Clinical trial design and policy expectations for dengue vaccines

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Age-dependent dengue transmission trends

Globally, incidence peaks between 5 and 14 years of age.

Seroprevalence in 9-year olds: a good proxy for high transmission and endemic settings.

Zeng et al. 2021. eClinicalMedicine

Source: Global Burden of Disease 2017

Seroprevalence in 9 year-olds (mean estimate)

Seroprevalence in 9 year olds
- <50%
- 50% - 60%
- >60%

Policy expectations

• A dengue vaccine that meets the public health needs:
• Efficacious and safe regardless of dengue serostatus
• Balanced efficacy against all four serotypes
• Long duration
• Ideally single dose
• Age indication: Infants, children and adolescents (for most endemic countries); without upper age limit (for low endemic countries and for travellers)
Immunological interaction between the 4 serotypes
Three dengue vaccine candidates, all are tetravalent and live attenuated; differences in the backbone and extent of chimerization

<table>
<thead>
<tr>
<th></th>
<th>Dengvaxia (Sanofi Pasteur)</th>
<th>TAK-003 (Takeda)</th>
<th>TV003/TV005 (NIH/Butantan/Merck)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Phase 3</td>
</tr>
<tr>
<td># Doses</td>
<td>3 doses over 12 months (0, 6, 12)</td>
<td>2 doses (0, 3 months)</td>
<td>Single dose</td>
</tr>
<tr>
<td>Indicated age</td>
<td>9 - 45</td>
<td>Phase 3 age range 4 - 16</td>
<td>Phase 3 age range 2 - 59</td>
</tr>
<tr>
<td>Other</td>
<td>Requires documented previous DENV infection</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Construct</td>
<td>![Construct Diagram]</td>
<td>![Construct Diagram]</td>
<td>![Construct Diagram]</td>
</tr>
<tr>
<td>Dengue proteins</td>
<td>8</td>
<td>16</td>
<td>32</td>
</tr>
</tbody>
</table>
Neutralizing/protective antibody responses following DENV infection and vaccination

- **First infection**
  - Cross neutralizing and protective Abs

- **12-24 months**
  - Monotypic neutralizing and protective Abs

- **Second infection**
  - Cross neutralizing and protective Abs
  - Serotype cross neutralizing Ab response (including to serotypes not "seen" by the immune system)

**LAV in naïve individuals**

Abs, antibodies; LAV, live attenuated viruses

**LAV in DENV-exposed individuals**
Serostatus-driven vaccine performance

- **Dengvaxia**
  - Seropositive persons: efficacious and safe, especially serotype 4
  - Seronegative persons: increased risk of severe dengue in seronegative persons:
    - RR 2-3
  - a “pre-vaccination screening strategy” is the recommended strategy, in which only dengue-seropositive persons are vaccinated.
  - Age 6-45
  - Low vaccine uptake due to the costs and complexities of the “test-and-vaccinate” policy

- **Qdenga TAK-003**
  - Seropositive persons: efficacious and safe, especially serotype 2
  - Seronegative persons: efficacious against serotypes 1 and 2. Absence of efficacy in serotypes 3 and 4
  - Safety risk cannot be excluded with the available data
  - WHO recommendation: use in settings with high dengue transmission intensity only, eg seroprevalence > 60%, age 6-16
  - No pre-vaccination screening
Viremia following a single dose of Butantan/Merck`s TV003 vaccine

The percentage of subjects with detectable viremia by PCR after a single dose in flavivirus-naïve subjects

<table>
<thead>
<tr>
<th></th>
<th>DENV-1</th>
<th>DENV-2</th>
<th>DENV-3</th>
<th>DENV-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYD, Day 7 (n=12)¹</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>CYD, Day 7 (n=84)²</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>CYD (n=25)³</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>CYD (n=95)⁴</td>
<td>7.4</td>
<td>0</td>
<td>12.6</td>
<td>44.2</td>
</tr>
<tr>
<td>TAK (n=74)⁵</td>
<td>0</td>
<td>68.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TV003 (n=36)⁶</td>
<td>63.9</td>
<td>69.4</td>
<td>52.8</td>
<td>52.8</td>
</tr>
</tbody>
</table>

1. Qiao et, 2011, viremia only measured on day 7 & 14, but cumulative viremia was not reported
2. Poo, et al, 2011, viremia only measured on day 7 & 14, but cumulative viremia was not reported
4. Torresi, et al 2017; CYD lot-to-lot consistency trial. Viremia measured on days 6, 8, 10, 14, & 20
5. Rupp et al 2015; Viremia measured on days 7, 9, 11, 14, &17
6. Russell et al, ASTMH 2019, Merck V181. Viremia collected on days 7 & 12 only
WHO Report

Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines

Kirsten S. Vannice\textsuperscript{a,1}, Annelies Wilder-Smith\textsuperscript{a b,1}, Alan D.T. Barrett\textsuperscript{c,1}, Kalinka Carrijo\textsuperscript{d,1}, Marco Cavalieri\textsuperscript{e,1}, Aravinda de Silva\textsuperscript{f,1}, Anna P. Durbin\textsuperscript{g,1}, Tim Endy\textsuperscript{h,1}, Eva Harris\textsuperscript{i,1}, Bruce L. Innis\textsuperscript{j,1}, Leah C. Katzelnick\textsuperscript{l,1}, Peter G. Smith\textsuperscript{k,1}, Wellington Sun\textsuperscript{l,1}, Stephen J. Thomas\textsuperscript{h,1}, Joachim Hombach\textsuperscript{a,1}
Current assays do not distinguish between type-specific antibodies, transient heterotypic antibody, and long-lasting heterotypic antibody.

Serotype-specific assays need to be used.
Vaccine infectivity and interference

• Vaccine infectivity:
  • Demonstrating replication for each of the four vaccine viruses, when administered as a live tetravalent vaccine, is highly desirable given the potential risk of interferences.

• Interference:
  • Antibody depletion assays to determine whether type-specific responses were generated for each of the four serotypes.
Immunobridging

Lack of immune correlates for protection

Lack of immune correlates for enhancement

Whilst for some flavivirus vaccines (e.g., JE, yellow fever etc), immunobridging has been accepted, RCT Phase 3 trials are still required for dengue.
Human Challenge Studies

- Can provide initial proof-of-concept that a vaccine may have potential for clinical benefit
- Was done for the NIH tetravalent vaccine
- Challenge should be done >12 months
- But greater confidence is required in dengue CHIM performance: highly attenuated challenge virus vs disease-causing virus
Clinical trial design requirements

• Baseline samples needed to determine baseline serostatus
• A-priori plans to stratify by serostatus, serotype and clinical endpoints
• Active surveillance
• Duration 3-5 years
• An extended follow-up period will allow for additional power to look at secondary analyses, eg VE by infecting serotype
• Multi-country trial over several seasons to ensure that all 4 serotypes are captured
Thank you
Dengvaxia: post-hoc results from the Phase 3 trials:
Cumulative incidence of hospitalised dengue by serostatus
Figure 3. Cumulative incidence of (A) virologically confirmed dengue (VCD) cases and (B) hospitalized VCD cases.
Risk of severe dengue associated with secondary versus primary infections

<table>
<thead>
<tr>
<th></th>
<th>Seronegative</th>
<th>Seropositive</th>
<th>RR</th>
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<tbody>
<tr>
<td><strong>2–8 years old</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputations methods, months 0–60</td>
<td>3.64</td>
<td>11.6</td>
<td>3.19</td>
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<tr>
<td><strong>9–16 years old</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputations methods, months 0–60</td>
<td>1.74</td>
<td>4.80</td>
<td>2.76</td>
</tr>
<tr>
<td><strong>2–16 years old</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputations methods, months 0–60</td>
<td>2.52</td>
<td>6.09</td>
<td>2.42</td>
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</tbody>
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