UPDATE ON DENGVAXIA: EFFICACY, SAFETY AND IMPLEMENTATION

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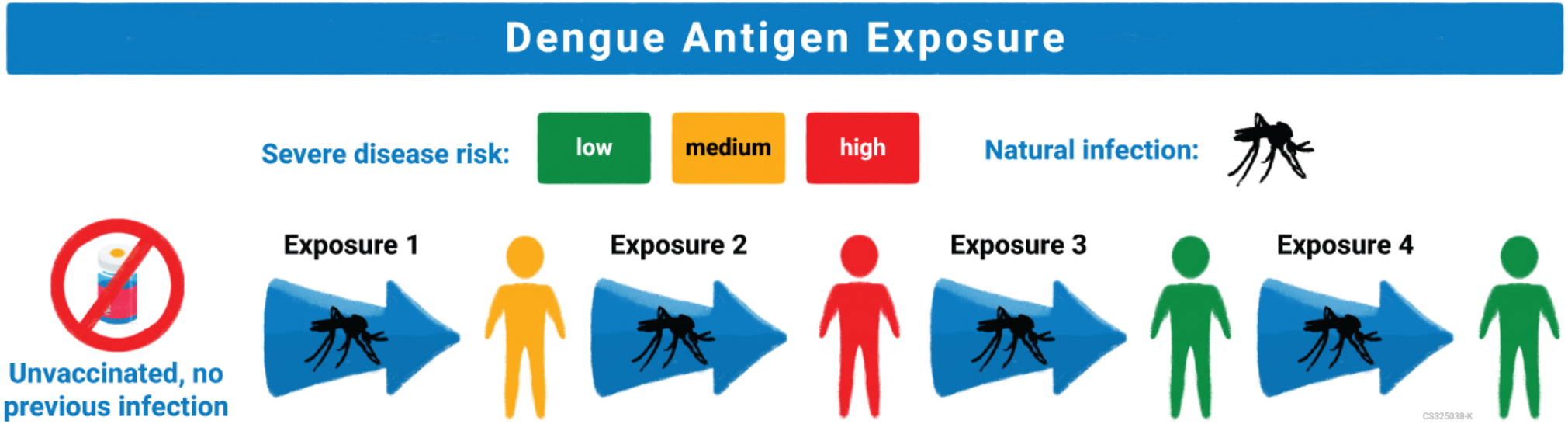
Severe dengue and multiple DENV infections

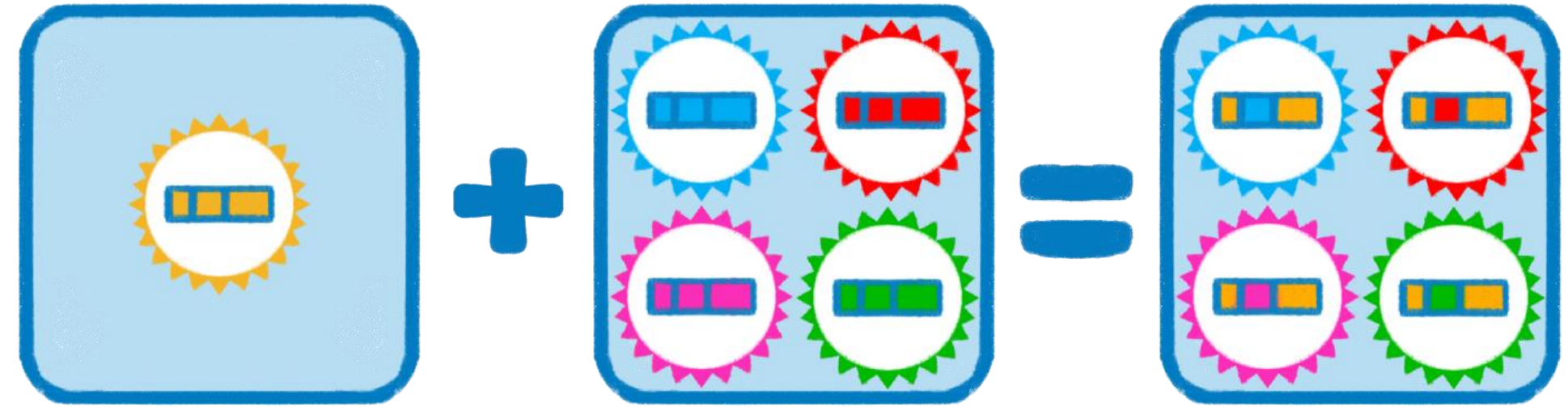


- Infection with DENV-1, 2, 3, 4 provides **lifelong DENV type-specific immunity** and **short-term cross-immunity**
- **Second DENV infections are more severe** in part because of **antibody-dependent enhancement** leading to plasma leakage and severe disease.

ABOUT DENGVAXIA

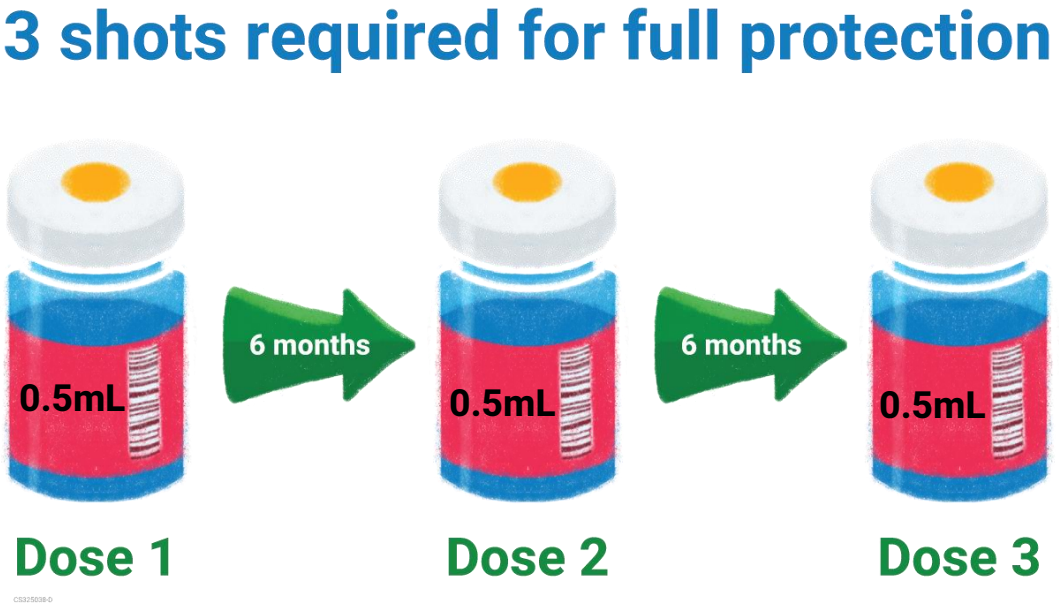
Dengvaxia™ technology

- Dengvaxia is a tetravalent, live-attenuated dengue vaccine.
- Yellow fever backbone with sequences from the homologous dengue virus serotypes 1, 2, 3, and 4.



Dengvaxia™ schedule

- **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.

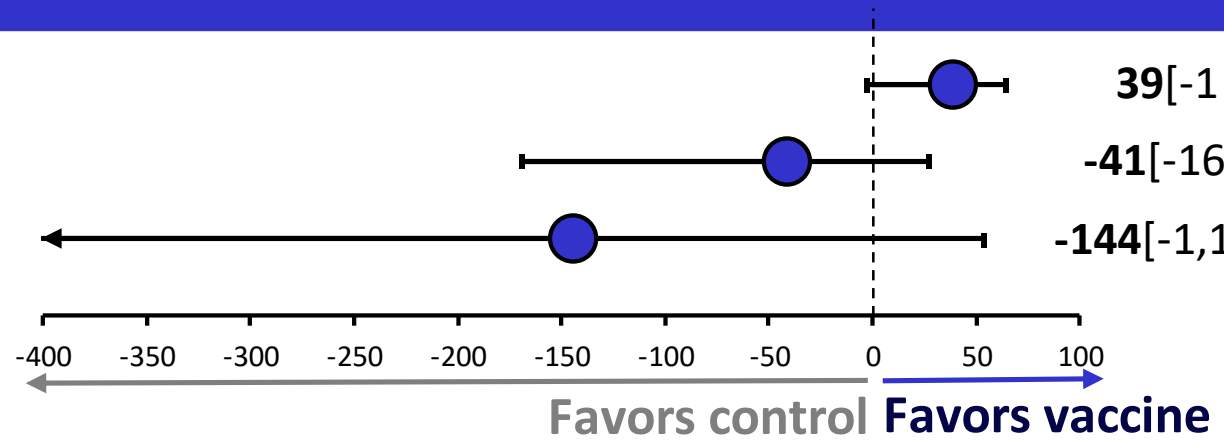
Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. New England Journal of Medicine. 2018 2018-07-26;379(4):327-40.

HARMS

Vaccine safety

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]



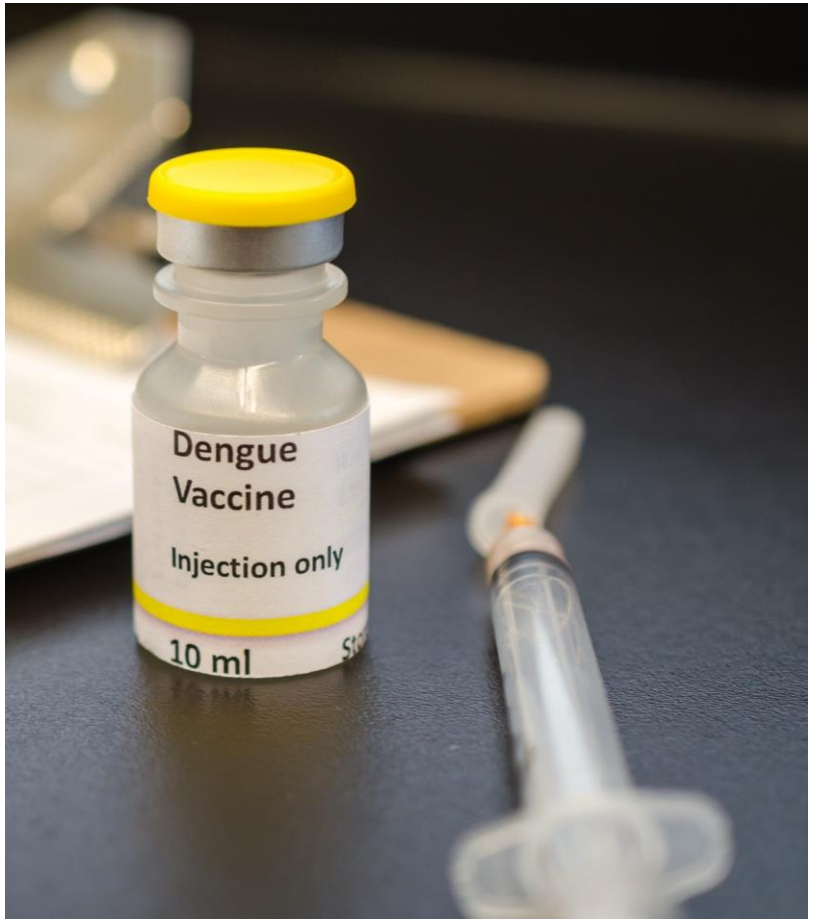
Note: Vaccine efficacy from hospitalization and severe dengue, calculated from hazard ratios (VE=(1-HR)*100). Cumulative incidence rates among seronegative participants calculated through month 25 for virologically confirmed symptomatic dengue and through month 60 for hospitalization and severe dengue.

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

Dengvaxia 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

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.

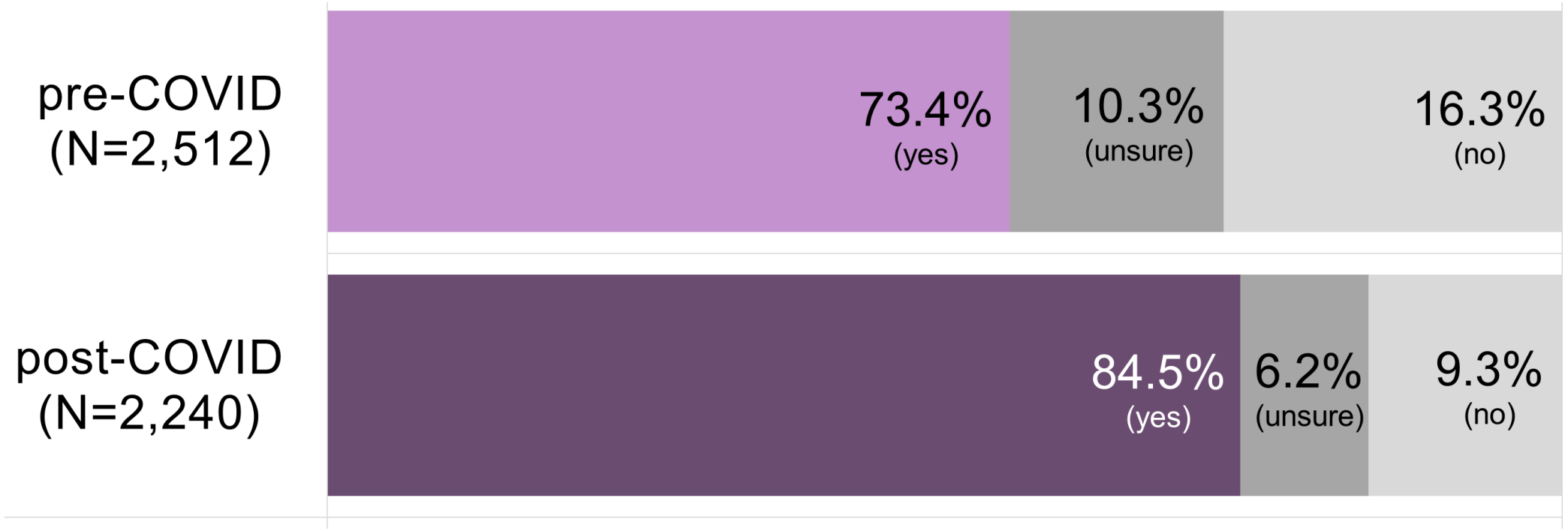
- Other tests meeting performance requirements might become available in the future. For the most up to date information, please visit https://www.cdc.gov/dengue/vaccine/hcp/testing.html

IMPLEMENTATION

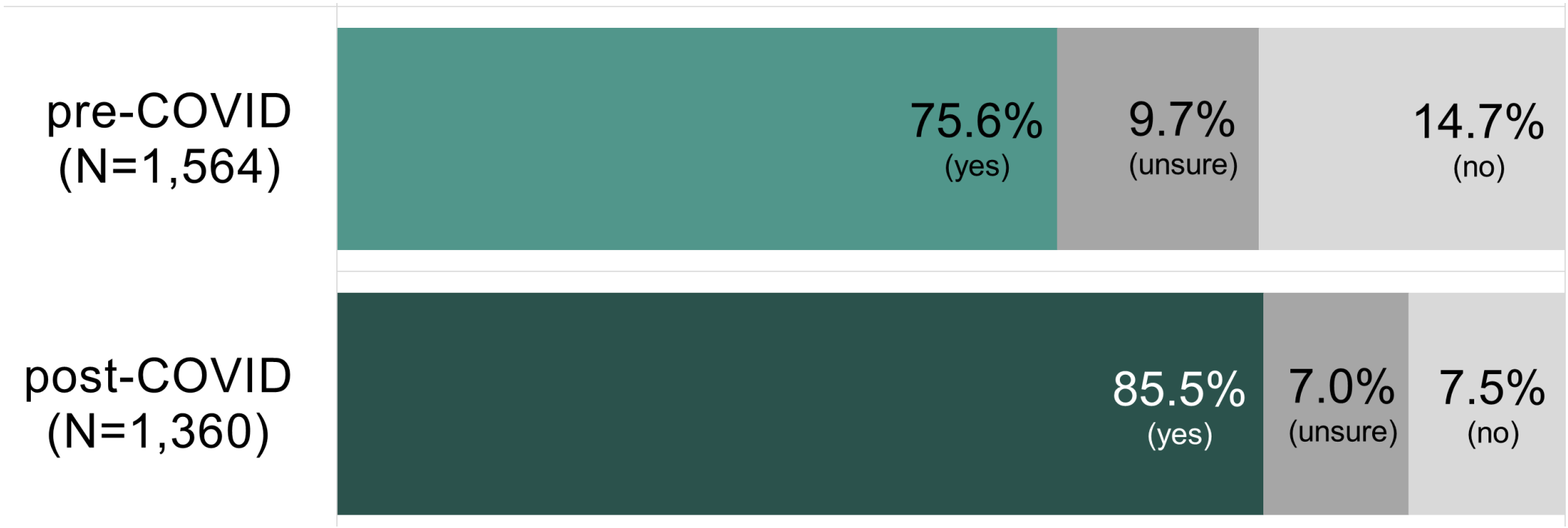
Puerto Rico

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

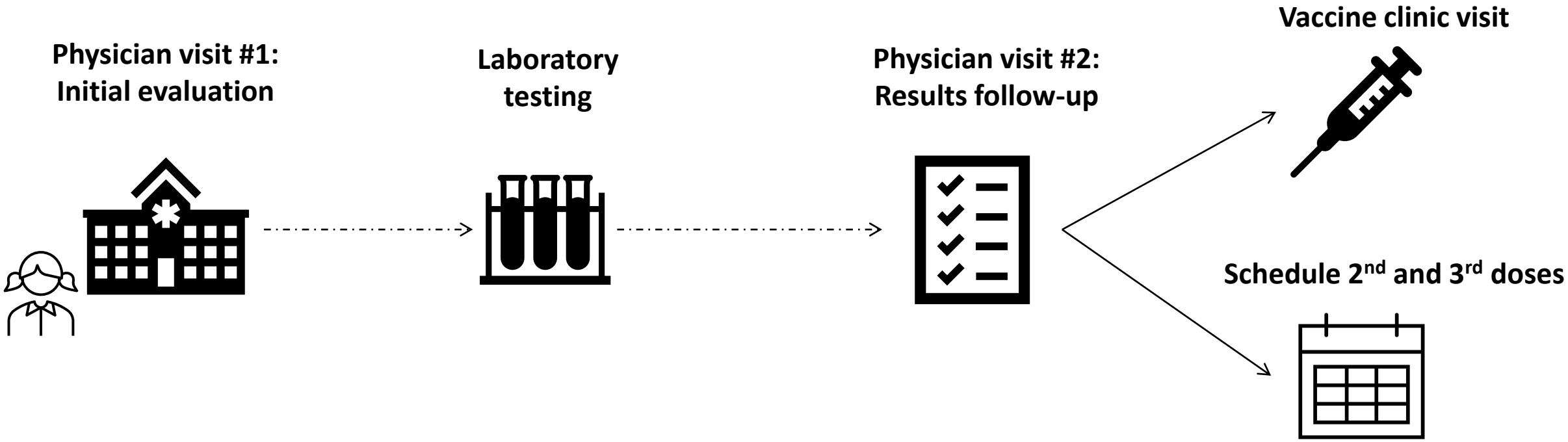
If there was an approved vaccine for dengue in Puerto Rico, would you get it?



If there was an approved vaccine for dengue in Puerto Rico, would you vaccinate your children?



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.com de Puerto Rico

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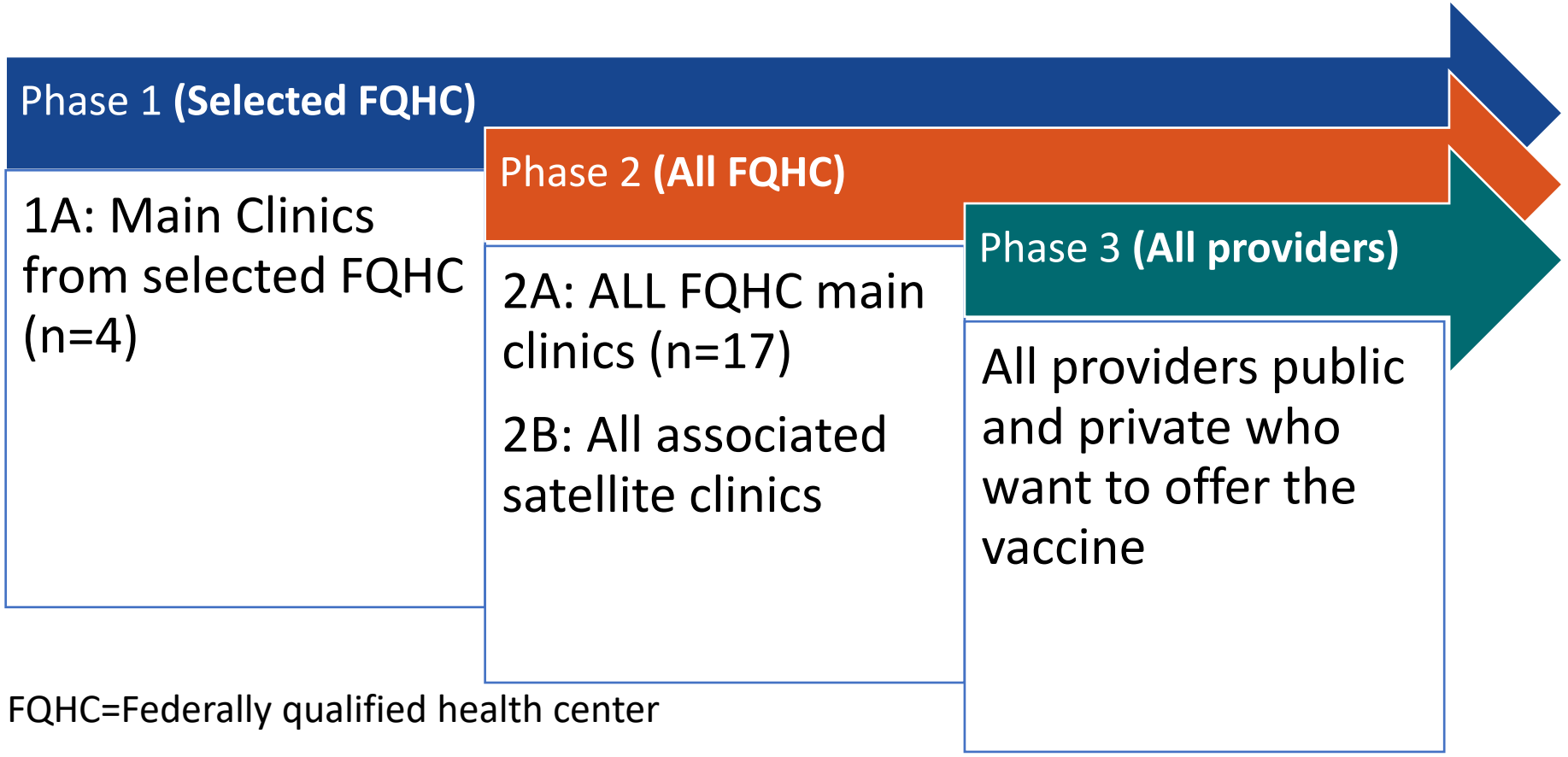
Phased implementation in Puerto Rico

- **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: January 2023



FQHC=Federally qualified health center

Challenges

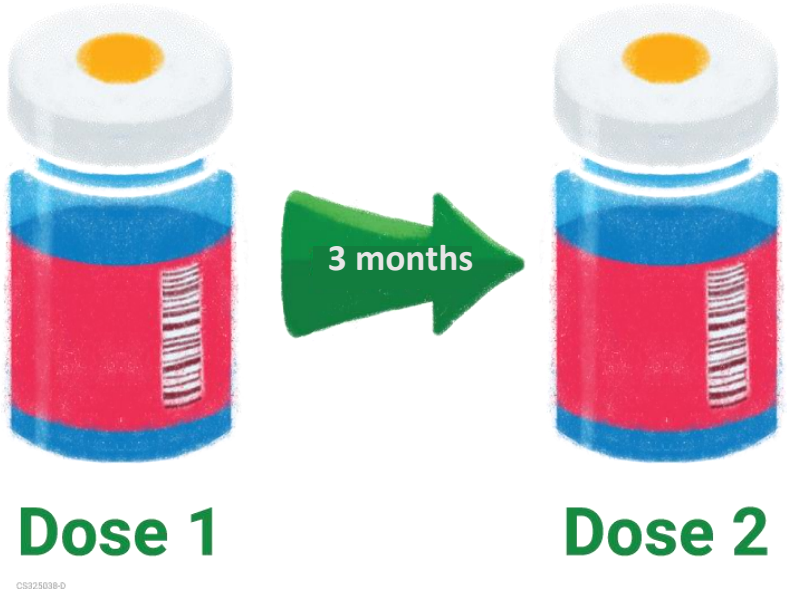
- Pre-vaccination screening requirement
- Tests not FDA approved implemented under CLIA
- All testing in Puerto Rico should be conducted by a licensed technician
- Messaging on a vaccine to prevent dengue only among seropositive
- Insurance coverage for the test has been complicated by lack of a specific billing code
  - Resolved in October 2022
- 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 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

- **October 2022**
  - European Medicine Agency recommended the approval of Takeda's Dengue Tetravalent Vaccine for the prevention of dengue disease caused by any serotype in individuals 4 years of age and older
    - Review was for European Union (EU) market and non-EU countries, under the 'EU-Medicines for all'
    - Final step in Europe is Marketing Authorization from the EMA, expected in the coming months.
  - Approved for use in Indonesia.
- **Other countries**
  - Plans to submit to regulatory agencies in Argentina, Brazil, Colombia, Malaysia, Mexico, Singapore, Sri Lanka, Thailand and U.S.

- 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/.

Summary

The Dengvaxia vaccine has an efficacy of ~80% among seropositive children against:

- Symptomatic virologically confirmed dengue
- Hospitalization for dengue
- Severe dengue

- Implementation has been challenging due to the pre-vaccination screening requirement, the two-test algorithm and reimbursement
- The dengue vaccine workgroup has started review of the Takeda TAK-003 dengue vaccine

ACIP Dengue Vaccines Workgroup

ACIP Members

Wilbur Chen (Chair)

Kathy Poehling

Beth Bell

Veronica McNally

CDC Co-Lead

Gabriela Paz-Bailey

Laura Adams

Ex Officio Members

Kaitlyn Morabito (NIH)

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Josh Wong

Mimi Eckert

Rachel Eidex

Alfonso Hernandez

Susan Hills

Terri Hyde

Mike McNeil

Jorge Munoz

Erin Staples

Cindy Weinbaum

Rita Helfand

THANK YOU!

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348
www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.