DengVaxia® for U.S. Travelers: Should We Mass Vaccinate?

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Dengvaxia® for U.S. Travelers: Should We Mass Vaccinate?

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Objectives
- Discuss dengue fever and current epidemic issues around the world
- Introduction into Dengvaxia® and it’s dosing schedule
- Evaluate current literature investigating safety and efficacy of Dengvaxia® for prevention of dengue fever
- Develop recommendations for appropriate use of Dengvaxia®.
- Discuss alternative measures

Patient Case
- AG is a 15 year old student planning to attend an international boarding school in Cambodia. He is set to start the new semester next academic year (13 months).
- AG is up-to-date on his travel vaccinations but his parents were concerned about the Dengue Fever. He discussed with his physician about the potential for it. They would like your opinion.
- Is AG a good candidate for Dengvaxia®?

BACKGROUND

Dengue Virus
- Dengue is a mosquito-borne disease (Aedes species mosquitoes)
- Considered the fastest spreading vector borne viral disease worldwide

Disclosures
- No conflicts of interest to disclose
Areas of Dengue Fever

https://www.cdc.gov/dengue/areaswithrisk/around-the-world.html

Dengue Endemic Areas

- Africa:
  - Sudan, Djibouti, Ethiopia, Kenya, Senegal, Tanzania
- Asia:
  - Bangladesh, Cambodia, Indonesia, Laos, Malaysia, Nepal, Philippines, Thailand, Vietnam, Taiwan
- Americas:
  - Chile, Antigua and Barbuda, Barbados, Belize, Haiti, Honduras, Jamaica, Nicaragua, Panama, Paraguay, Puerto Rico, Venezuela, etc.
- Europe:
  - Croatia, France, Madeira Islands
- Oceania/Pacific Islands:
  - Australia, Fiji, French Polynesia, Maldives, Papua New Guinea

https://www.cdc.gov/dengue/areaswithrisk/around-the-world.html

Epidemiology

- In 2018, 93 million United States travelers flew outside of the United States
  - 10 million travel to Dengue prone areas of the world
  - 284-528 million people per year are infected with dengue annually
  - 67-137 million have clinically apparent disease
  - In March of 2019, data from Pan American Health Organization (PAHO) documented an estimated 250,000 cases
  - 42% of the total cases in 2018

Impact on Population

- Dengue not only affects tourists but also:
  - Business travelers
  - Expatriates
  - Persons visiting friends and relatives
  - Migrants
- Occurs mostly in adults but can also affect pediatric travelers as well
- New evidence from GeoSentinel show an increase of dengue in the returning travelers over the past decade.

Pathophysiology of Dengue
Symptoms of Dengue

- Characterized by flu-like symptoms, fever, aches and pain, and rash.
- Symptoms begin within a week and can last 3-10 days.
- Some can end up hospitalized and can even result in death.

Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS)

DHF:
- Clinical manifestations:
  - Fever (>38°C)
  - Headache
  - Abdominal pain
  - Vomiting
  - Excessive thirst
  - Hemorrhaging

DSS:
- Clinical manifestations:
  - Weak, rapid pulse
  - Cold, clammy skin
  - Restlessness
  - Multiorgan failure

Progression to DHF/DSS

- The progress towards DHF/DSS occur after 3-5 days of fever.
- Most dangerous period that requires high vigilance from caregivers.

Distribution of DENV Serotypes

- In 2004, we saw a major shift in the distribution of DENV serotypes.

Serotypes of Dengue Virus

- Dengue Virus (DENV) serotypes 1,2,3,4
- Members of the Flaviviridae family
- Genus flavivirus
- The four dengue viruses are similar
- Share approximately 65% of their genomes
- Infection with each of the dengue serotypes results in the same disease and range of clinical symptoms.
- Each has different interactions with the antibodies in human blood serum.
Dengvaxia® (CYD-tetravalent Dengue Vaccine)

- FDA approved on May 1, 2019.
- Live attenuated, recombinant tetravalent vaccine.
- Attenuated from the Yellow Fever virus at the 17D backbone.
- Only approved for ages 9-16 years old with laboratory-confirmed previous dengue infection (seropositive).

**Viral Composition**

1. **YFV 17D genome encoded in DNA**
2. **F gene**
3. **Conversion with each dengue gene of DENV 1, 2, 3, or 4**

**Mechanism of Action**

1. Dengvaxia® is a live, tetravalent vaccine for prevention of Dengue Fever serotypes 1–4 of the virus.
2. After administering, Dengvaxia® elicits dengue-specific immune responses against the four dengue virus serotypes.
3. The exact mechanism of protection has not been determined.

**Dosing Schedule**

- 3 dose series
- 0.5ml(s) lyophilized powder to reconstitute with diluent.
- One dose subcutaneously every 6 months:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Dose</td>
<td>0</td>
</tr>
<tr>
<td>2nd Dose</td>
<td>6</td>
</tr>
<tr>
<td>3rd Dose</td>
<td>12</td>
</tr>
</tbody>
</table>

Note: It takes a full year to be vaccinated for Dengue.

**Adverse Effects**

- Injection site:
  - Pain, erythema, and swelling
- Systemic:
  - Asthenia, fever, headache, myalgia, and malaise

**Contraindications**

- Immunocompromised patients
- Hypersensitivity to vaccine components
Testing for Seropositive Status

- Currently there are no rapid test available for detection of Dengue serostatus
- Only tests available is MAC-ELISA and Plaque Reduction Neutralization Test (PRNT)
- MAC-ELISA for qualitative detection of dengue virus IgM antibodies
- PRNT for titer of neutralizing antibodies for Dengue Virus

Risk of Severe “Secondary” Like Infection

- Seronegative patients that receive Dengvaxia® will be exposed to the virus resulting in a primary immune response
- If exposed to the natural virus while traveling, it will result in a “secondary like” more severe infection
- Infection-enhancing phenomenon is referred to as the antibody-dependent enhancement
- After the secondary infection, individuals are believed to be generally protected against all serotypes

LITERATURE REVIEW

Sabchareon et al. (2012)

- Phase III Clinical Trial in Thailand from 02/2009 to 02/2010
- Randomized, double blinded trial

Sabchareon et al. (2012)

- Primary objective:
  - Assess protective efficacy against virologically confirmed, symptomatic dengue, irrespective of severity or serotype, occurring 1 month or longer after the third injection
- Intervention:
  - Dengvaxia® [0,6,12 months intervals]
  - Inactivated rabies virus vaccine [0,6,12 months intervals]
  - Placebo (NaCl 0.9%) [0,6,12 months intervals]

Sabchareon et al. (2012)

- Inclusion Criteria:
  - Ages 4-11
  - Participants in good health
  - Parents must be present at all scheduled visits
  - Females must avoid becoming pregnant
- Exclusion Criteria:
  - Febrile illness (>37.5°C)
  - Known pregnancy status
  - History of hypersensitivity to the vaccine components
Sabchareon et al. (2012)

- **Strengths:**
  - Large number of participants
  - Utilized PRNT testing to measure vaccine efficacy.
- **Weaknesses:**
  - Only assessed safety for 1 year post 3rd dose
  - Limited to patients age 4-11
  - Rabies virus for cohort 1

Hadinegoro et al. (2015)

- **Primary Objective:**
  - Assess incidence of hospitalization and vaccine efficacy for virologically confirmed dengue for 4 years after the end of the 25-months efficacy surveillance period.

Hadinegoro et al. (2015)

- Meta-Analysis of Phase 3 trial data in 5 Asian-Pacific countries (CYD14), 5 Latin American countries (CYD 15), and a primary and extension study in Thailand (CYD23/57).
- Stratified according to age
- Followed up with patients from studies for additional 50 months

<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients</th>
<th>Vaccine Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYD 23 (Ages 4-11)</td>
<td>3,203/4,002</td>
<td>2,131</td>
<td>1,072</td>
</tr>
<tr>
<td>CYD 15 (Ages 2-16)</td>
<td>19,898/20,869</td>
<td>13,268</td>
<td>6,630</td>
</tr>
<tr>
<td>CYD 14 (Ages 2-16)</td>
<td>10,165/10,275</td>
<td>6,778</td>
<td>3,378</td>
</tr>
</tbody>
</table>
Hadinegoro et al. (2015)

- Hospitalization after vaccination:
  - Cumulative relative risk >3 years after vaccinations:
    - 0.46 (CI 95%, 0.32 to 0.65) in CYD14
    - 0.28 (CI 95%, 0.18 to 0.44) in CYD15
    - 0.66 (CI 95%, 0.43 to 1.02) in CYD23/57

Kaplan–Meier plot for hospitalized or severe virologically confirmed dengue by age (<9 years; >9 years)

Serotypes

<table>
<thead>
<tr>
<th>Vaccine Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Efficacy (95% CI)</td>
<td></td>
</tr>
<tr>
<td>All Serotypes</td>
<td>65.6 (95% CI: 60.7-69.9)</td>
</tr>
<tr>
<td>Serotype 1</td>
<td>58.4 (95% CI: 47.7-66.6)</td>
</tr>
<tr>
<td>Serotype 2</td>
<td>73.6 (95% CI: 59.9-80.4)</td>
</tr>
<tr>
<td>Serotype 3</td>
<td>73.6 (95% CI: 64.4-80.4)</td>
</tr>
<tr>
<td>Serotype 4</td>
<td>83.2 (95% CI: 76.2-88.2)</td>
</tr>
<tr>
<td>Seropositive at Baseline</td>
<td>81.9 (95% CI: 67.2-90.0)</td>
</tr>
<tr>
<td>Seronegative at Baseline</td>
<td>52.5 (95% CI: 5.9-76.1)</td>
</tr>
</tbody>
</table>

Hadinegoro et al. (2015)

- Strengths:
  - Meta-Analysis of multiple trials that consist of multiple international centers
  - Analysis of different age groups

- Weaknesses:
  - Retrospective, therefore certain data points are limited
  - On-site investigations showed that major forms of bias were present

Sridhar et al. (2018)

- Case-cohort studies that reassessed all cases from 3 clinical trials (CYD14, CYD 15, and CYD23).
- Developed a dengue anti-nonstructural protein 1 (NS1) IgG enzyme-linked assay to test samples from month 13 to infer serostatus.
Sridhar et al. (2018)

- Primary objective:
  - Reassess serostatus in relation to virologically confirmed dengue (VCD), hospitalization for VCD, and symptomatic VCD according to their serostatus.

<table>
<thead>
<tr>
<th></th>
<th>Seronegative Group (Month 24-60)</th>
<th>Seropositive Group (Month 24-60)</th>
<th>Control Group (Month 24-60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for VCD</td>
<td>HR 1.57% (95% CI: 1.13-2.19)</td>
<td>HR 0.25% (95% CI: 0.14-0.31)</td>
<td>HR 1.09% (95% CI: 0.53-2.27)</td>
</tr>
<tr>
<td>Severe VCD</td>
<td>HR 0.40% (95% CI: 0.22-0.73)</td>
<td>HR 0.16% (95% CI: 0.07-0.37)</td>
<td>HR 0.17% (95% CI: 0.22-0.75)</td>
</tr>
</tbody>
</table>

Results from Dengvaxia® trial in Philippines

- Was first licensed in the Philippines in early April 2016
- Decided to mass vaccinate in the schools for children ages 9-10 and living in high endemic regions
  - Started to vaccinate 1 million 4th grade students
- Sanofi announced a safety update on November 2017
  - Seronegative patients should not receive vaccine

Results from Dengvaxia® trial in Philippines

- Turmoil ensued and several researchers, regulators, and the former Secretary of Health were held responsible
- Public riots broke out and resulted in a dramatic drop in vaccine confidence
  - 93% → 32% "strongly agree" that vaccines are important
- Measles and other vaccine preventable diseases resurfaced
Dealing with Pushback
• Events in Philippines can be a barrier for our mission to help reduce vaccine preventable diseases
• Mass vaccination programs potentially can result in chaotic riots and a sharp decline in public trust
• Statistics that might be utilized by Anti-Vaxers:
  • 1 million children at risk of potentially hospitalization and death
  • 600 children died as a result of a mass vaccination program

Non-Pharmacological Measures
• For those that are not eligible for Dengvaxia®:
  • Overall vector control:
    • Covering, emptying, and cleaning of domestic water storage containers on weekly basis
    • Use of window screens, long sleeve clothing, insecticides, and bed nets
    • Use DEET insect repellent
  • Monitor vectors during peak season

https://www.who.int/immunization/research/development/dengue_q_and_a/en/

BACK TO OUR PATIENT

Patient Case
• AG is a 15 year old student planning to attend an international boarding school in Cambodia. He is set to start the new semester next academic year (13 months).
• AG is up-to-date on his travel vaccinations but his parents were concerned about the Dengue Fever. He discussed with his physician about the potential for it. They would like your opinion.
• Is AG a good candidate for Dengvaxia®?

Patient Case
• Updates from his follow up with his physician:
  – Checked serostatus (seropositive)
  – Up-to-date on all vaccinations (Travel and Routine)
  • Due to past vacations
  – In good physical and mental health
Patient Case

• AG is a candidate for Dengvaxia® due to:
  – Seropositive status
  – Age
  – Traveling to endemic area
  – Timeframe
  – Traveler staying for a long period

FUTURE VACCINES

Vaccinations in the Pipeline

• TAK-003:
  • Takeda’s live-attenuated tetravalent dengue vaccine with serotype DENV-2 as the base, which provides the genetic “backbone” for all four vaccine viruses

• TV003:
  • Butantan’s live attenuated tetravalent vaccine utilizing reverse genetics to provide immunity to each of the four serotypes of DENV

Conclusion

• Dengvaxia® still has benefits for certain patient population
  • Expatriates or business travelers for a long duration

• In addition, we must screen intensely in order to ensure that patients are truly seropositive

• There are other Dengue vaccines in the pipeline that may provide better coverage

• Currently, best practice is to follow prevention strategies for vector control

Acknowledgement

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• James Weems, R.Ph.
• Nathan Pope, Pharm.D.

References

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Appendix A: Abbreviations
PAHO: Pan American Health Organization
DHF: Dengue Hemorrhagic Fever
DSS: Dengue Shock Syndrome
DENV: Dengue Virus
PRNT: Plaque Reduction Neutralization Test
MAC-ELISA: IgM antibody capture enzyme-linked immunosorbent assay
CYD: chimeric Yellow Fever chain- Dengue
Appendix B: CDC Map of Dengue Areas
Appendix C: Health Map of current Dengue Concentrations
Appendix: Vector Control Tips

1. Remove water from coolers and other small containers at least once in a week.

2. Use aerosol during day time to prevent the bites of mosquitoes.

3. Do not wear clothes that expose arms and legs.

4. Use mosquito nets or mosquito repellents while sleeping during daytime.