The Dengue Vaccine Landscape

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Mission – To accelerate the development and consideration of vaccines to prevent dengue
Background: Dengue

- Most common global vector-borne viral infection
- Global burden is increasing substantially driven by population growth, urbanization, globalization and ecological changes
- World needs dengue vaccine as part of an integrated approach to dengue prevention and control (including vector control, improved surveillance, etc.)
Dengue virus

- Positive sense, single stranded, 11kb RNA flavivirus
- 3 structural (prM/M, E, C) and 7 non-structural proteins
- 4 antigenically distinct serotypes (DENV-1, 2, 3, 4)
Dengue vaccine design strategies

DNA (prM + E) + adjuvant

Directed mutagenesis Chimeras

E recombinant
Expressed in Drosophila cells

E Domain I/II hinge; E Domain III

PIV + adjuvant
Purified, formalin-inactivated

Virus-like particles

YF 17D backbone
DENV-1,-2,-3,-4 prM and E

DENV-2 PDK-53 backbone
DENV-1,-3,-4 prM and E
Substantial challenges exist

- Mainly due to existence of four serotypes that interact with each other in significant and often unpredictable ways
  - Protection
  - Enhancement
  - Interference
Substantial challenges exist

• Biological assays to measure immune response are imprecise and of unclear clinical relevance
  – No current lab measurement is correlate of protection or risk
• No valid animal model
  – Monkeys have viremia but lower than humans and no disease
  – Immunodeficient mouse models have been developed but are not optimal
# Vaccines in active human clinical trials

<table>
<thead>
<tr>
<th>Category</th>
<th>Sponsor</th>
<th>Vaccine name</th>
<th>Approach</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Live attenuated with or without chimera</td>
<td>Sanofi Pasteur</td>
<td>CYD-TDV</td>
<td>Yellow fever 17D backbone and YF-DENV chimera</td>
<td>III License</td>
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<tr>
<td></td>
<td>Takeda</td>
<td>TDV</td>
<td>DENV-2 PDK-53 backbone and DENV-DENV chimera</td>
<td>II; soon III</td>
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<td></td>
<td>US NIH, Butantan, VaBiotech, Panacea, Serum Institute of India, Merck</td>
<td>TV003/TV005</td>
<td>Direct mutagenesis and DENV-2/4 chimera</td>
<td>Preclin II, III</td>
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<tr>
<td>Protein subunit</td>
<td>Merck</td>
<td>V180</td>
<td>DENV 80% E protein recombinant + adj</td>
<td>I</td>
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<tr>
<td>Inactivated whole virus</td>
<td>GSK/ Fiocruz/ US Army</td>
<td>DPIV</td>
<td>Formalin inactivated + adj</td>
<td>Preclin I</td>
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<tr>
<td>DNA</td>
<td>US Navy</td>
<td>TVDV</td>
<td>Plasmid DNA + adj</td>
<td>I</td>
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<tr>
<td>Heterologous prime-boost</td>
<td>US Army</td>
<td>TDENV-LAV +</td>
<td>Live attenuated/ inactivated whole</td>
<td>I</td>
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<td>TDENV-PIV</td>
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## Vaccines in preclinical development (NHPs)

Table 1: Active dengue vaccine candidates in preclinical development that have been evaluated in NHP models.

<table>
<thead>
<tr>
<th>Technological approach</th>
<th>Vaccine developer</th>
<th>Antigen</th>
<th>Valency under evaluation or evaluated in NHP</th>
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<tr>
<td>Recombinant subunit vaccines</td>
<td>IPK/CIGB</td>
<td>EDIII-p64k fusion proteins and EDIII-capsid fusion proteins expressed in <em>E. coli</em></td>
<td>Monovalent</td>
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<tr>
<td></td>
<td>VaxImmune</td>
<td>Bivalent 80E-STF2 fusion proteins expressed in baculovirus/insect cells</td>
<td>Tetravalent</td>
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<td></td>
<td>NHRI</td>
<td>Tetravalent consensus EDIII protein expressed in <em>E. coli</em></td>
<td>Tetravalent</td>
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<tr>
<td>DNA vaccines</td>
<td>NMRC</td>
<td>Tetravalent “shuffled” prM/E expressed from plasmid vector</td>
<td>Tetravalent</td>
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<tr>
<td></td>
<td>CDC</td>
<td>prM/E expressed from plasmid vector</td>
<td>Tetravalent</td>
</tr>
<tr>
<td>VLP Vaccines</td>
<td>ICGEB</td>
<td>EDIII-HBsAg VLPs or ectoE-based VLPs expressed in <em>P. pastoris</em></td>
<td>Tetravalent</td>
</tr>
<tr>
<td>Virus-vectored vaccines</td>
<td>Themis Bioscience/Institut Pasteur</td>
<td>Tetravalent EDIII and DENV-1 ectoM expressed from live-attenuated measles virus vector</td>
<td>Tetravalent</td>
</tr>
<tr>
<td></td>
<td>Global Vaccines</td>
<td>E85 expressed from single-cycle VEE virus vector</td>
<td>Tetravalent</td>
</tr>
<tr>
<td>Purified inactivated virus vaccines</td>
<td>NMRC</td>
<td>Psoralen-inactivated DENV</td>
<td>Monovalent</td>
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<tr>
<td></td>
<td>WRAIR/GSK/FIOCRUZ</td>
<td>Purified inactivated DENV</td>
<td>Tetravalent</td>
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<tr>
<td></td>
<td>Global Vaccines</td>
<td>Inactivated virus (+VEE-particle adjuvant)</td>
<td>Tetravalent</td>
</tr>
<tr>
<td>Live attenuated virus vaccines</td>
<td>Chiang Mai University/Mahidol University/NSTDA/BioNet-Asia</td>
<td>DEN/DEN chimeric viruses</td>
<td>Monovalent</td>
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<tr>
<td></td>
<td>Arbovax</td>
<td>DEN host range mutations</td>
<td>Tetravalent</td>
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<tr>
<td></td>
<td>Beijing Institute of Microbiology and Epidemiology</td>
<td>DEN-SA 14 14 2</td>
<td>Monovalent</td>
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<td></td>
<td>Novartis Institute for Tropical Diseases/Agency for Science, Technology and Research, Singapore</td>
<td>DEN targeted mutation (2’-O-methyltransferase mutant)</td>
<td>Bivalent</td>
</tr>
<tr>
<td>Heterologous prime-boost approaches</td>
<td>NMRC/WRAIR</td>
<td>Purified inactivated DENV or plasmid vector expressing prM/E (prime) and live attenuated DENV (boost)</td>
<td>Tetravalent</td>
</tr>
<tr>
<td>Simultaneous administration</td>
<td>FIOCRUZ</td>
<td>DENV prM/E expressed from live attenuated chimeric YF 17D/DEN virus with DNA vaccine</td>
<td>Monovalent</td>
</tr>
</tbody>
</table>
**Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial**

Arunee Sabchareon, Derek Wallace, Chukiat Sirichaeyeakul, Kriengsak Limkittikul, Pornthep Chanthavanich, Sarawuth Suwanndibbo, Vithaya Jiwanayavej, Wut Dulyachai, Kristina Pengsaa, T Anh Wartel, Annick Moureau, Melanie Saville, Aline Bouckenooge, Simonetta Viviani, Nadja G Tomieporth, Jean Long


**Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial**

Maria Rosario Capeding, Nego Huo Tran, Sri Razali S Hadinegoro, Hussein Imam Hj Muhammad Ismail, Towee Chotpitayasunandas, Mary Nureen Chua, Chan Quang Luong, Kusnandi Rosri, Dewi Nyoman Wirawan, Kevathy Nallusamy, Punnee Pitrutthithum, Usa Thiyakorn, In-Kyo Yoon, Diane van der Velden, Edith Langevin, Thalma Laut, Yanie Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadja G Tomieporth, Melanie Saville, Aline Bouckenooge, and the CYD15 Study Group


**Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America**

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tomieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group


**Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease**


Summary of CYD-TDV phase 2b and 3 trials

- Serotype-specific efficacy:
  - Poor efficacy against DENV-2
  - Moderate efficacy against DENV-1
  - Good efficacy against DENV-3 and 4
  - Immunogenicity by PRNT of unclear clinical relevance

- Better efficacy against severe dengue

- Better efficacy in older children and dengue-primed individuals (not independent)
  - Efficacy apparent after dose 1 in primed individuals

- Increased risk in very young children during 3rd year
Licensure of CYD-TDV in endemic countries

• Given efficacy profile and no observed safety signal in post-hoc analysis in older children, Sanofi Pasteur submitted the dossier for licensure in multiple dengue endemic countries in Asia and Latin America.

• In December 2015, CYD-TDV (Dengvaxia®) was licensed in Mexico, Philippines, and Brazil for use in 9-45 year olds in endemic areas.
TDV (Takeda) & TV003/TV005 (NIH)

3 most clinically advanced dengue vaccine candidates

<table>
<thead>
<tr>
<th>Structural</th>
<th>Non-structural</th>
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<tr>
<td>5'</td>
<td>C</td>
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</tbody>
</table>

**Sanofi Pasteur CYD-TDV:**
- Chimeric
- Full-length
- Unique DENV proteins 8

**Takeda TDV:**
- Chimeric
- Full-length
- 16

**NIH TV003/TV005:**
- Full-length
- Chimeric
- 32

**YFV**
- C
- prM
- E
- NS1
- NS2A
- NS2B
- NS3
- NS4A
- NS4B
- NS5

DENV:
- DENV-1
- DENV-2
- DENV-3
- DENV-4

**3'**
DPIV (GSK/ Fiocruz/ US Army)

- GSK, Fiocruz (Brazil) and U.S. Army have been collaborating on tetravalent purified formalin-inactivated whole virus vaccine
  - Used with alum or GSK proprietary adjuvants
  - Two dose schedule IM at 0 and 21 days (may be further modified)
  - US Army manufactured PIV (TDENV-PIV) with adjuvant has undergone Phase I trials in dengue naïve and non-naïve adults with good tetravalent neutralizing antibody responses
  - GSK manufactured PIV with adjuvant is in preclinical studies in monkeys
DPIV (GSK/ Fiocruz/ US Army)

- **Potential advantages**
  - Could be co-administered with other vaccines
  - Could be administered in immunocompromised
  - No/minimal viral interference
  - Potential accelerated schedule for indication in travelers and for “outbreak” control

- **Challenges**
  - No nonstructural proteins
  - Unclear maintenance of native conformation
  - Unclear relevance of neutralizing antibodies
  - Early in clinical development
V180 (Merck)

- Tetravalent recombinant protein subunit vaccine based on truncated envelope (E) protein (DENV-80E) expressed in *Drosophila* S2 expression system
  - Used with alhydrogel or ISCOMATRIX® proprietary adjuvant
  - Three dose schedule IM over 2 months (may be further modified)
  - Phase I dose-escalation trial in adults is ongoing
  - Also Phase I trial using prime-boost in combination with NIH dengue vaccine candidate is planned
V180 (Merck)

• Potential advantages
  – Could be co-administered with other vaccines
  – Could be administered in immunocompromised
  – No/minimal viral interference
  – Potential accelerated schedule for indication in travelers and for “outbreak” control

• Challenges
  – No nonstructural proteins
  – Unclear maintenance of native conformations
  – Unclear relevance of neutralizing antibodies
  – Early in clinical development
TVDV (US Navy)

- Tetravalent **DNA plasmid** vaccine with genes encoding premembrane (prM) and envelope (E) proteins
  - Used with Vaxfectin® proprietary adjuvant
  - Monovalent DENV-1 vaccine without adjuvant had poor neutralizing antibody response
  - Three dose schedule IM over 3 months (may be further modified)
  - Phase I dose-escalation trial in adults in U.S. is ongoing
TVDV (US Navy)

• Potential advantages
  – Could be co-administered with other vaccines
  – Could be administered in immunocompromised
  – No/minimal viral interference
  – Stable and relatively easy to produce

• Challenges
  – No nonstructural proteins
  – Unclear maintenance of native conformations
  – Poor neutralizing antibody response in humans when used without adjuvant
Summary

• Sanofi Pasteur’s Dengvaxia® has now been licensed in 3 dengue endemic countries; perhaps others in future
• Butantan’s TV003 (developed by NIH) has been approved for a phase 3 trial in Brazil
• Takeda’s TDV may enter phase 3 trial soon
• Three other candidates (DPIV, V180, TVDV) are in phase 1
• Clinical development of next wave of vaccine candidates will need to account for Dengvaxia®’s introduction
Thank you