Summary of Key Points WHO Position Paper on Dengue Vaccine, September 2018

For more information on the WHO Dengue position paper, please visit the WHO website:
www.who.int/immunization/documents/positionpapers
Introduction

This position paper replaces the WHO position paper on dengue vaccines published in 2016.

In November 2017, results of a retrospective analysis of data from clinical trials, using a new serological assay, became available.

The assay enabled classification of trial participants according to their dengue serostatus prior to receipt of the first vaccine dose.

These data revealed an excess risk of severe dengue in seronegative vaccine recipients compared to seronegative non-vaccinated individuals, while confirming long-term protection in seropositive individuals.

In view of these findings, SAGE provided revised recommendations in April 2018, on which this position paper is based.

Background

- Dengue is a rapidly expanding arboviral disease transmitted by *Aedes* mosquitoes.
- Four antigenically distinct serotypes (DENV1-4).
- Clinical spectrum:
  - 80% asymptomatic.
  - Self-limiting febrile illness.
  - Severe dengue (~2-4% of symptomatic).
  - Secondary infections are associated with a higher risk of more severe dengue.
  - CFR 0.1—1%.

Epidemiology of dengue

Table 1 | Estimated burden of dengue in 2010, by continent

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>Inapparent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Millions (credible interval)</td>
<td>Millions (credible interval)</td>
</tr>
<tr>
<td>Africa</td>
<td>15.7 (10.5–22.5)</td>
<td>48.4 (34.3–65.2)</td>
</tr>
<tr>
<td>Asia</td>
<td>66.8 (47.0–94.4)</td>
<td>204.4 (151.8–273.0)</td>
</tr>
<tr>
<td>Americas</td>
<td>13.3 (9.5–18.5)</td>
<td>40.5 (30.5–53.3)</td>
</tr>
<tr>
<td>Oceania</td>
<td>0.18 (0.11–0.28)</td>
<td>0.55 (0.35–0.82)</td>
</tr>
<tr>
<td>Global</td>
<td>96 (67.1–135.6)</td>
<td>293.9 (217.0–392.3)</td>
</tr>
</tbody>
</table>

Bhatt et al, Nature 2013. doi:10.1038/nature12060
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
Dengue Vaccine development

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

**Phase I**
- DPIV
  - GlaxoSmithKline, Biomanguinhos, WRAIR
- DEN-80E
  - Merck
- TVDV
  - Naval Medical Research Center
- TLAV-TPIV
  - WRAIR

**Phase II**

**Phase IIb**
- TV003/TV005
  - US National Institutes of Health
  - Butantan

**Phase III**
- CYD-TDV
  - Dengvaxia™
  - Sanofi Pasteur
- DENVax
  - Takeda

**Registration**

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1. US National Institutes of Health

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To address the question of the potential risk in seronegative individuals, a new assay was utilized on sera collected at month 13 (post-dose 3) from all trial participants to retrospectively classify trial participants by serostatus prior to vaccination.

Rationale for the assay was that the NS1 protein in Dengue virus is different from the NS1 protein in Yellow Fever virus.

Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) in the 25 months after dose 1 (2-16 year-olds)

<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 hospitalised dengue comparing vaccinated to controls in the 66 months after dose 1 (2-16 year-olds)

<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>0.29</td>
<td>0.21, 0.42</td>
</tr>
<tr>
<td>Sero-negative</td>
<td>1.65</td>
<td>1.04, 2.61</td>
</tr>
</tbody>
</table>

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

<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>
Cumulative risk of hospitalized dengue

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
- In high transmission intensity settings, even seronegative recipients gain eventual benefit
- Mathematical models adopting these assumptions fit the original trial data well
## Incidence rates (IRs) and attributable risks (ARs) in <9y and 9+y age groups (MI method)

<table>
<thead>
<tr>
<th></th>
<th>Seropositive</th>
<th></th>
<th></th>
<th>Seronegative</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IR, control</td>
<td>IR, vaccine group</td>
<td>AR (%)</td>
<td>IR, control</td>
<td>IR, vaccine group</td>
<td>AR (%)</td>
</tr>
<tr>
<td>9+ yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized</td>
<td>1.883</td>
<td>0.375</td>
<td>-1.508</td>
<td>1.093</td>
<td>1.571</td>
<td>0.4782</td>
</tr>
<tr>
<td>Severe (IDMC)</td>
<td>0.480</td>
<td>0.075</td>
<td>-0.405</td>
<td>0.174</td>
<td>0.404</td>
<td>0.230</td>
</tr>
<tr>
<td>&lt; 9 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized</td>
<td>5.051</td>
<td>2.430</td>
<td>-2.621</td>
<td>3.345</td>
<td>5.722</td>
<td>2.377</td>
</tr>
<tr>
<td>Severe (IDMC)</td>
<td>1.160</td>
<td>0.614</td>
<td>-0.547</td>
<td>0.364</td>
<td>1.229</td>
<td>0.865</td>
</tr>
</tbody>
</table>
Policy options

1. Screen and vaccinate – screen every potential vaccine recipient with a rapid diagnostic test (RDT) to determine serostatus, and only vaccinate those testing seropositive

2. Mass-vaccination with seroprevalence threshold – vaccinate populations in areas where transmission intensity exceeds a certain threshold – e.g. >80% seroprevalence in 9 year old children
WHO position

The live attenuated dengue vaccine CYD-TDV has been shown in clinical trials to be efficacious and safe in persons who have had a dengue virus infection in the past (baseline seropositive individuals), but carries an increased risk of hospitalized and severe dengue in those who experience their first natural dengue infection after vaccination (baseline seronegative individuals).

Countries should consider introduction of the dengue vaccine CYD-TDV only if the minimization of risk among seronegative individuals can be assured.
For countries considering vaccination as part of their dengue control programme, **pre-vaccination screening** is the **recommended strategy**.

With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past).
WHO position: pre-vaccination screening

Screening tests would need to be highly specific to avoid vaccinating truly seronegative persons.

Screening test would also need to be highly sensitive to ensure that a high proportion of seropositive persons are vaccinated.

No screening test is likely to be 100% specific due to potential cross-reactivity with other flaviviruses.
Need to explain limitations of RDTs and vaccine efficacy

Given that no assay will be 100% specific, some truly seronegative individuals may be vaccinated due to a false positive test result.

Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not 100%.

Hence, the limitations of CYD-TDV will need to be clearly communicated to populations offered vaccination.
Countries need to consider local factors

Decisions about implementing a “pre-vaccination screening” strategy with the currently available tests will require careful assessment at the country level, including consideration of:

- the sensitivity and specificity of available tests
- local priorities
- dengue epidemiology
- country-specific dengue hospitalization rates
- affordability of both CYD-TDV and screening tests.
If pre-vaccination screening is not feasible, vaccination without individual screening could be considered in areas with recent documentation of seroprevalence rates of at least 80% by age 9 years.

Decisions about implementing a seroprevalence criterion-based vaccination strategy without individual screening will require population serosurveys at high resolution, i.e. at district and sub-district level.

Careful assessment is required with regard to the feasibility and cost of population seroprevalence studies.

Communication needs to ensure appropriate and full disclosure of the risks of vaccination of persons with unknown serostatus.
Maintain Dengue Control Measures

There is a continued need to adhere to other disease preventive measures and to seek prompt medical care in the event of dengue-like symptoms, regardless of whether vaccinated or not.

Vaccination should be considered as part of an integrated dengue prevention and control strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.
There is an urgent need for the development of highly specific and sensitive RDTs for determination of dengue serostatus.

Research is also needed to evaluate vaccine schedules with fewer doses, and to assess the need for booster doses.

Locally applicable cost-effectiveness studies are needed to support policy decisions.

Research on how best to implement and integrate pre-vaccination screening in an immunization programme is recommended.

The development of safe, effective, and affordable dengue vaccines for use irrespective of serostatus remains a high priority.