



DENGUE VACCINE: CONSIDERATIONS FOR HEALTHCARE PROFESSIONALS



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- Dengue virology, epidemiology, and clinical considerations
- Dengvaxia dengue vaccine efficacy, safety, and indications for use
- Pre-vaccination laboratory screening for previous dengue infection

Topics

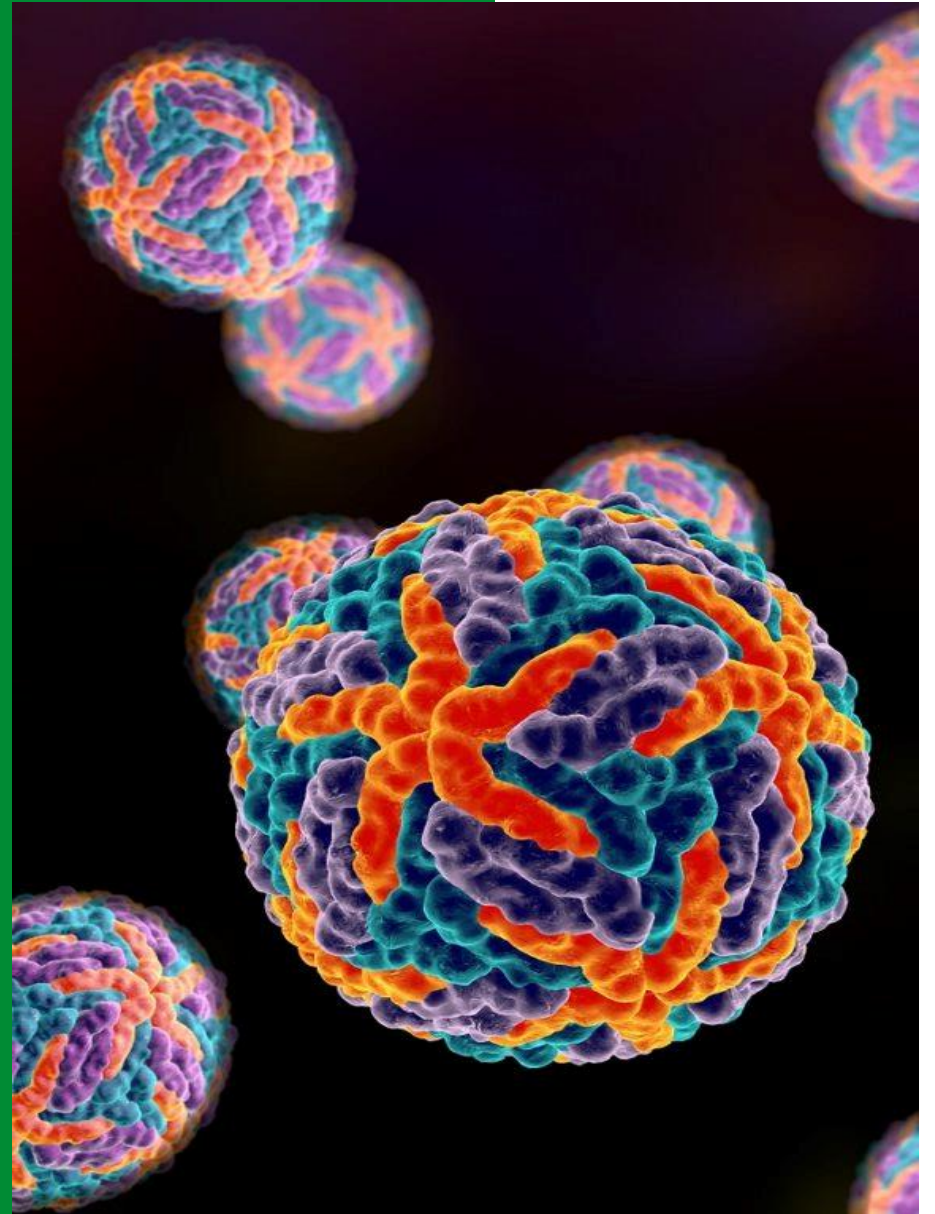




DENGUE VIRUS AND EPIDEMIOLOGY

About Dengue

- Dengue is the disease caused by dengue viruses (DENV): DENV-1, DENV-2, DENV-3, and DENV-4.
- Once infected, individuals have life-long immunity against re-infection from the **same serotype**.
- People can be infected with DENV up to 4 times in their life.



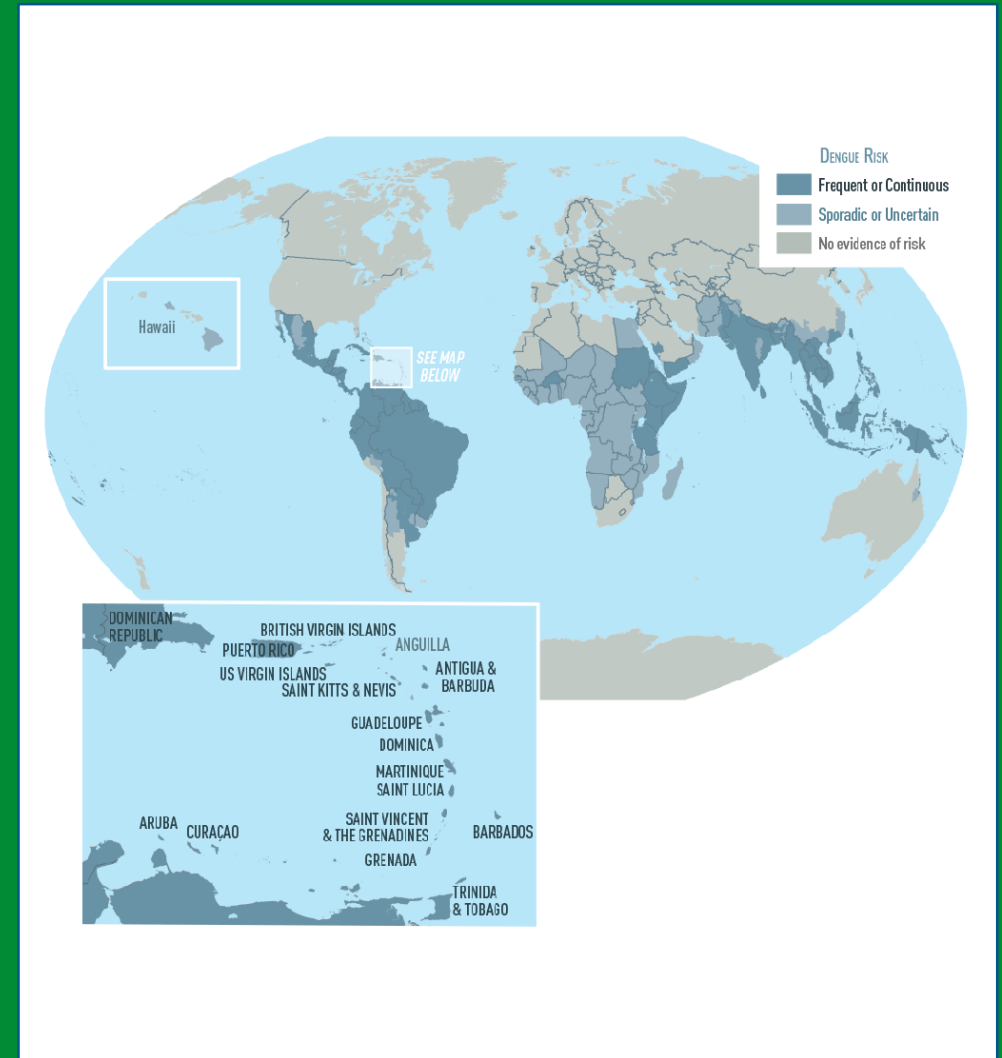
Dengue transmission occurs through...

- The bite of an infected *Aedes* species (*Ae. aegypti* or *Ae. albopictus*) mosquito.
 - Symptoms occur 5–7 days after the bite.
- Other routes of transmission include:
 - Bloodborne transmission
 - Perinatal transmission
 - Breast milk transmission

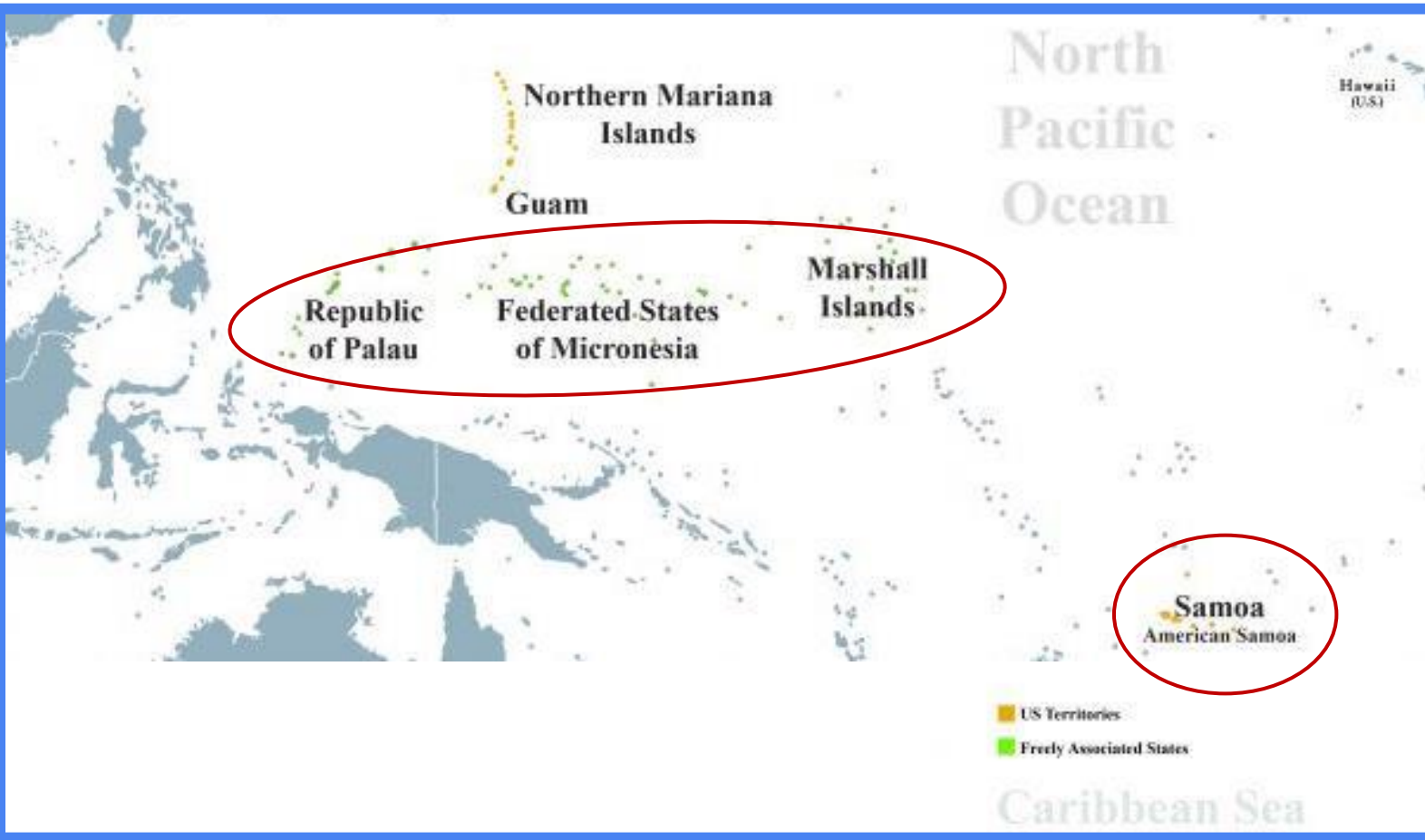


Areas with Risk of Dengue

- Dengue is the most common mosquito-borne virus in the world.
- About half of the world's population, about 4 billion people, live in areas with a risk of dengue.
- Each year, up to 400 million people get infected with dengue.
- Approximately 100 million people get sick from infection, and 40,000 die from severe dengue.



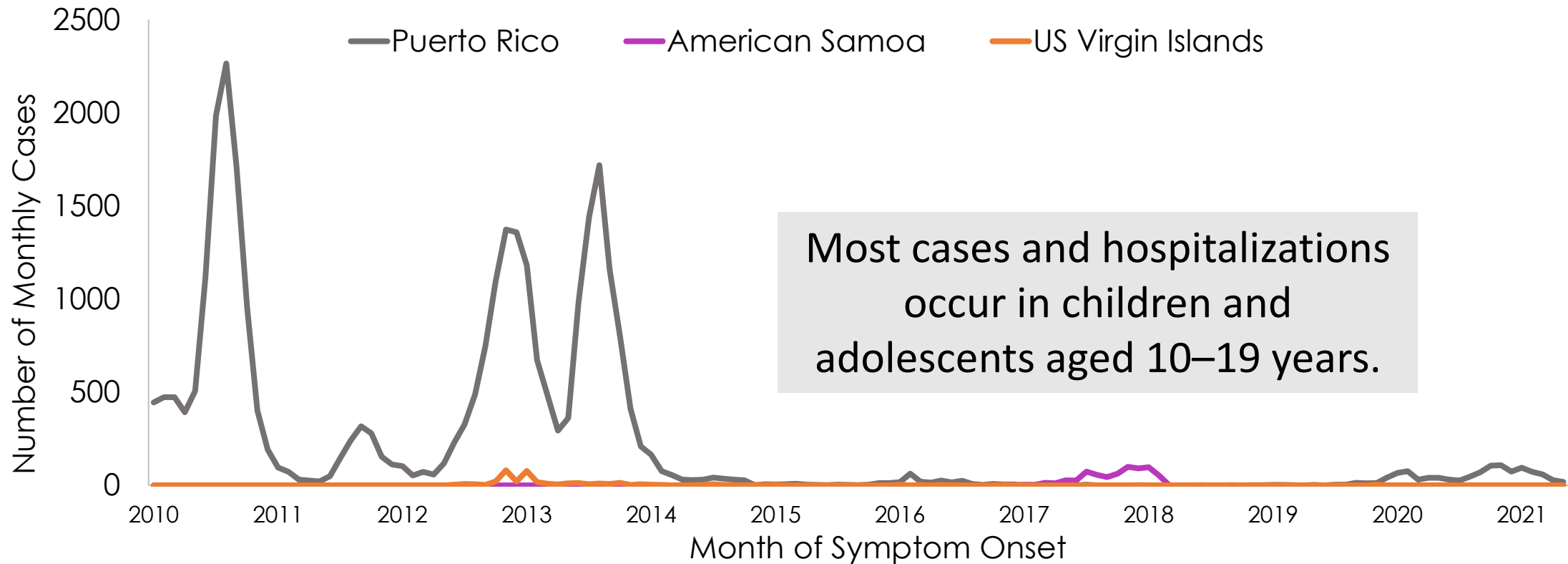
Dengue in the United States, U.S. Territories, and Freely Associated States



Dengue is endemic in the areas indicated.



Large, Cyclical Epidemics of Dengue Occur Every 3-7 Years in Endemic Areas of the U.S.

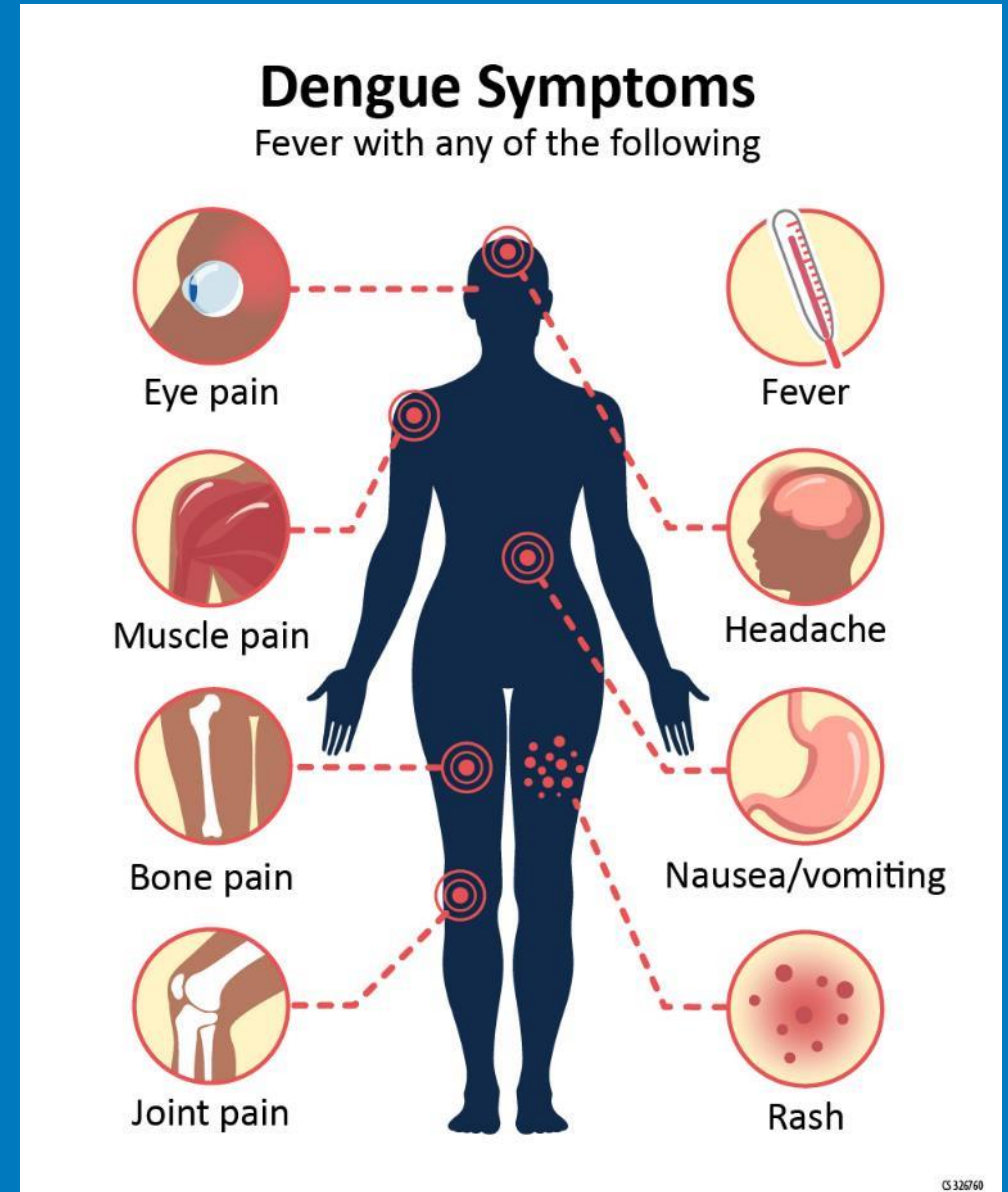


A healthcare worker, likely a nurse or doctor, is shown in a clinical setting. She is wearing a blue surgical cap, clear safety glasses, and a blue surgical mask. She is looking upwards and to the right with a focused expression. The background is a blurred clinical environment with a teal color cast. An IV drip is visible in the upper right corner. A solid blue horizontal bar is overlaid on the left side of the image, containing the text.

DENGUE CLINICAL CONSIDERATIONS

Clinical Manifestations of Dengue

- An estimated 1 in 4 dengue virus infections are symptomatic.
- Dengue most commonly presents as a mild, undifferentiated febrile illness.
- Mortality can be as low as 0.2% with treatment or as high as 15% left untreated



Clinical Manifestations of Severe Dengue

- Severe dengue occurs in approximately 1 in 20 patients with dengue.
- Severe dengue is characterized by plasma leakage leading to:
 - Severe organ impairment
 - Shock
 - Fluid accumulation
 - Bleeding



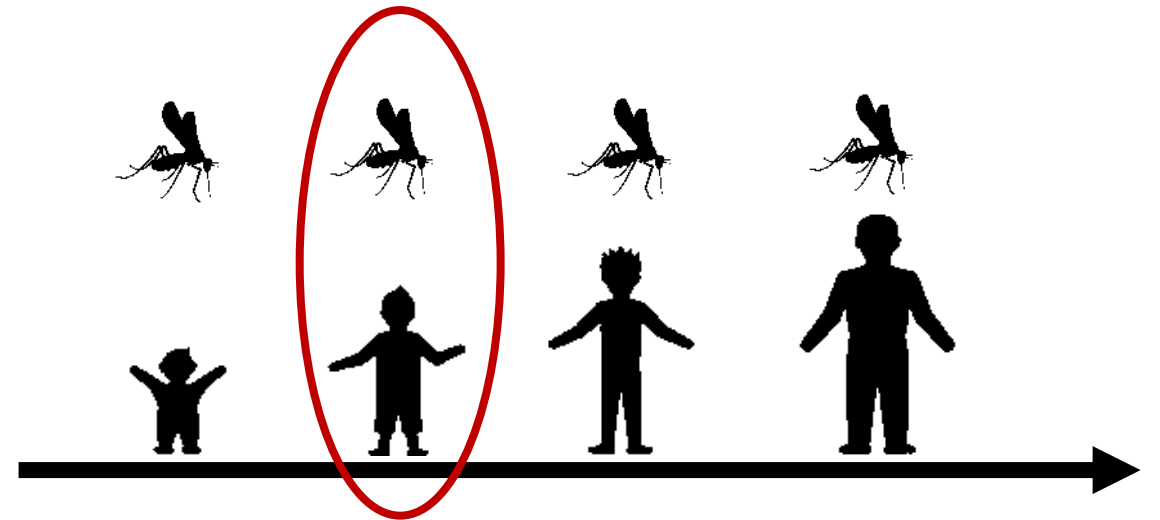
Hospital chapel converted to a dengue ward during dengue outbreak in Honduras in 2019.

Warning Signs for Severe Dengue

- Abdominal pain or tenderness
- Persistent vomiting (≥ 3 times in 24 hours)
- Extravascular fluid accumulation (e.g., pleural or pericardial effusion, ascites)
- Mucosal bleeding
- Liver enlargement
- Progressive increase in hematocrit (hemoconcentration)
- **For more information on dengue clinical presentation, please visit:**
 - <https://www.cdc.gov/dengue/healthcare-providers/clinical-presentation.html>

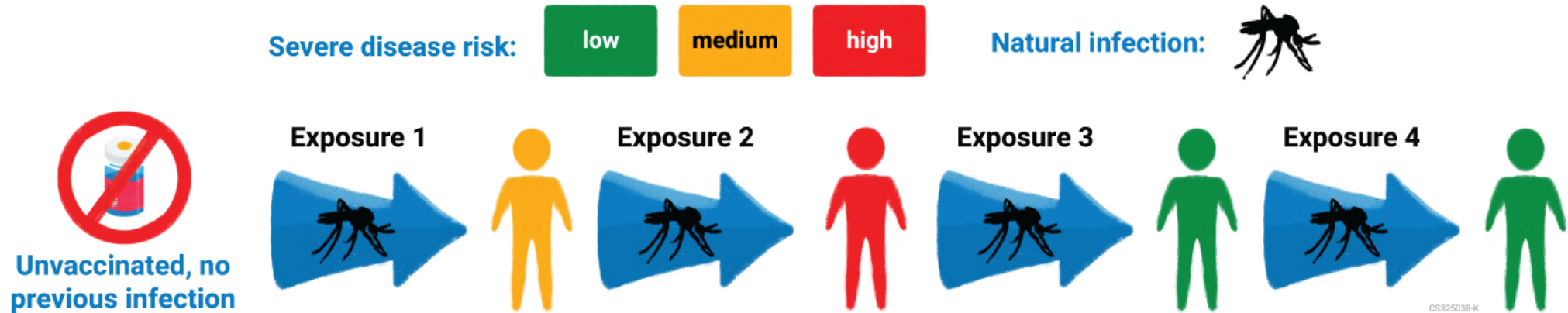
Risk Factors for Severe Dengue

- Risk factors:
 - Serotype and strain
 - Host factors (age, underlying conditions, pregnancy, etc.)
- The second infection with DENV is associated with the highest risk for severe dengue.
- For more information on risk factors for severe dengue, please visit:
 - https://www.cdc.gov/dengue/training/cme/ccm/Severe%20Disease%20in%20Infants_F.pdf

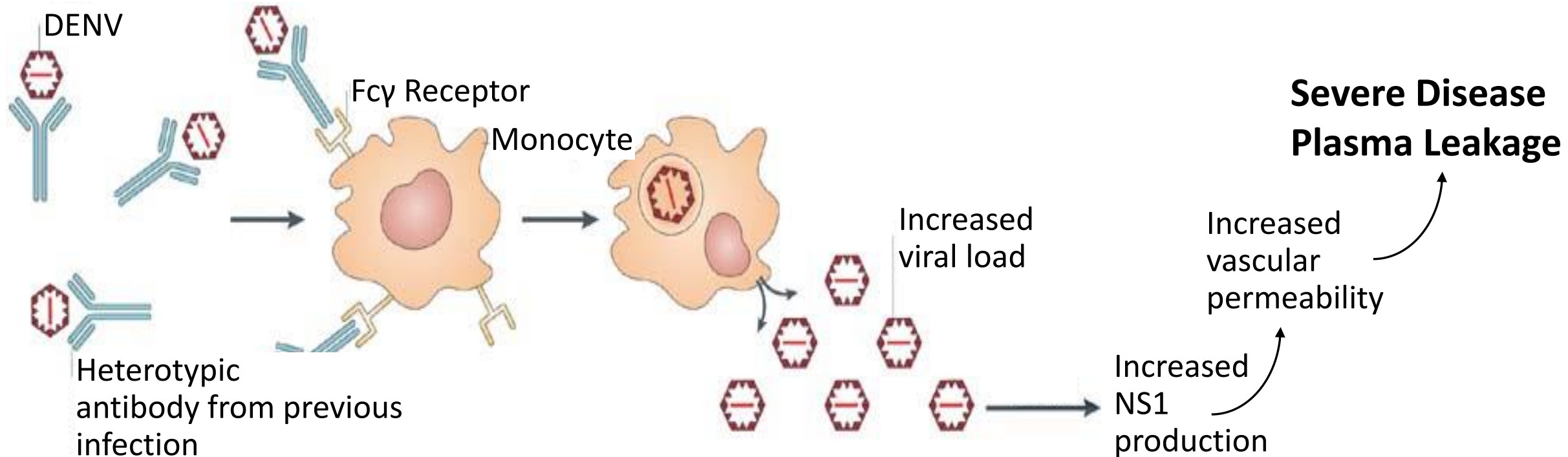


Severe Dengue and Multiple DENV Infections

Dengue Antigen Exposure



Antibody-dependent Enhancement (ADE) of Dengue Infection



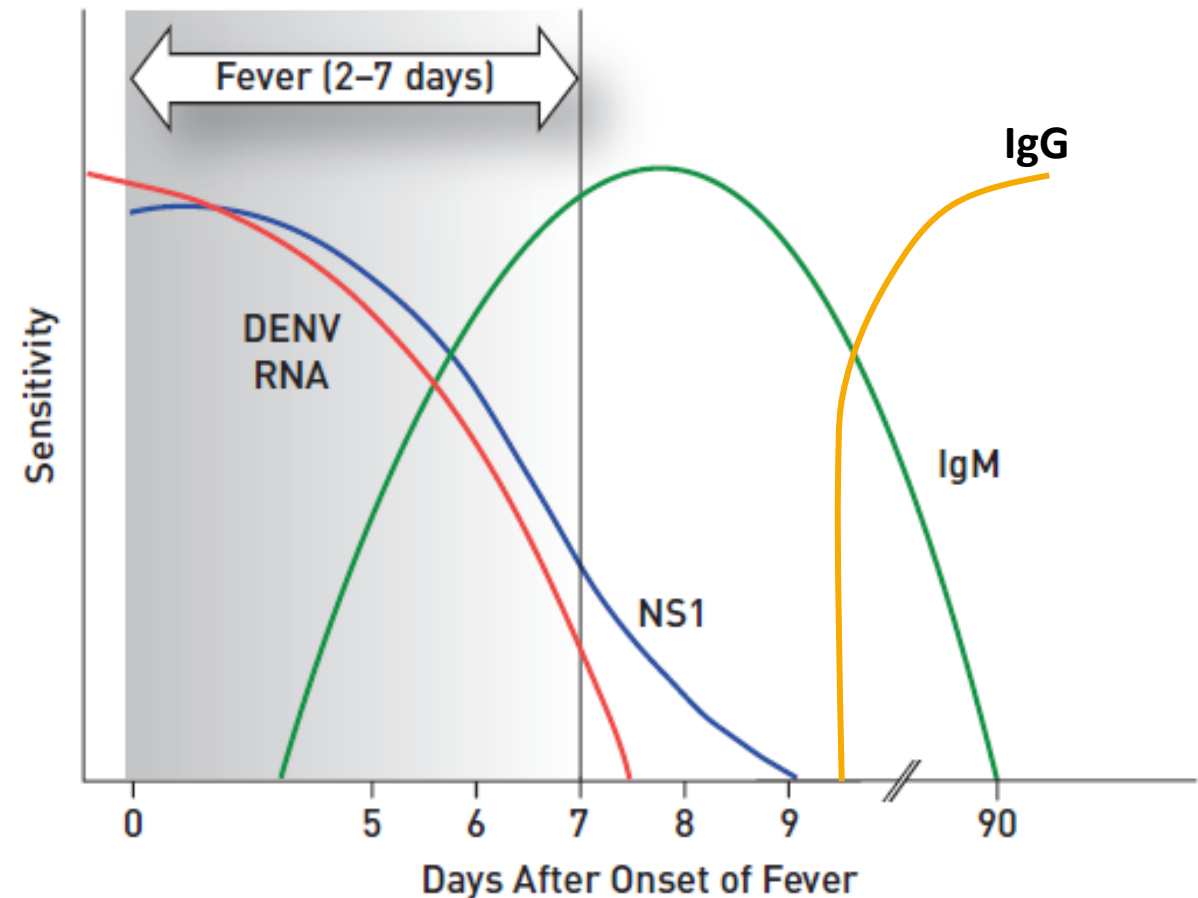
Nature Reviews | Microbiology

Beatty et al, *Science Trans Med* 2015

Diagnostic Testing for Acute Dengue Infection

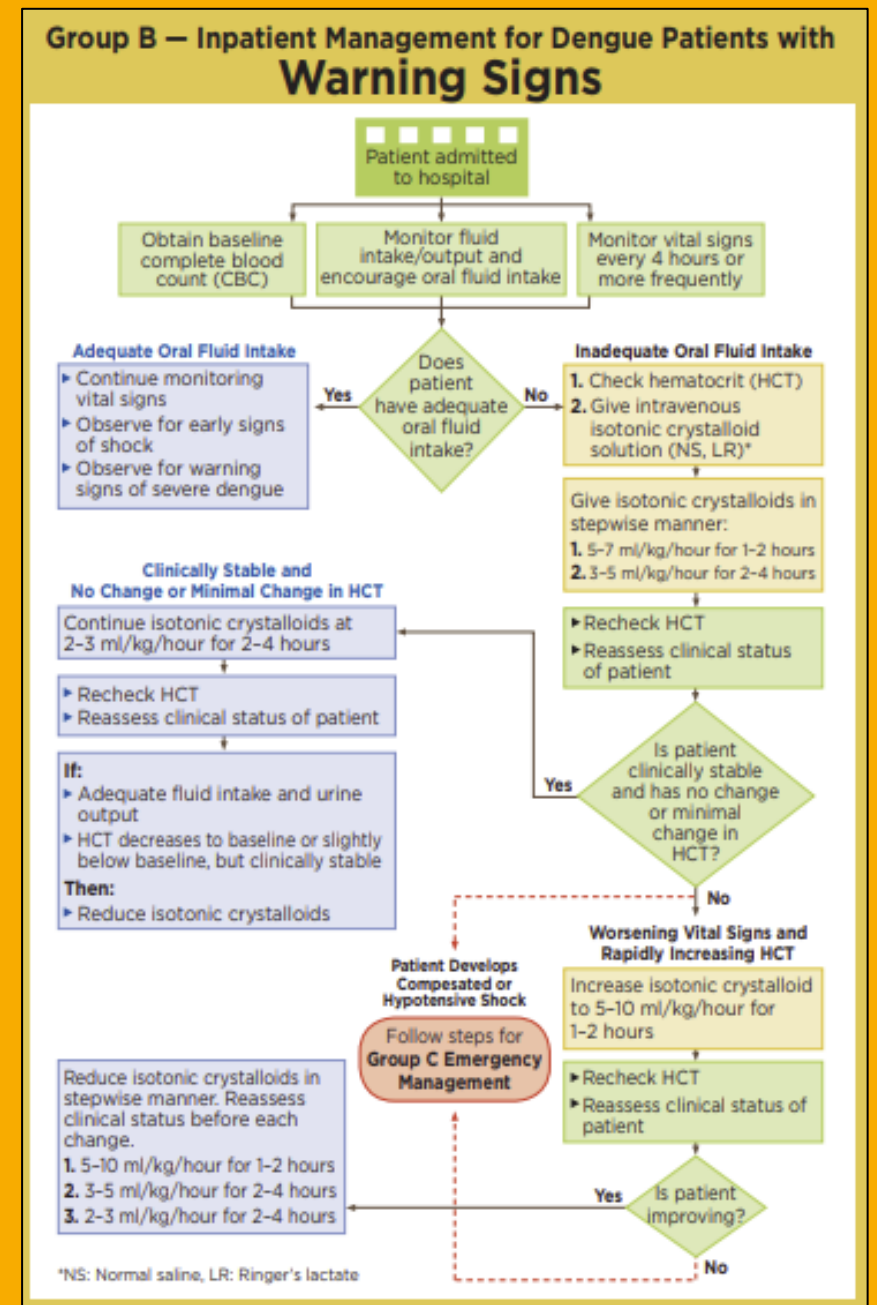
- Tests that confirm dengue virus infection:
 - **NS1**
 - **RT-PCR**
- Tests that can cross-react with other flaviviruses:
 - **IgM**
 - **IgG**
- For more information on diagnostic testing, please visit:
 - <https://www.cdc.gov/dengue/healthcare-providers/diagnosis.html>

Relative sensitivity of detection of dengue virus nucleic acid, antigen, IgM, and IgG after primary infection



Treatment of Dengue

- For dengue without warning signs, supportive care and continued monitoring for development of warning signs.
- For dengue with warning signs and severe dengue, volume management and management of complications.
- No specific antivirals to treat dengue
- For more information on clinical management, please visit:
 - <https://www.cdc.gov/dengue/training/cme.html>



Dengue Prevention

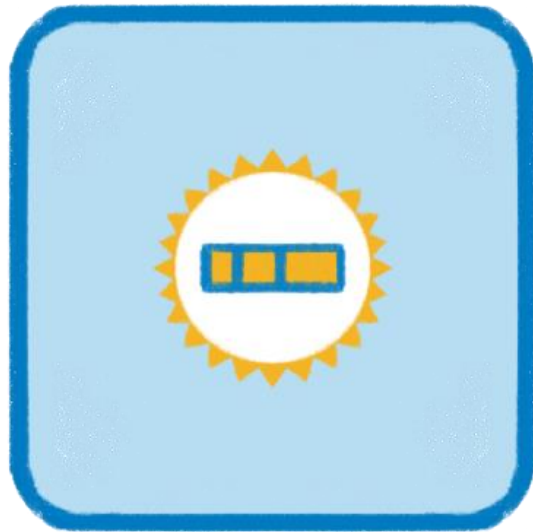
- Use EPA-approved insect repellants
- Wear long-sleeved shirts and pants
- Install insect screens on windows and doors or air-conditioning.
- Weekly, remove standing water where mosquitoes lay eggs



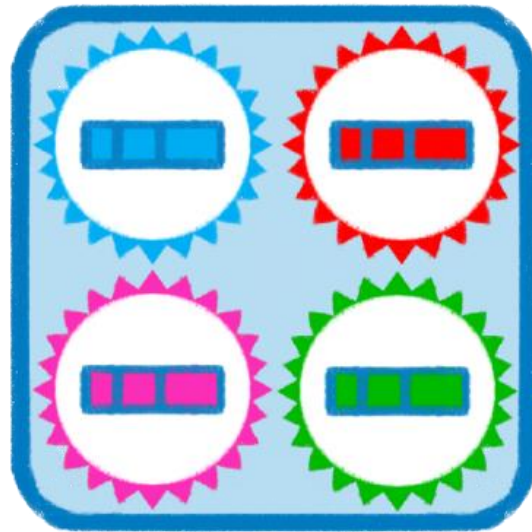
A close-up photograph of a person wearing a blue surgical cap and a clear face shield. The person's eyes are visible through the shield. They are holding a small, clear glass vial with a silver cap. The vial contains a clear liquid. The background is a soft, out-of-focus blue.

ABOUT DENGVAXIA

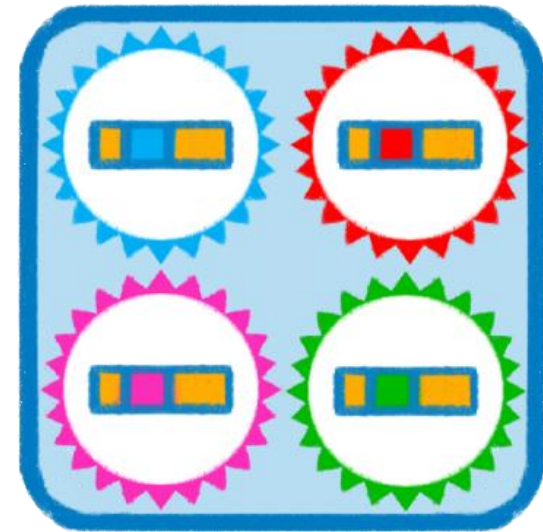
Dengvaxia Technology



Yellow Fever Vaccine



4 Dengue Serotypes



Dengvaxia

Dengvaxia Preparation and Administration

- **Preparation:** Requires mixing of diluent and lyophilized vaccine antigen in single use vials.
- **Administration:** Subcutaneous

3 shots required for full protection



For more information, visit:

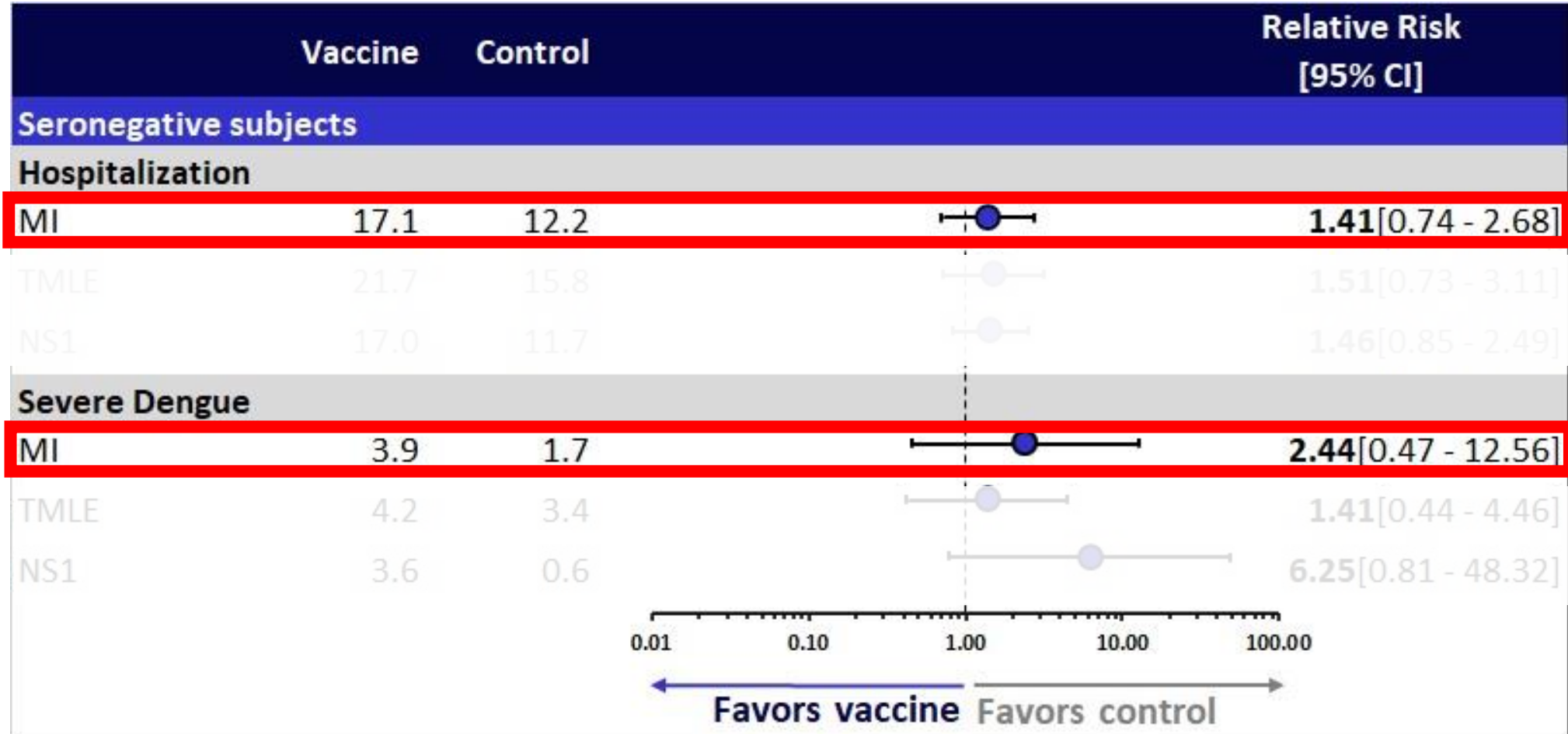
- <https://www.cdc.gov/dengue/vaccine/hcp/schedule-dosing.html>
- <https://www.cdc.gov/dengue/vaccine/hcp/storage-handling.html>

Dengvaxia and previous dengue infection

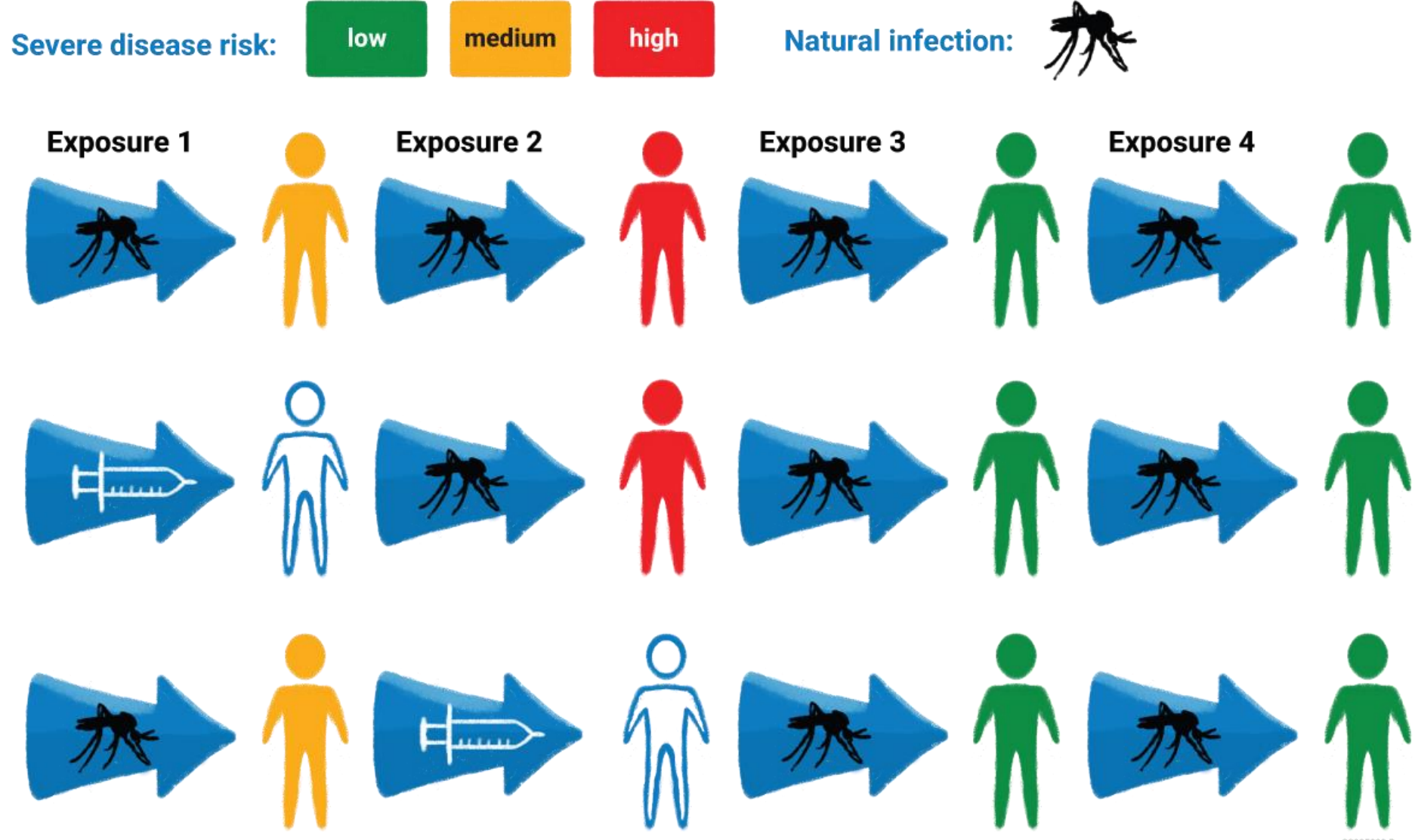
Clinical trials found **different outcomes after Dengvaxia vaccination** between children with and without previous dengue infection.

- 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 of hospitalization and severe dengue** if they were vaccinated and then had a DENV infection.

Risk of Hospitalization and Severe Dengue at 5 Years, Seronegative Participants 9-16 years



Dengue Antigen Exposure



CS325038-P

FDA licensed Dengvaxia in 2019 for persons aged 9–16 living in endemic areas and with laboratory confirmation of previous dengue virus infection.



A young woman with dark, curly hair is lying on her stomach on a grassy lawn, reading an open book. She is wearing a mustard-colored t-shirt and blue jeans. In the background, a pink bicycle is parked on the grass, and there are trees with green and yellow leaves, suggesting an outdoor setting like a park or campus. The lighting is bright and natural, indicating daytime.

**DENGVAXIA
SAFETY AND
EFFICACY**

Dengvaxia Protects from Dengue, Hospitalization, and Severe Disease

Vaccine efficacy for children 9–16 years old with a previous history of dengue infection

Outcome	Efficacy
Symptomatic virologically confirmed dengue*	82%
Hospitalization for dengue**	79%
Severe dengue**	84%
*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 Efficacy by DENV Serotype for Symptomatic Dengue

Vaccine efficacy for children 9–16 years old with a previous history of dengue infection

Serotype	Efficacy
DENV-1	67%
DENV-2	67%
DENV-3	80%
DENV-4	89%

Most Common Side Effects Among Participants 9-16 Years*

Side Effect	Frequency (%)
Headache	40%
Injection site pain	32%
Myalgias	29%
Malaise	25%
Asthenia	25%

*Serostatus Combined.

Data from: Dengvaxia [Package Insert]. Switfwater, PA: Sanofi; 2019.

Dengvaxia Contraindications and Precautions

- Severe allergic reaction to previous dose of vaccine or any component of the vaccine
- Severe immunodeficiency or immunosuppression*

Composition of Dengvaxia

Ingredient	Function
Chimeric yellow fever–dengue (CYD) serotypes 1–4	Active Ingredients
Essential amino acids (including L-phenylalanine)	Stabilizer
Non-essential amino acids	Stabilizer
L-Arginine hydrochloride	Stabilizer
Sucrose	Stabilizer
D-trehalose dihydrate	Stabilizer
D-sorbitol	Stabilizer
Trometamol	Stabilizer
Urea	Stabilizer
Sodium Chloride	Excipient

*For more information on immunodeficiency and immunosuppression, please visit:

- Paz-Bailey G, Adams L, Wong JM, Poehling KA, Chen WH, McNally V, et al. Dengue Vaccine: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021. MMWR Recomm Rep. 2021 Dec 17;70(6):1-16.
- Centers for Disease Control and Prevention. General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices - Altered Immunocompetence. 2021; Available from: <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html>.

List of vaccine components from: Dengvaxia [Package Insert]. Swiftwater, PA: Sanofi; 2019. Accessible at <https://www.fda.gov/media/124379/download>

Dengvaxia was unanimously **recommended for routine use** by Advisory Committee on Immunization Practices (ACIP) on June 24, 2021.





Indications and Use

Three doses of Dengvaxia administered 6 months apart at 0, 6, and 12 months 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 Checklist

Have you verified your patient ...	Yes	No
Is 9-16 years old?	✓	
Is living in a dengue endemic area?*	✓	
Has documentation of laboratory-confirmed previous dengue infection (see next section)?	✓	
Has no history of severe allergic reaction to a previous dose of Dengvaxia or any component of this vaccine?	✓	
Has no diagnosis or history of severe immunosuppression due to disease or therapy?	✓	



If "NO" to any, **DO NOT** vaccinate.



If "YES" to all, then **PROCEED** with patient education and vaccination.

*Endemic areas include the U.S. territories of American Samoa, Puerto Rico, and the U.S. Virgin Islands, and freely associated states, including the Federated States of Micronesia, the Republic of the Marshall Islands, and the Republic of Palau.

For more information, visit:

- https://www.cdc.gov/mmwr/volumes/70/rr/rr7006a1.htm?s_cid=rr7006a1_w



**SCREENING FOR
PREVIOUS
DENGUE VIRUS
INFECTION**

Screening for Previous Dengue Infection

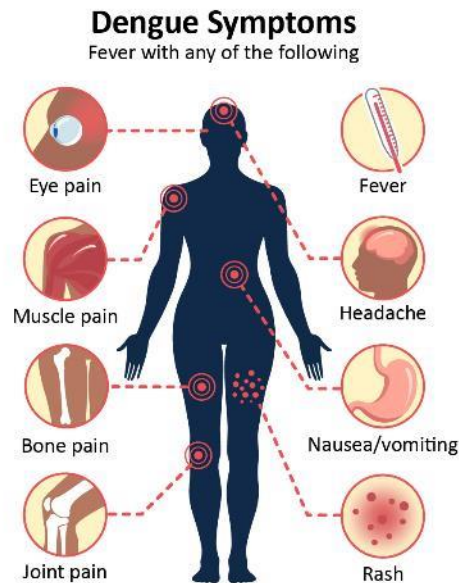
Test result from the acute phase of previous dengue disease:

- Positive DENV RT-PCR test
- Positive NS1 antigen test

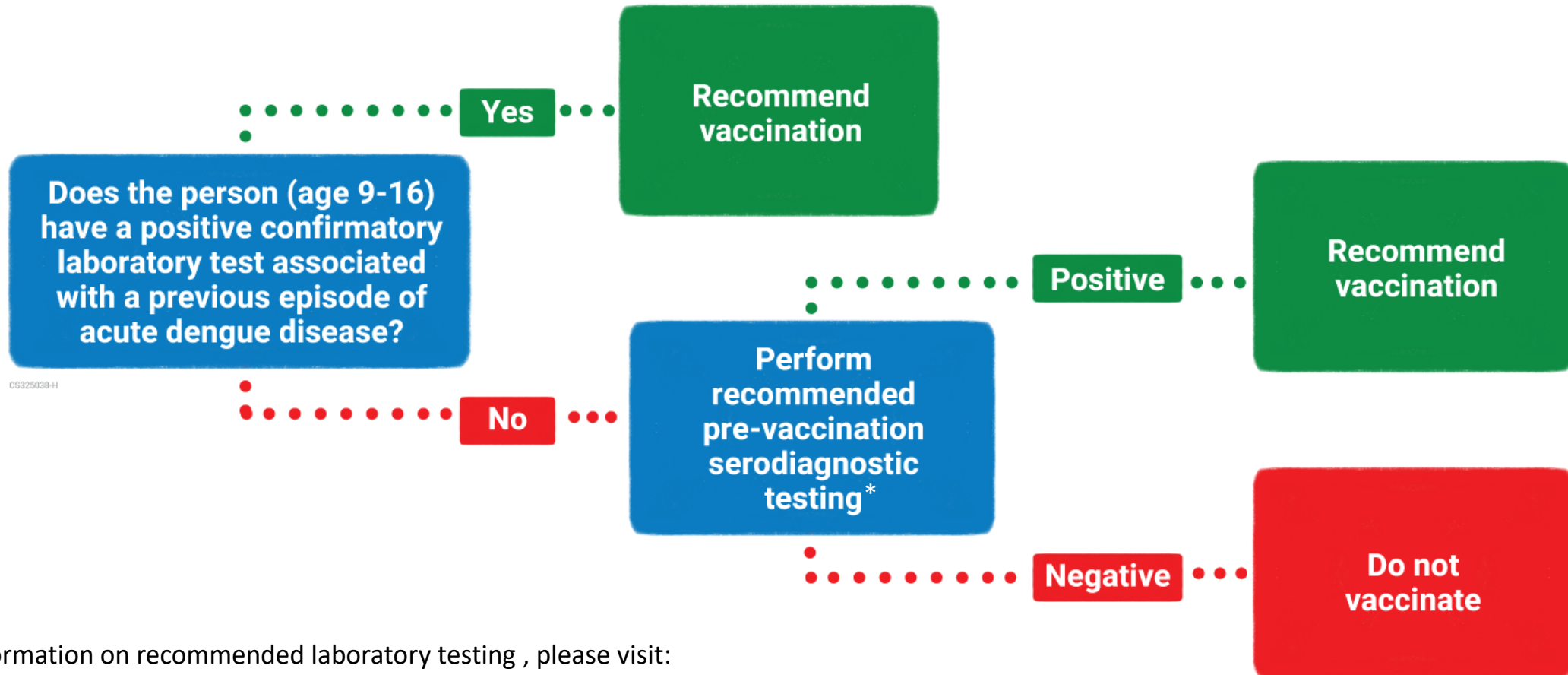
OR

Test results on pre-vaccination screening testing for previous dengue infection:

- Positive results on certain DENV IgG antibody tests meeting test performance requirements



Algorithm for Assessing Previous Dengue Virus Infection Among Children 9–16 Years Old Living in Endemic Areas



CS325038-H

*For more information on recommended laboratory testing , please visit:

- Centers for Disease Control and Prevention. Laboratory Testing Requirements for Vaccination with Dengvaxia Dengue Vaccine. 2021; Available from: <https://www.cdc.gov/dengue/vaccine/hcp/testing.html>.

Minimum Sensitivity and Specificity of Pre-vaccination IgG Screening Tests

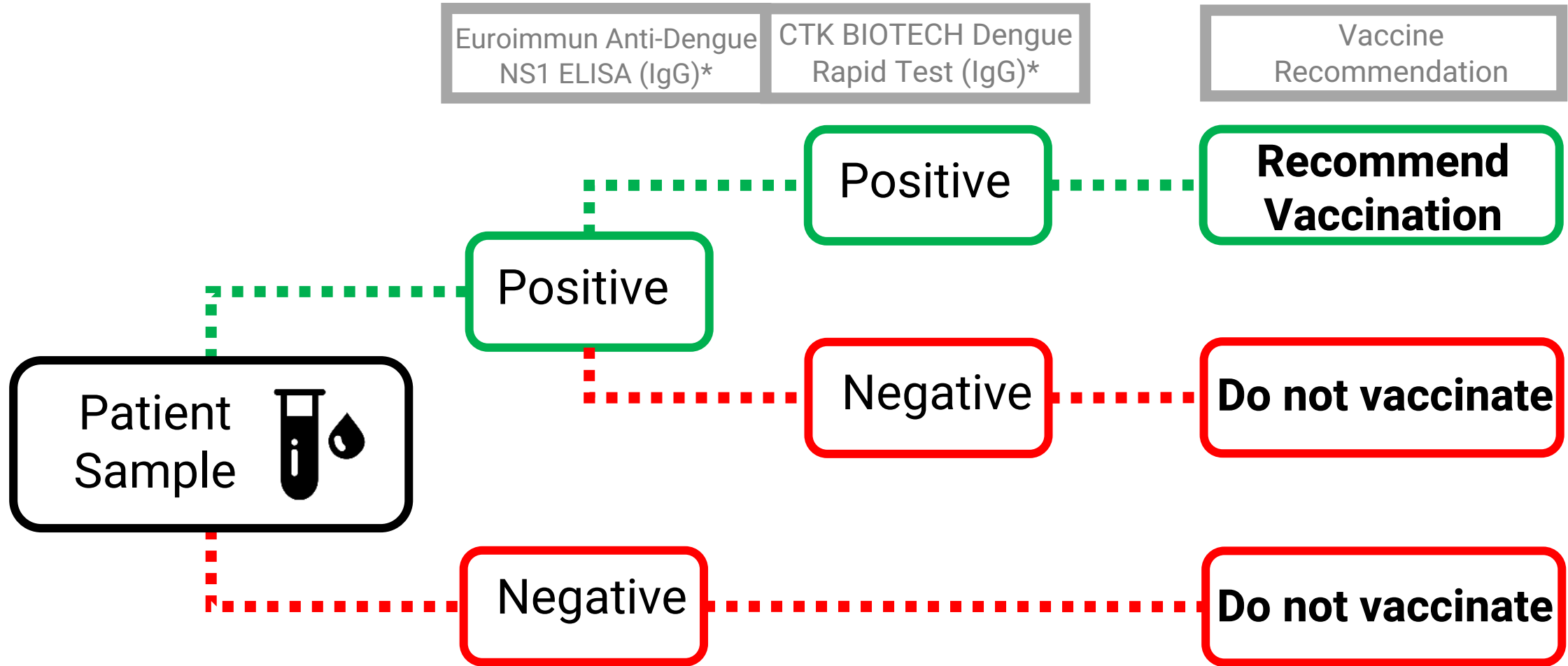
Characteristic	Minimum
Sensitivity	≥75%
Specificity*	≥98%
Positive Predictive Value	≥90%
Negative Predictive Value	≥75%

*Zika virus and other epidemiologically-relevant flaviviruses are included in the evaluation for specificity.

Currently Available Testing Meeting the Required Criteria for Pre-vaccination Screening

- These IgG tests, **when used together in a two-test algorithm**, meet the test performance requirements:
 - EUROIMMUN Anti-Dengue Virus NS1 Type 1-4 ELISA (IgG)
 - CTK BIOTECH OnSite Dengue IgG Rapid Test
- Only individuals with positive results on **both** tests are eligible 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>

Pre-vaccination 2-test Screening Algorithm



*A testing algorithm with the order of the tests reversed (i.e., the CTK BIOTECH OnSite Dengue IgG Rapid Test is performed first and the Euroimmun Anti-Dengue Virus NS1 Type 1–4 ELISA (IgG) is performed as the second, confirmatory test) is also valid for confirming eligibility for vaccination with Dengvaxia.

For more information, visit:

- <https://www.cdc.gov/dengue/vaccine/hcp/testing.html>



- Dengue virology, epidemiology, and clinical considerations
- Dengvaxia dengue vaccine efficacy, safety, and indications for use
- Pre-vaccination laboratory screening for previous dengue infection

Topics



Pediatricians and families want a dengue vaccine.



Vaccination is expected to reduce burden of dengue on local healthcare systems.

More Information

- CDC Dengue Vaccine Website:
 - Spanish: <https://www.cdc.gov/dengue/es/vaccine/index.html>
 - English: <https://www.cdc.gov/dengue/vaccine/index.html>
- CDC Dengue Website:
 - Spanish: <https://www.cdc.gov/dengue/es/index.html>
 - English: <https://www.cdc.gov/dengue/index.html>
- Dengue Clinical Case Management Course:
 - English: <https://www.cdc.gov/dengue/training/cme.html>
- FDA Dengvaxia Package Insert:
 - English: <https://www.fda.gov/vaccines-blood-biologics/dengvaxia>

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.

