DENGUE VACCINE: CONSIDERATIONS FOR HEALTHCARE PROFESSIONALS

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January 24, 2022
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Topics

• Dengue virology, epidemiology, and clinical considerations
• Dengvaxia dengue vaccine efficacy, safety, and indications for use
• Pre-vaccination laboratory screening for previous dengue infection
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 is endemic in the areas indicated.

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

Most cases and hospitalizations occur in children and adolescents aged 10–19 years.

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 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
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](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](https://www.cdc.gov/dengue/training/cme/ccm/Severe%20Disease%20in%20Infants_F.pdf)
Severe Dengue and Multiple DENV Infections

Dengue Antigen Exposure

Severe disease risk: low | medium | high

Natural infection: 🦟

UNvaccinated, no previous infection

Exposure 1

Exposure 2

Exposure 3

Exposure 4
Antibody-dependent Enhancement (ADE) of Dengue Infection

Increased viral load
Increased NS1 production
Increased vascular permeability
Severe Disease Plasma Leakage

Heterotypic antibody from previous infection


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

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

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Control</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seronegative subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>17.1</td>
<td>12.2</td>
<td>1.41 [0.74 - 2.68]</td>
</tr>
<tr>
<td>TMLE</td>
<td>21.7</td>
<td>15.8</td>
<td>1.51 [0.73 - 3.11]</td>
</tr>
<tr>
<td>NS1</td>
<td>17.0</td>
<td>11.7</td>
<td>1.46 [0.85 - 2.49]</td>
</tr>
<tr>
<td><strong>Severe Dengue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>3.9</td>
<td>1.7</td>
<td>2.44 [0.47 - 12.56]</td>
</tr>
<tr>
<td>TMLE</td>
<td>4.2</td>
<td>3.4</td>
<td>1.41 [0.44 - 4.46]</td>
</tr>
<tr>
<td>NS1</td>
<td>3.6</td>
<td>0.6</td>
<td>6.25 [0.81 - 48.32]</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic virologically confirmed dengue*</td>
<td>82%</td>
</tr>
<tr>
<td>Hospitalization for dengue**</td>
<td>79%</td>
</tr>
<tr>
<td>Severe dengue**</td>
<td>84%</td>
</tr>
</tbody>
</table>

*Followed over 25 months  
**Followed over 60 months
Dengvaxia Efficacy by DENV Serotype for Symptomatic Dengue

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

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DENV-1</td>
<td>67%</td>
</tr>
<tr>
<td>DENV-2</td>
<td>67%</td>
</tr>
<tr>
<td>DENV-3</td>
<td>80%</td>
</tr>
<tr>
<td>DENV-4</td>
<td>89%</td>
</tr>
</tbody>
</table>
Severe Adverse Events and Deaths Among Participants 9-16 Years*

<table>
<thead>
<tr>
<th>Serostatus combined, 9-16</th>
<th>Vaccine</th>
<th>Control</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE 28d</td>
<td>0.6</td>
<td>0.8</td>
<td>0.84 [0.63 - 1.12]</td>
</tr>
<tr>
<td>SAE 6m</td>
<td>2.8</td>
<td>3.2</td>
<td>0.86 [0.75 - 0.99]</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.3</td>
<td>0.3</td>
<td>0.97 [0.61 - 1.56]</td>
</tr>
</tbody>
</table>

*Serostatus Combined

Figure from: 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.
### Most Common Side Effects Among Participants 9-16 Years*

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>40%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>32%</td>
</tr>
<tr>
<td>Myalgias</td>
<td>29%</td>
</tr>
<tr>
<td>Malaise</td>
<td>25%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Serostatus Combined.
Dengvaxia Contraindications and Precautions

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

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


Composition of Dengvaxia

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chimeric yellow fever—dengue (CYD) serotypes 1–4</td>
<td>Active Ingredients</td>
</tr>
<tr>
<td>Essential amino acids (including L-phenylalanine)</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>Non-essential amino acids</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>L-Arginine hydrochloride</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>D-trehalose dihydrate</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>D-sorbitol</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>Trometamol</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>Urea</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>Excipient</td>
</tr>
</tbody>
</table>
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**

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

*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.

If “NO” to any, **DO NOT** vaccinate.

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

For more information, visit:
- [https://www.cdc.gov/mmwr/volumes/70/rr/rr7006a1.htm?c_id=rr7006a1_w](https://www.cdc.gov/mmwr/volumes/70/rr/rr7006a1.htm?c_id=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

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

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

Dengue Symptoms
Fever with any of the following

- Eye pain
- Muscle pain
- Bone pain
- Joint pain
- Rash
- Fever
- Headache
- Nausea/vomiting

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

For more information on recommended laboratory testing, please visit:
Minimum Sensitivity and Specificity of Pre-vaccination IgG Screening Tests

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>≥75%</td>
</tr>
<tr>
<td>Specificity*</td>
<td>≥98%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>≥90%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>≥75%</td>
</tr>
</tbody>
</table>

*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

Patient Sample

Euroimmun Anti-Dengue NS1 ELISA (IgG)*  CTK BIOTECH Dengue Rapid Test (IgG)*  Vaccine Recommendation

Positive

Positive

Recommend Vaccination

Negative

Negative

Do not vaccinate

Do not vaccinate

* 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
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.