Arbovirus vaccines: Dengue, Zika vaccines - Advances and challenges.

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Director for Latin America
Dengue: the most common arboviral infection worldwide

- 390 million dengue infections per year
- 96 million (67–136 million) manifest clinically
- 75% reduction in 2016
Zika infection and outbreaks 1947-2017
Monthly Zika illness case counts reported to the Pan American Health Organization (PAHO) during August 2015 to July 2018
Dengue and its adaptive immunity

Primary DENV infection

Secondary heterologous DENV infection
Dengue: critical issues for vaccine development

- Four DENV serotypes all capable of causing the full spectrum of disease (need for a tetravalent vaccine)
- Life-long homotypic protection afforded after infection but only short term (few months) heterotypic protection is afforded
- Secondary infection with a different serotype is strongly associated with severe disease
# Current Live attenuated dengue vaccines

<table>
<thead>
<tr>
<th>Status</th>
<th>Dengvaxia (Sanofi Pasteur)</th>
<th>TDV (Takeda)</th>
<th>TV003 (NIH/Butantan)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Doses</td>
<td>Licensed</td>
<td>Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td></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 - &lt;16(^1)</td>
<td>Phase 3 age range 2 - 59(^2)</td>
</tr>
<tr>
<td>Other</td>
<td>Seropositive to dengue</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

**Construct**

- **DENV-1**
- **DENV-2**
- **DENV-3**
- **DENV-4**
- **YFV**

1. NCT02747927
2. NCT02406729

Courtesy of Anna Durbin, JHSPH
# Efficacy\(^1\) of CYD-TDV

<table>
<thead>
<tr>
<th>Trial</th>
<th>Region</th>
<th>Vaccine recipients enrolled</th>
<th>Age</th>
<th>Overall Efficacy (95% CI)</th>
<th>Efficacy, hospitalization</th>
<th>Efficacy, severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYD23(^2)</td>
<td>Thailand</td>
<td>2,669</td>
<td>4-11</td>
<td>30.2 (-13.4-56.6)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>CYD14(^3)</td>
<td>SE Asia</td>
<td>6,851</td>
<td>2-14</td>
<td>56.5 (43.8-66.4)</td>
<td>67%</td>
<td>80%</td>
</tr>
<tr>
<td>CYD15(^4)</td>
<td>Latin America</td>
<td>13,920</td>
<td>9-16</td>
<td>60.8 (52.0-68.0)</td>
<td>80%</td>
<td>91.7%</td>
</tr>
</tbody>
</table>

1. Per protocol analysis. Period of primary efficacy evaluation was > 28 days after the third dose to month 25 (12 month period)
### Risk of Hospitalization for confirmed Dengue and of Severe VCD in subjects 2 to 16 Years of Age in Asia and Latin America (Dengvaxia Phase III)

<table>
<thead>
<tr>
<th>Serostatus, End Point, and Method</th>
<th>Vaccine Group</th>
<th>Control Group</th>
<th>Relative Risk or Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seropositive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for VCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI, month 0 onward</td>
<td>152.4/1816.1</td>
<td>227.5/886.2</td>
<td>0.32 (0.23–0.45)</td>
</tr>
<tr>
<td>TMLE, month 0 onward</td>
<td>99.2/1742.3</td>
<td>199.5/846.7</td>
<td>0.25 (0.12–0.53)</td>
</tr>
<tr>
<td>NS1, T9, month 13 onward</td>
<td>124/1750</td>
<td>175/822</td>
<td>0.34 (0.26–0.43)</td>
</tr>
<tr>
<td>Severe VCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI, month 0 onward</td>
<td>35.1/1816.1</td>
<td>53.4/886.2</td>
<td>0.31 (0.17–0.58)</td>
</tr>
<tr>
<td>TMLE, month 0 onward</td>
<td>28.2/1742.3</td>
<td>49.9/846.7</td>
<td>0.27 (0.15–0.48)</td>
</tr>
<tr>
<td>NS1, T9, month 13 onward</td>
<td>31/1750</td>
<td>44/822</td>
<td>0.33 (0.21–0.53)</td>
</tr>
<tr>
<td><strong>Seronegative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for VCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI, month 0 onward</td>
<td>201.6/567.9</td>
<td>62.5/307.8</td>
<td>1.75 (1.14–2.70)</td>
</tr>
<tr>
<td>TMLE, month 0 onward</td>
<td>244.0/547.2</td>
<td>65.5/296.8</td>
<td>2.10 (0.94–4.70)</td>
</tr>
<tr>
<td>NS1, T9, month 13 onward</td>
<td>187/512</td>
<td>53/272</td>
<td>1.89 (1.35–2.65)</td>
</tr>
<tr>
<td>Severe VCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI, month 0 onward</td>
<td>44.9/567.9</td>
<td>8.6/307.8</td>
<td>2.87 (1.09–7.61)</td>
</tr>
<tr>
<td>TMLE, month 0 onward</td>
<td>44.6/547.2</td>
<td>9.3/296.8</td>
<td>2.62 (1.03–6.70)</td>
</tr>
<tr>
<td>NS1, T9, month 13 onward</td>
<td>37/512</td>
<td>5/272</td>
<td>3.93 (1.53–10.10)</td>
</tr>
</tbody>
</table>
The Dengvaxia Sanofi vaccine "safety issue"
Updated SAGE-WHO review of Dengvaxia

• Overall population level benefit of vaccination remains favorable, but the vaccine performs differently in seropositive versus seronegative individuals.

• There is an increased risk of hospitalized and severe dengue in seronegative individuals starting about 30 months after the first dose.

• In areas of 70% dengue seroprevalence, over a 5-year follow-up:
  — For every 4 severe cases prevented in seropositive, there would be one excess severe case in seronegative per 1,000 vaccinees;
  — For every 13 hospitalizations prevented in seropositive vaccinees, there would be 1 excess hospitalization in seronegative vaccinees per 1,000 vaccinees.
TDV summary (Takeda vaccine)

- Similar GMTs achieved with different regimens
- Better multi-valent seroconversion frequencies with 2 dose regimen in dengue-naïve
- RR of dengue = 0.29 in those who received TDV compared with placebo
- Current formulation in Phase 3 clinical trial in Asia and Latin America (dosing: 0 & 3 months)

<table>
<thead>
<tr>
<th></th>
<th>Tota</th>
<th>Grp 1</th>
<th>Grp 2</th>
<th>Grp 3</th>
<th>Grp 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1794</td>
<td>n=20</td>
<td>n=39</td>
<td>N=998</td>
<td>N=19</td>
</tr>
</tbody>
</table>

Confirmed dengue cases

- 30
- 4
- 3
- 14
- 9

Serotype recovered

- DEN-1
- DEN-2
- DEN-3
- DEN-4
- Unk

<table>
<thead>
<tr>
<th></th>
<th>Grp 1</th>
<th>Grp 2</th>
<th>Grp 3</th>
<th>Grp 4</th>
</tr>
</thead>
<tbody>
<tr>
<td># cases</td>
<td>10</td>
<td>11</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

All participants were monitored for episodes of febrile illness throughout the study. Within 5 days of fever or febrile illness suspected to be due to dengue infection, blood samples were collected and analyzed for the presence of dengue by RT-PCR or NS1 ELISA.
Takeda’s Dengue Vaccine Candidate Meets Primary Endpoint in Pivotal Phase 3 Efficacy Trial

January 29, 2019

Cambridge, Mass., and Osaka, Japan, January 29, 2019 – Takeda Pharmaceutical Company Limited [TSE:4502 / NYSE:TAK] ("Takeda") today announced that the pivotal Phase 3 trial of its dengue vaccine candidate met the primary efficacy endpoint. This first analysis of the Tetravalent Immunization against Dengue Efficacy Study (TIDES) trial showed that the company’s investigational live-attenuated tetravalent dengue vaccine (TAK-003) was efficacious in preventing dengue fever caused by any of the four serotypes of the virus.
TV003/TV005 – NIH/Butantan vaccine

- Attenuated by deletions in 3’ UTR (3 components) and chimerization (1 component)
  - Contains 32 dengue proteins
- TV003 contains $3 \log_{10}$ PFU of each monovalent component, TV005 contains a 10-fold higher dose of rDEN2/4Δ30
- Asymptomatic rash most common vaccine-associated adverse event (correlated with tetravalent antibody response)
- Viremia detected in ~65% vaccinees (all 4 components detected)
  - $HID_{50}$ of each component is ≤ 10 PFU
Current status and challenges of Dengue vaccines

- Dengvaxia just approved by FDA – ACIP to discuss its use in endemic US territories
- First vaccine to potentially need a **rapid diagnostic test** before administration (major challenge ahead)
- Takeda vaccine results to be denuded soon, will the **safety signal** be also an issue? Long term data needed
- NIH-Butantan - very low dengue incidence in Latin America 2017 & 2018 delaying efficacy results
Zika virus structure

- ENV dimer
- M protein
- Lipid membrane
- Genomic RNA
- C protein

<table>
<thead>
<tr>
<th>C</th>
<th>prM</th>
<th>ENV</th>
<th>NS1</th>
<th>NS2A</th>
<th>NS2B</th>
<th>NS3</th>
<th>NS4A</th>
<th>NS4B</th>
<th>NS5</th>
</tr>
</thead>
</table>
Zika immunity and dengue

Unanswered Questions
- Microcephaly and other birth defects?
- Transplacental transmission?
- Sexual transmission? Persistence in immune-privileged tissues?
- More severe ZIKV disease?
- More severe DENV disease?
- Interference with DENV vaccine responses?
- Guillain-Barré syndrome?

DENV1 (prime) → high neutralizer → ZIKV (boost) → weak neutralizer

Antibodies vs. time

Polyclonal B cells → VH3-23/VK1-5 expanded clone

Zika Virus Infection
- Viremia
- Fever
- Rash
- Myalgia
- Conjunctivitis

Protective Immunity

Aedes mosquito

Keratinocytes

Dendritic cell

Center for Global Health
colorado school of public health
Experience with other Flavivirus Vaccines

• **Yellow Fever Vaccine** (*live-attenuated*)
  - Effective against 7 genotypes
  - Protective titer ≥1:10
  - High efficacy rates

• **JEV and TBE Vaccines** (*inactivated virus*)
  - Protective titer ≥1:10
  - High efficacy rates

• **Dengue Vaccines** (*live recombinant and chimeric*)
  - Protective titer undefined
  - Variable efficacy

• **Investigational WNV vaccines**
  - Multiple platforms have been tested
  - Correlate of protection undefined

• **E protein is primary target for neutralizing antibody**
### ZIKV Vaccine Evaluation

<table>
<thead>
<tr>
<th>Concept</th>
<th>Vaccine</th>
<th>Antigens</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-inactivated virus</td>
<td>Formalin-inactivated virus</td>
<td>All</td>
<td>Takeda, Walter Reed, Sanofi Pasteur, Valneva</td>
</tr>
<tr>
<td>Replicating virus</td>
<td>Chimeric Dengue prM-E</td>
<td>prM-E</td>
<td>NIAID</td>
</tr>
<tr>
<td></td>
<td>Live-attenuated virus All</td>
<td>All</td>
<td>UTMB by mutation, Codagenix by codon-deoptimization</td>
</tr>
<tr>
<td></td>
<td>Chimeric Yellow Fever prM-E</td>
<td>prM-E</td>
<td>Sanofi Pasteur</td>
</tr>
<tr>
<td>Nucleic acid</td>
<td>DNA plasmids M-E</td>
<td>M-E</td>
<td>Beth Israel</td>
</tr>
<tr>
<td>Gene delivery</td>
<td>DNA plasmids prM-E</td>
<td>prM-E</td>
<td>NIAID, Inovio</td>
</tr>
<tr>
<td></td>
<td>mRNA prM-E</td>
<td>prM-E</td>
<td>Moderna, UPenn</td>
</tr>
<tr>
<td></td>
<td>Self-amplifying RNA prM-E</td>
<td>prM-E</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Vector Gene delivery</td>
<td>VSV Vector prM-E</td>
<td>prM-E</td>
<td>Harvard</td>
</tr>
<tr>
<td></td>
<td>Adenovirus Vector M-E</td>
<td>M-E</td>
<td>Beth Israel (J&amp;J)</td>
</tr>
<tr>
<td></td>
<td>Measles Vector prM-E</td>
<td>prM-E</td>
<td>Institut Pasteur (with Themis)</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Antigen</td>
<td>Induction of NAbs</td>
<td>Short-term protection in mice</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>-------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>ZPIV</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>DNA</td>
<td>prM-ENV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ad</td>
<td>prM-ENV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>mRNA</td>
<td>prM-ENV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MVA</td>
<td>NS1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MV</td>
<td>prM-ENV</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>ZIKV-LAV</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Viremia in vaccinated and control cynomolgus macaques challenged with ZIKV

*Vaccinated animals had a significantly reduced number of viremic days compared to control animals (p < 0.0002; Alum, Alhydrogel® 85).

ZIKV DNA Vaccine-Induced Antibody and Protection

VRC8400 control
VRC5283 4mg X2
VRC5283 1mg X2
VRC5288 4mg X2
VRC5288 1mg X1

NT Antibody

Viral Load

Weeks Post-Vaccination

Days Post-Challenge
Plasma viremia after challenge at gestational day 30

Control Dams (n=12)

Vaccinates (n=12)

Data from Koen Von Rompay
UC Davis
ZIKV DNA Vaccine Development

- 2013:
  - Zika virus outbreak in French Polynesia
  - First reports of Zika infection in Brazil

- 2014:
  - Zika virus spread to over 20 countries in Western hemisphere

- 2015:
  - Pre-IND
  - May 2015
  - DNA Vaccine Sequence Selected
  - Apr 24, 2016

- 2016:
  - Feb 2016
  - Jun 2016
  - Drug Product Manufacturing
  - May 23, 2016
  - IRB Review
  - July 21, 2016
  - IND Submission
  - Jul 2016
  - Product Release
  - Aug 2, 2016
  - First vaccination VRC 319 (Phase 1)
  - First vaccination VRC 320 (Phase 1)
  - Sep 2016
  - Preclinical data published
  - Dec 12, 2016

- 2017:
  - Mar 30, 2017
  - First vaccination In Phase 2a/2b

Projected Date: Mar 30, 2017
Estimated cost-effectiveness of a Zika vaccine according to target populations
Challenges ahead for Zika vaccines

• **Neutralizing antibodies** are likely to be an important immune marker of protection;

• **WHO standardization and validation of assays** are critical for appropriate assessment of the immune response to Zika vaccine

• **Passive transfer studies** in animals showing protection against disease, infection, and CZS with human sera useful approximation

• **Clinical disease endpoint efficacy** studies may be challenging or even infeasible given the current epidemiology of ZIKV;

• **Post-licensure studies** will be required for all approved ZIKV vaccines: the specific studies will depend on the regulatory pathway, the indication, and vaccine characteristics.