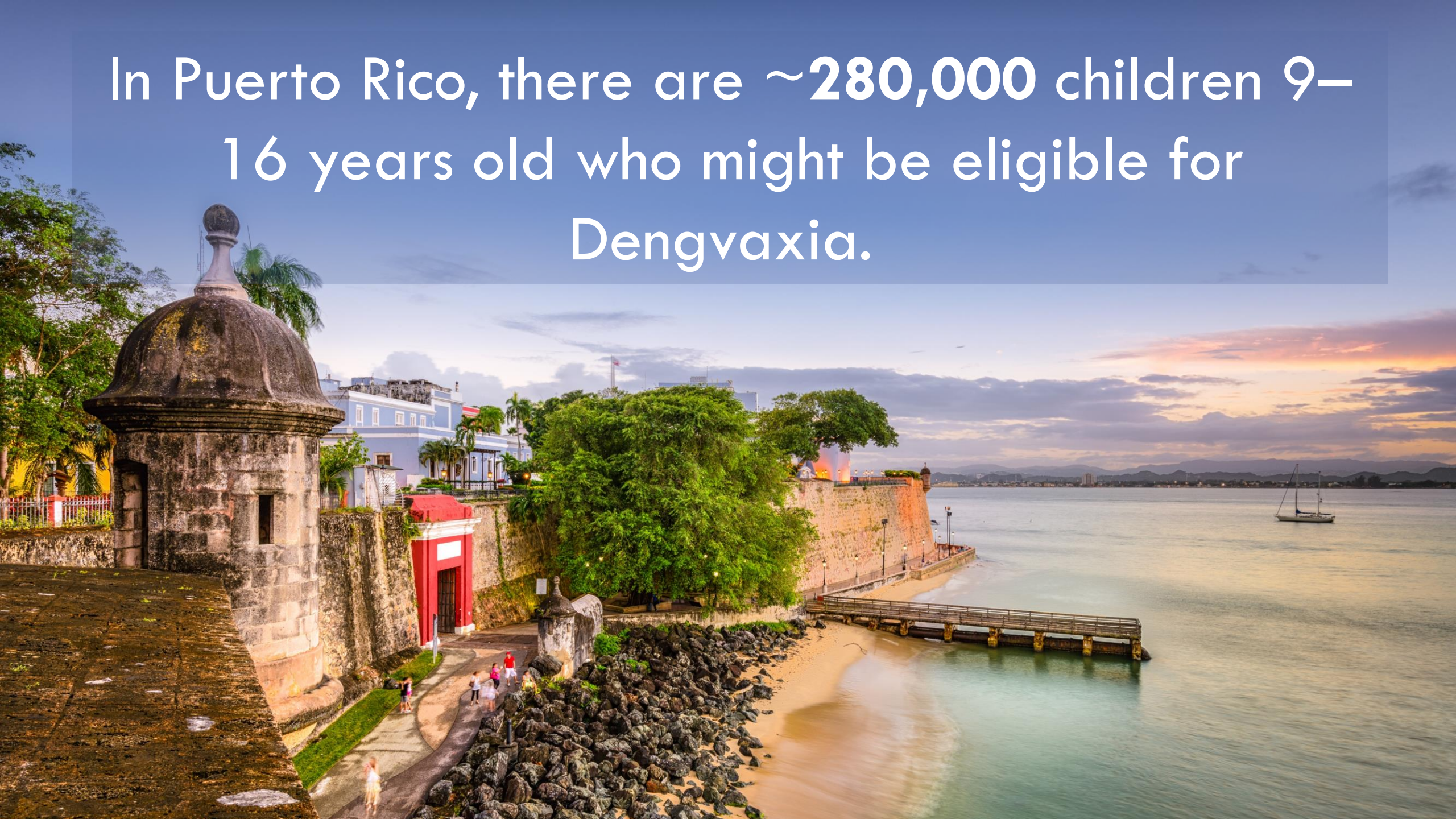
51 vaccine-induced hospitalizations in 102,884 vaccinees (completed series)

Espana G, Leidner A, Waterman S, Perkins A. Cost-effectiveness of Dengue Vaccination in Puerto Rico. https://www.medrxiv.org/content/10.1101/2020.10.07.20208512v1
Sensitivity and specificity modified by Espana G. for this presentation.

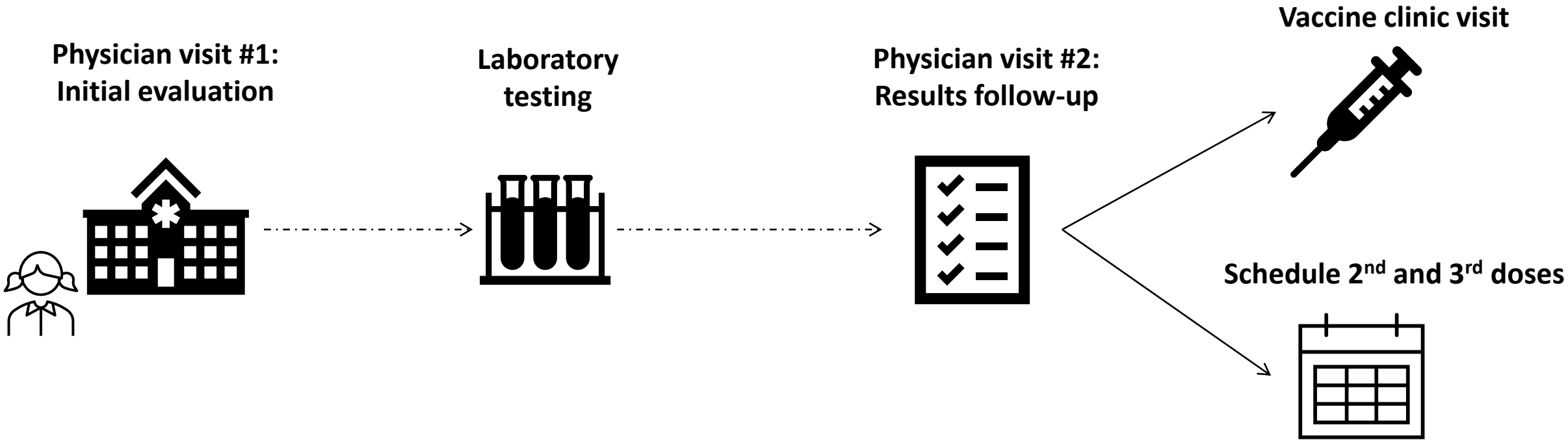
IMPLEMENTATION

Puerto Rico

In Puerto Rico, there are ~**280,000** children 9–16 years old who might be eligible for Dengvaxia.



Multiple visits to healthcare providers and/or the laboratory are required to determine eligibility for Dengvaxia ™ and start the series.



The first dengue vaccine in Puerto Rico was administered on September 7, 2022.

elVocero de Puerto Rico .com

Search...

DEN GOBIERNO DEPORTES ECONOMÍA ESCENARIO OPINIÓN PROGRAMAS

n la primera vacuna contra el

Pro Med en Santurce

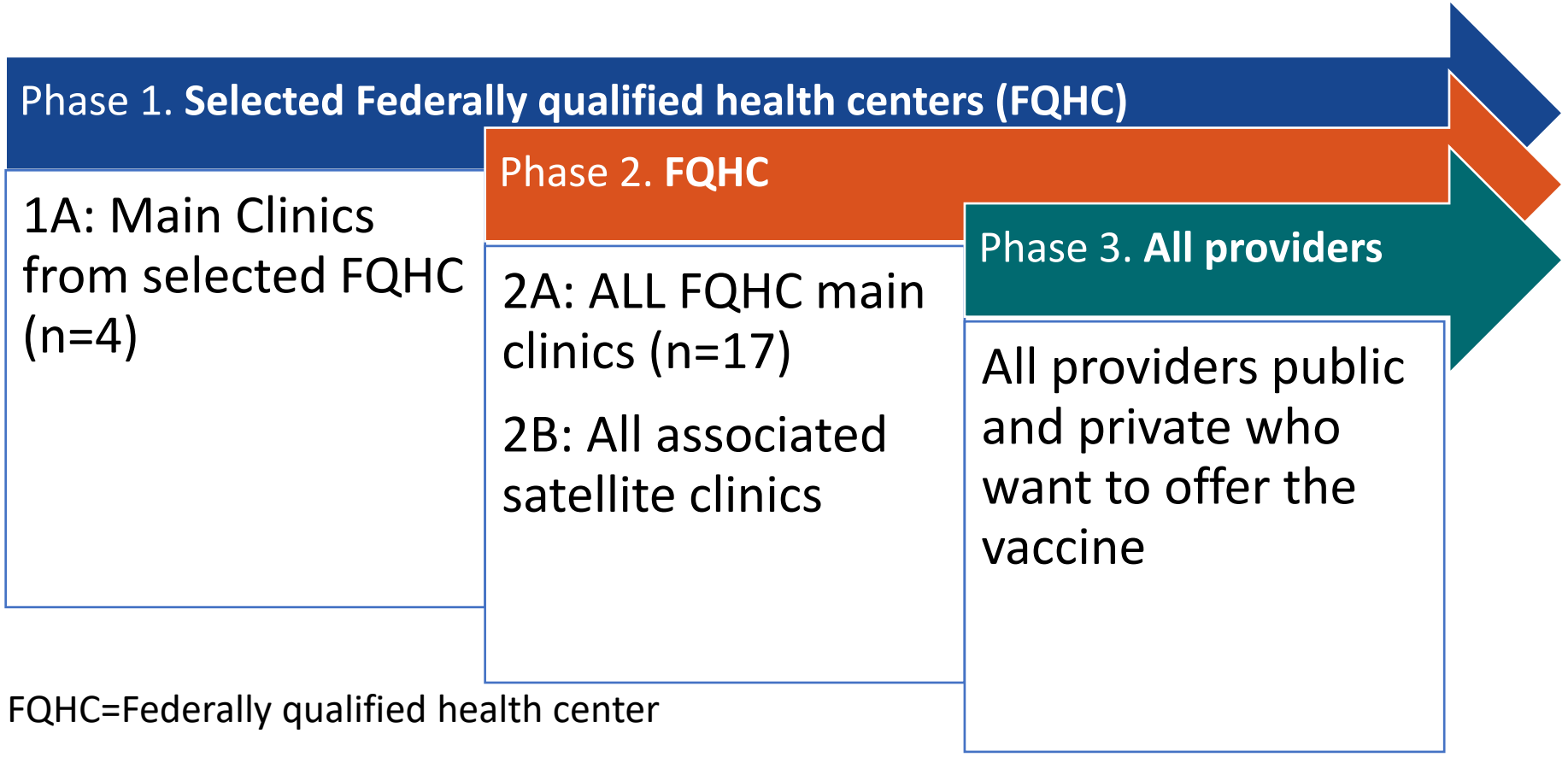
RO 07/09/2022 Actualizado hace 10 horas

Phased implementation in Puerto Rico

- **Phase 1 → Phase 2**
  - ❑ Three-month assessment of phase 1 providers complete

  Target date: November 2022
- **Phase 2 → Phase 3**
  - ❑ Three-month assessment of phase 2 providers complete

  Target Date: February 2023



FQHC=Federally qualified health center

Challenges for Dengvaxia implementation

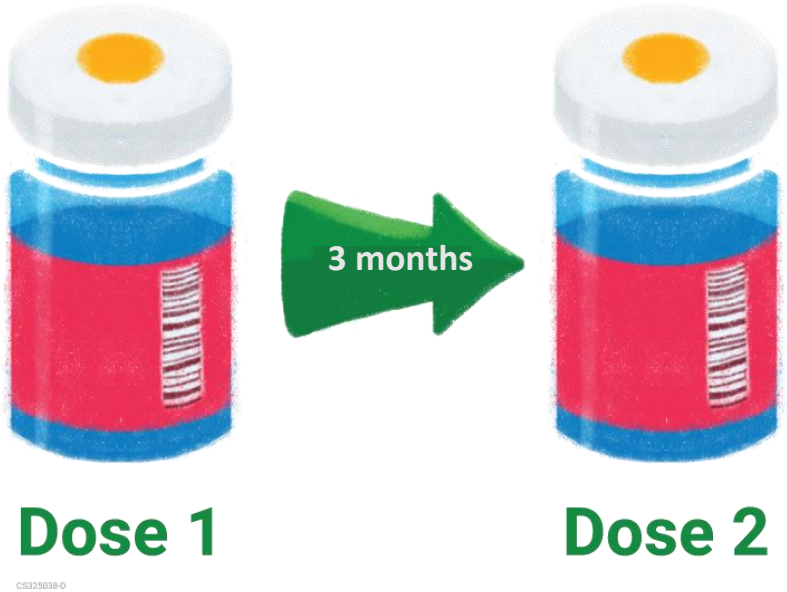
- Multiple visits before vaccination due to screening requirement.
- Tests not FDA approved implemented under CLIA.
- All testing in Puerto Rico should be conducted by a licensed technician.
- Messaging on a vaccine to prevent dengue only among seropositive.
- Insurance coverage for the test was challenging.
- Competing priorities like COVID-19 vaccination.

NEW VACCINE

Takeda TAK-003

TAK-003 Vaccine Construct and Schedule

- **Construct:** Tetravalent live attenuated DENV-2 virus backbone and three chimeric viruses expressing E and prM proteins of all four DENV serotypes.
- **Schedule:**



Wong JM, Adams LE, Durbin AP, Munoz-Jordan JL, Poehling KA, Sanchez-Gonzalez LM, et al. Dengue: A Growing Problem With New Interventions. Pediatrics. 2022 Jun 1;149(6).

TAK-003 (Takeda) Timeline

- In 2022 approved by European Medicine Agency for the prevention of dengue disease caused by any serotype in individuals 4 years of age and older.
- Approved for use in Indonesia and UK.
- Submitted to FDA and under review at ACIP and WHO SAGE, reccomendations expected at the end of 2023.

- **Other countries**
  - Plans to submit to regulatory agencies in Argentina, Brazil, Colombia, Malaysia, Mexico, Singapore, Sri Lanka, and Thailand.

- Takeda Pharmaceutical Company Limited. Takeda's QDENGA®▼ (Dengue Tetravalent Vaccine [Live, Attenuated]) Approved in Indonesia for Use Regardless of Prior Dengue Exposure. 2022 [updated August 22, 2022]; Available from: https://www.takeda.com/newsroom/newsreleases/2022/takedas-qdenga-dengue-tetravalent-vaccine-live-attenuated-approved-in-indonesia-for-use-regardless-of-prior-dengue-exposure/.

Vaccine Efficacy* Outcome: **Virologically Confirmed Dengue**

Overall VE

61.2% (56.0, 65.8%)

VE in Seropositives

64.2% (58.4, 69.2%)

VE in Seronegatives

53.5% (41.6–62.9%)

VE in Seropositives by Serotype		
DENV-1	**56.1%**	**(44.6, 65.2%)**
DENV-2	**80.4%**	**(73.1, 85.7%)**
DENV-3	**52.3%**	**(36.7, 64.0%)**
DENV-4	**70.6%**	**(39.9, 85.6%)**

VE in Seronegatives by Serotype		
DENV-1	**45.4%**	**(26.1, 59.7%)**
DENV-2	**88.1%**	**(78.6, 93.3%)**
DENV-3	-15.5%	(-108.2, 35.9%)
DENV-4	-105.6%	(-628.7, 42.0%)

*57 months after first dose, significant results **bolded.** Number for seropositive placebo participants 4,855 and vaccine 9,666; Seronegative placebo 1,832 and vaccine 3,714.

Unpublished data presented by Takeda to ACIP and ASTMH

Vaccine Efficacy* Outcome: **Hospitalization**

Overall VE

84.1% (77.8, 88.6%)

VE in Seropositives

85.9% (78.7, 90.7%)

VE in Seronegatives

79.3% (63.5, 88.2%)

VE in Seropositives by Serotype

DENV-1	**66.8% (37.4, 82.3%)**
DENV-2	**95.8% (89.6, 98.3%)**
DENV-3	**74.0% (38.6, 89.0%)**
DENV-4	**100% (NE, NE)†**

†DENV-4 Placebo events: 3 TAK-003 events: 0

VE in Seronegatives by Serotype

DENV-1	**78.4%**	**(43.9, 91.7%)**
DENV-2	**100%**	**(NE, NE)§**
DENV-3	-87.9%	(-573.4, 47.6%)¶
DENV-4	100 %	(NE, NE)**

§DENV-2 Placebo events: 23 TAK-003 events: 0
¶DENV-3 Placebo events: 3 TAK-003 events: 11
**DENV-4 Placebo events: 1 TAK-003 events: 0

*57 months after first dose, significant results **bolded.** Number for seropositive placebo participants 4,855 and vaccine 9,666; Seronegative placebo 1,832 and vaccine 3,714.

Unpublished data presented by Takeda to ACIP and ASTMH

Vaccine safety

- **Solicited AEs were higher among recipients of TAK-003** compared to placebo.*
  - Local: TAK-003 43%; placebo 26%
  - General: TAK-003 46%; placebo 40%

- **Unsolicited AEs were similar** between recipients of TAK-003 and placebo.*
  - Common TAK-003 unsolicited AEs:
    - injection site pruritus (0.7%)
    - bruising (0.6%)
    - pyrexia (0.2%)

*Adverse events were analyzed using the safety set.

Vaccine safety: serious adverse events (SAE)

- **SAEs were similar** among recipients of TAK-003 (8%) and placebo (10%).
  - 1 TAK-003 and 4 placebo recipients had SAEs related to the intervention

- **Common SAEs** (>0.2%) among recipients included:
  - **Dengue fever** (TAK-003: 0.5%; placebo: 2%).
  - **Dengue hemorrhagic fever** (TAK-003: 0.1%; placebo 0.5%).

- Incidence of death was 0.1% in both TAK-003 (n=16) and placebo (n=9) recipients.
  - **No deaths attributed to TAK-003.**

NEW VACCINE

TV003

TV003 Vaccine Construct and Schedule

- **Construct:** Tetravalent, live-attenuated vaccine. Attenuated DENV1, DENV3 and DENV4 and a chimeric virus for DENV2 on a DENV4 backbone.

- **Schedule:**

Dose 1

Wong JM, Adams LE, Durbin AP, Munoz-Jordan JL, Poehling KA, Sanchez-Gonzalez LM, et al. Dengue: A Growing Problem With New Interventions. Pediatrics. 2022 Jun 1;149(6).

TV003 (Merck / Butantan Institute) Status

- Developed by the US National Institutes of Health (NIH).
- Licensed to Merck in the U.S. and the Instituto Butantan in Brazil.
- Phase 3 trials in Brazil ongoing, 2-year follow-up recently released.
  - Efficacy against VCD was 89% for seropositives and 73% seronegatives.
  - Higher efficacy for seropositive than seronegative (DENV1 97% and 86%, DENV2 84% and 58%).
  - Estimated study completion August 2024.

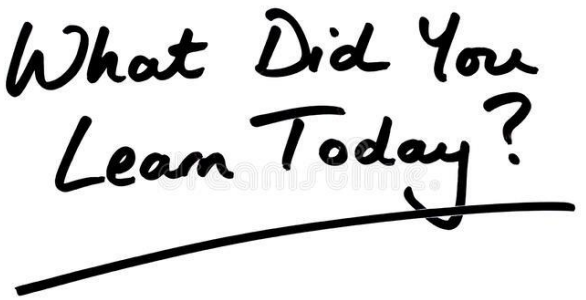
Wong JM, Adams LE, Durbin AP, Munoz-Jordan JL, Poehling KA, Sanchez-Gonzalez LM, et al. Dengue: A Growing Problem With New Interventions. Pediatrics. 2022 Jun 1;149(6).
Phase III Trial to Evaluate Efficacy and Safety of a Tetravalent Dengue Vaccine. [September 7, 2022]; Available from: https://clinicaltrials.gov/ct2/show/results/NCT02406729.

	Dengvaxia™ (Sanofi Pasteur)	TAK-003 (Takeda)	TV003 (Merck / Butantan Institute)
Currently available in U.S.	✓	✗	✗
Status	Recommended by ACIP*	Submitted to FDA	Phase 3 trials
Number of doses	3	2	1
Ages eligible	9–16 years	4+	2+
Prevaccination screening required*	✓	?	?

*only recommended for individuals with previous DENV infection confirmed by laboratory test including serology (i.e., antibody testing), positive RT-PCR during acute dengue infection, or positive NS1 during acute infection.

Summary

- Dengue viruses are transmitted by mosquitoes, most common arbovirus globally.
- The second dengue infection with a heterologous virus has the highest risk of severe disease.
- Dengue is **endemic** in **six** US territories and freely associated states.
- Dengvaxia vaccine approved for children 9-16 years who had dengue before and may increase risk of severe disease if administered to seronegatives.
- A second dengue vaccine, TAK-003, is currently under review at FDA and ACIP.
- A third dengue vaccine, TV003, is in phase 3 trials.

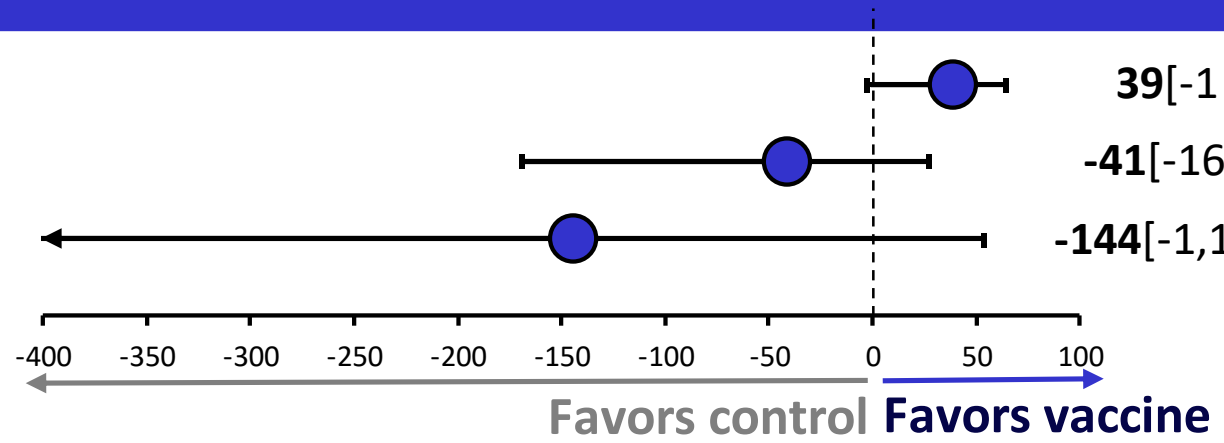


Thank you

ACIP Dengue Vaccine Workgroup
Laura Adams, CDC
Josh Wong, CDC

Higher risk of hospitalization and severe disease following vaccination in seronegative children aged 9–16 years

	Vaccine	Control	Vaccine Efficacy [95% CI]
Seronegative subjects	**Incidence Rates**		
Symptomatic Dengue	5.41	8.28	**39**[-1 - 63]
Dengue Hospitalization	1.57	1.09	**-41**[-168 - 26]
Severe Dengue	0.40	0.17	**-144**[-1,156 - 53]



Note: Vaccine efficacy from hospitalization and severe dengue, calculated from hazard ratios (VE=(1-HR)*100). Cumulative incidence rates among seronegative participants calculated through month 25 for virologically confirmed symptomatic dengue and through month 60 for hospitalization and severe dengue.

Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340

Dengvaxia serious adverse events

- Vaccine: urticaria, asthma, acute polyneuropathy, tension headache, severe dengue, polymyalgia rheumatica, severe dengue, dengue hospitalization, acute disseminated encephalomyelitis
- Placebo: visual impairment, miscarriage, nerve paralyses, angioedema

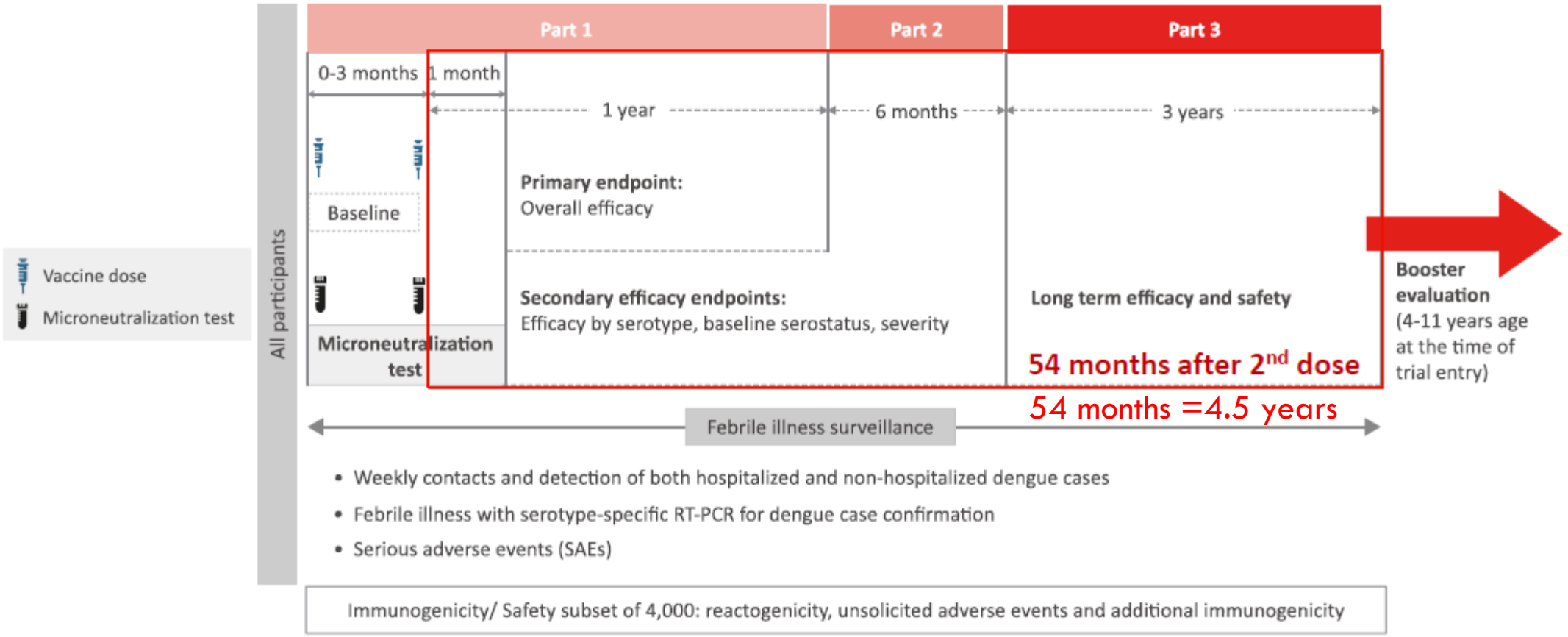
Dengvaxia side effects

- Most common side effects within 14 days following vaccination include:
  - Headache
  - Injection site pain
  - Myalgias
  - Malaise
  - Asthenia
- No difference between placebo and control arm

Takeda Trial Design

DEN-301: Pivotal study design

20,071 children (aged 4–16 years) received either TAK-003 or placebo in a 2:1 ratio[1,2]



Dengvaxia Trial Design

Design: Participants were randomly assigned to Dengvaxia or placebo in a 2:1 ratio in CYD14 and CYD15.

CYD14: 10,275 participants aged 2–14 years in the Asia-Pacific region

CYD15: 20,869 participants aged 9–16 years in Latin America

Baseline Serostatus: Determined in ~2000 children at trial entry