SAGE deliberations on CYD-TDV ("Dengvaxia®")

Annelies Wilder-Smith
Consultant, Vaccines for Arboviral Diseases, WHO-IVB

- Scientific Coordinator ZikaPLAN
- Director, Partnership for Dengue Control, Fondation Merieux

SAGE meeting April 2018
Homotypic and heterotypic antibodies

Vaccine efficacy varied by:

- Serotype
- Serostatus
- Severity of disease
- Age

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

S.R. Hadinegoro, J.L. Arredondo-Garcia, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze,
So what data drove the SAGE 2016 decisions?
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases in Vaccine group (n)</th>
<th>Cases in Placebo group (n)</th>
<th>Pooled (2-16 years)</th>
<th>Pooled (9-16 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic VCD</td>
<td>563</td>
<td>694</td>
<td>60.3% (55.7-64.5)</td>
<td>65.6% (60.7-69.9)</td>
</tr>
<tr>
<td>Hospitalized VCD</td>
<td>57</td>
<td>104 (15%)</td>
<td>72.7% (62.3-80.3)</td>
<td>80.8% (70.1-87.7)</td>
</tr>
<tr>
<td>Severe VCD</td>
<td>13</td>
<td>31 (4.5%)</td>
<td>79.1% (60.0-89.0)</td>
<td>93.2% (77.3-98.0)</td>
</tr>
</tbody>
</table>
### Longer-term Follow Up for Hospitalized Dengue: 2-5 year age group

<table>
<thead>
<tr>
<th>Time Period (Follow up)</th>
<th>CYD group cases</th>
<th>Control group cases</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1 (Active)</td>
<td>8</td>
<td>6</td>
<td>0.64 (0.20-2.32)</td>
</tr>
<tr>
<td>Year 2 (Active)</td>
<td>9</td>
<td>7</td>
<td>0.64 (0.21-2.02)</td>
</tr>
<tr>
<td>Year 3 (Hospital)</td>
<td>15</td>
<td>1</td>
<td>7.45 (1.15-313.80)</td>
</tr>
<tr>
<td>Year 4 (Hospital)</td>
<td>20</td>
<td>7</td>
<td>1.42 (0.58-3.99)</td>
</tr>
<tr>
<td>Year 5 (Hospital/SEP)</td>
<td>6</td>
<td>2</td>
<td>1.49 (0.27-15.15)</td>
</tr>
<tr>
<td><strong>Cumulative Years 1-5</strong></td>
<td><strong>58</strong></td>
<td><strong>23</strong></td>
<td><strong>1.26 (0.76-2.13)</strong></td>
</tr>
</tbody>
</table>
Seronegatives aged > 9

- From the immunogenicity subset up to year 4:
  - 7/387 (1.8%) hospitalized vaccinees
  - 4/204 (2%) hospitalized controls

<table>
<thead>
<tr>
<th></th>
<th>CYD vaccine n*</th>
<th>Placebo n*</th>
<th>Vaccine Efficacy, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 9 years</td>
<td>16</td>
<td>17 (x2)</td>
<td>52.5 (5.9 to 76.1)</td>
</tr>
</tbody>
</table>

SAGE GRADE 2 = evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome

Insufficient data to determine increased risk in seronegative vaccinees aged 9-16
What recommendation would you have given if you had served on the WHO SAGE in April 2016?

• Unclear whether safety signal in 2-5 years olds was due to age or to a higher proportion of this age group being seronegative at vaccination, or both.

• Finding led Sanofi to seek vaccine licensure from age 9+ years, distant from the age group in which the signal was apparent. No signal in other age groups.

• Modelling of cost-effectiveness of the vaccine suggested most efficient to use when the target population had seroprevalence 70% or greater.

• Question remained as to whether vaccinated seronegatives 9y+ might be at increased risk of severe disease.

• This was highlighted as important unanswered question by both GACVS and SAGE; and Sanofi Pasteur was asked to provide more data in seronegatives
WHO recommendations for settings with seroprevalence > 70%

• **Public Health benefit**— Vaccine preventable disease incidence, seropositivity drives efficacy; booster by natural infection

• **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
Critique – Halstead position prior to use

• Known antibody – antibody dependent enhancement of infection (2003)*
• ‘Irrelevance of vaccine safety calculation when a vaccine has potential for immune enhancement’
• Critique of method used to calculate VE**

Scott B. Halstead; Critique of World Health Organization Recommendation of a Dengue Vaccine, The Journal of Infectious Diseases, Volume 214, Issue 12, 15 December 2016, Pages 1793–1795,
**Scott B. Halstead; Dengue Vaccine Efficacy: Not a Zero Sum Game, The Journal of Infectious Diseases, Volume 214, Issue 12, 15 December 2016, Pages 2014
Status of CYD-TDV  
(as of May 2018)

• Licensed by 20 countries
  – Asia, Latin America, Australia

• Indication varies
  – Typically 9-45 years
  – Singapore (12-45 year-olds), Indonesia (9-16 year-olds) and Paraguay (9-60 year-olds)

• Vaccine introduction in public health programmes in two countries
  – **Philippines**: Routine, school-based programme - 4th grade children (9-10 year olds) in highly endemic regions (~1,000,000 children) – programme suspended.
  – **Brazil**: Paraná State – about 500,000 doses in 30 most highly endemic municipalities (28 municip. age 15-27y, 2 municip. age 9-44y.)
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 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.

“Those findings highlight the complex nature of dengue infection. We are working with health authorities to ensure that practitioners, vaccination and patients are fully informed of the new findings, with the goal of enhancing the impact of Dengvaxia in dengue-endemic countries,” said Dr. Su-Ping Ng, Global Medical Head, Sanofi Pasteur.

About half of the world’s population lives in countries where four serotypes of dengue virus are in circulation. Every year an estimated 390 million dengue infections are reported. People can be infected with dengue up to four times in their lifetime and they can get severely ill after any of these infections. Surveillance data from some endemic countries indicates that between 70 and 90 percent of people will have been exposed to dengue at least once by the time they reach adolescence. There are many factors that can lead to severe dengue infection. However, the highest risk of getting more severe disease has been observed in people infected for the second time by a different dengue virus.

Dengvaxia is currently indicated in most of the countries for individuals 9 years of age and older living in a dengue-endemic area in this indicated population. Dengvaxia has been shown to prevent 95 percent of severe dengue and 80 percent of hospitalisations due to dengue over the 23 month phase of the large-scale clinical study conducted in 10 countries in Latin America and Asia where dengue is widespread.

Proposed label updates

The company proposes that national regulatory agencies update the prescribing information, known as the label, in countries in many countries, requiring that healthcare professionals assess the likelihood of prior dengue infection in an individual before vaccinating. Vaccination should only be recommended when the potential benefits outweigh the potential risks (in countries with high burden of dengue disease). For individuals who have not been previously infected by dengue virus, vaccination should not be recommended.
Study design overview (CYD14 & 15)

Randomized CYD:Placebo 2:1

Vaccine doses

Month 0 6 12 13 24 25 ~48 72

per protocol (PP)

intention to treat (ITT)

ACTIVE SURVEILLANCE

HOSPITAL SURVEILLANCE ONLY

SURVEILLANCE EXPANSION (ACTIVE SURV. RESTARTED)

Preliminary data available to Oct/Nov 2015*

End of follow-up 2017/18

Vaccine doses

End of follow-up 2017/18
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)
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 Sero-</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevented number of hospitalisations over 10 years*</td>
<td></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>High</td>
<td></td>
<td></td>
<td></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>
</tbody>
</table>
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

1 excess severe dengue in vaccinated seronegatives by 4 severe 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

1 excess severe dengue in vaccinated seronegatives by 10 prevented severe cases in vaccinated seropositives.
Considerations at SAGE 2018

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

<table>
<thead>
<tr>
<th>Population Seroprevalence Criteria without Screening</th>
<th>Pre-Vaccination Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BENEFIT</strong></td>
<td><strong>BENEFIT</strong></td>
</tr>
<tr>
<td>Overall substantial population benefit in areas with high seroprevalence predicted.</td>
<td>Maximizing the benefit (high efficacy and good safety) in seropositive while avoiding harm in correctly identified seronegatives.</td>
</tr>
</tbody>
</table>

**HARM**
An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.

**HARM**
Some seronegative individuals will be put at increased risk of severe dengue if vaccinated due to a false positive screening test result.
Heterogeneity of seroprevalence between and within countries


https://mrcdata.dide.ic.ac.uk/_dengue/dengue.php
Temporal and spatial heterogeneity of dengue transmission

Spatial heterogeneity at small scale

Salje et al. Dengue diversity across spatial and temporal scales. Science 2017


Spatial heterogeneity dependent on socioeconomic factors, population density, ecological factors:

Kamphaeng Phet, Thailand, school based cohort study:

Seroprevalence differences within 5-10km:
1255 children, aged 9: 67 to 92%.
For all school children: 46 to 94% (Tim Endy, Katie Anderson, personal communication)

3. Population eligible for vaccination

**Population Seroprevalence Criteria without Screening**

- Subnational areas with seroprevalence >80% in 9 year olds are predicted by modelling to be rare, those with seroprevalence >90% by the age of 9y very rare.

**Pre-Vaccination Screening**

- Modelling predicts vaccine eligibility will be higher on a population basis compared to the seroprevalence criteria strategy, as all seropositive persons in the population are eligible.

- Strategy can be used in both high and moderate transmission settings, although pre-test probability will be higher in high transmission settings.
4. Risk perception

**Population Seroprevalence Criteria without Screening**

- Loss in vaccine confidence (dengue vaccines and possibly other vaccines).
- Inability of vaccinees to know own serostatus may lead to increased vaccine hesitancy.

**Pre-Vaccination Screening**

- Risk of false positive test: seronegative individuals will be misclassified as seropositive and unintentionally vaccinated as no test will be 100% specific.
5. Implementation challenges

**Population Seroprevalence Criteria without Screening**

- Dengue transmission exhibits a high spatiotemporal heterogeneity. To identify subnational areas with seroprevalence above 80% by age 9 years, multiple small-scale age-stratified seroprevalence studies need to be conducted.
- Providing appropriate information to those eligible for vaccination of the potential risks and benefits will be more challenging than for other vaccines.

**Pre-Vaccination Screening**

- Pre-vaccination blood sampling may lead to decreased acceptance of the vaccination programme.
- No rapid diagnostic test (RDT) has been validated or licensed for the indication of screening for past dengue infection.
- Unlikely that any test will have a 100% specificity, thereby still putting some truly seronegatives at risk.
- Tests with high sensitivity are needed to ensure that a large proportion of seropositives will benefit from CYD-TDV.
6. Population impact

**Population Seroprevalence Criteria without Screening**

Given that areas with seroprevalence above 80% by age 9y are predicted to be rare, population impact is likely to be low.

**Pre-Vaccination Screening**

Population impact on reduction of hospitalized dengue modelled at approximately 20% over 30 years.
Recommendation

Pre-Vaccination Screening

- For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” would be the preferred option, in which only dengue-seropositive persons are vaccinated

-
Explanatory hypothesis: "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