Title: What is the prospect of a safe and effective dengue vaccine for travelers?

Running title: Prospect of a dengue vaccine for travelers

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Editorial: What is the prospect of a safe and effective dengue vaccine for travelers?

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**Highlight**: Dengue affects hundreds of millions of persons each year and is a risk for travelers to dengue-endemic regions. The first licensed dengue vaccine is approved for use only in persons who are known to have previous dengue infection, limiting its potential for use in travelers. Two other dengue vaccines are currently in Phase 3 clinical trials with preliminary efficacy results expected soon. These vaccines differ from the currently licensed vaccine and, should they demonstrate efficacy, may offer the possibility of a dengue vaccine for travelers.

With the increasing geographic expansion of dengue\(^1\) and incidence of the disease in travelers\(^2^\text{-}^4\), offering pre-travel vaccination against dengue would provide protection for hundreds of thousands of persons traveling to dengue-endemic countries, including tourists, persons traveling for business, military personnel and humanitarian aid workers.

The first tetravalent live-attenuated dengue vaccine was licensed in 2015. This vaccine, CYD-TDV, utilized the yellow fever 17D backbone. The World Health Organization recommended its use only in highly endemic countries as defined by a dengue seroprevalence of 70\% and above,\(^5\) but long-term safety follow up revealed an increased risk of severe dengue from 30 months onwards after the administration of the first dose in individuals who had not had a previous dengue infection, eg those who were seronegative.\(^6\) However, in seropositive persons the vaccine was
efficacious and safe, decreasing severe disease by 93% and hospitalization by 81%.

Subsequently, WHO recommended that CYD-TDV should only be used in seropositive persons. Therefore, since most travelers are seronegative, this vaccine will not benefit the majority of travelers. The serostatus-dependent performance of the CYD-TDV vaccine entails that travelers would need to be screened, and only seropositive travelers would receive the vaccine. Given that severe dengue is more of a concern in those travelers who had a previous dengue infection and may be at increased risk of severe disease during repeat travel to dengue endemic countries, CYD-TDV may still have a role to play in travel medicine practice. Although the vaccine is licensed for 3 doses, 6 months apart, a single dose will provide documented short-term efficacy for up to 6 months. The drawback though is that currently CYD-TDV is not licensed in any non-dengue endemic countries, except for Australia. Hence, most travelers currently have no access to CYD-TDV. In October 2018, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended giving marketing authorization for CYD-TDV in individuals aged 9 to 45 years who live in an area where dengue is endemic and have already experienced a dengue virus infection, but they do not include the indication for travelers (https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-dengvaxia_en.pdf). The vaccine is currently being considered by the US Food and Drug Administration.

What is the prospect for a dengue vaccine that would be safe and efficacious in both seropositive and seronegative travelers? There are two other live-attenuated tetravalent dengue vaccines in late stage clinical trials. DENVAX, developed by the US Centers for Disease Control and Prevention (CDC) and Takeda, consists of an
attenuated DENV-2 (DEN2-PDK-53) from Thailand, and three chimeric viruses containing the prM and envelope proteins of DENV-1, -3 and -4 inserted into the DEN2-PDK-53 backbone. This vaccine has performed very well in phase 1 and 2 clinical trials with neutralizing antibody to all four serotypes in non-human primates and humans. The vaccine efficacy is currently being evaluated in approximately 20,000 recipients in Asia and Latin America using a 2-dose regimen given 3 months apart. Preliminary results are expected mid-2019.

The other live attenuated dengue vaccine was developed by the U.S. National Institutes of Health. It contains three full-length DENV with all their wild-type structural and non-structural proteins; only DENV-2 is a chimeric virus and does not contain DENV-2 nonstructural proteins. Since CD8+ T cell epitopes are predominantly localized to the nonstructural proteins, it elicits a broad cellular immune response based on three DENV serotypes. A single dose results in balanced infectivity and neutralizing antibody responses. Two formulations of the vaccine have been tested, TV003 and TV005, the only difference being a 10-fold higher dose of the DENV-2 component is given in TV005. Both formulations demonstrated 100% efficacy against DENV-2 in flavivirus-naïve individuals in a human challenge study (Kirkpatrick et al and manuscript in preparation). The vaccine has been licensed by several manufacturers and the TV003 vaccine manufactured by the Institute Butantan is currently in Phase 3 clinical trial in Brazil. Preliminary efficacy results are expected in late 2019.

Table 1 compares the three leading dengue vaccine candidates. While CYD-TDV uses the yellow fever vaccine backbone, the DENVAX and TV003/TV005 vaccines
use a combination of attenuated and chimeric viruses constructed on dengue backbones. The fact that these two vaccines contain more dengue proteins than CYD-TDV increases the potential for higher efficacy. Whether or not these vaccines will provide balanced tetravalent protection and thus, whether they will have the same serostatus-dependent problem as CYD-TDV is not yet known. Given that both of these vaccines have more convenient dosing schedules than CYD, these second-generation dengue vaccines would be a more attractive option for travelers. The results of the Phase 3 trials are eagerly awaited.

Authors Statements

Anna P. Durbin: The National Institutes of Health has contracted with Johns Hopkins University to conduct clinical trials of the TV003/TV005 live attenuated dengue vaccine. Dr. Durbin has served as the Principal Investigator for those clinical trials.

Duane J. Gubler: Dr Gubler helped develop DENVAX and is a patent holder of this vaccine. He has provided advice and consultation on vaccine development to Sanofi Pasteur, Merck and Takeda.

Author Contributions: APD and DJG contributed to the contents of the editorial.
References


Table 1: Comparison of the three leading dengue vaccine candidates

<table>
<thead>
<tr>
<th></th>
<th>CYD-TDV (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>
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<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>
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<td><strong>Indicated age</strong></td>
<td>9 - 45</td>
<td>Phase 3: age range 4 - &lt;16</td>
<td>Phase 3: age range 2 - 59</td>
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<td><strong>Construct</strong></td>
<td>Yellow fever 17D backbone</td>
<td>DENV-2 backbone</td>
<td>Full-length genomes for DENV-1, -3 and -4. Backbone for DENV-2: DENV-4</td>
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<tr>
<td><strong># DENV proteins</strong></td>
<td>8</td>
<td>16</td>
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