Dengue Vaccines

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Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine

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Dengue

- Four antigenically distinct serotypes (DENV1-4)
- 50-100 million cases every year
- Clinical spectrum:
  - 80% asymptomatic
  - Self-limiting febrile illness
  - Severe dengue (~2-4% of symptomatic)
  - Secondary infections are associated with higher risk of more severe dengue
  - CFR 0.1—1%

Dengue Vaccine

(http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/)

Phase I
- DPIV
  - GlaxoSmithKline, Biomanguinhos, WRAIR

Phase II
- DEN-80E
  - Merck

Phase IIb
- TVDV
  - Naval Medical Research Center

Phase III
- TLAV-TPIV
  - WRAIR

Registration
- CYD-TDV
  - Dengvaxia™ Sanofi Pasteur

- TV003/TV005
  - US National Institutes of Health\(^1\) Butantan

- DENVax
  - Takeda
Homotypic and heterotypic antibodies

- Vaccine efficacy varied by:
  - Serotype (serotype 4 and 3)
  - Serostatus (seropositive)
  - Severity of disease (more severe)
  - Age (older age)

*NEJM 2015*
WHO recommendations for settings with seroprevalence > 70% (April 2016)

• Licensed for age 9 and above

• Public Health benefit—Vaccine preventable disease incidence, seropositivity drives efficacy

• Safety benefit – high proportion of seropositives; seronegatives will have a higher or equal risk of secondary infections through natural exposure than potential vaccine induced secondary-like infections
Sanofi updates information on dengue vaccine

New analysis of long-term Dengvaxia® data found differences in vaccine performance based on prior dengue infection. Company will ask regulators to update product label to reflect new information.

PARIS, FRANCE — November 29, 2017 — Sanofi will ask health authorities to update information provided to physicians and patients on its dengue vaccine Dengvaxia® in countries where it is approved. The request is based on a new analysis of long-term clinical trial data, which found differences in vaccine performance based on prior dengue infection.

Based on up to six years of clinical data, the new analysis evaluated long-term safety and efficacy of Dengvaxia® in people who had been infected with dengue prior to vaccination and those who had not. The analysis confirmed that Dengvaxia® provides persistent protective benefit against dengue fever in those who had prior infection. For those not previously infected by dengue virus, however, the analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection.

For individuals who have not been previously infected by dengue virus, vaccination should not be recommended.
ILIGTAS
SO
PANGANIB ANG
750,000 BATANG
BINAKUNAHAN
NG
DENGVAXIA!
GABRIELA
Metro Manila
PAANO NA ANG
AMING MGA ANAK?
-GABRIELA CALOOCAN
Politics comes into play in dengue vaccine scare

Parents of vaccine ‘victim’ seek justice

*Philippines Suspends Dengue Shots After Drug Firm’s Warning*
Myths, Misconceptions and Lies

- “Insomnia and declining school grades is due to neurotropic disease of Dengvaxia.
- Systemic disease is due to viscerotropic disease of Dengvaxia”
- “Genocide”

• Collateral damage:
  • Loss of vaccine confidence, reduced vaccine uptake, first measles outbreaks....
How did Sanofi Pasteur determine serostatus-dependent performance?

Vaccine efficacy against symptomatic VCD in the 25 months after dose 1 (2-16 year-olds - MI method)

<table>
<thead>
<tr>
<th>Sero-status at dose 1</th>
<th>Vaccine efficacy</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sero-positive</td>
<td>72%</td>
<td>58%, 82%</td>
</tr>
<tr>
<td>Sero-negative</td>
<td>32%</td>
<td>-9%, 58%</td>
</tr>
</tbody>
</table>

Relative risk of severe VCD comparing vaccinated to controls in the 66 months after dose 1 (2-16 year-olds - MI method)

<table>
<thead>
<tr>
<th>Sero-status at dose 1</th>
<th>Relative risk (CYD:Control)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sero-positive</td>
<td>0.28</td>
<td>0.15, 0.52</td>
</tr>
<tr>
<td>Sero-negative</td>
<td>3.00</td>
<td>1.10, 8.15</td>
</tr>
</tbody>
</table>

Time to hospitalized VCD – MI method - age 9-16 years

Cumulative % hospitalised VCD

Time from M0 (months)
How do we explain the CYD-TDV observations?
Viremia induced by CYD

<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 (0)</td>
<td>0 (0)</td>
<td>0 (17)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>CYD, Day 7 (n=84)²</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>2.1 (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>
</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
Homotypic vs heterotypic antibody response in CYD-TDV (Dengvaxia): depletion assays

- Samples were depleted of serotype specific antibodies to determine proportion of cross-reactive response
- Serotype specific antibodies dominated the DENV-4 response (CYD-4 most often detected post-vaccination)
- Cross-reactive antibodies dominated the DENV-2 response

Henein et al, JID 2017
Explanatory hypothesis for excess cases in seronegative trial participants:
“Silent infection” mode of action

- Vaccination primes the immune system similarly to infection:
  1. Temporary high degree of cross-immunity in at least seronegative recipients
  2. Seronegative recipients have secondary-like breakthrough infection once cross-immunity wanes
  3. Seropositive recipients have tertiary-like breakthrough infection once cross-immunity wane

Summary: CYD-TDV vaccine
Serostatus dependent performance

• Dengvaxia is efficacious and safe in seropositive persons

• Dengvaxia increases the risk of severe dengue in seronegative persons

How to best use the first licensed dengue vaccine?
Public health net benefit of Dengvaxia

Impact for vaccinated subjects over 10 years (direct protection only)

Results for a vaccinated cohort of 1,000,000 vaccinees

<table>
<thead>
<tr>
<th>Endemic setting</th>
<th>Sero+</th>
<th>Hospitalisations</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sero-</td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90%</td>
<td>6419 [5713;7101]</td>
<td>348 [82;992]</td>
<td>6767 [5795;8093]</td>
</tr>
<tr>
<td>80%</td>
<td>6535 [5834;7116]</td>
<td>-7 [-436;612]</td>
<td>6528 [5398;7728]</td>
</tr>
<tr>
<td>70%</td>
<td>5611 [5219;6332]</td>
<td>-572 [-874;287]</td>
<td>5039 [4344;6045]</td>
</tr>
<tr>
<td>60%</td>
<td>4303 [3833;5148]</td>
<td>-1484 [-1740;698]</td>
<td>2820 [2093;4450]</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>2978 [2724;3181]</td>
<td>-2039 [-2224;1758]</td>
<td>939 [500;1423]</td>
</tr>
<tr>
<td>40%</td>
<td>2243 [2124;2484]</td>
<td>-1904 [-2337;1314]</td>
<td>340 [-213;1170]</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>143 [115;219]</td>
<td>-217 [-290;188]</td>
<td>-74 [-176;31]</td>
</tr>
<tr>
<td>20%</td>
<td>74 [43;80]</td>
<td>-231 [-701;122]</td>
<td>-157 [-658;42]</td>
</tr>
<tr>
<td>Very low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>9 [6;11]</td>
<td>-57 [-89;44]</td>
<td>-48 [-83;33]</td>
</tr>
</tbody>
</table>

*Prevented number of hospitalisations over 10 years*
Ethical Dilemma

70% seroprevalence:
Every 1 excess case of hospitalized dengue in vaccinated seronegatives would be offset by 7 hospitalized cases prevented in vaccinated seropositives

85% dengue seroprevalence:
Every 1 excess case of hospitalized dengue in vaccinated seronegatives would be offset by 18 cases prevented in vaccinated seropositive persons
SAGE Working Group Considerations

A number of dimensions:

– Population benefit versus individual risk
– Ethical considerations
– Risk perceptions and communication
– Screening tests versus serosurveys
– Programmatic issues
– Vaccine coverage estimates

_Came down to an evaluation of:_

- Population Seroprevalence Criteria without Screening
- Pre-Vaccination Screening
## 1. Benefits and Harm

| Population Seroprevalence Criteria without Screening | Pre-Vaccination Screening |
|------------------------------------------------------+----------------------------|
| **BENEFIT**                                         | **BENEFIT**                 |
| Overall substantial population benefit in areas with high seroprevalence predicted. | Maximizing the benefit (high efficacy and good safety) in seropositive while avoiding harm in correctly identified seronegatives. |
| **HARM**                                            | **HARM**                    |
| An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term. | Some seronegative individuals will be put at increased risk of severe dengue if vaccinated due to a false positive screening test result. |
## 2. Risk

<table>
<thead>
<tr>
<th>Population Seroprevalence Criteria without Screening</th>
<th>Pre-Vaccination Screening</th>
</tr>
</thead>
</table>
| • If vaccine is introduced in a setting with 80% seroprevalence, 20% of the vaccinated population will be put at risk.  
• Loss in vaccine confidence (dengue vaccines and possibly other vaccines).  
• Inability of vaccinees to know own serostatus may lead to increased vaccine hesitancy. | • Risk of false positive test: seronegative individuals will be misclassified as seropositive  
• In a setting with 80% seroprevalence and a test with 98% specificity, 0.4% of the population would be unintentionally vaccinated. |
For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” is the recommended strategy, in which only dengue-seropositive persons are vaccinated.
What about travellers?

Perspective

Sero status-dependent performance of the first licensed dengue vaccine: implications for travellers

Annelies Wilder-Smith, MD, PhD*

Low seroprevalence in travellers
Not licensed in most non-dengue endemic countries
3 doses (however, short-term efficacy after one dose is as high as after 3 doses)
# Second-generation dengue vaccines

<table>
<thead>
<tr>
<th></th>
<th>Dengvaxia (Sanofi Pasteur)</th>
<th>TDV (Takeda)</th>
<th>TV003 (Butantan)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Status</strong></td>
<td>Licensed</td>
<td>Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td><strong># Doses</strong></td>
<td>3 doses over 12 months (0, 6, 12)</td>
<td>2 doses 3 months apart</td>
<td>1 dose</td>
</tr>
<tr>
<td><strong>Indicated age</strong></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><strong>Construct</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong># DENV proteins</strong></td>
<td>8</td>
<td>16</td>
<td>32</td>
</tr>
</tbody>
</table>

1. NCT02747927
2. NCT02406729

*Legend:*
- **DENV-1**
- **DENV-2**
- **DENV-3**
- **DENV-4**
- **YFV**
Thank you
Heterogeneity of seroprevalence between and within countries

**Thailand.** Vongpunsawad et al. PLoS ONE 2017


**Singapore** Ang et al, Epi News Bulletin 2014

https://mrcdata.dide.ic.ac.uk/_dengue/dengue.php
Optimal age for pre-vaccination screening strategy