Dengue vaccine availability - opportunities and challenges for Latin America

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Universidad Central de Venezuela
Is dengue a real health problem in Latin America?

<table>
<thead>
<tr>
<th>Americas Sub-region</th>
<th>habitants</th>
<th>Severe Dengue**</th>
<th>Deaths</th>
<th>Case Fatality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America, Central America &amp; Mexico</td>
<td>286,895</td>
<td>57.7</td>
<td>1,330</td>
<td>63</td>
</tr>
<tr>
<td>Andean</td>
<td>210,859</td>
<td>151.7</td>
<td>1,379</td>
<td>275</td>
</tr>
<tr>
<td>Southern Cone</td>
<td>1,750,826</td>
<td>638.5</td>
<td>892</td>
<td>655</td>
</tr>
<tr>
<td>Hispanic Caribbean</td>
<td>80,275</td>
<td>313.8</td>
<td>670</td>
<td>39</td>
</tr>
<tr>
<td>Caribbean</td>
<td>9,993</td>
<td>51.7</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2,338,848</td>
<td>244.8</td>
<td>4,274</td>
<td>1,032</td>
</tr>
</tbody>
</table>

*Sum of Dengue + Severe Dengue

**Includes all forms of Severe Dengue including Dengue Shock Syndrome and Dengue Haemorrhagic Fever

PAHO, 2016

Severe cases | Deaths | Lethality (%)
Of the more than 2.38 million cases reported by the Region of the Americas in 2016 (>70% of the world’s total), Brazil alone contributed about 1.5 million cases, approximately 3 times higher than in 2014.
Dengue disease burden

Dengue causes 1.39% to 4.9% of all DALYs due to NTDs in Latin America.


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Dengue economic burden in Latin America

- Dengue illness in the Americas has a substantial economic burden estimated to cost $2.1 billion per year on average (in 2010 US dollars)
- Approximately 60% of this cost related to indirect or ‘productivity’ losses, and the figure excluded prevention costs
- The burden for dengue in the Americas exceeds that from other viral illnesses, such as human papillomavirus (HPV) or rotavirus

Vector control has failed to prevent epidemics and DENV’s expanding geographic distribution. There is a growing consensus that eliminating dengue as a public health burden can only be achieved by integrating vector control with vaccines. Achee NL, et al. *PLoS Negl Trop Dis* 9(5): e0003655
Integrated dengue control strategy

Source: PAHO/WHO
Introducing a dengue vaccine

Factors considered when the national ITAG makes recommendations

- Disease burden in other countries
- Actions in other countries
- Ease of distribution of vaccine
- Method of administration of vaccine
- Priority of vaccine related to other possible health interventions
- Priority of vaccine related to other VPD
- Economic impact of the disease
- Vaccine effectiveness

ITAG: Immunization Technical Advisory Group

M. Bryson et al. / Vaccine 28S (2010) A13–A17
Is dengue vaccine profitable?

Global Dengue Vaccine Market Share Analysis (%)
By End User (2016)

2017 – 2027 at a CAGR of 17.5%

49.5% Government Institutes
28.0% Hospitals
22.5% NGOs

SP reported €30 million in Dengvaxia® sales by Q3, 2015

compound annual growth rate
Dengue vaccines candidates galore...

Torresi J, et al. Human Vaccines & Immunother 2017
Dengue vaccines candidates galore...

Torresi J, et al. *Human Vaccines & Immunotherapeutics* 2017
• Association between PRNT titers and disease risk
• Qualitative differences in immune responses induced by CYD serotypes; in naïve vaccinees, homotypic responses are mostly induced against a few serotypes (eg serotype 4); while broader cross-reactive responses are induced in seropositives

• Immune response induced against ST1 and ST2 not lower than against the other serotypes in a FcγR+ cell-based neutralization assay

• Better protection in flavivirus seropositive at baseline, also possibly influenced by age

• Ongoing / planned
  • Further document the role of CMI responses in protection
  • Ab specificity and affinity/avidity
  • Long-term immunogenicity
  • Potential role of boosters
  • Role of HLA
  • Perform systems vaccinology studies in future trials, possibly coupled to a human challenge model

• To be explored further
  • Role of the force of infection
  • Transmission of wt viruses to mosquitoes upon infection in vaccinees (existence of indirect protection?)

• No immune escape in a PRNT assay of wt DEN strains circulating in the CYD23 area

• Potential increased fitness of these wt strains (unique clade) requiring higher responses?

• Ongoing
  • Sequencing of wt DEN strains from CYD14 and CYD15 cases to explore the potential impact of genotype in the observed protection

• Key epitopes present on the CYD Dengue viruses (reactivity with human mAbs)

• Higher potency of the vaccine may be associated with higher immunogenicity
  • In vivo protective activity of monovalent CYD2 (monkeys)
  • Similar glycosylation for all 4 CYD serotypes

• Ongoing / planned: further characterization of structure and protein context
Dengue Vaccine: Efficacy Studies in Asia and LatAm Consistently Demonstrate a Reduction in Dengue Disease

Both Studies Met their Primary Efficacy Endpoints and Showed Consistent Safety Profile for the Observed Active Phase\(^{(2,3,7)}\)

Key Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction in Symptomatic Dengue</th>
<th>Reduction in Severe Disease</th>
<th>Reduction in Hospitalized Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYD 14, Asia</td>
<td>56.5%</td>
<td>80%</td>
<td>67.2%</td>
</tr>
<tr>
<td>CYD 15, LatAm</td>
<td>60.8%</td>
<td>95%</td>
<td>80.3%</td>
</tr>
</tbody>
</table>

(1) World Health Organization, 2014; Dengue Factsheet
(2) Ooi et al., 2014; Lancet
(3) Villar et al., 2014; NEJM
(4) Post Dose 3
(5) DHF, WHO 1997 criteria, intent to treat
(6) Intent To Treat
(7) For a summary of the Dengue Vaccine safety profile, please refer to slide 116 from the Nav 20, 2014 IR Thematic Seminar on New Medicines
**CYD-TDV (Dengvaxia®)**

- **Global Efficacy** 60% intention to treat and 59% per protocol
- **Efficacy by serotype** (intention to treat) – DENV1 55%, DENV2 43%, DENV3 71% and DENV4 77%
- **Global efficacy/seropositivity**: seronegatives: 38% (RR = 0.62; 95% CI: 0.37, 1.03; I² = 0%; p = 0.82) and seropositives: 78% (RR = 0.22; 95% CI: 0.14, 0.35; I² = 0%; p = 0.36)
- **Safety** – local events: erythema 45% & swelling 67%; systemic events – no statistical difference between control & the intervention groups
- The efficacy and safety of dengue vaccines need to continue to be evaluated after commercialization

VE of dengue vaccine

<table>
<thead>
<tr>
<th>Criteria and Trial</th>
<th>Vaccine Group</th>
<th>Control Group</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All severity hospitalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYD14</td>
<td>10/3316</td>
<td>27/1656</td>
<td>81.6 (60.7 to 92.0)</td>
</tr>
<tr>
<td>CYD15</td>
<td>17/13,914</td>
<td>43/6940</td>
<td>80.3 (64.7 to 89.5)</td>
</tr>
<tr>
<td>CYD14+CYD15</td>
<td></td>
<td></td>
<td>80.4 (70.1 to 87.7)</td>
</tr>
<tr>
<td>Severe (IDMC) hospitalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYD14</td>
<td>2/3316</td>
<td>11/1656</td>
<td>90.9 (58.4 to 99.0)</td>
</tr>
<tr>
<td>CYD15</td>
<td>1/13,914</td>
<td>11/6940</td>
<td>95.5 (68.8 to 99.9)</td>
</tr>
<tr>
<td>CYD14+CYD15</td>
<td></td>
<td></td>
<td>93.3 (77.3 to 98.0)</td>
</tr>
<tr>
<td>DHF (WHO 1997) hospitalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYD14</td>
<td>2/3316</td>
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</tr>
<tr>
<td>CYD14+CYD15</td>
<td></td>
<td></td>
<td>92.9 (76.1 to 97.9)</td>
</tr>
</tbody>
</table>

Seronegative at baseline

<table>
<thead>
<tr>
<th></th>
<th>Vaccine Group</th>
<th>Control Group</th>
<th>Vaccine Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYD14</td>
<td>7/129</td>
<td>8/59</td>
<td>61.6 (-21.1 to 88.1)</td>
</tr>
<tr>
<td>CYD15</td>
<td>9/258</td>
<td>9/149</td>
<td>43.2 (-61.6 to 80.0)</td>
</tr>
<tr>
<td>CYD14+CYD15</td>
<td></td>
<td></td>
<td>52.0 (5.9 to 76.1)</td>
</tr>
</tbody>
</table>
VE vs. VPDI
Two sides of a coin

SUCCESS

FAILURE/EQUIVOCAL

NNV for Dengvaxia® in Latam:
28 VCD cases
201 Hospitalized VCD cases
661 Severe hospitalized VCD cases

Introducing a routine CYD-TDV vaccination program at 9 years of age in settings meeting the criteria outlined below is expected to result in a 10% to 30% reduction in symptomatic and hospitalized dengue illness over 30 years. “Catch-up” campaigns targeting older age groups may be considered if additional impact is desired and the extra costs can be met.

- ...populations to be targeted for vaccination: prior infection with DENV (any serotype), as measured by seroprevalence, should be ≥70% in the age group, in order to maximize public health impact and cost-effectiveness.
- Vaccination of populations with seroprevalence 50-70% is acceptable but the impact of the vaccination program may be lower.
- CYD-TDV is not recommended when seroprevalence <50% in the age group targeted.
Seroprevalence studies are an important parameter and, when available, they are fundamental for decision making. However, the lack of them should not be a reason to delay or defer the application of dengue vaccine to populations who need it urgently.

The delay in incorporating vaccines with proven effectiveness and impact, has been a source of unnecessary morbidity and mortality in the case of previous vaccines.

Regional surveillance systems need to be strengthen and diagnostic algorithms improved incorporating more specific diagnostic methods, in order to better evaluate the effectiveness of the vaccine in a complex context in which the interpretation of serological diagnosis for dengue tests is difficult due to the co-circulation of Zika virus and wide YF vaccine coverage in the population.

International Dengue Initiative, 2017 (Vaccine, under consideration)
Target population: 500,000 out of 10 millions (all individuals 15-27 years of age in 28 municipalities and 9-44 years of age in the two municipalities with the top dengue burden).

Up to April 2017, thirteen countries have registered Dengvaxia® and only two (Philippines & Brazil) have introduced it.
As CYD-TDV expresses only protein E and prM of all 4 serotypes of DENV, tests that detect IgM against other viral proteins could be an attractive alternative to diagnose DENV infection in vaccinated subjects:

- NS1-based IgM capture ELISA and IgG capture ELISA
- Detection of isotypes of antibodies against the virus that does not persist for a long time is another option (Anti-IgA antibodies?)
- Dengue virus RNA in urine?

- There is a need to define the best dengue test algorithm for identification of probable dengue disease using serology in vaccinated individuals
- Current ‘probable’ case definition based only on IgM and IgG serology appears inadequate

Adding to the confusion...
Some caveats though…

- Will Antibody Dependant Enhancement play a role in vaccinated individuals who acquire a new dengue infection?
- How long is vaccine-induced immunity expected to last?
- In hyperendemic countries, how earlier in life can vaccination be initiate?
- Is current serology-based surveillance appropriate in areas with intense vaccine use?
- What would be a good correlate to population seroprevalence?
WELL... LOOK DOCTOR......HOW TO EXPLAIN THAT I ALREADY HAVE ALL MY VACCINES? REALLY!!

THANKS A LOT!

GRACIAS...