



# Arboviral Diseases: Updates in Dengue & Chikungunya Vaccination

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Delaware Immunization Summit

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# Disclosures

- No financial or other conflicts of interest.

*I may use vaccine manufacturer or trade names, for identification purposes only.*



# What is an Arbovirus?

- Arbovirus = **arthropod-borne virus**
- Transmitted primarily via bites of arthropods
  - Mosquitos, ticks, sandflies, midges
- Some may *also* be spread via blood transfusion, organ/bone marrow transplantation, needlestick, sexual contact, perinatally (including breastfeeding)

California encephalitis  
Chikungunya  
Dengue  
Eastern equine encephalitis (EEE)  
Japanese encephalitis  
Powassan  
St. Louis encephalitis  
Tick-borne Encephalitis  
West Nile  
Yellow Fever  
Zika  
...and others

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- Human vaccines have been developed for several

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**Chikungunya**

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St. Louis encephalitis

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West Nile

**Yellow Fever**

Zika

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# DENGUE VIRUS DISEASE

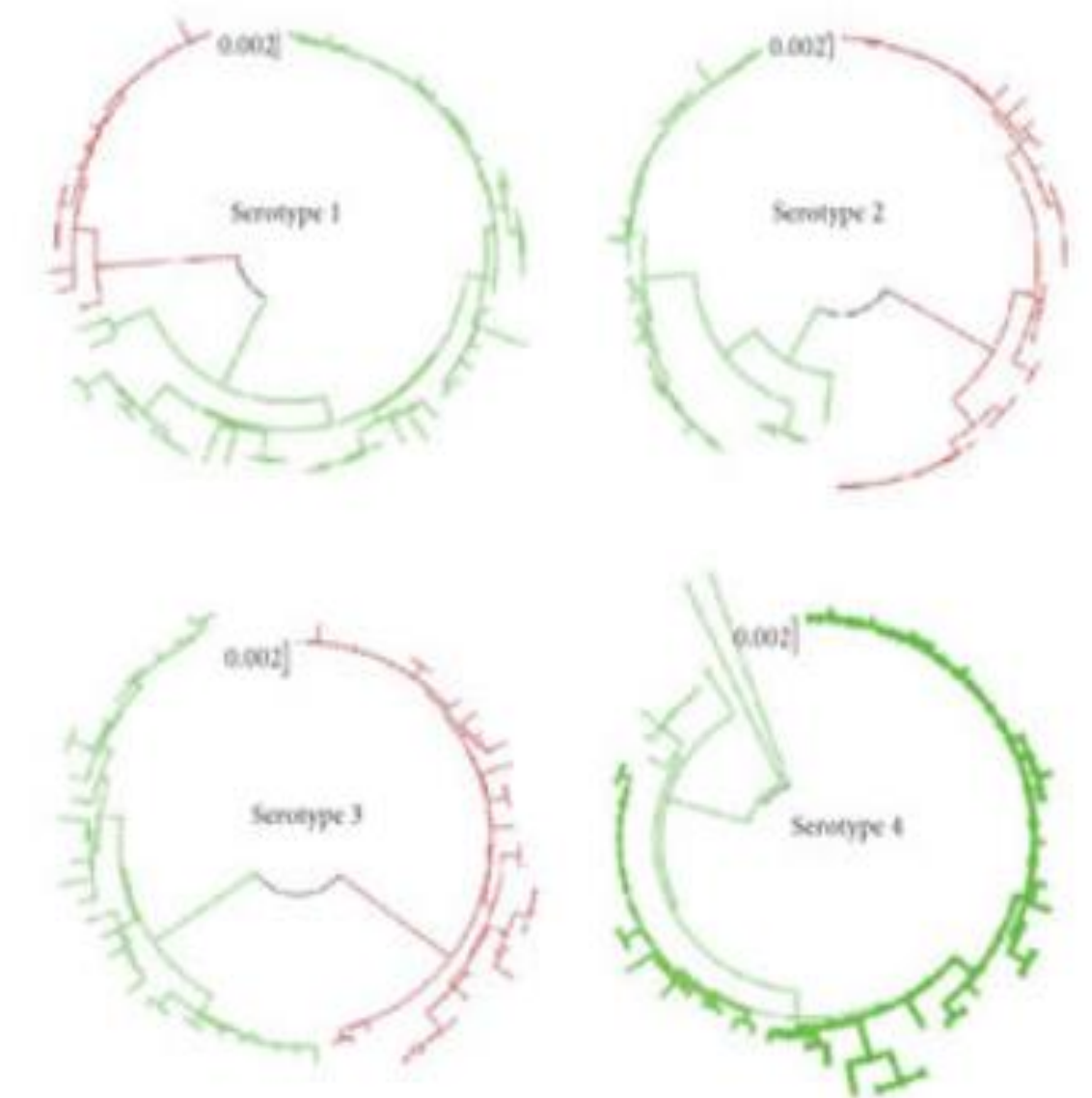
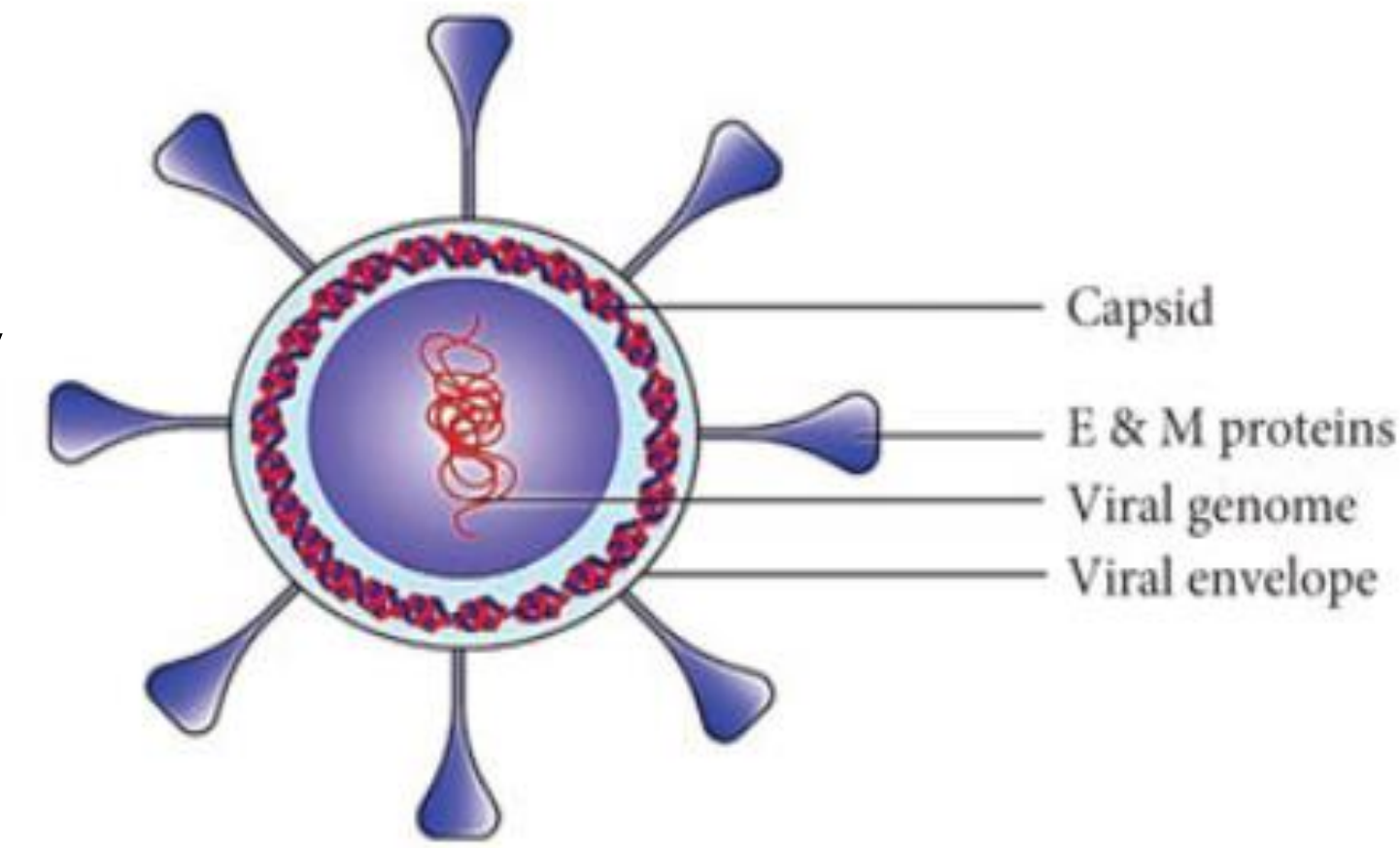
# Dengue Virology

- Dengue illness caused by any of 4 distinct but closely related dengue viruses (DENV)
  - DENV-1, DENV-2, DENV-3, DENV-4
- Infection leads to lifelong type-specific immunity but only short-term (months to <2 years) cross-immunity
- Individuals may be infected up to 4 times
  - 60-80% infections asymptomatic
- Spread by saliva of *Aedes* species mosquitoes



- Not transmitted person-to-person
  - Maternal-fetal (rare)
  - Transfusion/transplant/needlestick injuries
  - Sexual transmission reported

Photo courtesy of CDC



Islam MT, et al. *Biomed Res Internat* 2021

# Dengue Virus Illness

## Dengue Fever

- Fever
- **Retroorbital pain**
- Myalgias/arthralgias
- Nausea & vomiting
- Rash
- Sx typically last 2-7 days and resolve on their own

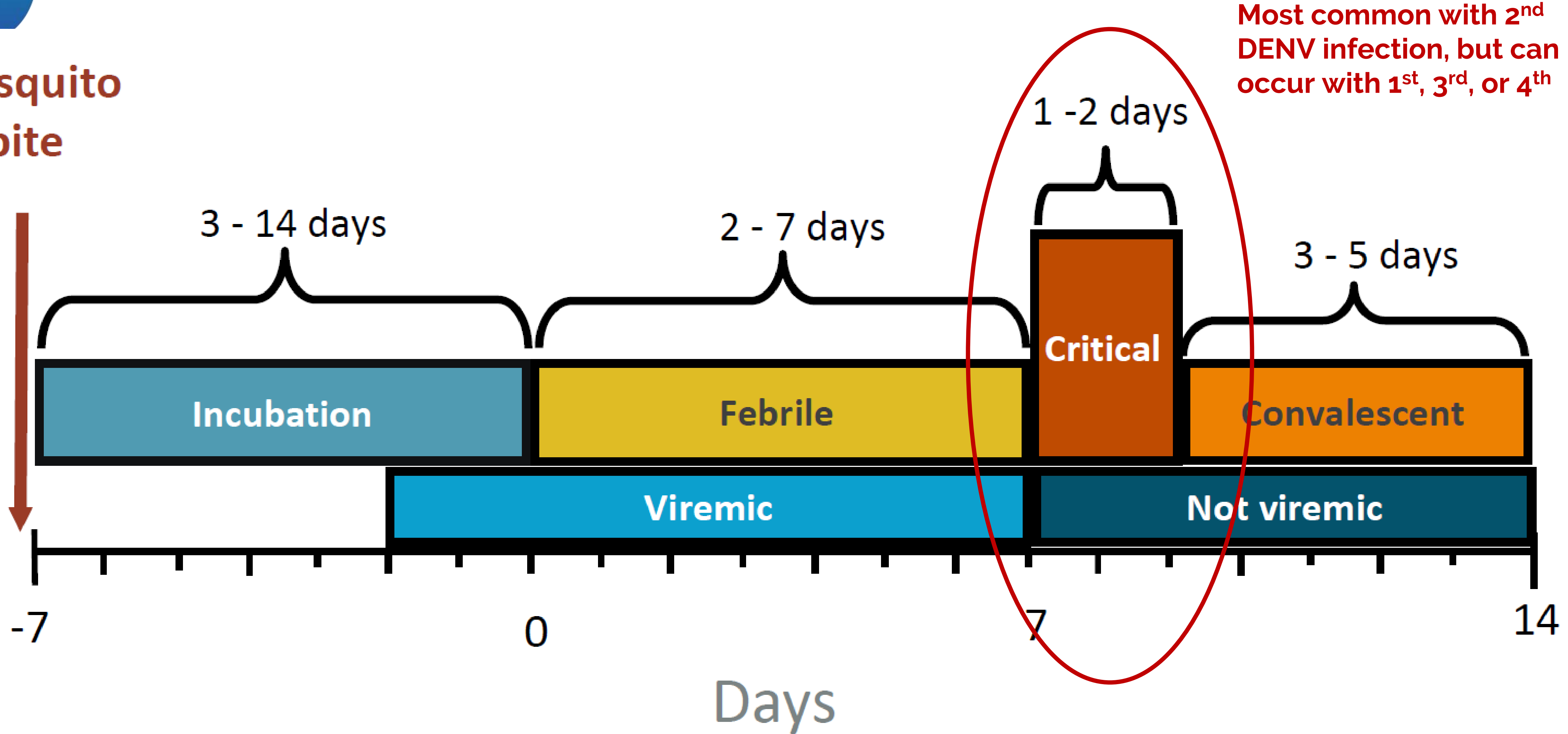


## Severe Dengue (Hemorrhagic Fever) – 5%

- **Medical emergency** – warning signs:
  - Intense abdominal pain or tenderness
  - Persistent vomiting
  - Fluid accumulation (pleural or pericardial effusion, ascites)
  - Mucosal bleeding (nose, gums, vagina, GI, kidney)
  - Altered mental status (irritability, drowsiness)
  - Hepatomegaly
  - Progressive increase in hematocrit (2 measurements taken 6hr apart)
  - Can progress to shock, end-organ impairment, death
- Warning signs usually begin 24-48 hours after fever has resolved

# Clinical Course

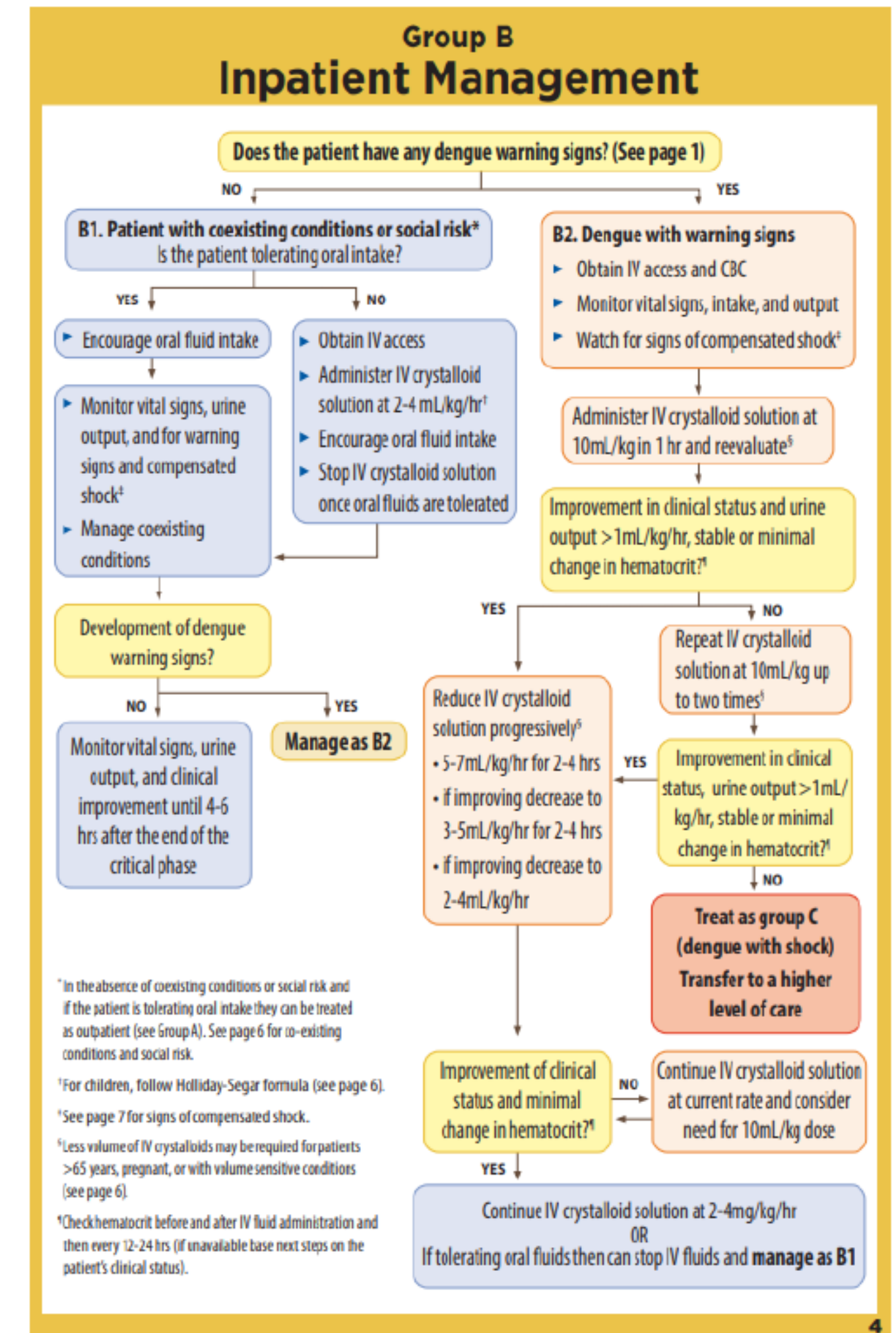
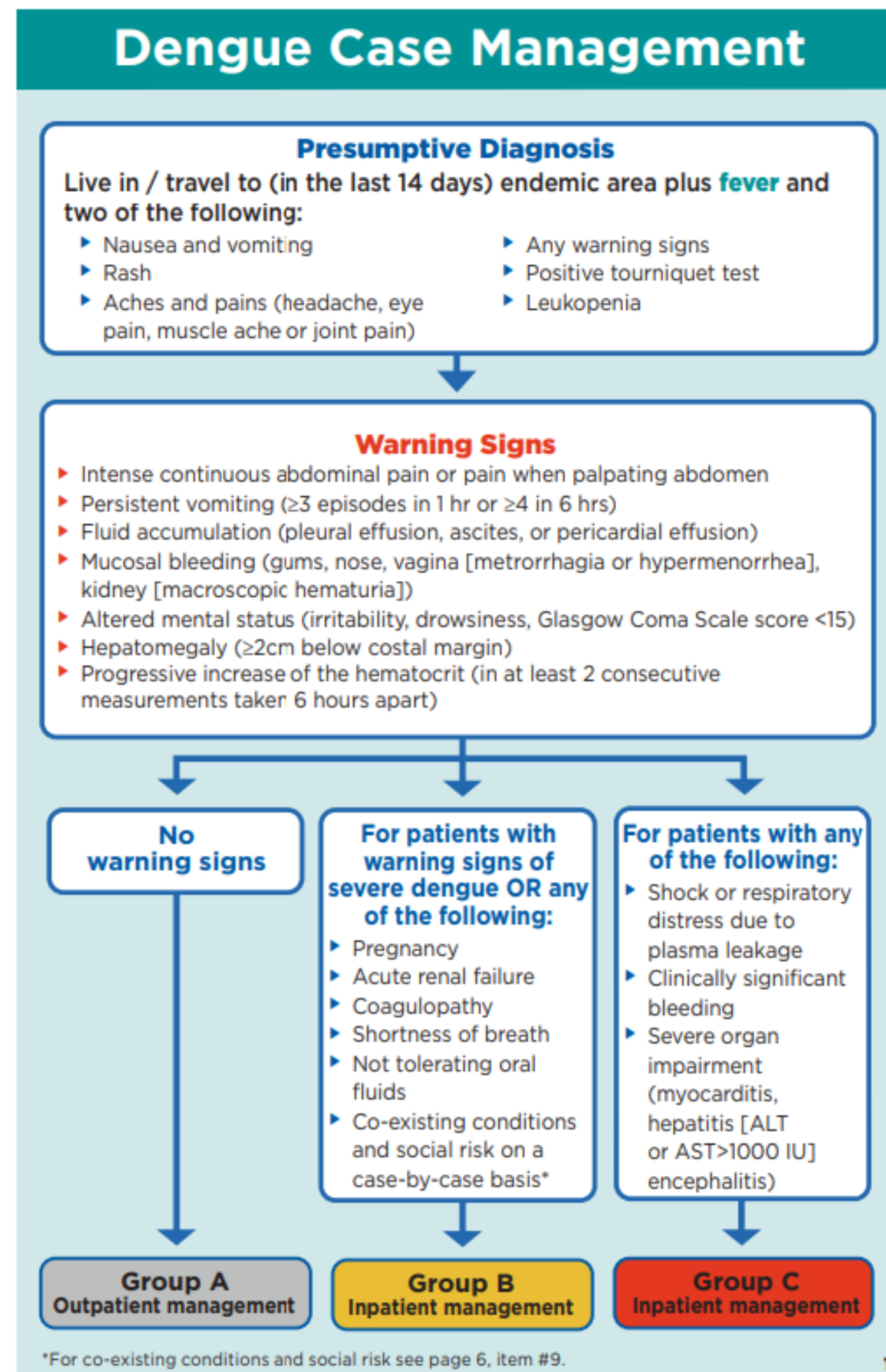
Mosquito bite





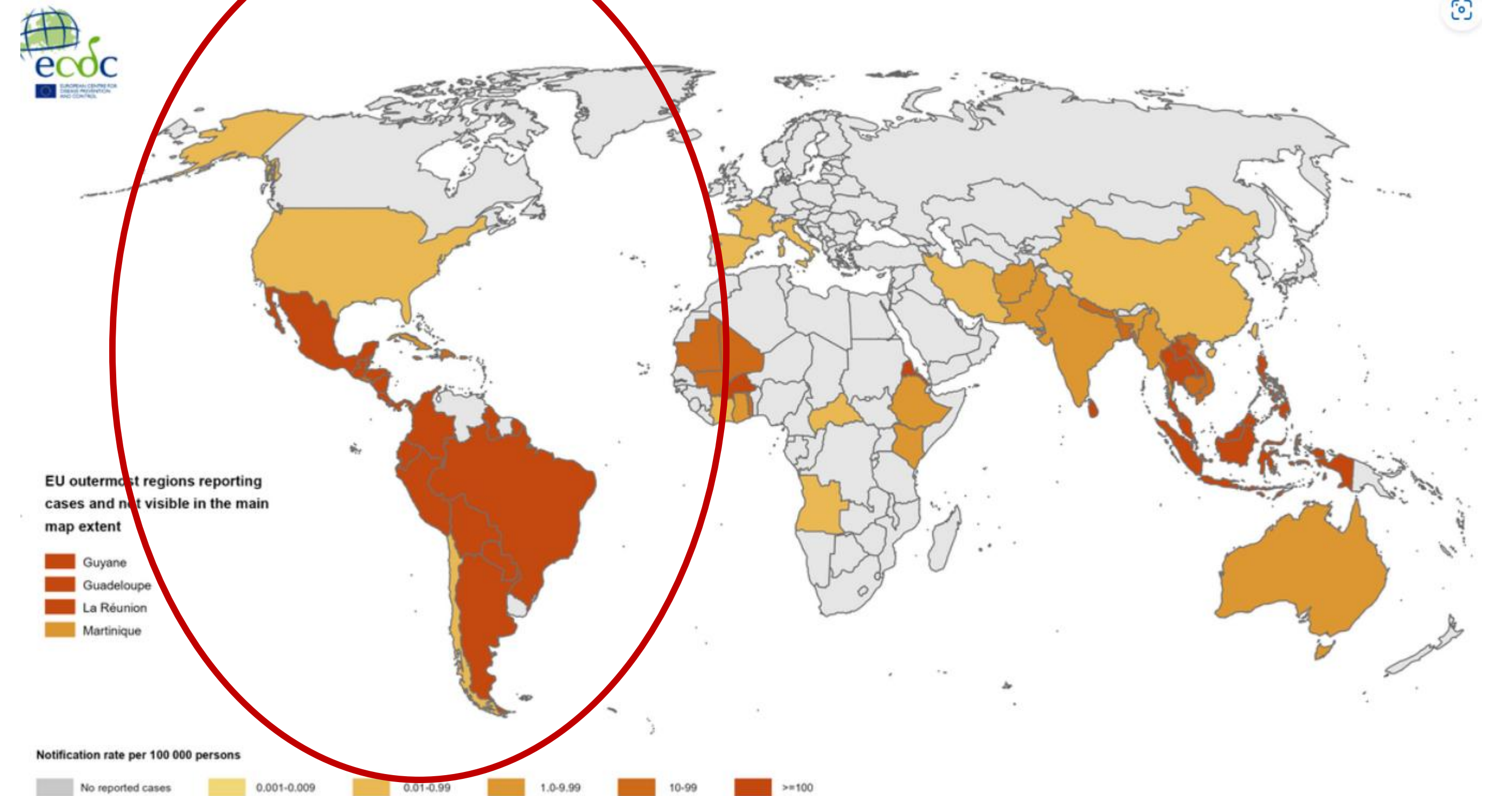
# Dengue: Treatment

- No specific antiviral available
- Standard of care: protocolized IV fluid management (WHO guidelines)
- Up to 13% mortality if severe disease untreated → <0.05% with appropriate management



# Global Dengue

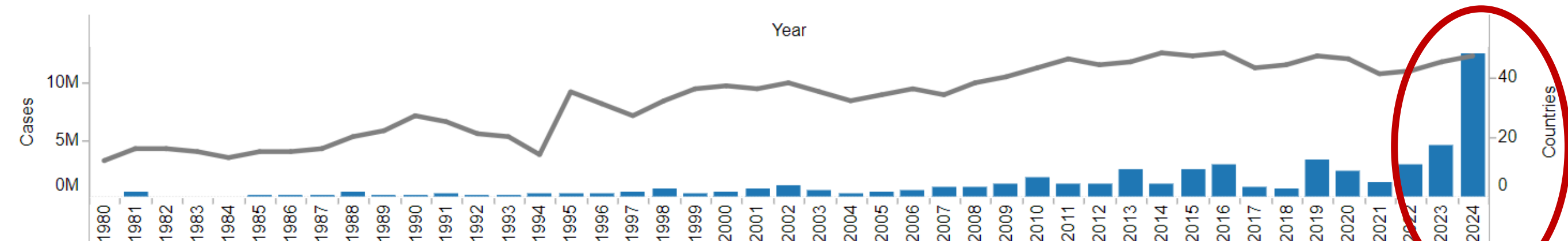
- Year-round risk in many countries, with outbreaks commonly every 2-5 yr
- 2024: >13 million cases worldwide
  - >8500 deaths
  - 3X cases reported in 2023
- >20 countries reporting outbreaks; 103 countries/territories with reported cases
- June 2024: CDC issued global Level 1 travel notice (“practice usual precautions”)
  - Mosquito bite prevention



Dengue Cases

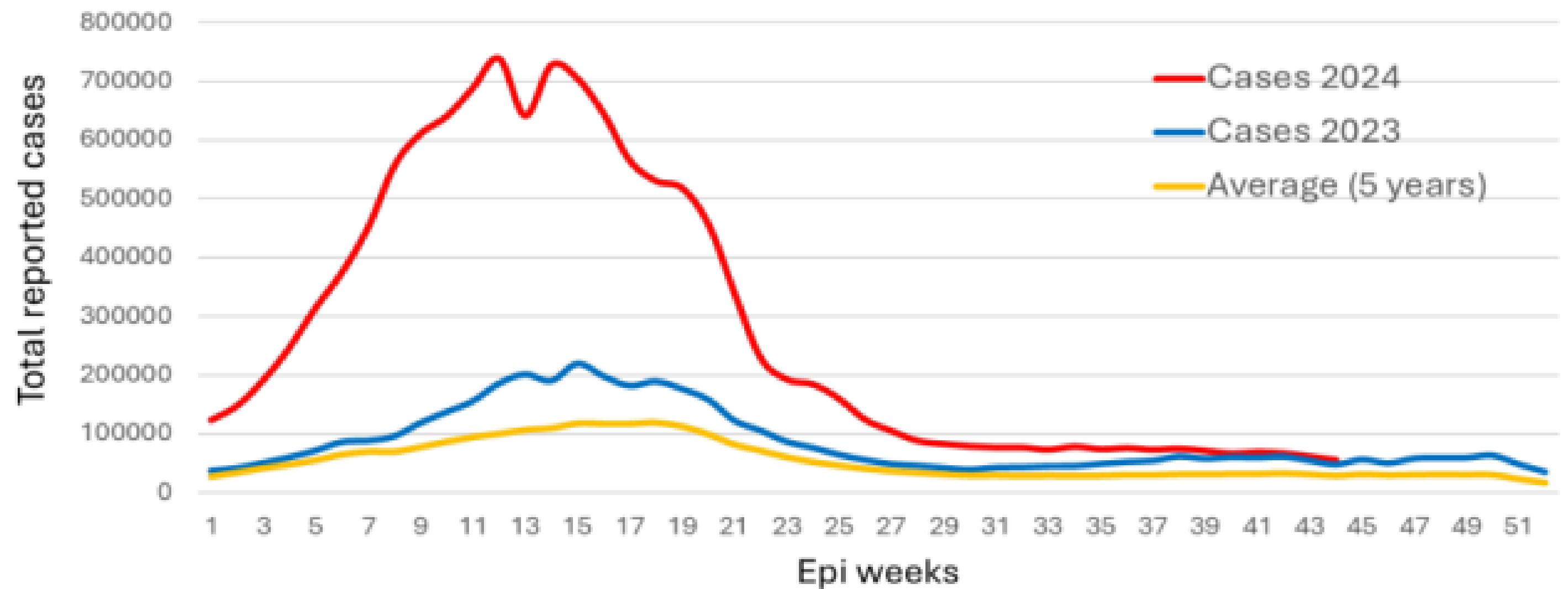
Year: 2024

Region	Total	Confirmed	Severe	Deaths
The Americas	12,522,878	6,658,687	21,026	7,598

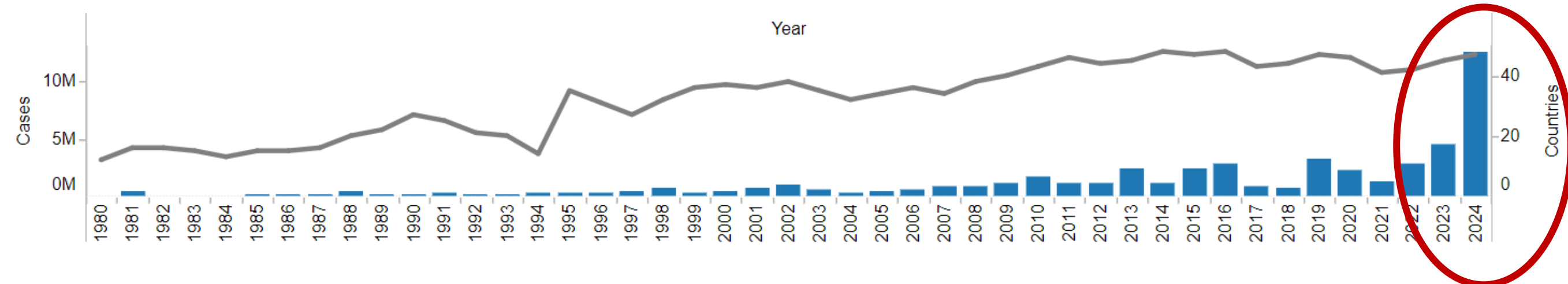


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# Dengue in U.S., 2010-2023

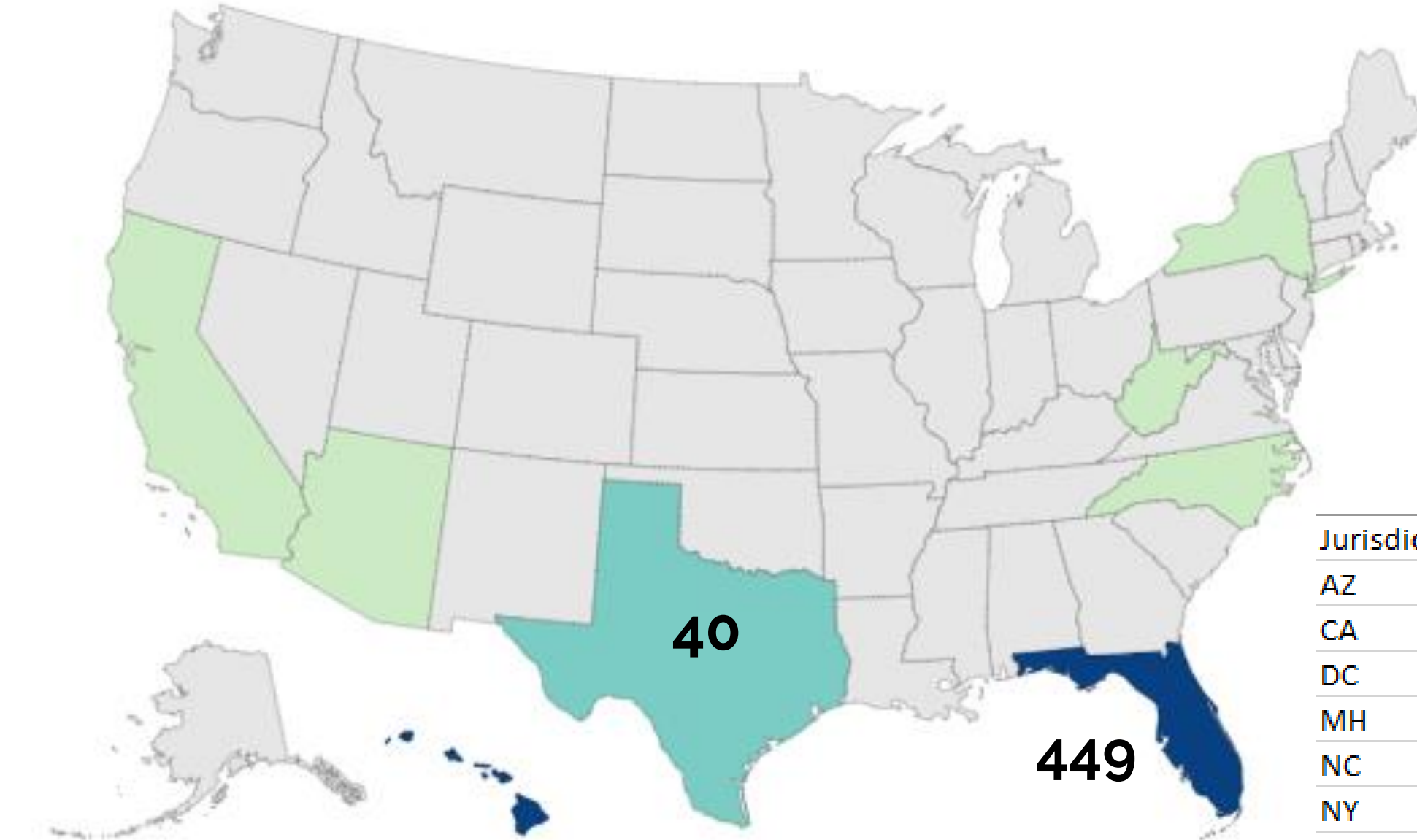
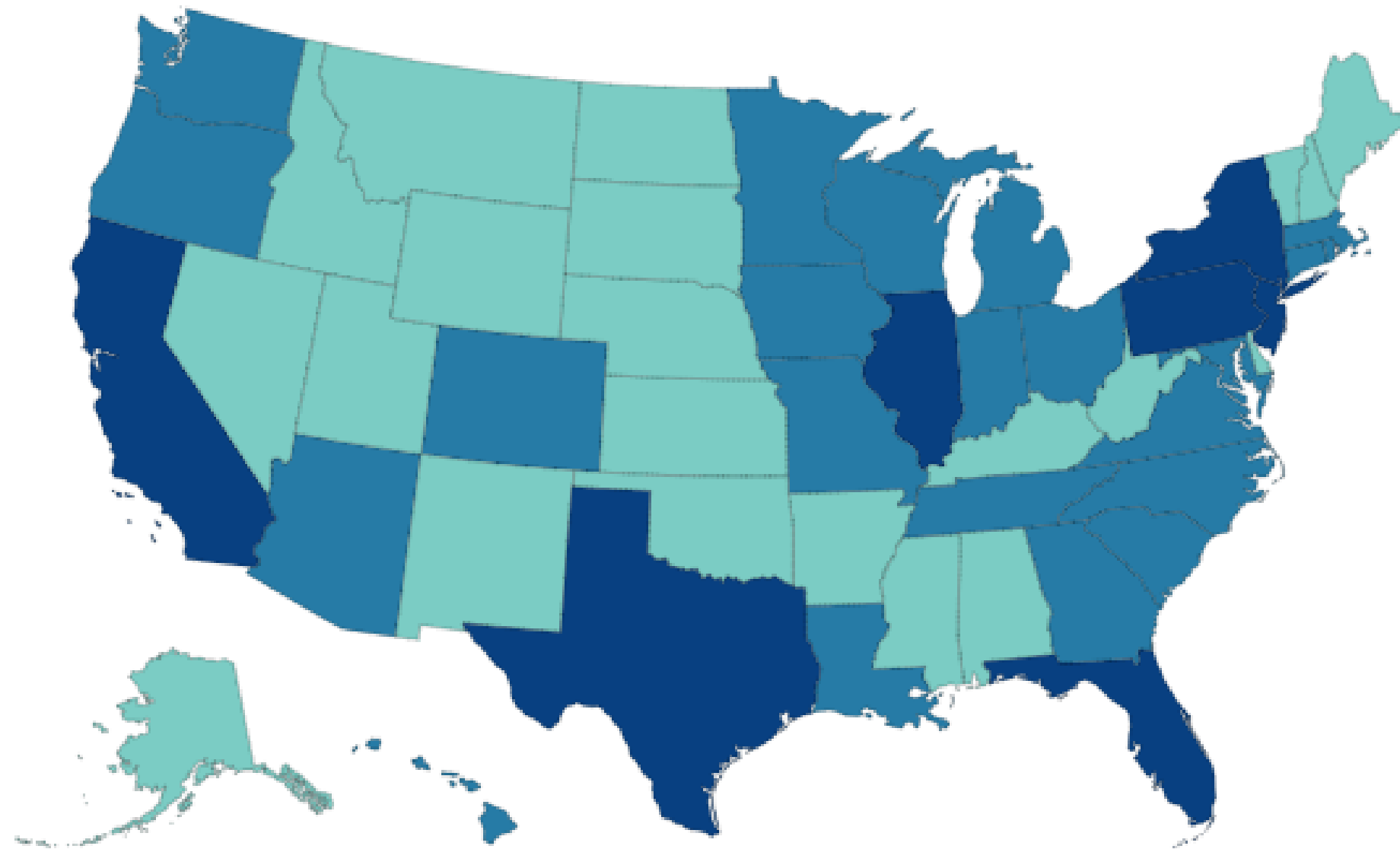
Cases for all years

**45,531**

Dengue cases reported from 2010-2023

Travel-associated

Locally acquired



Territories and freely associated states

AS GU PR VI MP FM PW MH

Territories and freely associated states

AS GU PR VI MP FM PW MH

Legend

>94% of cases in U.S. states

○ No reported cases ○ 1 to 4 ○ 5 to 49 ○ 50 to 249 ○ 250+

**Cases**  
**10,912**  
Cases reported for year and travel status selected above

**Jurisdictions**  
**56**  
Jurisdictions reporting cases for year and travel status selected above

Cases

**34,619**

Cases reported for year and travel status selected above

Jurisdictions

**16**

Jurisdictions reporting cases for year and travel status selected above

Jurisdiction	Count
AZ	2
CA	2
DC	1
MH	1
NC	2
NY	1
WV	1
GU	16
TX	40
FM	58
PW	72
AS	660
FL	449
HI	250
PR	32712
VI	352



# Dengue in U.S., 2024

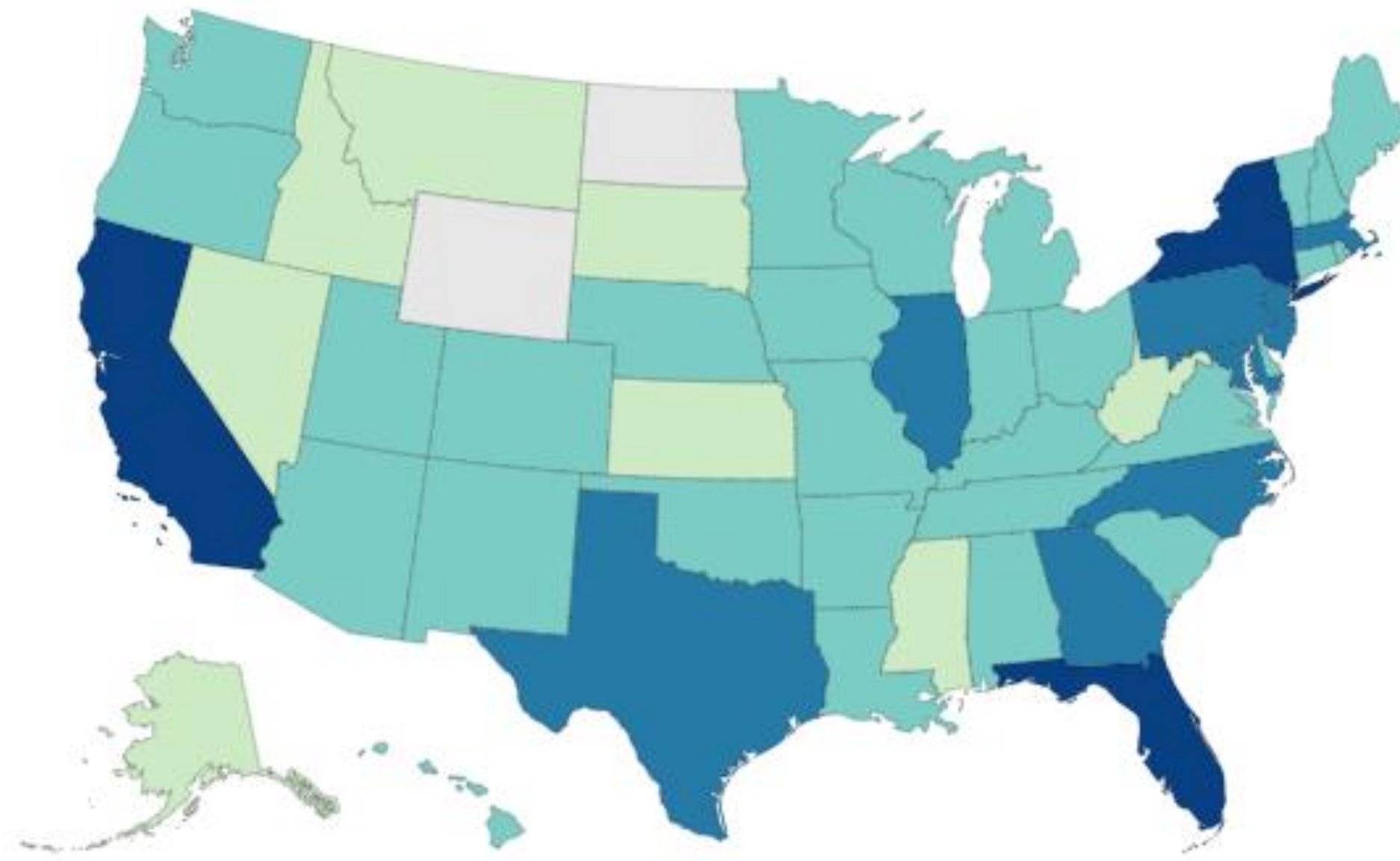
Cases

**7,858**

*Dengue cases in 2024 for travel status selected above*

## Travel-associated

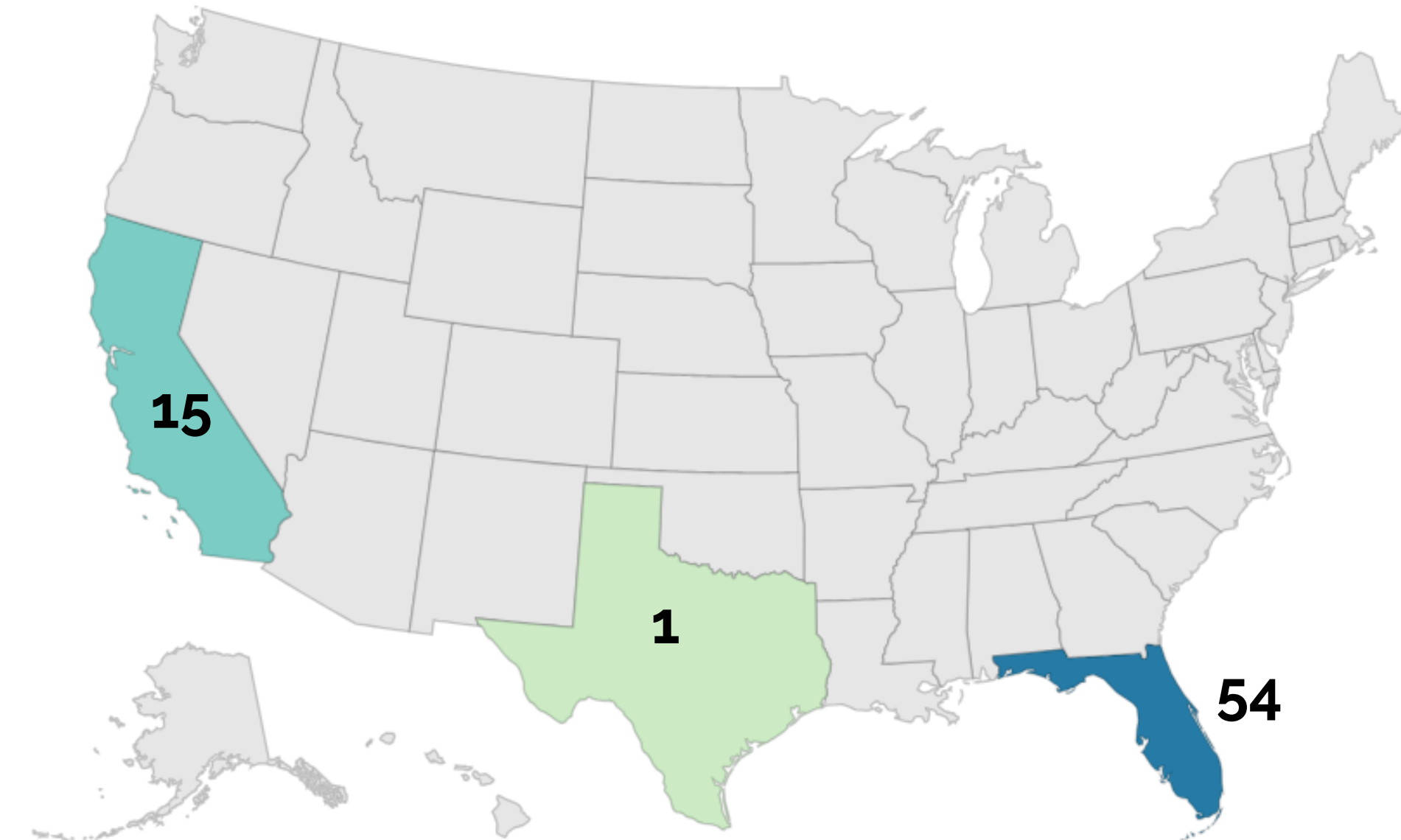
## Locally acquired



Territories and freely associated states

AS GU **PR** **VI** **MP** FM PW MH

**99% of cases in U.S. states**



Territories and freely associated states

AS GU **PR** **VI** MP FM PW MH

**164**

**4917**

Cases

**2,707**

*Dengue cases in 2024 for travel status selected above*

Jurisdictions

**52**

*Jurisdictions reporting cases in 2024 for travel status selected above*

Cases

**5,151**

*Dengue cases in 2024 for travel status selected above*

Jurisdictions

**5**

*Jurisdictions reporting cases in 2024 for travel status selected above*

# Locally Acquired Dengue, U.S., 2024

## Cases

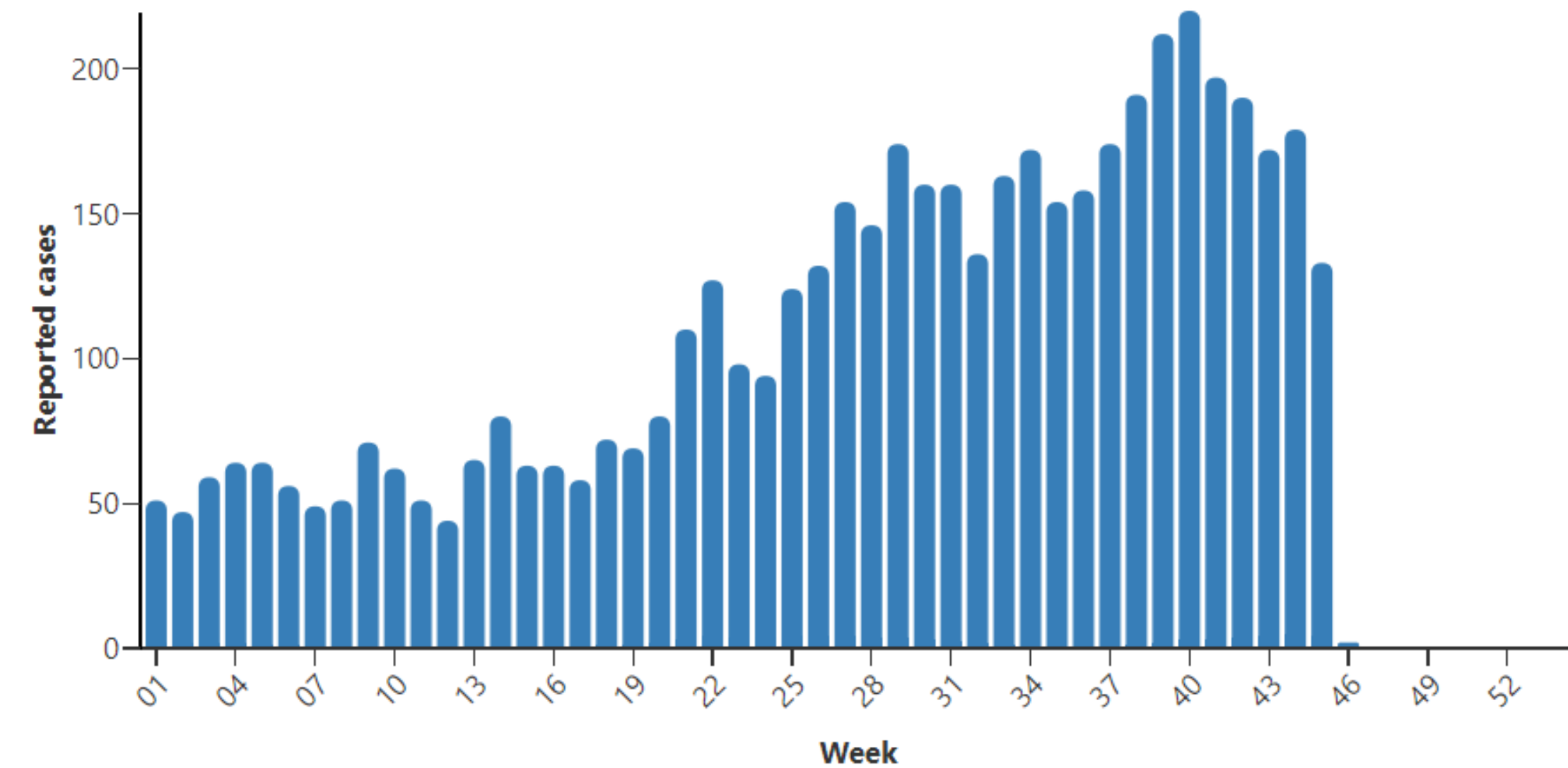
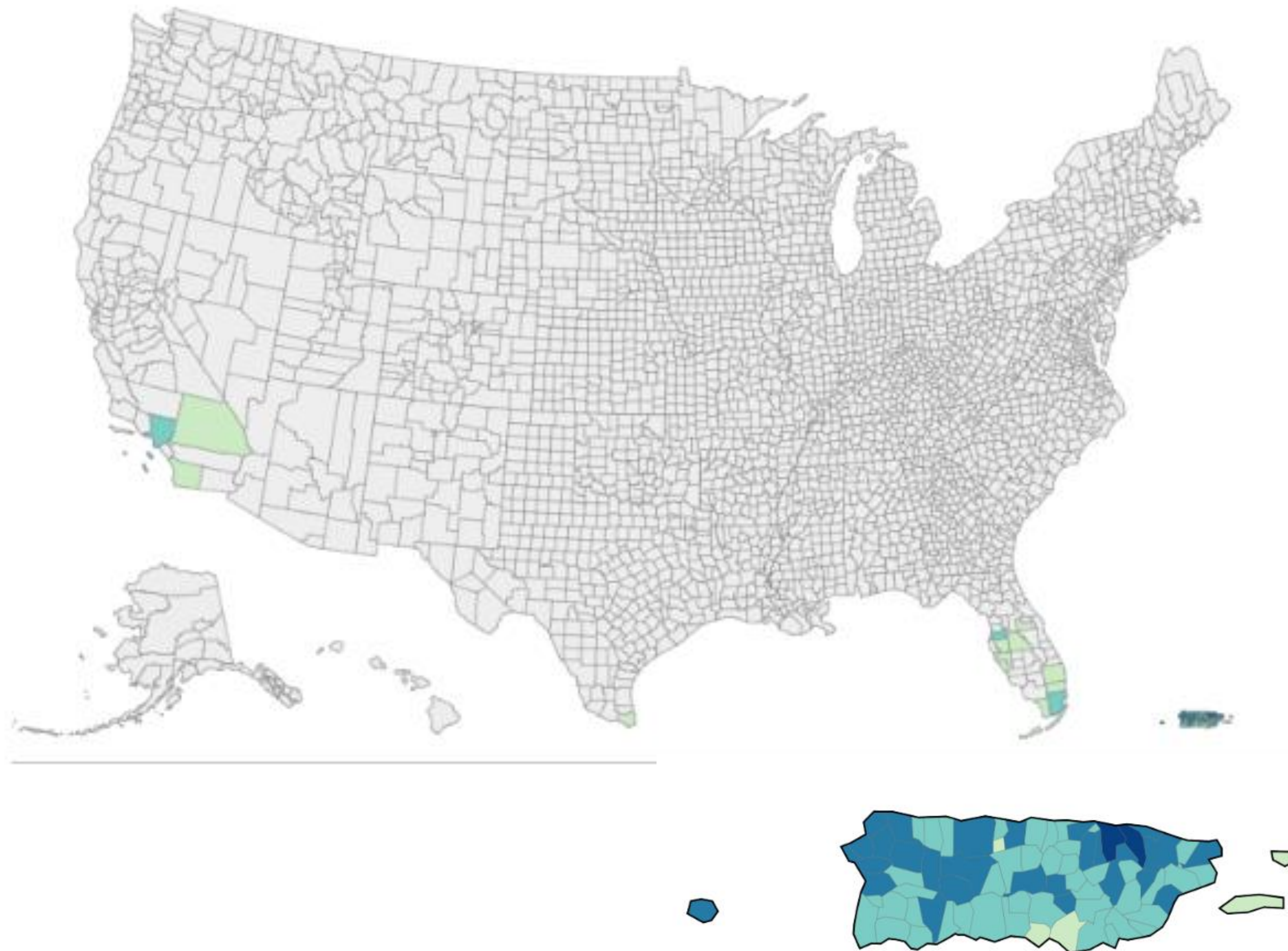
**5,151**

Dengue cases in 2024 for travel status selected above

## Jurisdictions

**5**

Jurisdictions reporting cases in 2024 for travel status selected above



**March 2024: Puerto Rico declared PH emergency (extended to 12/31/24)**



# Aedes Mosquitoes



*Aedes aegypti*

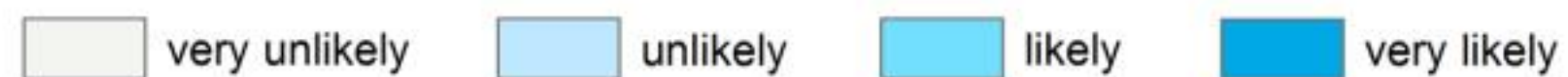


*Aedes albopictus*

***Aedes aegypti* mosquitoes**



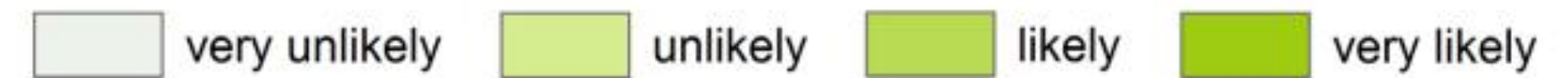
**Mosquitoes' ability to live and reproduce**



***Aedes albopictus* mosquitoes**

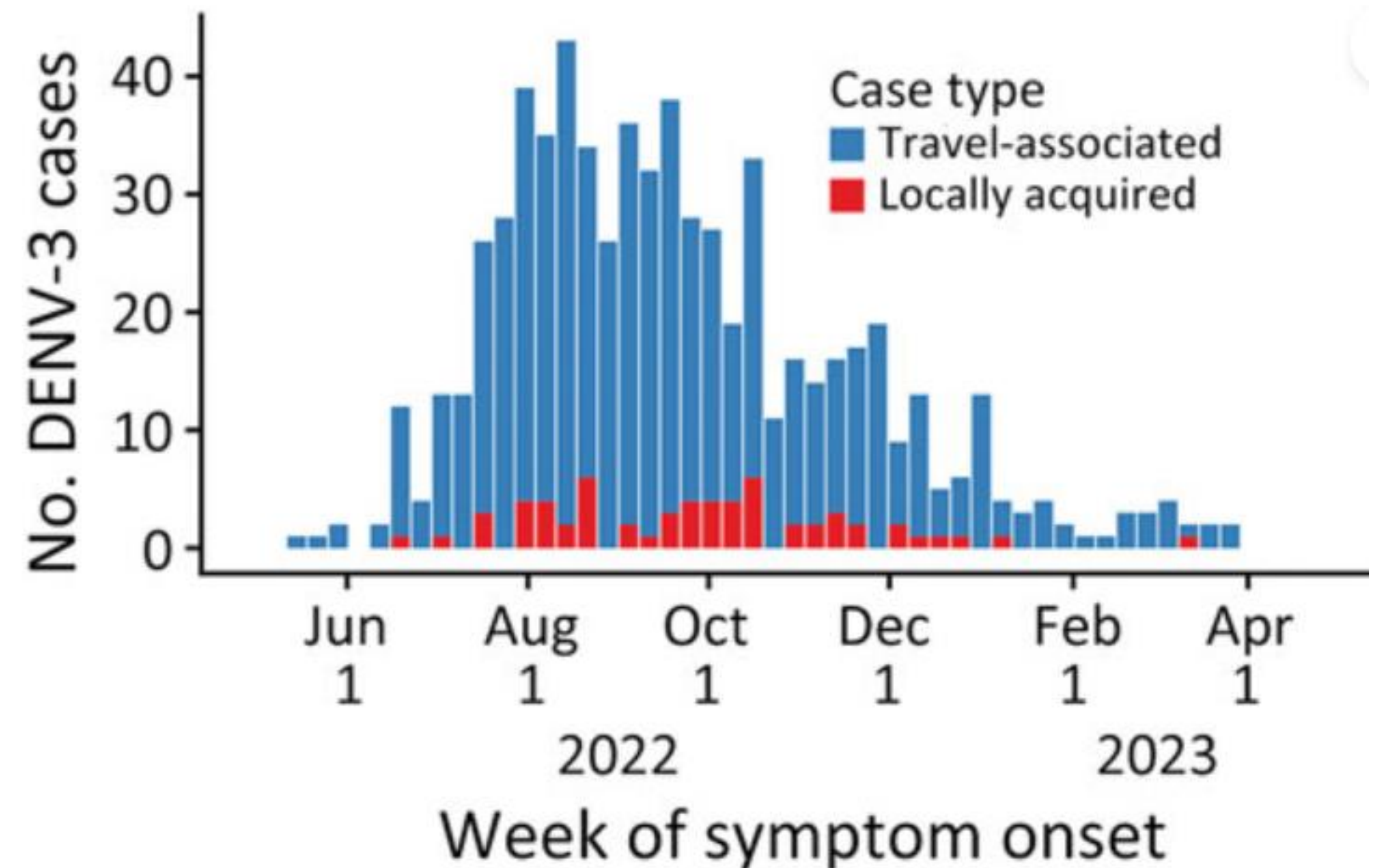


**Mosquitoes' ability to live and reproduce**



# Travel Introductions → Local Spread

- FL, May 2022- April 2023
- 1037 DENV cases reported (93% travel-related)
- DENV-3 identified among 601 travel-associated & 61 locally acquired dengue cases
  - Primarily travel from Cuba
- All 203 sequenced genomes belonged to same lineage
- Most locally acquired cases occurred shortly after introduction, with little sustained transmission



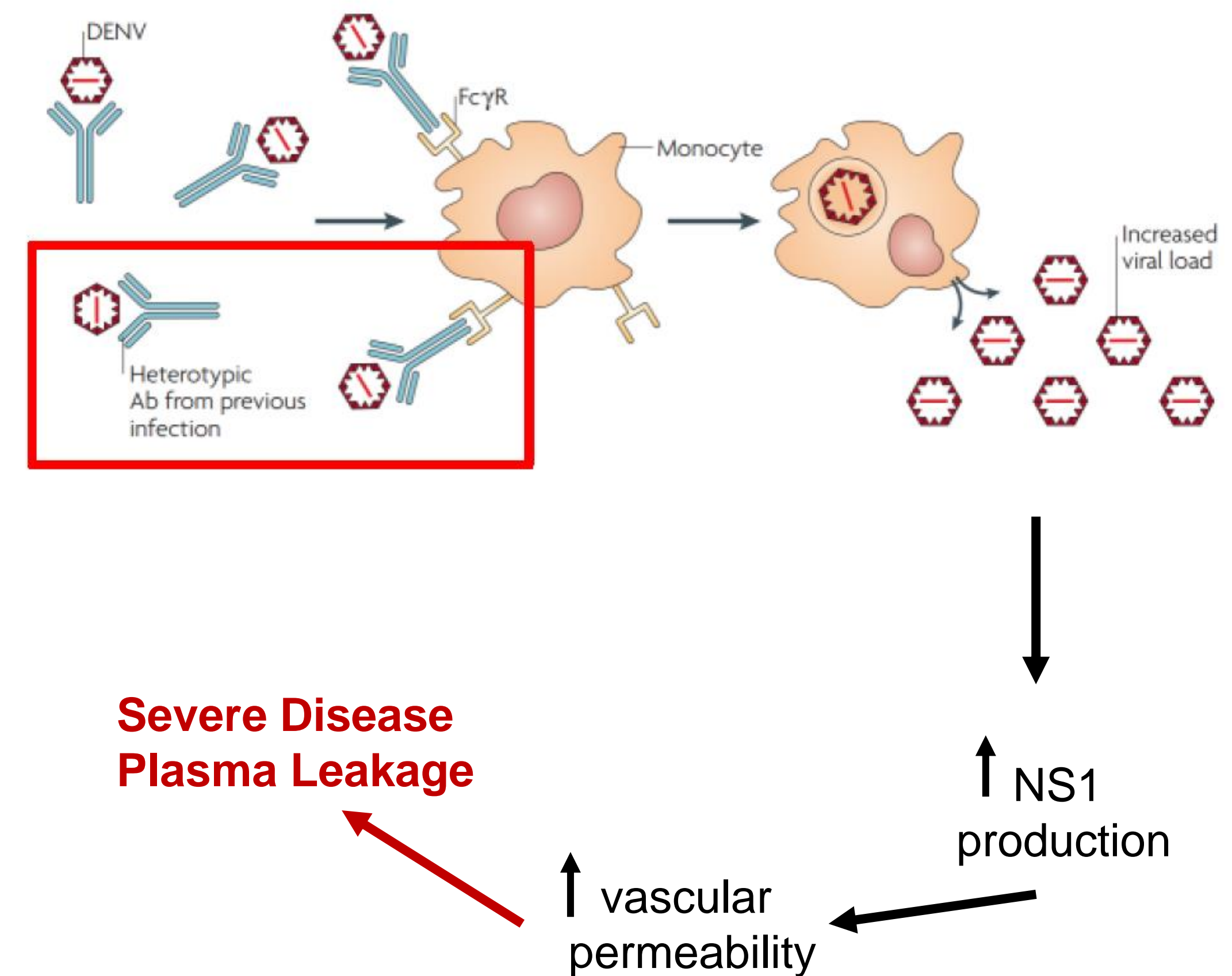


# Dengue Vaccine Development

## Challenges:

- Four DENV types, all capable of severe disease/death
- No immune correlate of protection
- Lack of sufficient animal model
- Immune assays unable to precisely define DENV type-specific immune responses
- Requirement for very large efficacy trials to demonstrate benefit across diverse populations & endpoints
- Potential for antibody-dependent enhancement

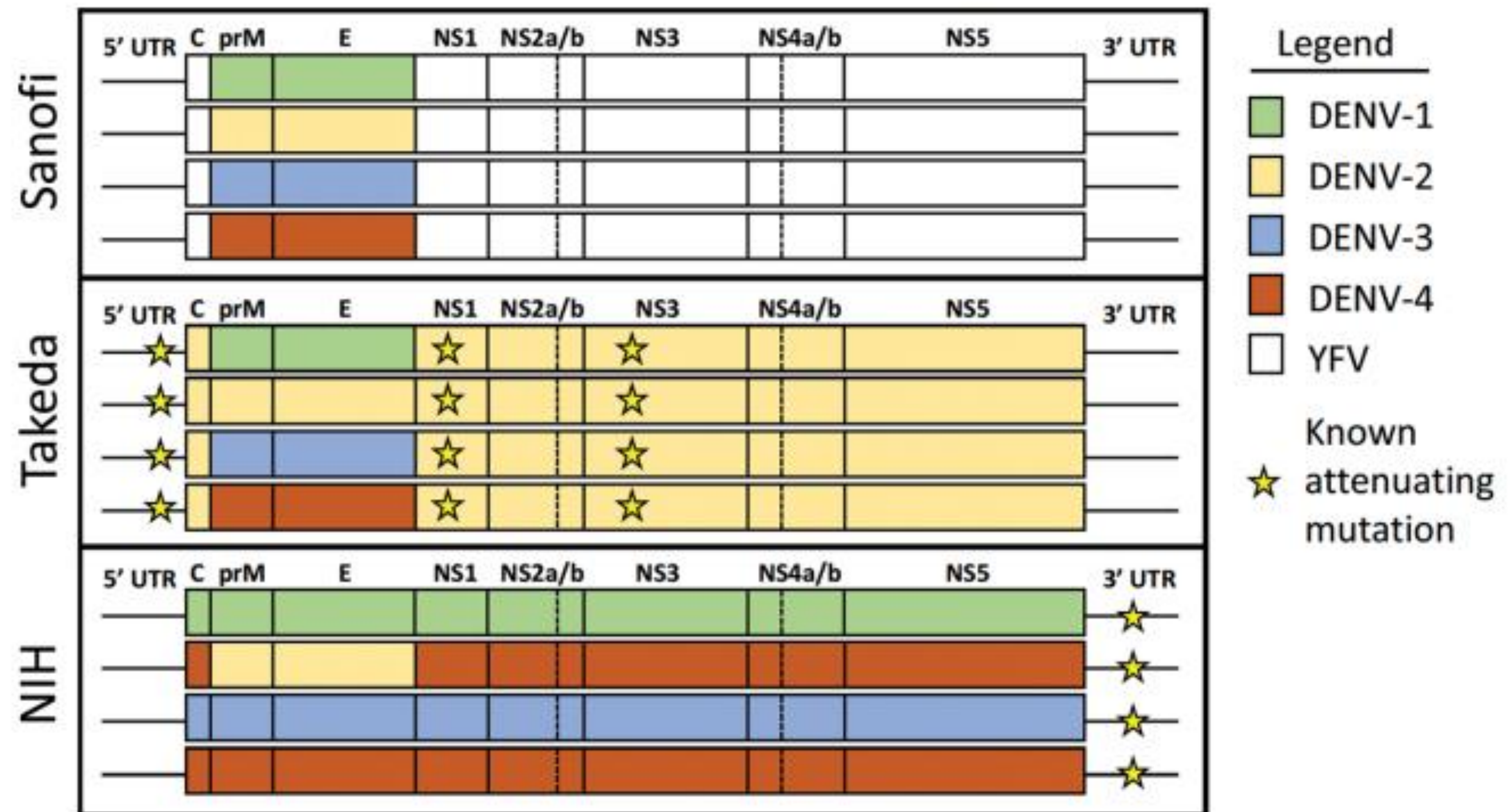
**Antibody-Dependent Enhancement (ADE) can lead to severe dengue in secondary infections.**



# Dengue Vaccines

- Dengvaxia<sup>®</sup> (Sanofi)
  - Live attenuated, YFV backbone
  - 3 doses (0, 6, 12 mo.)
- TAK-003 (Qdenga<sup>®</sup>, Takeda)
  - Live attenuated, DENV2 backbone
  - 2 doses (0, 3 mo.)
- NIH TV003/TV005
  - Live attenuated
  - Butantan-DV, Merck V181
  - Phase III trials ongoing
  - Single dose

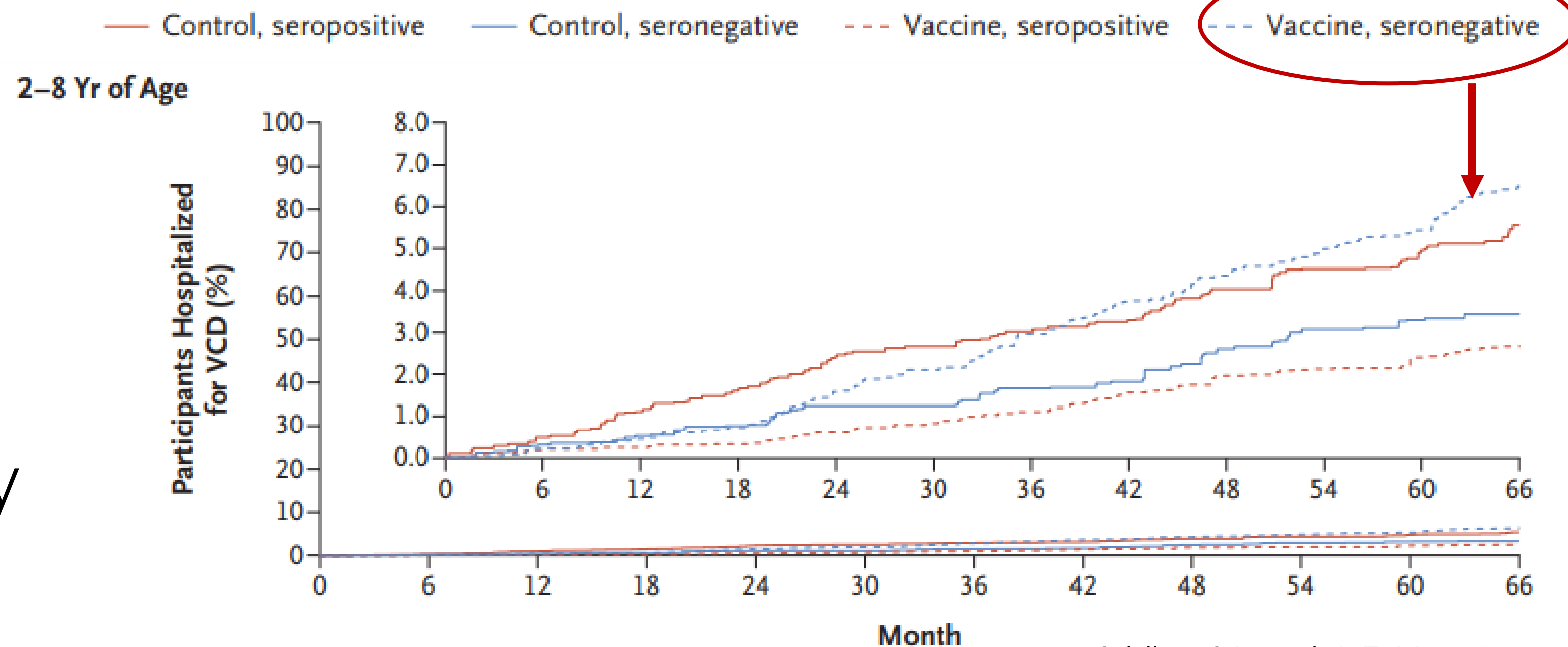
Live Attenuated Dengue Vaccine Constructs



Thomas SJ, *npj Vaccines* 2023

# Dengvaxia®

- First approved in Mexico 2015, then >20 countries
- Safety signal noted in year 3 of phase III trial → youngest, non-immune recipients experienced higher rates of hospitalization & severe dengue compared to unvaccinated
  - HR 0.32 for baseline seropositive
  - HR 1.75 for baseline seronegative
- WHO recommended use only in children known to be previously infected



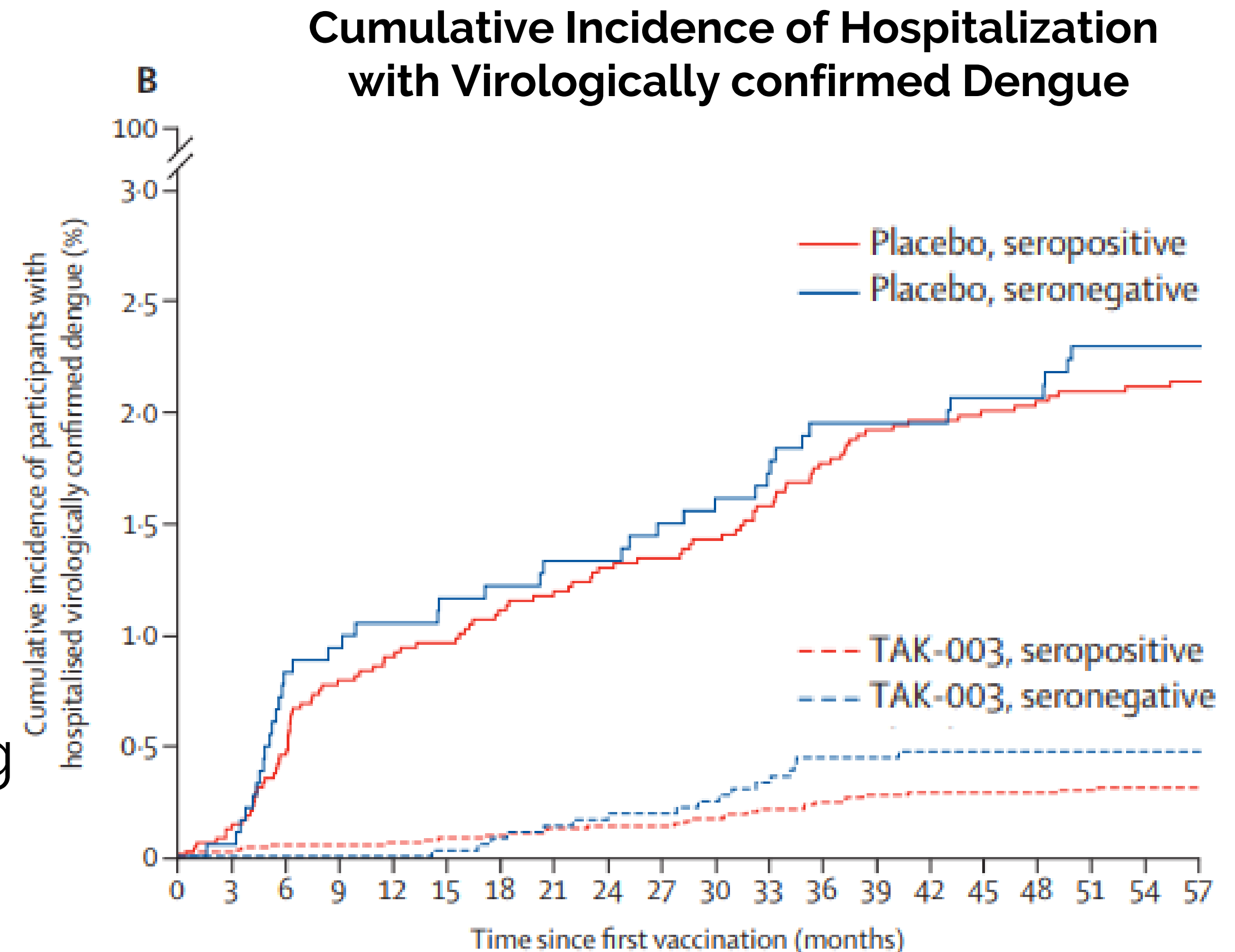


# Dengvaxia<sup>®</sup>, cont.

- 2021: CDC/ACIP recommended for use in children 9-16 yr living in endemic areas with lab-confirmed prior infection
  - Serology required prior to vaccination
  - 3 dose series (0, 6, 12 mo)
- Puerto Rico: vaccination program started Sept 2022
  - Uptake low: as of June 2024, 264 doses in 145 individuals administered
- Sanofi announced discontinuation in June 2024
  - Low demand in PR (only public program in place) and globally
  - Existing product will continue to be available until expiration in Aug 26 (latest start of series should be Aug 2025)

# TAK-003 (Qdenga<sup>®</sup>)

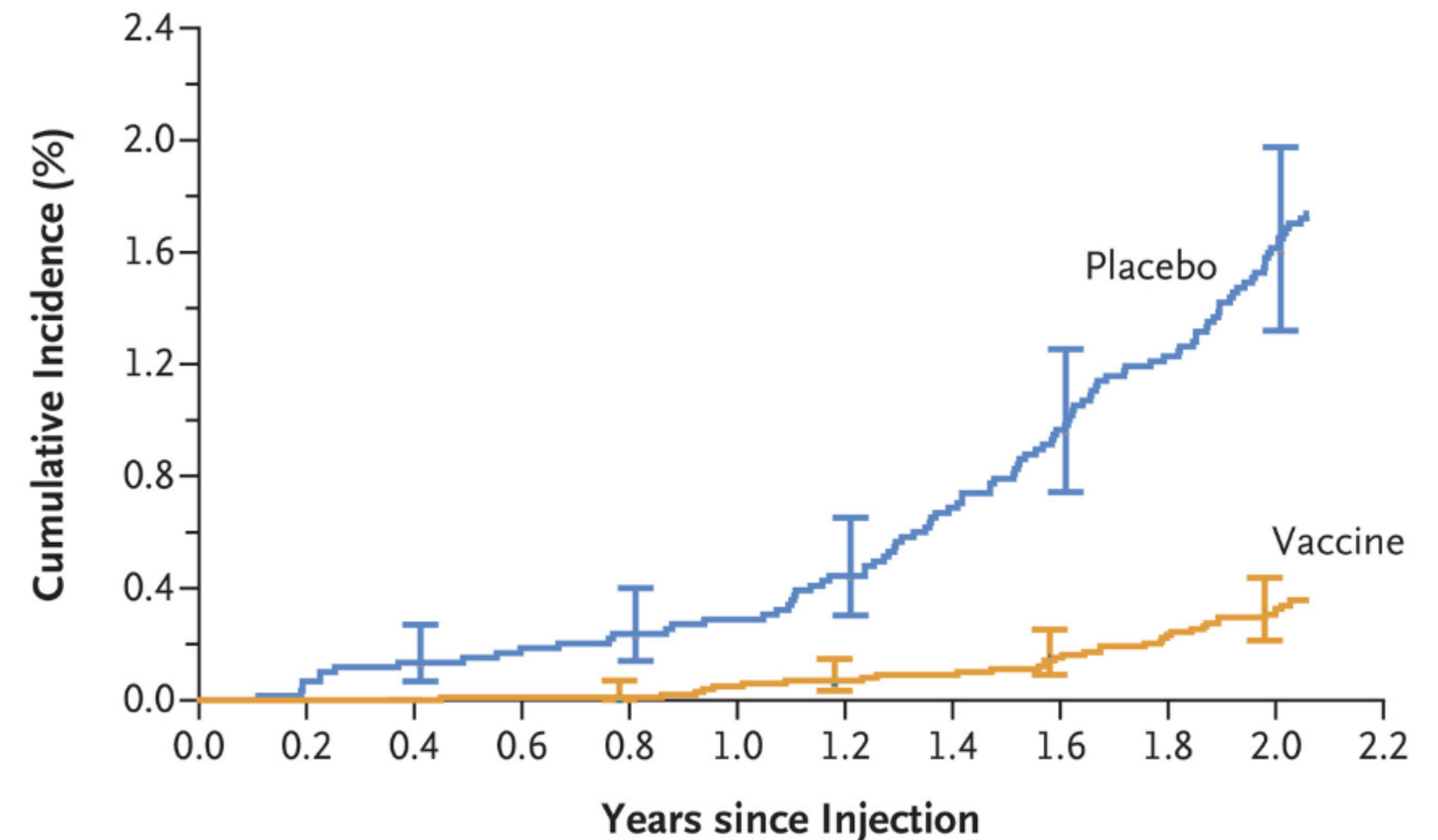
- Overall vaccine efficacy (VE):
  - 61.2% vs virologically confirmed dengue
  - 84.1% vs. hospitalization
- In baseline seropositives: 52-80% VE
- In baseline seronegatives:
  - 45% VE for DENV1, 88% for DENV2
  - Lack of efficacy for DENV3
  - Insufficient evidence for DENV4
  - No signal of increased risk
- Approved for use by EMA in 2022, including in travelers,  $\geq 4$  years
- WHO recommends use in ages 6-16y in endemic regions



# Butantan-DV (TV003)

- Ongoing phase 3 RCT in Brazil enrolling 2-59 yo
- Overall 2-yr VE:
  - 79.5% among seronegative
  - 89.2% among seropositive
  - 89.5% vs. DENV1
  - 69.6% vs. DENV2
  - DENV3/4 not observed
- Subsequent median 3.7 yr follow-up: overall 67.3% VE
  - 5 yr follow-up data expected late 2024
- Merck initiating trials of its formulation

Cumulative Incidence of Virologically Confirmed Dengue



**No. at Risk**

Placebo	5,946	5,865	5,811	5,741	5,668	5,571
Vaccine	10,213	10,014	9,925	9,840	9,750	9,628



# Dengue: Summary

- Ongoing global dengue outbreak (largest in history in Americas)
  - Active public health emergency in Puerto Rico
- Increasing local acquisition in continental US related to multiple travel-related introductions and presence of *Aedes* mosquitoes
  - Clinical awareness of dengue symptoms, testing & management needed, even without travel history
- Effective and safe dengue vaccines finally available, but uptake has been low, even in setting of large outbreaks (PR, Brazil)
- No dengue vaccines currently recommended for travelers
- No dengue vaccines currently under FDA review
- Ultimately, dengue control will require multifaceted approach

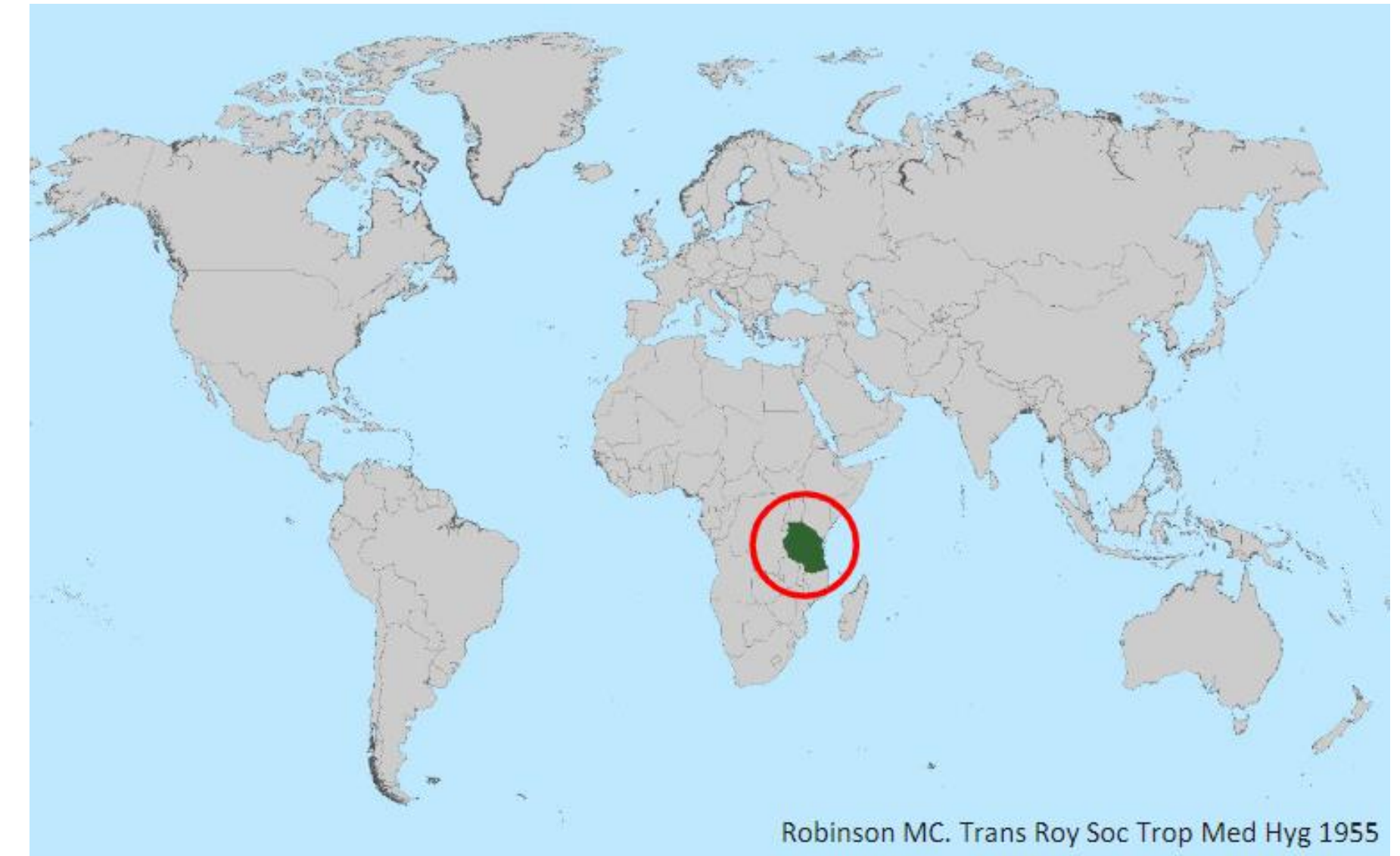


# CHIKUNGUNYA



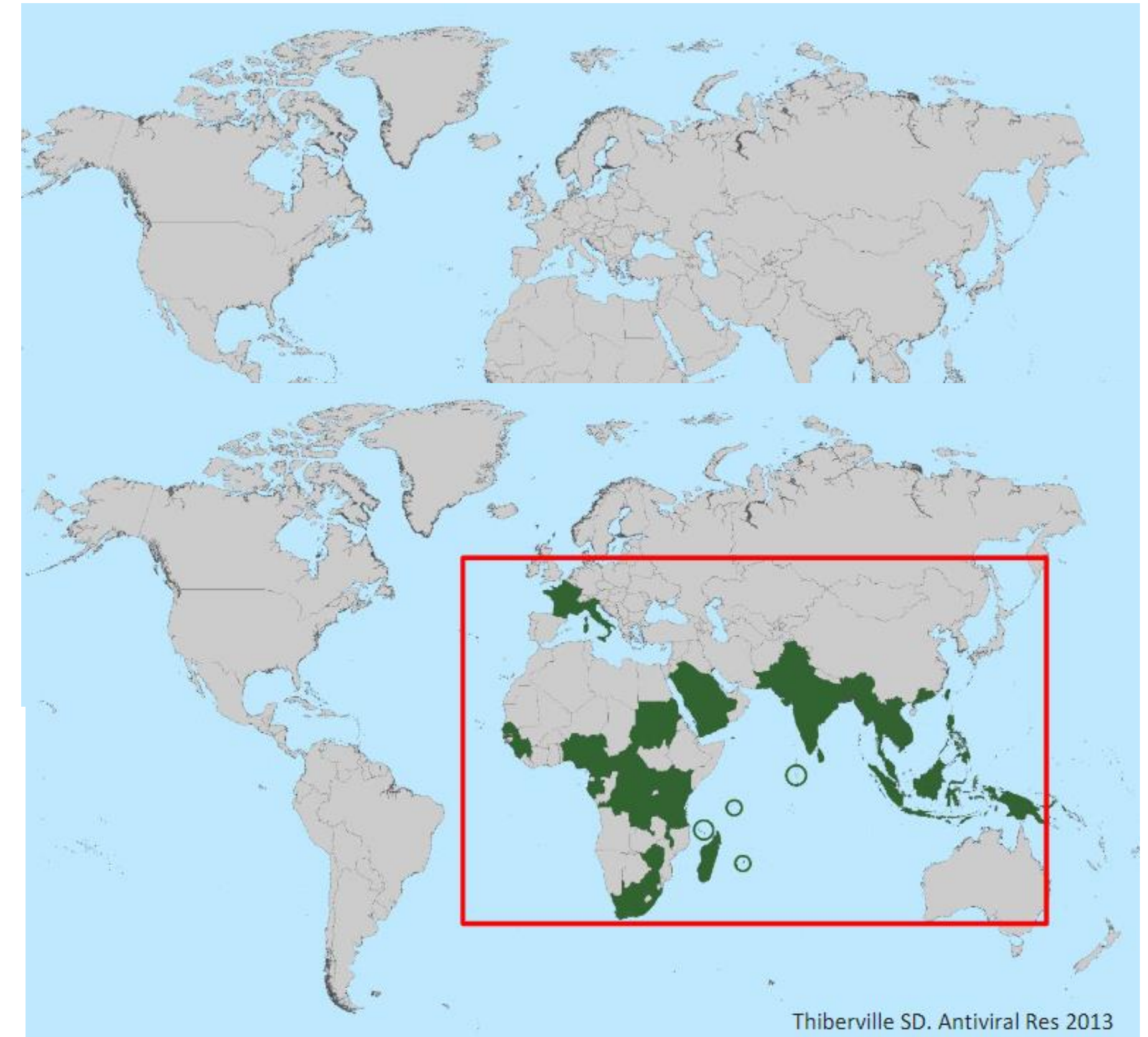
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  - Can also spread intrauterine, intrapartum, via needlestick, lab exposure (all rare)
- Expanded in Africa and to Asia, Indian Ocean 1953-2012
- Introduction to and spread in the Americas, 2013-2015



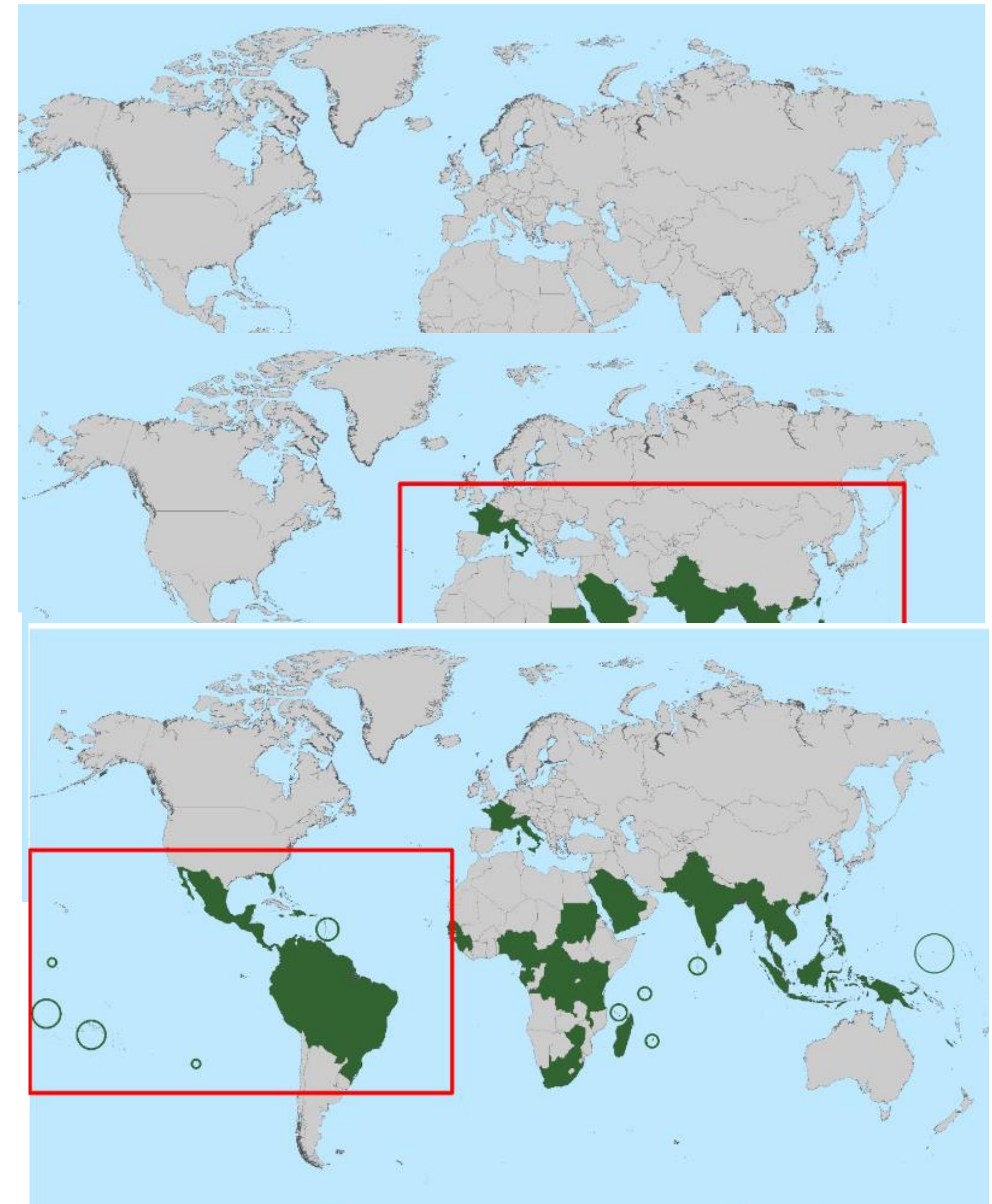
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# Chikungunya: Clinical Features

- Incubation 3-7 days
- Abrupt onset of fever, often with severe polyarthralgia
  - “Chikungunya = “to become contorted” or “to walk bent over”
- Common: joint swelling, muscle pain, headache, nausea, fatigue, rash
- Acute symptoms usually resolve in 7-10 days but joint pain & fatigue often persist for months/years (50% at 3 mo; ~1/3 at 12 mo)
  - More common in older age, more severe acute illness, pre-existing joint disease
  - Fatigue, depression, alopecia, impaired memory, sleep d/o, lower QoL
- Once infected, immunity lifelong
- No specific antiviral treatment



# Severe Chikungunya

## Syndromes

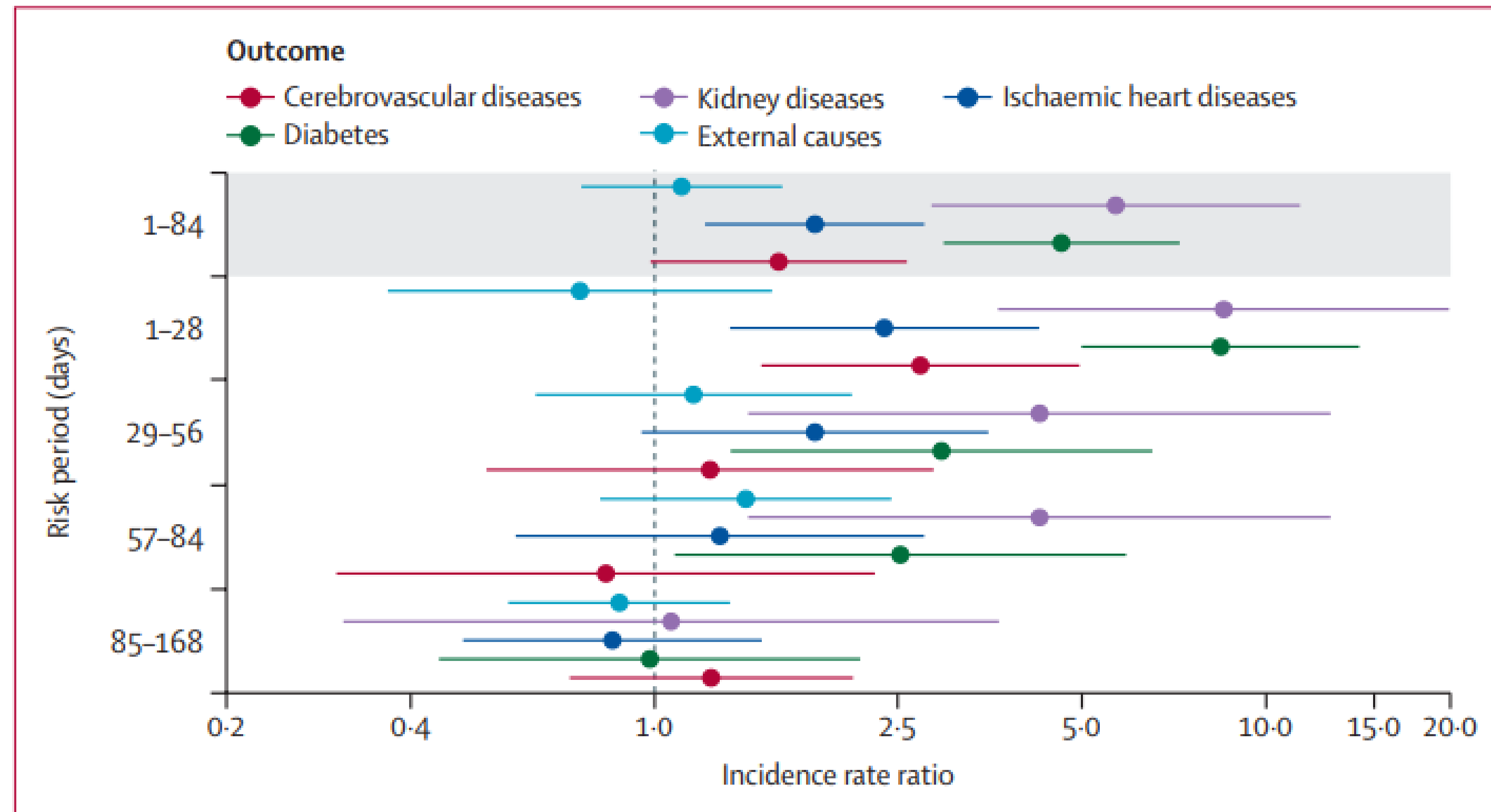
- Ocular disease
- Myocarditis
- Hepatitis
- Acute kidney disease
- Severe bullous lesions
- Neurologic disease
  
- Mortality low (0.07%)
  - Vulnerable hosts

## Risk factors

- Age < 1 year or > 65 years
- Underlying medical conditions (e.g., hypertension, diabetes, heart disease)
- Intrapartum transmission

# Deaths Following CHIKV Infection

- Population-based cohort study in Brazil
- Incidence rate ratio (IRR) for all-cause natural death following CHIKV infection:
  - 8.8 (95% CI 7.2-10.7) within 7d
  - 1.6 (95%CI 1.3-2.0) at 57-84d
- Death within 28 d significantly elevated for:
  - Cerebrovascular disease
  - Diabetes
  - Ischemic heart disease
- No evidence of increased risk after 85d



# CHIKV in Pregnant Persons

- Clinical disease similar in pregnant vs. non-pregnant individuals
- Adverse outcomes such as fetal loss, stillbirth, preterm birth documented but rare
- Infection commonly results in adverse neonatal outcomes if pregnant person infected around the time of delivery
  - Intrapartum transmission occurs ~30-50% cases
  - Encephalopathy, sepsis-like illness, cardiac, dermatologic, hemorrhagic manifestations
  - Neurocognitive outcomes often poor
- Young infants infected via mosquitos also at risk for severe disease, especially during first few months



Bin S et al, Clin Case Rep 2023



A

Jebain J et al, ID Cases 2020

1. Gerardin P et al, PLoS Medicine 2008



Valampampil JJ et al, Ind J Ped 2009



# Chikungunya Outbreaks

- More common during tropical rainy season but can occur in dry seasons
- More likely in regions with no or mild outbreaks in recent past
- Often rapidly increase in size & affect 30-60% of population
- Period of intense transmission typically short (3-6 months)
- Interval between outbreaks unpredictable and variable, can be >20 years; related to:
  - Pre-existing population immunity
  - Build-up of non-immune population
  - Environmental factors
- Once introduced, huge outbreaks unlikely to recur but continued large outbreaks likely
  - Some countries report outbreaks regularly, but in different locations
  - High ongoing risk in south/SE Asia during monsoon season

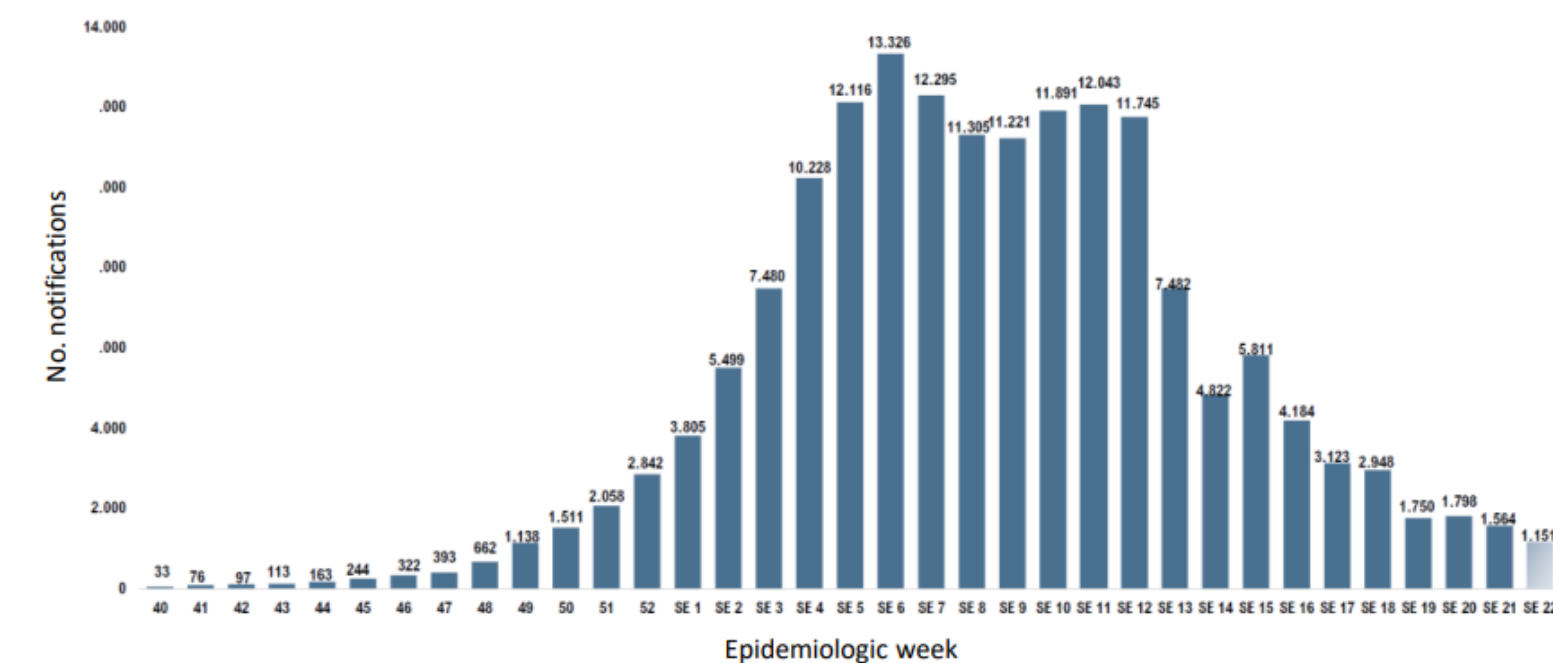


# Example: Paraguay, 2023

- Nearly 170,000 cases
  - ~8600 (9%) hospitalizations
  - 253 (<1%) deaths
- <10,000 notifications by end of 2022 → >50,000 notifications by week 6, 2023
- Case fatality rate highest among neonates
- 75% of those who died had comorbidities

**Chikungunya notifications\***  
**October 1, 2022 – June 3, 2023**

**167,239 cases**



\*Confirmed and probable cases and suspected arboviral infection

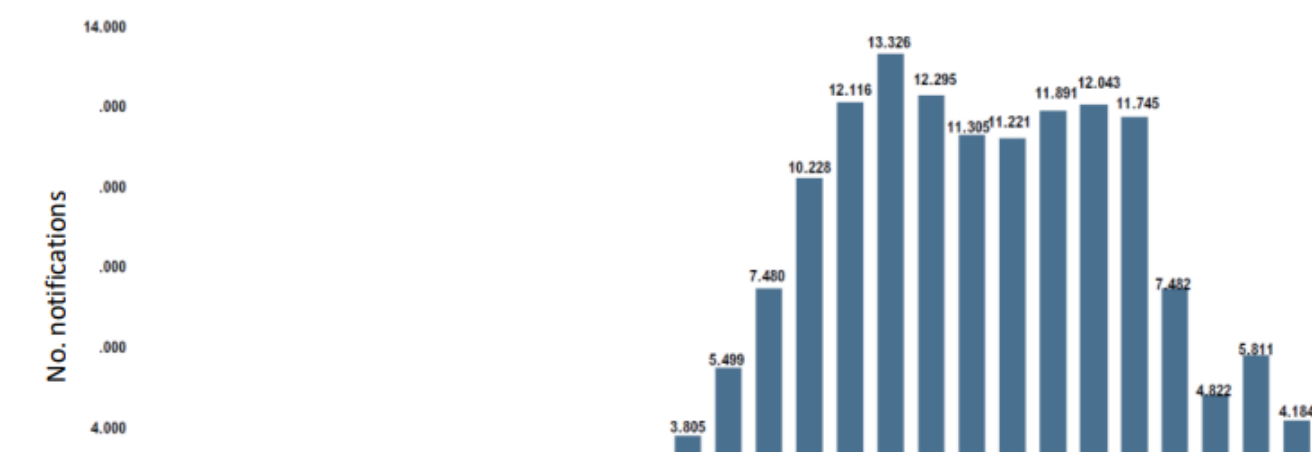
Source: Ministry of Public Health and Social Welfare, Paraguay

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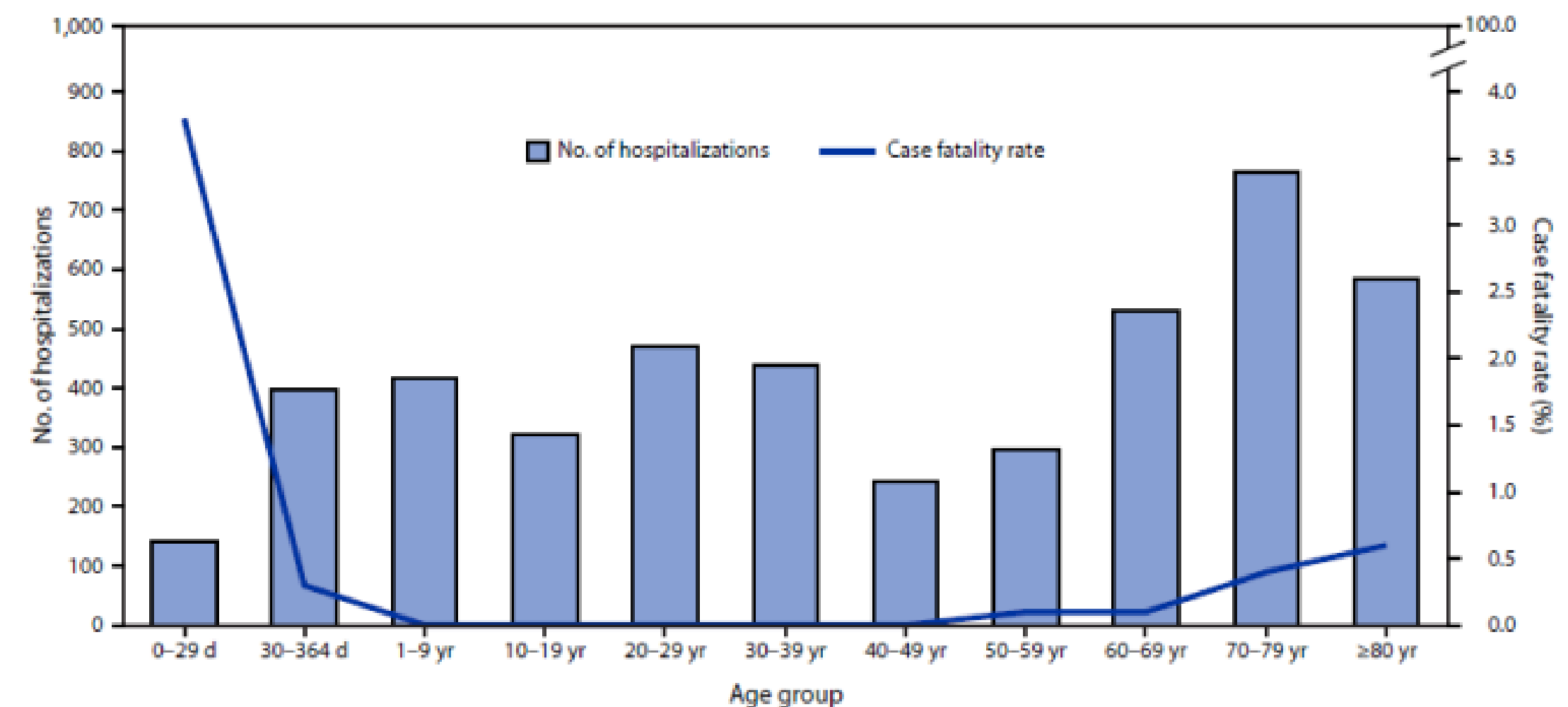
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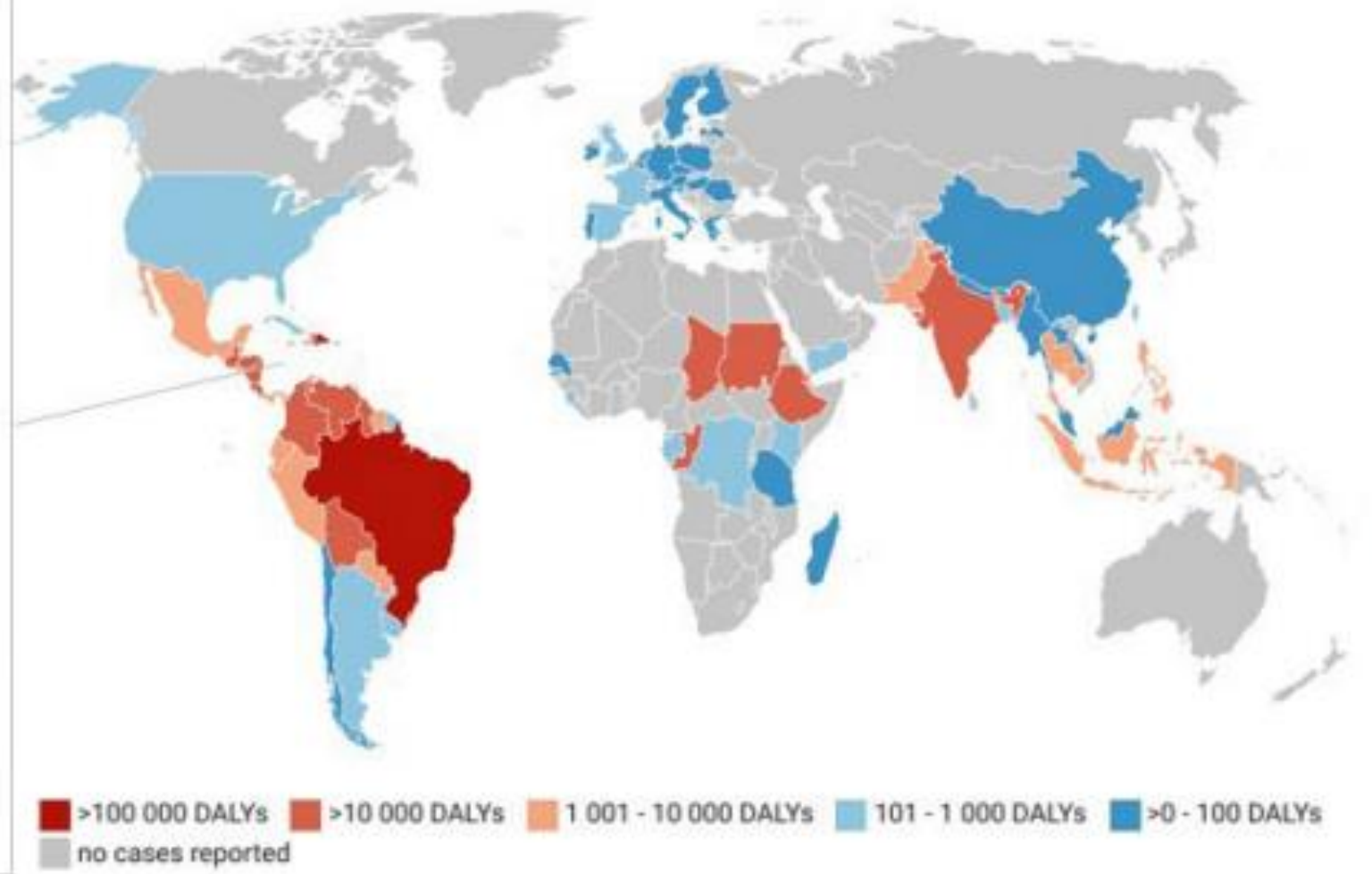


Number of hospitalizations (N=4,604) and case fatality rate among probable and confirmed chikungunya cases by age group, October 1, 2022–March 11, 2023



# CHIKV: Economic Impact

The global chikungunya DALY burden between 2011 and 2020



**2011-2020:**

18.7 million cases in 110 countries  
 → 1.95 million disability-adjusted life years (DALYs)

-76% from chronic illness

\$2.8 billion direct costs

\$47.1 billion indirect costs

**Table 2** Number of chikungunya cases, DALYs, and cost outcomes per super region between 2011 and 2020.

	Reported cases	Corrected for underreporting	DALYs	Direct costs	Indirect costs
Latin America and the Caribbean	3 054 869	14 926 878	1 559 482	\$2 488 465 640	\$40 387 345 194
Southeast Asia, East Asia, and Oceania	245 468	2 265 287	236 665	\$235 373 724	\$5 579 768 265
Sub-Saharan Africa	128 289	1 024 913	107 078	\$28 105 258	\$473 276 350
South Asia	81 788	288 159	30 105	\$14 314 425	\$246 292 422
High Income	14 546	36 259	3 788	\$50 893 981	\$324 201 070
North Africa and the Middle East	14 511	140 850	14 715	\$4 852 610	\$77 771 115
Central Europe, Eastern Europe, and Central Asia	54	202	21	\$170 937	\$1 245 276
<b>Total (95% CI *)</b>	<b>3 539 525</b>	<b>18 682 548</b>	<b>1 951 854</b> (748 848 – 4 630 891)	<b>\$2 822 176 575</b> (\$2 295 775 588 – \$4 067 780 477)	<b>\$47 089 899 692</b> (\$15 173 735 585 – \$98 870 351 923)

# Chikungunya Cases in U.S.

- Prior to 2006, chikungunya rarely detected in U.S. travelers
- 2006-2013: average 28 people/yr, all travelers from Asia, Africa or Indian Ocean
- Late 2013: 1<sup>st</sup> case identified in Caribbean
- 2014: chikungunya detected in US travelers returning from affected areas in Americas, & local transmission identified in FL, TX, PR & USVI
- No locally acquired cases reported in U.S. since 2019

Year	US States Locally acquired	US States Travel-associated†	US Territories Locally acquired	US Territories Travel-associated
2014	12‡	2,799	4,659	51
2015	1‡	895	237	0
2016	0	248	180	1
2017	0	156	39	0
2018	0	116	8	0
2019	0	192	2	0
2020	0	33	0	0
2021	0	36	0	0
2022	0	81	0	0
2023	0	154	0	0
2024	0	141	0	0

*Data are preliminary and subject to change. Data are current as of November 1, 2024.*

\*Includes confirmed and probable disease cases

†Includes cases acquired through other routes (e.g., laboratory transmission)

# Local Transmission in U.S. States

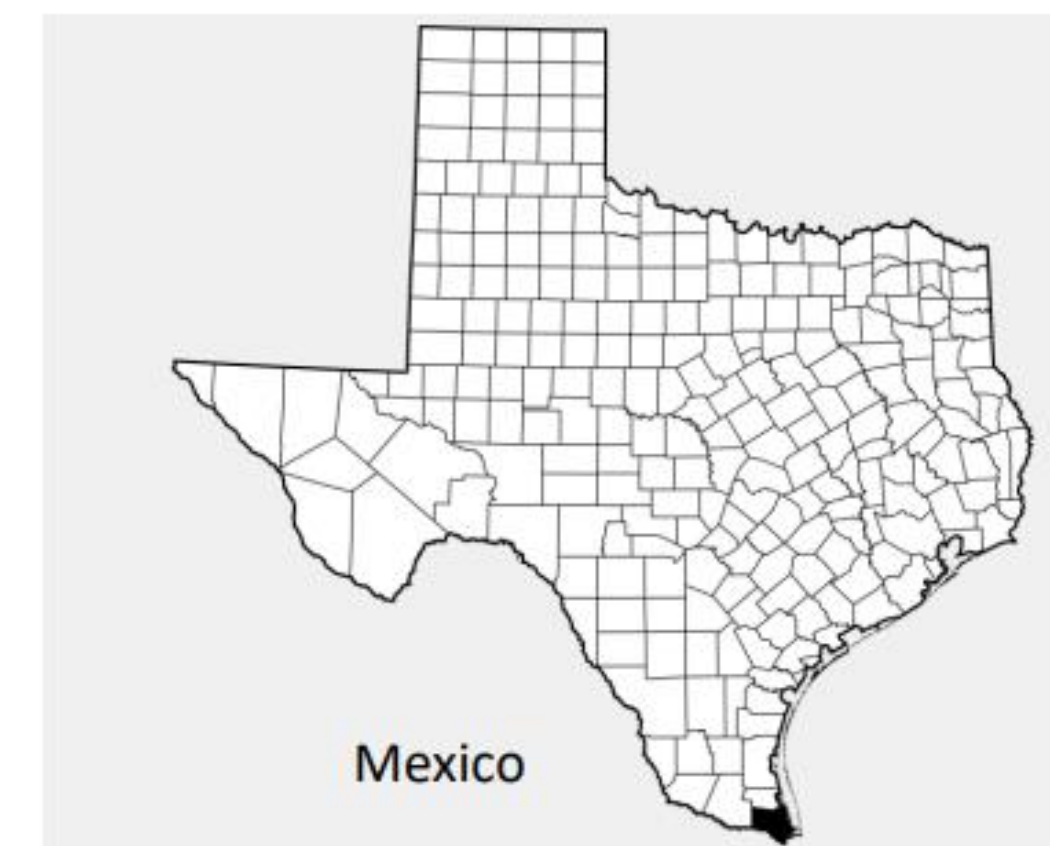
## Florida

- 1<sup>st</sup> local transmission in continental U.S. in 2014
- During outbreak in Americas & increase in travel-associated cases
- 11 additional cases identified in 4 counties



## Texas

- N = 1
- November 2015
- Cameron County



Location of Cameron County, Texas



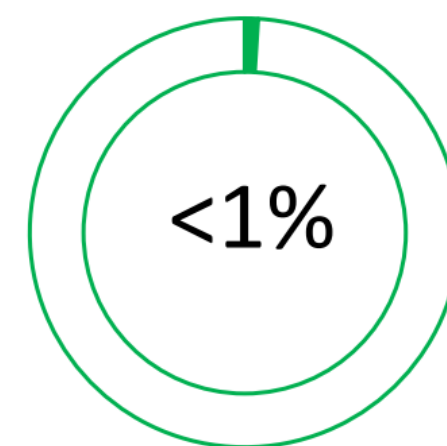
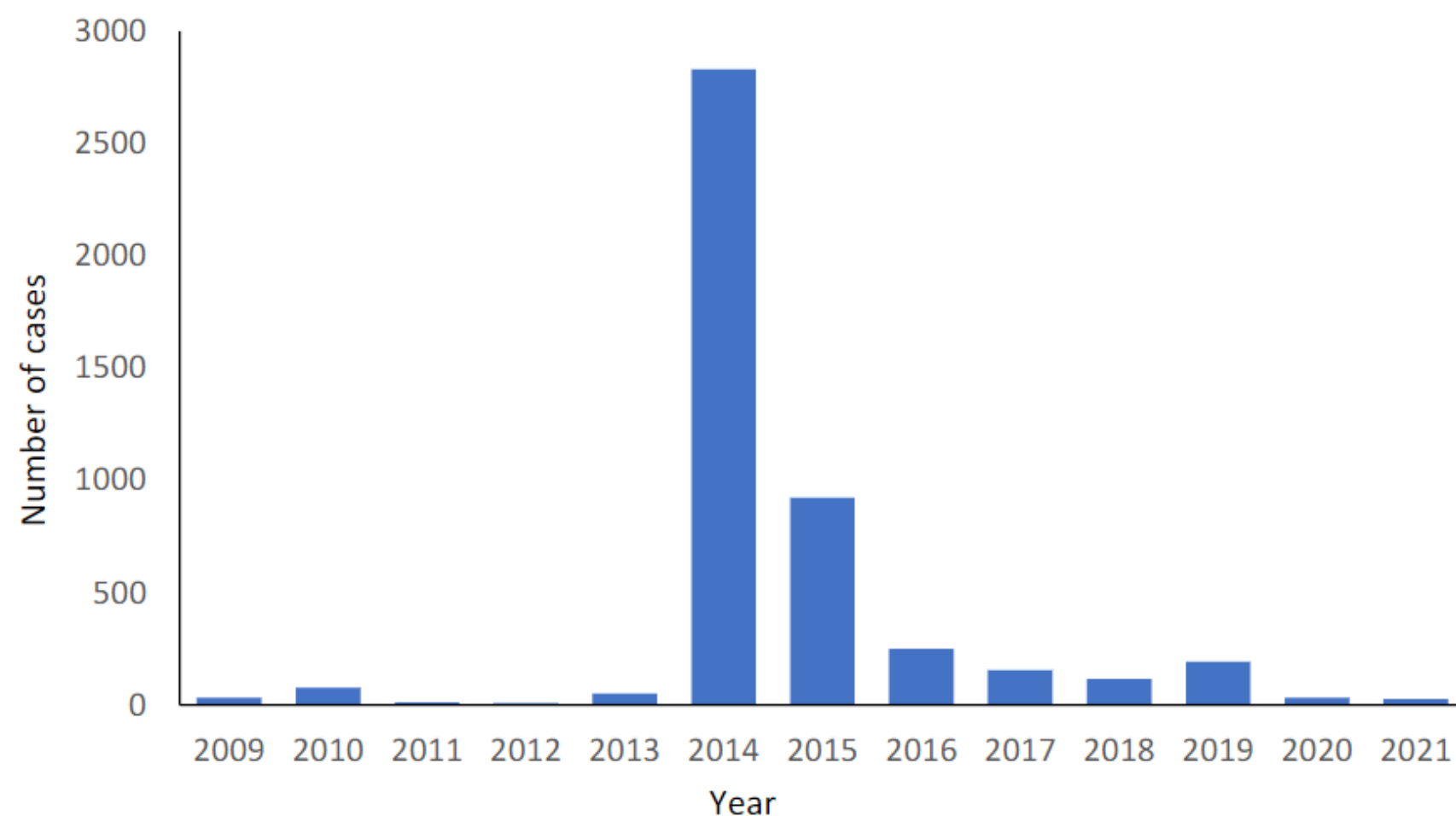
# Chikungunya in U.S. Territories & Affiliated States

- 3 territories (PR, USVI, American Samoa) & 2 affiliated states (Yap, Marshall Islands) have had explosive chikungunya outbreaks
  - All occurred 2013-2015
- PR & USVI: ~30% of population likely infected
  - 20-25% of population with clinical illness during 6-mo period
- No evidence of confirmed transmission since 2017 (PR) or earlier in islands with smaller populations

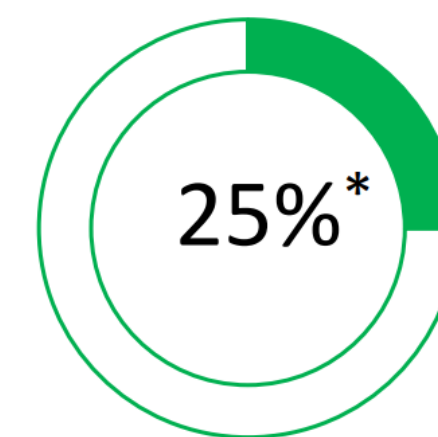
# Chikungunya Among U.S. Travelers

- ~100-200 cases reported annually
- Most commonly acquired in Asia & Americas
- Greatest risk factor is traveling to area with outbreak

Chikungunya cases in US travelers, 2009–2021\*



Percentage of all U.S. persons traveling to areas with chikungunya risk visiting Paraguay



Percentage of all reported U.S. traveler chikungunya cases who indicated they had traveled to Paraguay

Year	US States Locally acquired	US States Travel-associated†	US Territories Locally acquired	US Territories Travel-associated
2014	12‡	2,799	4,659	51
2015	1‡	895	237	0
2016	0	248	180	1
2017	0	156	39	0
2018	0	116	8	0
2019	0	192	2	0
2020	0	33	0	0
2021	0	36	0	0
2022	0	81	0	0
2023	0	154	0	0
2024	0	141	0	0

Data are preliminary and subject to change. Data are current as of November 1, 2024.

\*Includes confirmed and probable disease cases

†Includes cases acquired through other routes (e.g., laboratory transmission)



# Laboratory Workers

- At least 44 chikungunya virus infections identified among laboratory workers worldwide over ~ 50 years
  - 43 cases overt disease, 1 asymptomatic infection, no deaths
- 4 disease cases in US laboratorians since chikungunya became notifiable disease in 2015
  - One case hospitalized for observation, no deaths
- Identified cases underestimate infections as no formal laboratory surveillance system
- Transmission: aerosol, percutaneous, mucosal (possible)



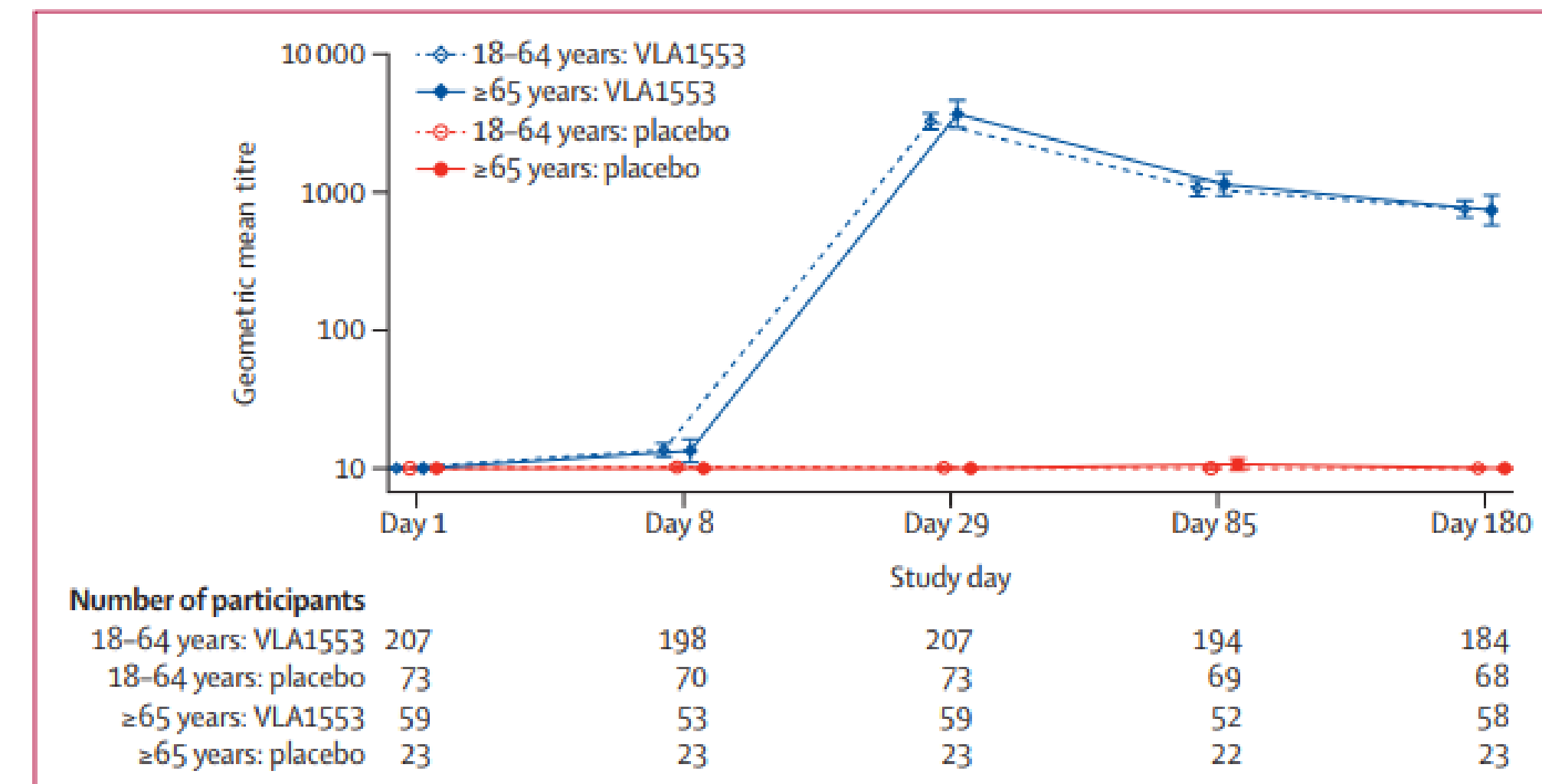


# CHIKV Vaccines: Accelerated Approval Pathway

- Traditional FDA approval challenging
  - Chikungunya outbreaks unpredictable & can be of short duration
  - No established immune correlate of protection
- Accelerated pathway:
  - May be granted by FDA for unmet medical need
  - Effectiveness demonstrated by controlled clinical trials showing vaccine has effect on surrogate endpoint likely to predict clinical benefit
  - Marker of protection for chikungunya vaccine based on neutralizing Ab titer estimated from validated non-human primate model
  - Includes post-licensure requirements for controlled trials to confirm clinical benefit

# Chikungunya Vaccine (IXCHIQ<sup>®</sup>)

- Live attenuated vaccine, manufactured by Valneva
  - Nov 2023: Initial licensure for adults  $\geq 18$  years (accelerated pathway)
  - Only vaccine licensed globally
  - Adolescents 12-17 yr: expected FDA submission 2024 & ACIP vote 2025
  - Children 1-11 yr: clinical trial began Dec 2023
- Single dose primary schedule
- Contraindications:
  - Immunocompromised persons
  - History of severe allergic reaction to any component
- Warnings/precautions:
  - May cause severe or prolonged chikungunya-like adverse reaction
  - Vaccine viremia during first week  $\rightarrow$  no data on risk of vertical transmission





# Benefits and Risks

## Seroprotection

- 2 studies, 622 subjects
  - Seroresponse at 28 days =  $\geq 98\%$
- 1 study, 360 subjects:
  - Seroresponse at 12 months = 99%
- 98% seroprotection persists for 2 years

## Side Effects (w/in 10d)

- Solicited local reactions
  - 15% in vaccinees vs. 11% in placebo
- Solicited systemic adverse events (AE)
  - 50% in vaccinees vs. 27% in placebo
  - Most common: HA, fatigue, myalgia (25-30% of vaccinees)
- Any related severe systemic AEs
  - 1.6% in vaccinees vs. 0% in placebo
    - Fever, arthralgia, myalgia
- Arthralgia/arthritis
  - Arthralgia: 17% vaccinees vs. 5% placebo
- Serious AE within 6 mo:
  - 1.5% in vaccinee vs. 0.8% placebo (2 events)
- No longterm AEs noted at 2 yrs



# ACIP Recommendation (2/24)

- Recommended for:
  - Persons  $\geq 18$  yrs traveling to area with chikungunya outbreak
  - Laboratory workers with potential exposure to CHIKV
- May be *considered* for:
  - Persons  $\geq 18$  yrs traveling to area without outbreak but with evidence of chikungunya transmission within past 5 yr
    - Age  $>65$  years, particularly those with underlying conditions, and likely to have at least moderate exposure\*, OR
    - Persons staying for cumulative period of  $\geq 6$  months

*\*moderate exposure = 2 weeks (cumulative) of exposure to mosquitoes in indoor/outdoor settings*

# Current CDC Travel Considerations

## Chikungunya in the state of Telangana, India

Level 4 - Avoid All Travel

Level 3 - Reconsider Nonessential Travel

Level 2 - Practice Enhanced Precautions

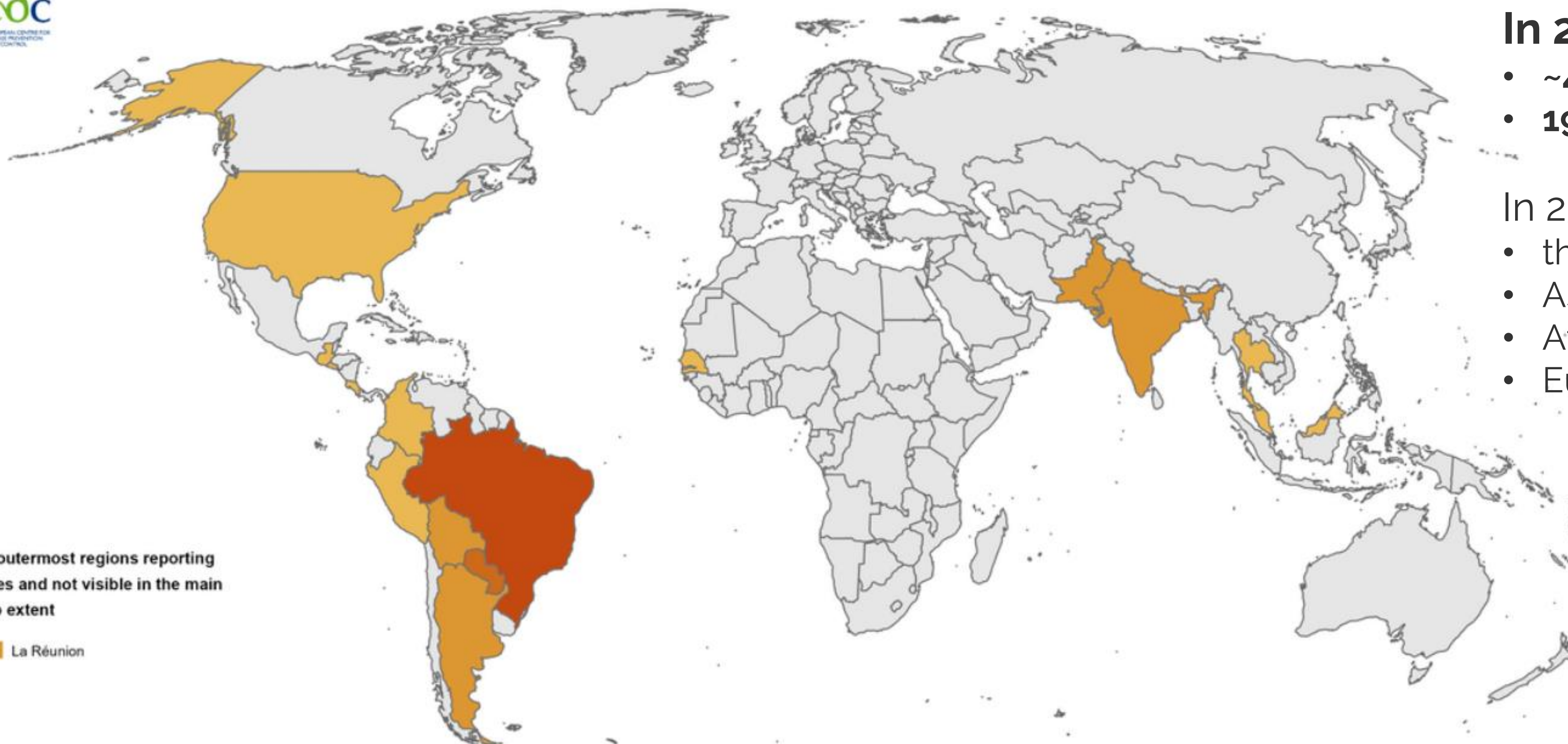
Level 1 - Practice Usual Precautions



Countries with evidence of chikungunya virus transmission to humans during last 5 years



# CHIKV case notification rate per 100,000 population, August to October 2024



**In 2024 (as of 8 Nov):**

- ~480,000 CHIKVD cases
- 190 deaths (Brazil)

**In 23 countries:**

- the Americas (15)
- Asia (6)
- Africa (1)
- Europe (1)

**EU outermost regions reporting cases and not visible in the main map extent**

■ La Réunion



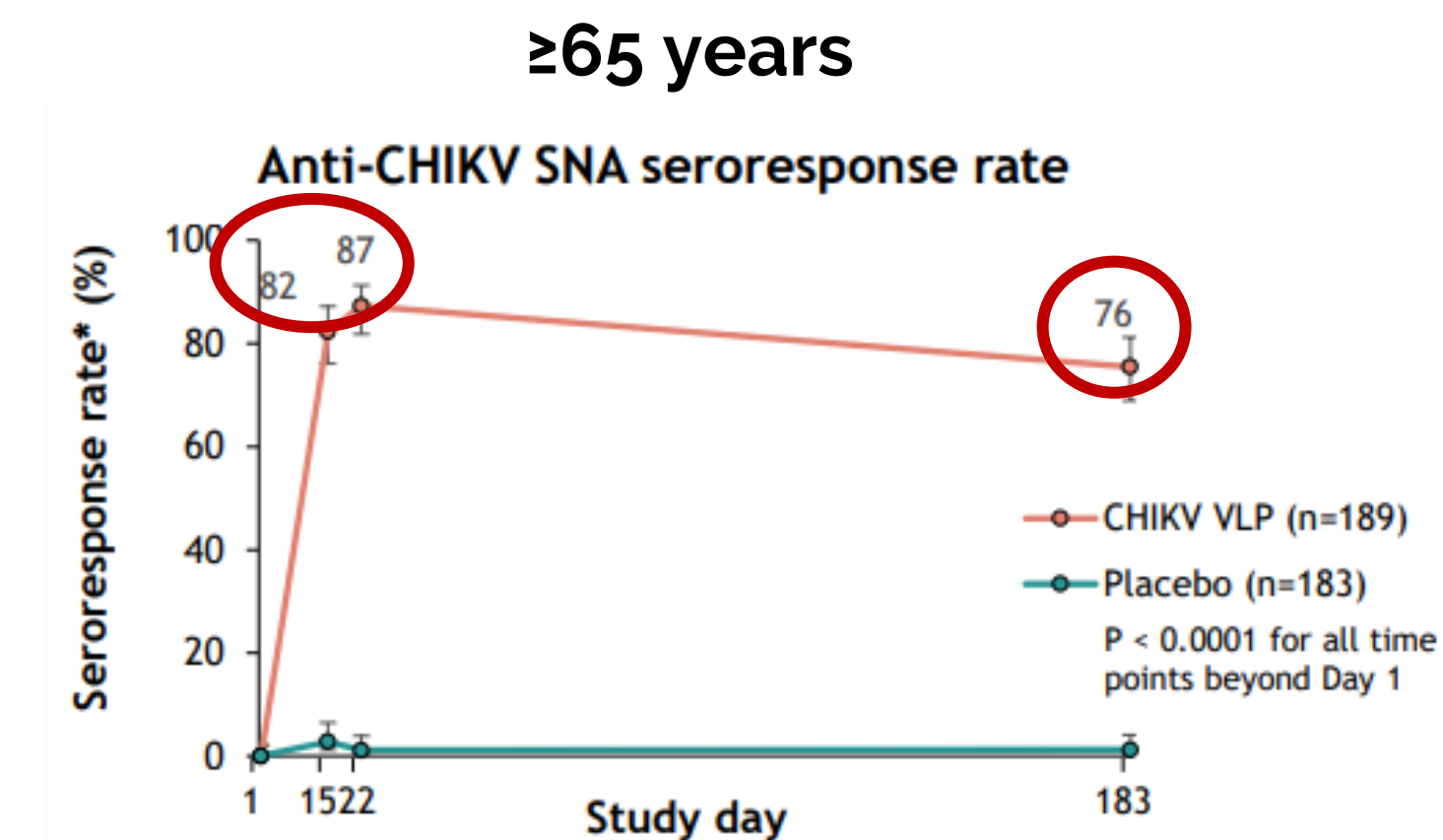
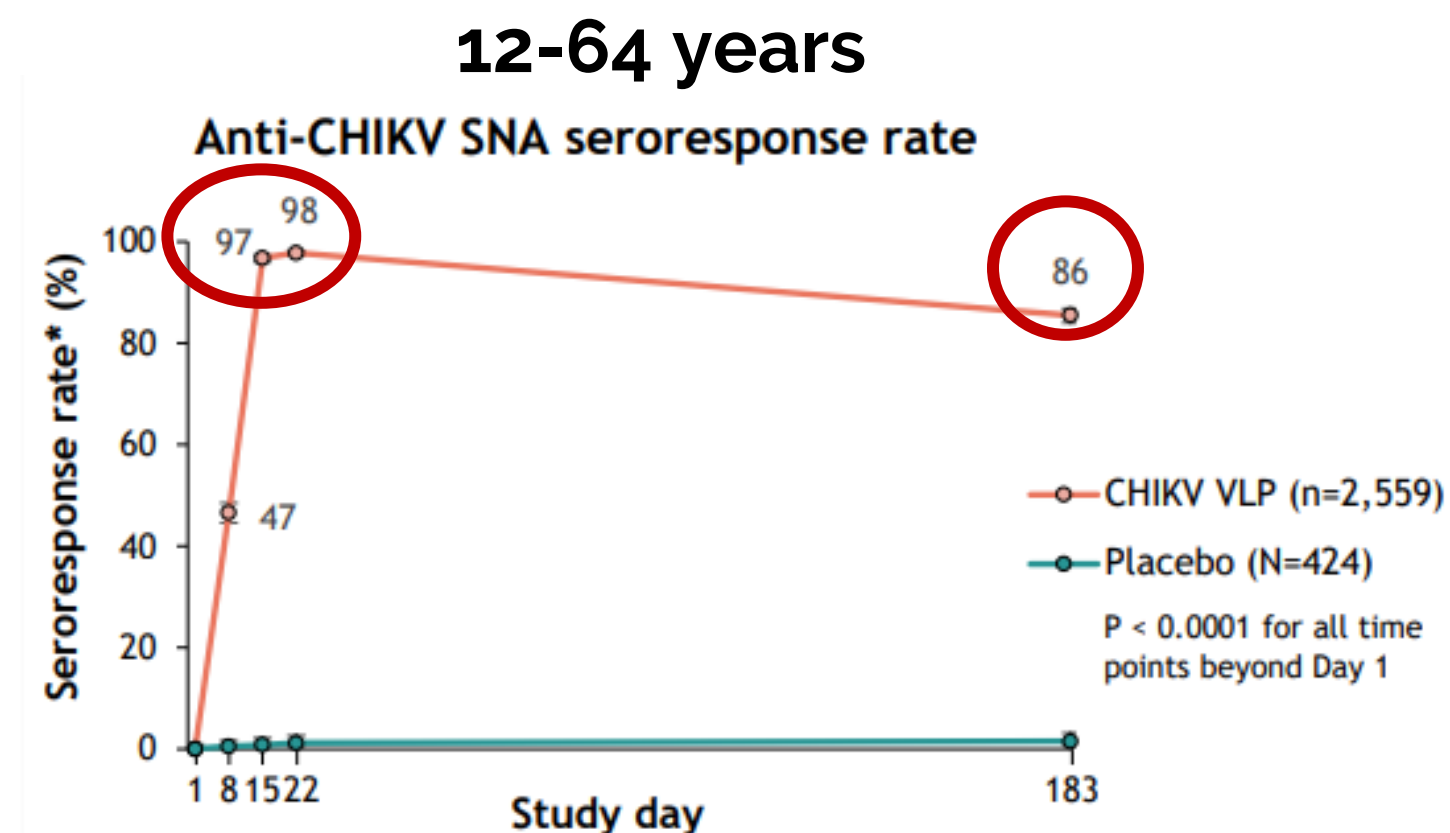


# Pregnancy: Vaccine Recs

- Pregnant persons should avoid risk of chikungunya virus infection if possible (i.e., avoiding travel)
- Pregnancy a precaution, not a contraindication
  - In general, defer to after pregnancy
  - If high risk of infection & exposure cannot be avoided, consider vaccination after discussion of risks/benefits
  - If vaccinating, avoid first trimester (< 14 weeks) and after 36<sup>th</sup> week gestation
    - Pregnancy loss noted in 2 individuals inadvertently vaccinated (1 anembryonic)
    - Vaccine reactogenic → avoid fever in 1<sup>st</sup> TM
    - Avoidance of late pregnancy to limit risk of vaccine-induced viremia in intrapartum period & theoretical risk of perinatal transmission
- Breastfeeding also a precaution, not a contraindication

# Bavarian Nordic Chikungunya Vaccine

- Adjuvanted virus-like particle vaccine (CHIKV VLP)
- Age: adolescents & adults  $\geq 12$  years
- Single dose
- Has received Breakthrough Therapy & Fast Track designations from the FDA
- BLA submitted to FDA June 2024, licensure possible early 2025
- 2 phase III double-blind placebo-controlled RCTs:
  - Conducted in multiple U.S. sites in healthy volunteers
  - Outcome: Presumptive seroprotective antibody response
  - Demonstrated favorable safety profile







# Chikungunya: Summary

- CHIKV outbreaks unpredictable & often explosive, can be localized or widespread
- Low mortality rate but high rate of chronic morbidity
- Huge outbreaks similar to 2014-16 in Americas unlikely to recur, but large outbreaks likely
- Currently 1 vaccine available for travelers & laboratory workers, hopefully soon to be 2 options in 2025
  - Appear highly effective based on immunologic response; phase 4 effectiveness trials needed

**Any Questions?**

