



Dengue: the latest in vaccines

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April 30, 2024

CDC disclaimer

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of [the Centers for Disease Control and Prevention

Outline

- Basic concepts on dengue
- Dengue vaccines
 - Dengvaxia
 - TAK-003 (QDENGGA)
 - TV003



Why you should you care about dengue?



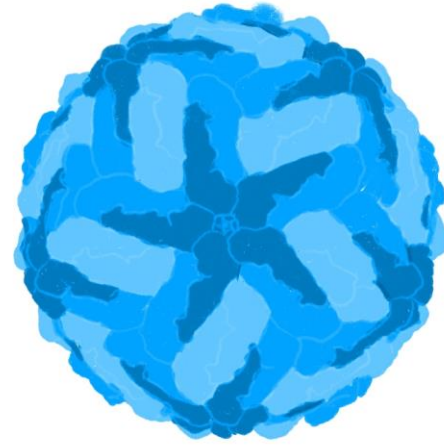
Chapel converted to hospital ward during dengue outbreak in Honduras



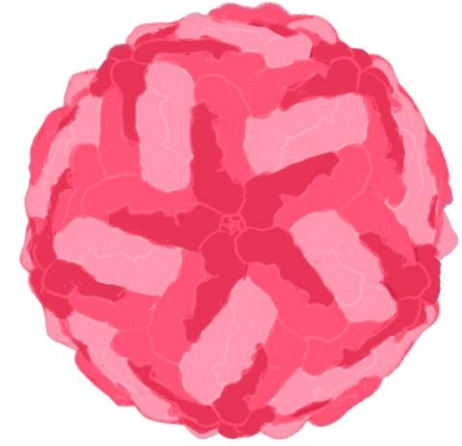
Patients in the corridor of the emergency room in Honduras

Dengue Virus (DENV)

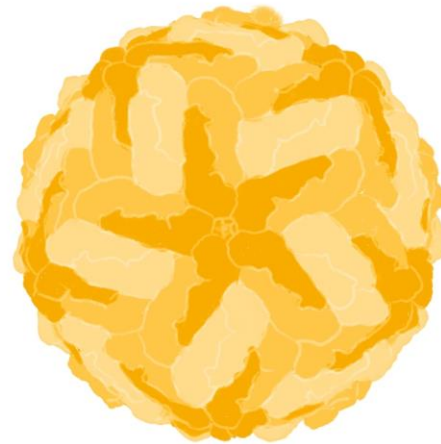
- DENV-1, 2, 3, 4
 - Lifelong DENV type-specific immunity
 - Short-term cross-immunity (~1–2 years)
- Transmitted through the bite of Aedes species mosquitoes



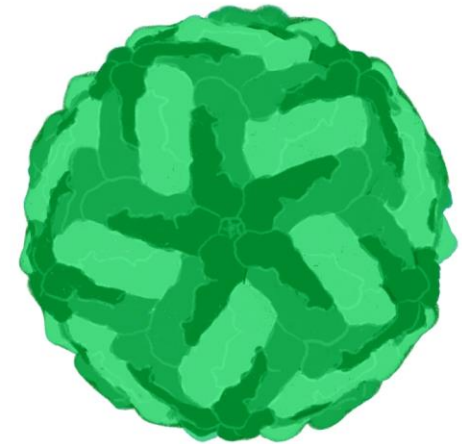
Dengue 1



Dengue 2

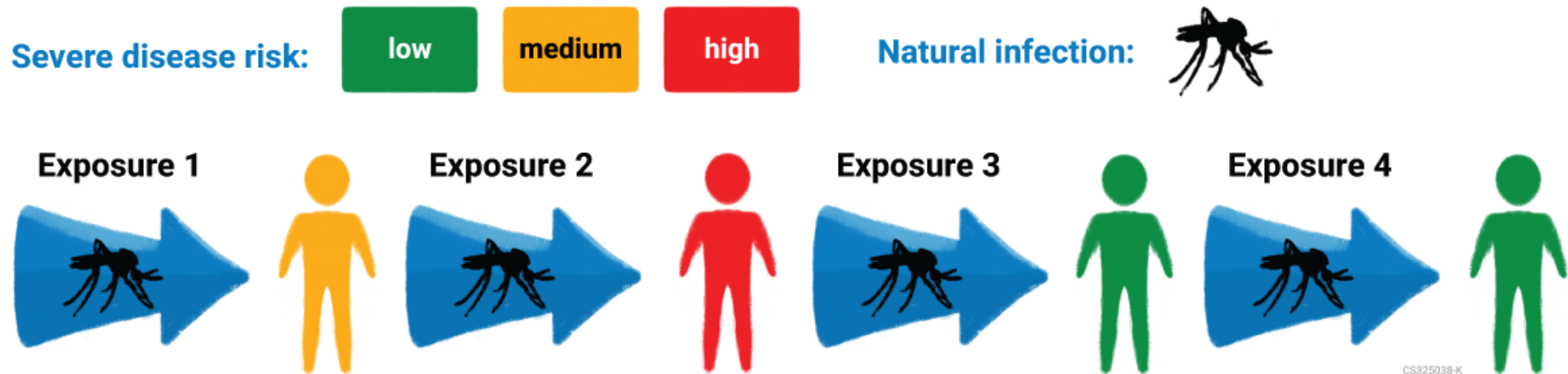


Dengue 3

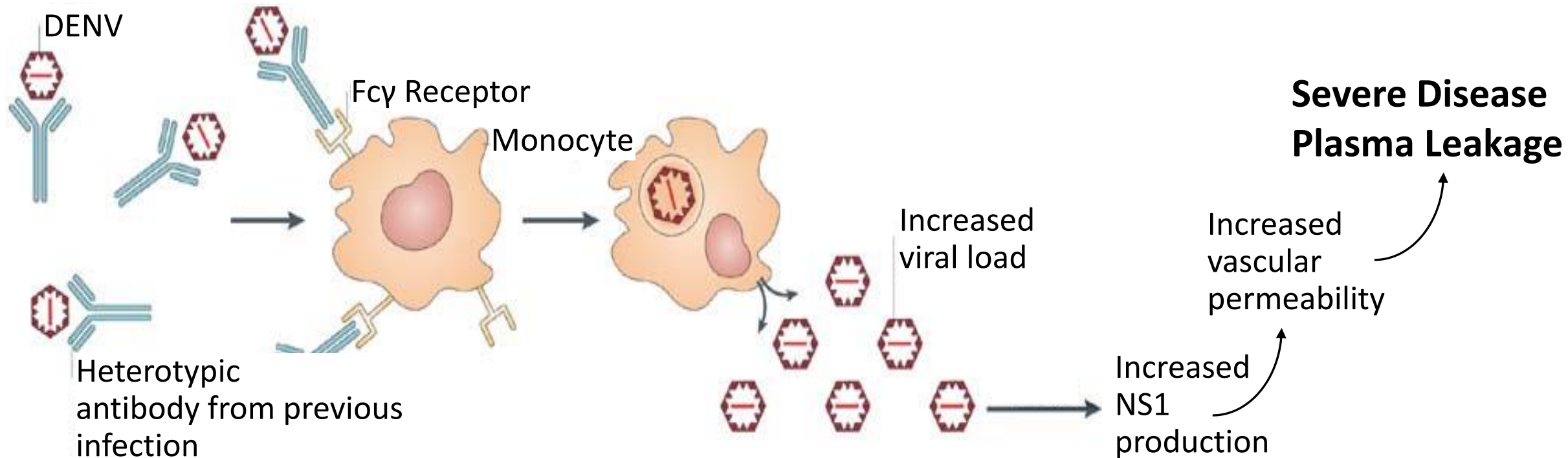


Dengue 4

Secondary DENV infections are at highest risk for severe dengue.



Antibody-dependent enhancement (ADE) of dengue infection



Nature Reviews | Microbiology

Beatty et al, *Science Trans Med* 2015

Implications for dengue vaccines

- Dengue vaccine must protect against all four DENV serotypes
- Vaccines may provide short term heterotypic protection
- A long period of observation following vaccination (2-3 years) is needed to identify immune enhancement

What is an ideal dengue vaccine?

What is an ideal dengue vaccine?



Significant efficacy/safety demonstrated in:

What is an ideal dengue vaccine?

			Ideal Vaccine
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Significant efficacy/safety demonstrated in:

- Seropositives (serotypes combined)



- Seropositives (**all 4 serotypes**)



What is an ideal dengue vaccine?

			Ideal Vaccine
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Significant efficacy/safety demonstrated in:

- Seropositives (serotypes combined)



- Seropositives (**all 4 serotypes**)



- Seronegatives (serotypes combined)



- Seronegatives (**all 4 serotypes**)



What is an ideal dengue vaccine?

			Ideal Vaccine
Significant efficacy/safety demonstrated in:			
- Seropositives (serotypes combined)			✓
- Seropositives (all 4 serotypes)			✓
- Seronegatives (serotypes combined)			✓
- Seronegatives (all 4 serotypes)			✓
Implementation/feasibility			
Number of doses			1
Time to finish primary series			N/A


What is an ideal dengue vaccine?

			Ideal Vaccine
Significant efficacy/safety demonstrated in:			
- Seropositives (serotypes combined)			✓
- Seropositives (all 4 serotypes)			✓
- Seronegatives (serotypes combined)			✓
- Seronegatives (all 4 serotypes)			✓
Implementation/feasibility			
Number of doses			1
Time to finish primary series			N/A
Age recommendation			All ages

What is an ideal dengue vaccine?

	Dengvaxia™			Ideal Vaccine
Significant efficacy/safety demonstrated in:				
- Seropositives (serotypes combined)				✓
- Seropositives (all 4 serotypes)				✓
- Seronegatives (serotypes combined)				✓
- Seronegatives (all 4 serotypes)				✓
Implementation/feasibility				
Number of doses				1
Time to finish primary series				N/A
Age recommendation				All ages
Recommended for travelers				✓
Prevaccination screening* NOT recommended				✓

*Laboratory test to determine eligibility

A child with curly hair and a backpack is walking away from the camera through a brightly colored school hallway. The walls are painted in vibrant shades of yellow, red, and blue. The child is wearing a white t-shirt and a blue denim backpack. The scene is captured from a low angle, emphasizing the child's presence in the space.

APPROVED VACCINE

Dengvaxia

Dengvaxia construct and schedule

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


3 shots required for full protection



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

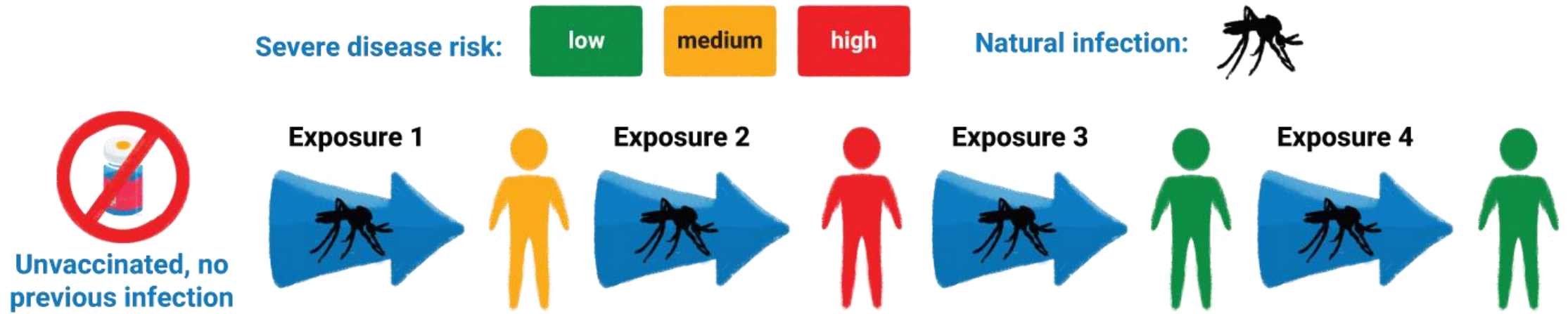
- 
- 2000s: Dengvaxia developed
 - 2010: Phase 3 trials started
 - 2015
 - Trial results show increased risk of severe disease among aged 2-5 years.
 - 2016
 - WHO recommends the vaccine among children ≥ 9 years old in endemic areas.
 - 2017
 - Case-cohort study showed increased risk of severe dengue and hospitalization among seronegative children vaccinated compared to controls
 - **WHO revised their recommendations to vaccinate children with laboratory-confirmed evidence of a past infection.**

Dengvaxia™ and previous dengue infection

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

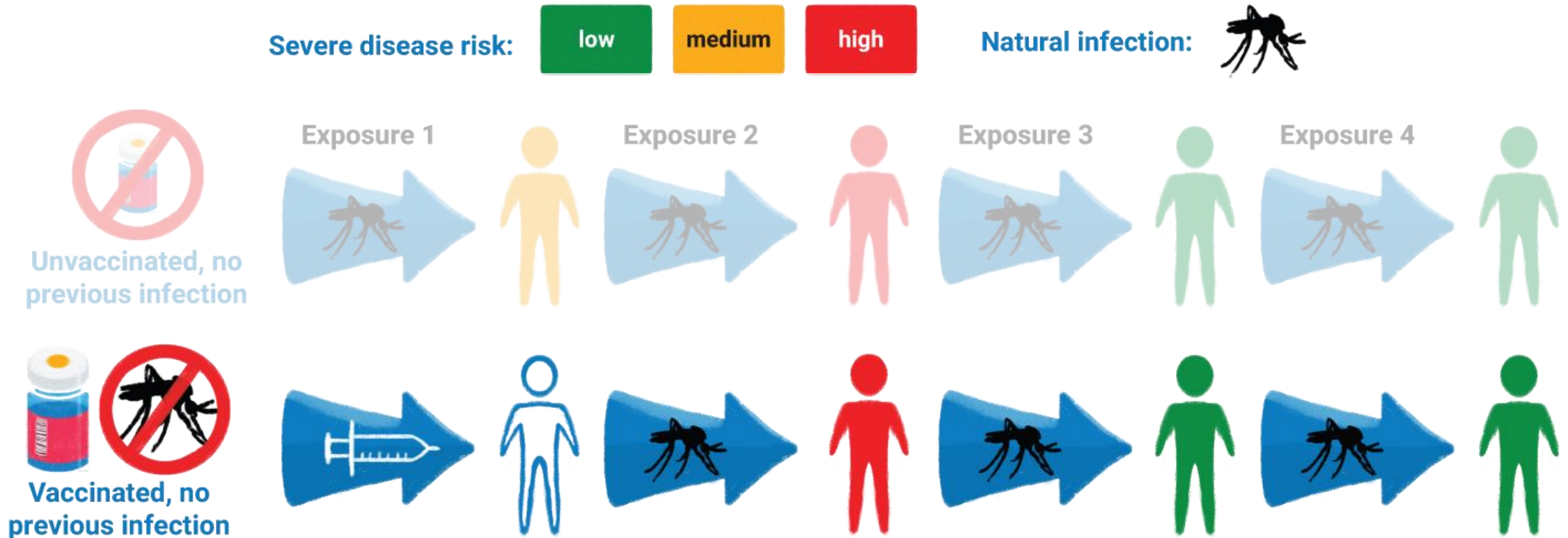
- Children **without previous dengue infection** had a **higher risk for hospitalization and severe dengue** if they were vaccinated and then had a DENV infection.
- Children **with previous dengue infection** were **protected from hospitalization and severe dengue** if they were vaccinated with Dengvaxia™.

How does Dengvaxia increase risk among seronegatives?



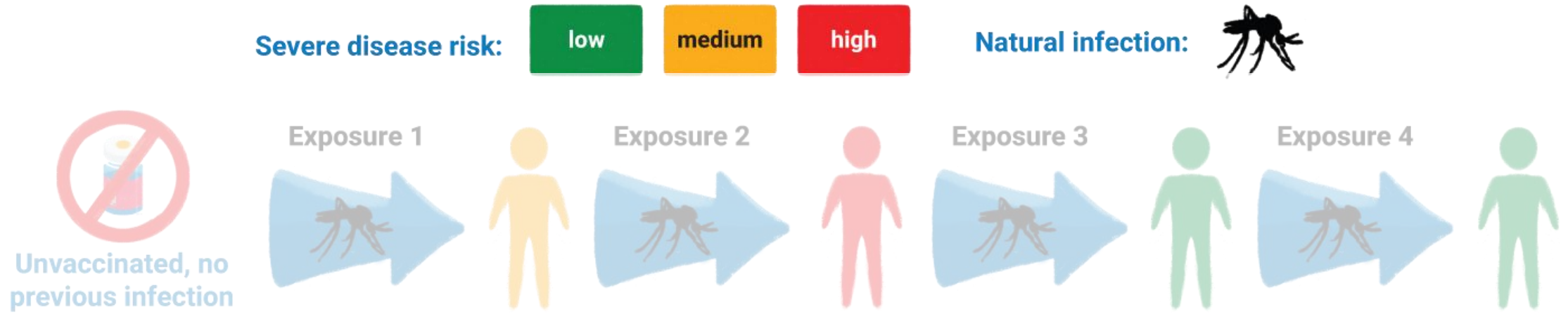
Secondary DENV infections are at highest risk for severe dengue (unvaccinated).

How does Dengvaxia increase risk among seronegatives?

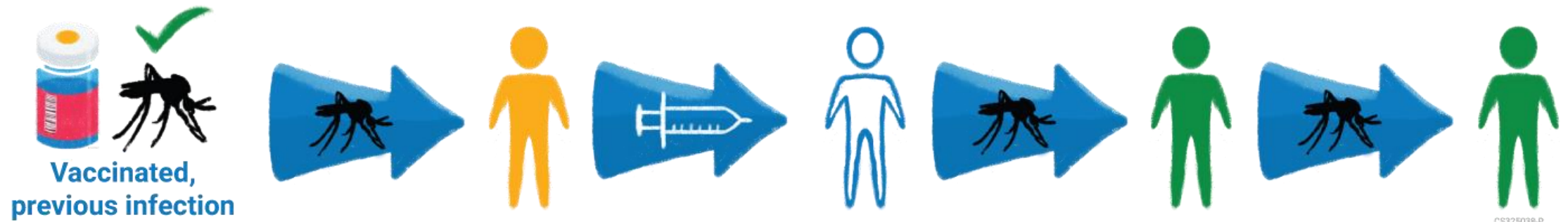


Vaccination with Dengvaxia of a seronegative individual heightens the risk of a **severe primary infection.**

How does Dengvaxia increase risk among seronegatives?



Vaccination of a seropositive individual reduces the risk of a severe secondary infection.



Dengvaxia efficacy, persons 9–16 years with previous DENV infection

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.

Dengvaxia and an ideal dengue vaccine

	Dengvaxia™			Ideal Vaccine
Significant efficacy/safety demonstration				
- Seropositives (serotypes combined)	✓			✓
- Seropositives (all 4 serotypes)	✓			✓
- Seronegatives (serotypes combined)	✗			✓
- Seronegatives (all 4 serotypes)				✓
Implementation/feasibility				
Number of doses	3			1
Time to finish primary series	1 year			N/A
Age recommendation	9–16 years			All ages
Recommended for travelers	✗			✓
Prevaccination screening NOT recommended	✗			✓

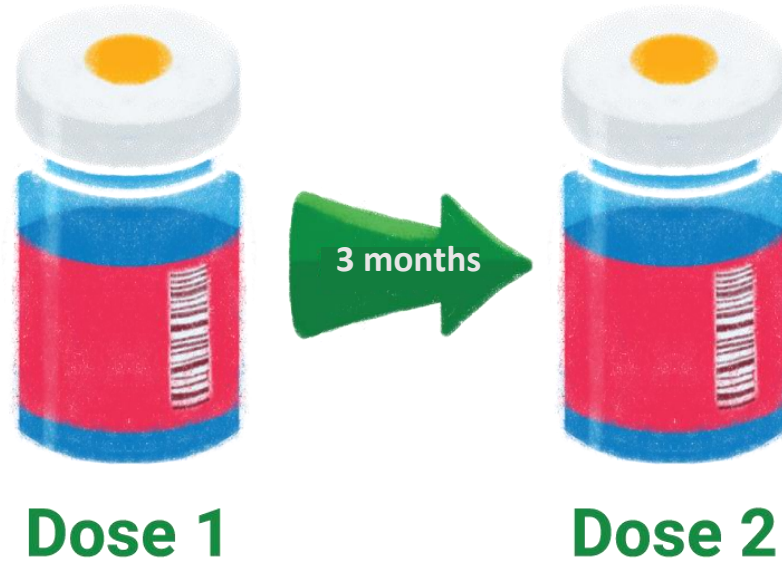
A child with dark, curly hair is seen from behind, wearing a white t-shirt and a blue denim backpack. They are walking away from the camera down a brightly lit school hallway. The lockers on either side are painted in vibrant colors like yellow, red, and blue. The overall atmosphere is bright and cheerful.

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:**

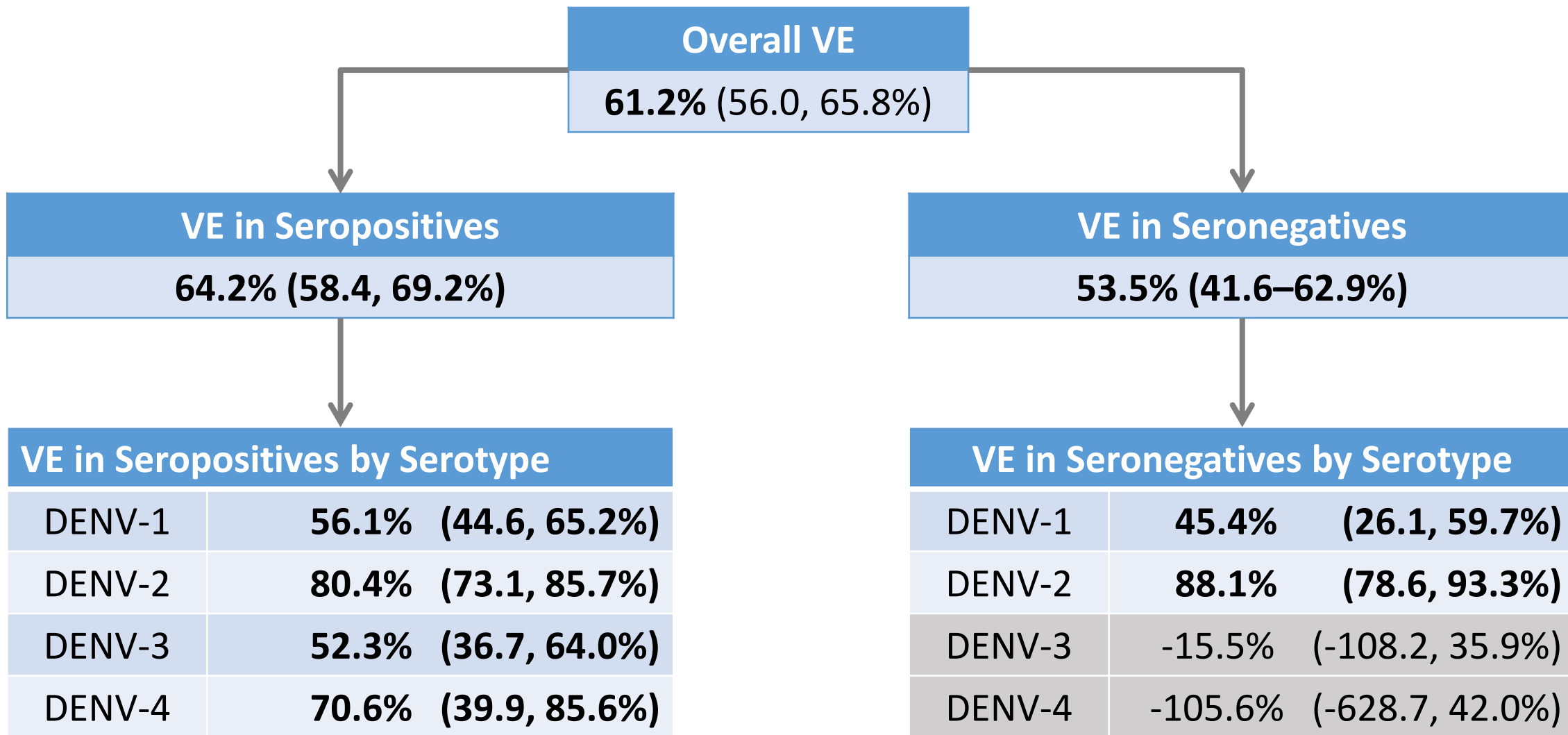


CS325038-D

WHO SAGE recommendations for TAK-003

Sept 25, 2023

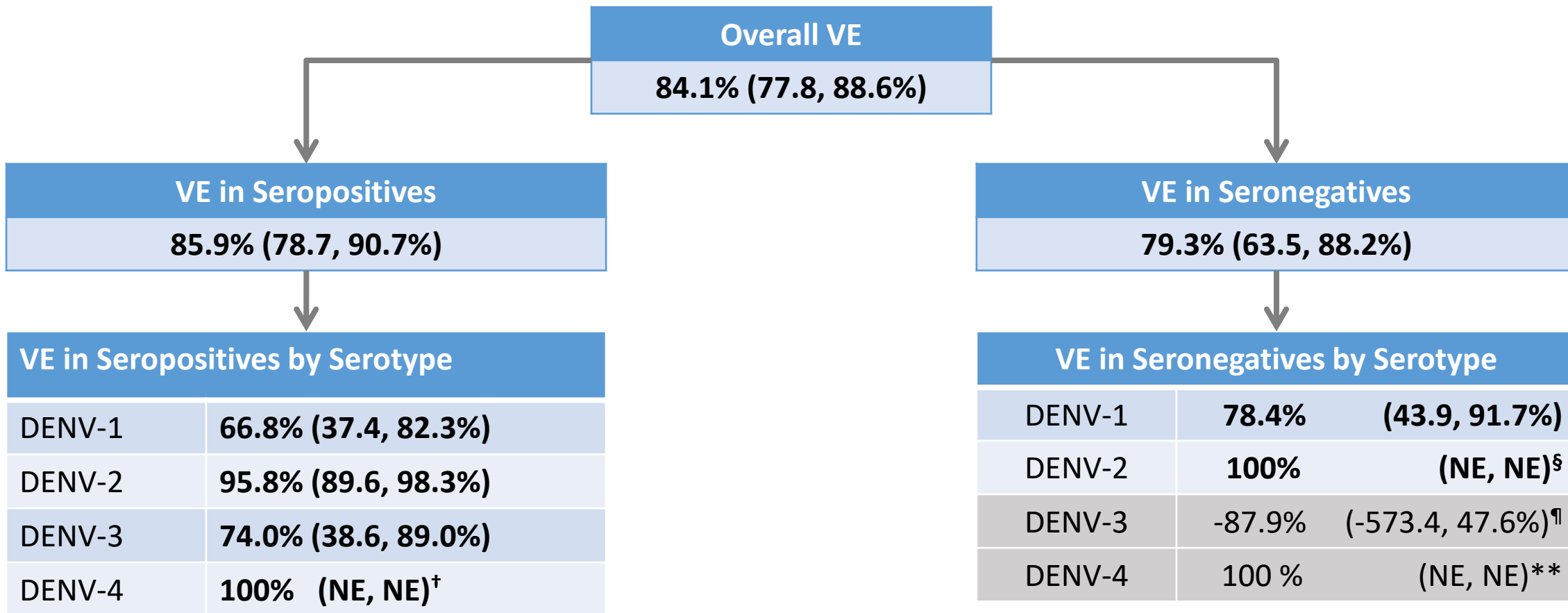
- TAK-003 should be considered for introduction in settings with **high dengue transmission intensity**
- Threshold cut-offs for minimal seroprevalence to initiate vaccination should be decided by countries
 - >60% by the age of 9 years indicator of high dengue transmission
 - Peak dengue-associated hospitalizations <16 years indicator of high dengue transmission.
- To be introduced to children aged **6 to 16 years** of age
- Post-licensure studies to understand effectiveness/risk profile against DENV-3 and DENV-4 in seronegative persons
- Licensed in several countries and implemented in Brazil as part of immunization program.



*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.

TAK-003 Vaccine Efficacy*

Outcome: Hospitalization



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

[§]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.

Dengvaxia, TAK-003 and an ideal dengue vaccine

	Dengvaxia™	TAK-003		Ideal Vaccine
Significant efficacy/safety demonstrated in:				
- Seropositives (serotypes combined)	✓	✓		✓
- Seropositives (all 4 serotypes)	✓	✓		✓
- Seronegatives (serotypes combined)	✗	✓		✓
- Seronegatives (all 4 serotypes)	✗	✗		✓
Implementation/feasibility				
Number of doses	3	2		1
Time to finish primary series	1 year	3 months		N/A
Age recommendation	9–16 years	6-16		All ages
Recommended for travelers	✗	✓		✓
Prevaccination screening NOT recommended	✗	✓		✓

A child with dark, curly hair is seen from behind, wearing a white t-shirt and a blue denim backpack. They are walking away from the camera down a brightly lit school hallway. The lockers on either side are painted in vibrant colors like yellow, red, and blue. The overall atmosphere is bright and cheerful.

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

CS325030-0

TV003 status

- Developed by the US National Institutes of Health (NIH).
- Licensed to Merck, Butantan, Serum Institute of India and others.
- Phase 3 trials in Brazil ongoing, 2-year follow-up released.
- Submitting to Brazil regulatory agency (ANVISA) late 2024



Efficacy against VCD of TV003 through 2 years post-vaccination

	Overall efficacy	DENV-1	DENV-2
Overall	79.6 (70.0-86.3)	89.5 (78.7-95.0)	69.6 (50.8-81.5)
Seropositive	89.2 (77.6-95.6)	96.8 (81.0-99.8)	83.7 (63.1-93.5)
Sero-naive	73.6 (57.6-83.7)	85.5 (61.1-94.0)	57.9 (20.8-78.1)

There were not any cases of DENV-3 or DENV-4 detected in the first 2 years of the trial

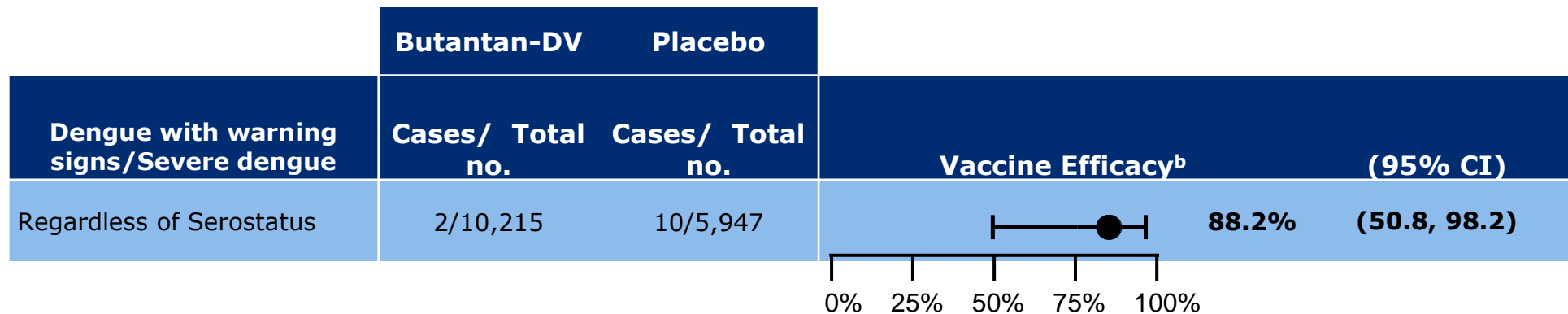
Kallas E, et al, NEJM 2024

Slide provided by Dr. Anna Durbin



Vaccine efficacy against dengue with warning signs or severe dengue

Through the data cut-off (2 or more years of follow up for each participant)**



- The case definitions correspond to those used by the Brazilian Ministry of Health from 2013 which adopts the definitions proposed by the 2009 World Health Organization classification

Nogueira M et al. ASTMH Chicago, IL, US Oct 2023.
Slide provided by Dr. Anna Durbin



What are we forecasting for TV003?

	Dengvaxia™	TAK-003	TV003	Ideal Vaccine
Significant efficacy/safety demonstrated in:				
- Seropositives (serotypes combined)	✓	✓	✓	✓
- Seropositives (all 4 serotypes)	✓	✓	?	✓
- Seronegatives (serotypes combined)	✗	✓	✓	✓
- Seronegatives (all 4 serotypes)	✗	✗	?	✓
Implementation/feasibility				
Number of doses	3	2	1	1
Time to finish primary series	1 year	3 months	N/A	N/A
Age recommendation	9–16 years	6-16	?	All ages
Recommended for travelers	✗	✓	?	✓
Prevaccination screening NOT recommended	✗	✓	?	✓

Summary of current state of dengue vaccines

- Safety is key for all vaccines, and highly scrutinized for dengue vaccines.
- Implementing the currently recommended vaccines is important for dengue control
- TAK-003 post-licensure studies will provide more information on efficacy and safety for DENV3 and DENV4
- TV003 is completing phase 3 trials and may be licensed in Brazil in the next year

CDC Dengue Branch, San Juan, Puerto Rico

