UPDATE ON DENGUE VACCINES

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DENGUE INFECTION

- RNA Virus
- Family flaviviridae
- DEN 1, DEN 2, DEN 3, DEN 4
  - Homotypic immunity
  - Heterotypic immunity
- Aedes aegypti, Aedes albopictus

ASYMPTOMATIC

SYMPTOMATIC
- UNDIFFERENTIATED FEVER
- DENGUE FEVER (DF)
- DENGUE HEMORRHAGIC FEVER (DHF) gr I, II, III,
- DENGUE SHOCK SYNDROME (DSS) gr IV
Number of dengue cases and incidence in Thailand from 2010 to 2015

พยาธิกาเนิด (Pathophysiology & Pathogenesis)

1. การติดเชื้อซ้ำ (Secondary infection: Immunological process)
   มีการกระตุ้นกลไกทางภูมิคุ้มกัน
   - Cytokines
   - Activated T cell
   - IL-6 & IL-8 production by endothelial cell
   - Activated complement

2. ความรุนแรงของเชื้อ (Viral Virulence)
   - สายพันธุ์ของเชื้อ (Serotypes)
   - ปริมาณของเชื้อไวรัสในกระแสเลือด (Magnitude of viremia)
Viral virulence

• Dengue-2 virus from the Southeast Asian may be specifically associated with DHF.


• Secondary infection with dengue-2 virus following primary infection with dengue-1, 3, 4 virus was a risk factor for DHF.

Challenges

• Existence of 4 serotypes interact with each other in significant and often unpredictable ways
  – Protection, Enhancement, Interference

• Biological assays to measure immune response are imprecise and unclear of clinical relevance.

• Seroconversion alone does not predict protection

• No valid animal model
Dengue Vaccine Candidates in Clinical Development
as of March 3, 2016

Phase I

- TDENV PIV by GSK, WRAIR & Fiocruz (Inactivated)
- TDENV-LAV+ TDEN-PIV by WRAIR (Heterologous prime boost)

Phase II

- TDV by Takeda (Live attenuated)
- TV003/TV005 by NIAD (Live attenuated)

Phase III

- TV003 by Butantan Institute* (Live attenuated)
- CYD-TDV by Sanofi Pasteur (Live attenuated)

Registration

Details

TDENV PIV: uses a purified inactivated vaccine.
TDENV-LAV + TDEN-PIV: uses a live attenuated vaccine and a purified inactivated vaccine.
TVDV: uses premembrane and envelope proteins-encoding genes of DENV-1, 2, 3, 4 expressed under control of the human cytomegalovirus promoter/enhancer of the plasmid vector VR1012.
TV003/TV005: uses full-length DENV-1, 3, 4 and a chimeric DENV-2 vaccine.
V180: uses wildtype premembrane and truncated envelope protein via expression in the Drosophila S2 cell expression system.
TDV: uses a mixture of of four attenuated viruses, all carrying the same attenuated DENV-2 backbone, but structural genes of each of the four DENV serotypes.
CYD-TDV (Dengvaxia): uses the yellow fever virus as a backbone, carrying prM and E protein genes from wild type DENV-1, 2, 3, 4.

*Uses NIAID (NIH) vaccine formulation. NIH licensed its strains to several developing and developed country manufacturers.
## 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>
</tr>
</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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Protein subunit</td>
<td>Merck</td>
<td>V180</td>
<td>DENV 80% E protein recombinant+adj</td>
<td>I</td>
</tr>
<tr>
<td>Inactivated whole virus</td>
<td>GSK/ Fiocruz/ US Army</td>
<td>DPIV</td>
<td>Formalin inactivated-adj</td>
<td>Preclin I</td>
</tr>
<tr>
<td>DNA</td>
<td>US Navy</td>
<td>TVDV</td>
<td>Plasmid DNA+adj</td>
<td>I</td>
</tr>
<tr>
<td>Heterologous prime-boost</td>
<td>US Army</td>
<td>TDENV-LAV+TDENV-PIV</td>
<td>Live attenuated/inactivated whole</td>
<td>I</td>
</tr>
</tbody>
</table>
New vaccine development: Using genetic engineering technique.

YFV 17D genome cloned as cDNA

5' - C prM E Non-Structural genes - 3'

Exchange with coat protein genes of DENV, JEV or WN

5' - C

Non-Structural genes

3'

Chimeric cDNA transcribed to RNA

Virus grown in cell culture

RNA transfection

RNA replication machinery is from YFV 17D

Envelope is the immunizing Ag from a heterologous flavivirus

Dengvaxia (CVD – TDV)

- Each monovalent CYD recombinant is obtained by replacing the genes encoding the prM and E proteins of the attenuated yellow fever (YF) 17D virus genome with the corresponding genes of the 4 wild-type dengue viruses.

- The final formulation contains 4.5–6.0 log10 median cell-culture infectious doses (CCID50) of each of the live attenuated dengue serotype 1, 2, 3 and 4 vaccine viruses.
The envelope and precursor membrane genes from each serotype were combined with the genes encoding the capsid and non-structural proteins from the yellow fever (YFV 17D) vaccine strain.

- Freeze-dried and contains no adjuvant or preservatives.
- 3-dose schedule at 0, 6, 12 month

DENV-1 (strain PUO-359/TVP-1140, isolated in 1980 in Thailand)
DENV-2 (strain PUO-218, isolated in 1980 in Thailand)
DENV-3 (strain PaH881/88, isolated in 1988 in Thailand)
DENV-4 (strain 1228 (TVP-980), isolated in 1978 in Indonesia)

Phase IIb Efficacy Asia-Pacific (CYD23/57*) Proof-of-concept study\textsuperscript{1,4}

- Country: Thailand
- Age group: 4–11 years
- Sample size: 4002
- Long-term follow-up: 5 years postdose 3

*CYD57 is the long-term follow-up of CYD23.

4. sanofi pasteur, 2015, data on file.
Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial (N=4,002, 4-11 yo)

Serotype-specific and overall efficacy against virologically confirmed dengue

Efficacy % (95% CI)

All  D1       D2       D3       D4
30.2  55.6     9.2      75.3     100
(-13  6 - 56  6) (-21  6 - 84  0) (-375  0 - 99  6) (24  8 to 100  0)
PHASE III LARGE-SCALE RANDOMIZED EFFICACY STUDIES IN ENDEMIC COUNTRIES

CYD14 Asia
NCT01373281
5 Countries, 11 Sites
2–14 years, 10, 275 volunteers

Thailand
2 sites

Vietnam
2 sites

Malaysia
2 sites

Indonesia
3 sites

CYD15 Latin America
NCT01374516
5 Countries, 22 sites
9–16 years, 20,869 volunteers

Mexico
5 sites

Honduras
1 site

Puerto Rico
2 sites

Colombia
9 sites

Brazil
5 sites

ACTIVE PHASE
Active Surveillance/Detection of Dengue Cases Including hospitalized dengue cases

HOSPITAL PHASE
Additional follow-up for safety of hospitalized dengue cases for 4 years after the end of the active phase

Per Protocol (PP)
13 mo 25 mo
VE against symptomatic VCD, irrespective of disease severity or serotype, occurring >28 days post-dose 3

Intent to Treat (ITT)
25 mo
Efficacy, Immunogenicity and safety

The overall (baseline) seroprevalence in trial participants aged 9–16 years in the Phase 3 studies was approximately 80%.
STUDY DESIGN: RANDOMIZED, OBSERVER-MASKED, PLACEBO-CONTROLLED, MULTICENTER, PHASE III TRIALS\textsuperscript{1,2,3}

**Inclusion criteria**
- Children
  - 2-14 years – CYD14
  - 9-16 years – CYD15
- Good health
- No plans to leave study area

**Exclusion criteria**
- Febrile illness (until resolution)
- Receiving other vaccines (until 4 weeks after vaccination)
- Congenital or acquired immunodeficiency

**Randomization**
- 2:1

**Vaccination with**
\begin{align*}
\text{CYD-TDV} \Rightarrow \text{Vaccination with placebo*} \\
0 \quad 6 \quad 12 & 13 \quad 18 \quad 25 \quad \text{Year 6}
\end{align*}

**Active phase**
Active surveillance/detection of dengue cases
Symptomatic VCD defined as:
- Acute febrile illness (temp $\geq 38^\circ C$ on $\geq 2$ consecutive days)
- Virologically confirmed PCR and/or dengue NS1 Ag ELISA

**Hospital phase**
Additional follow-up for safety of hospitalized dengue cases

\textbf{Inclusion criteria}:
- Participants who received placebo were designated as the control group.
- CYD-TDV=Chimeric Yellow Fever 17D-Tetravalent Dengue Vaccine
- VCD: Virologically Confirmed Cases

ClinicalTrials.gov, 2014, NCT01374516.
OVERVIEW OF EFFICACY RESULTS AGAINST SEVERE AND HOSPITALIZED VCD

Intent-to-treat analysis (follow-up from months 0–25)

STUDY (n episodes)

1. VE in severe dengue cases
   - CYD14 (n=32)
   - CYD15 (n=12)

2. VE in DHF dengue cases
   - CYD14 (n=28)
   - CYD15 (n=11)

3. VE* in hospitalized dengue cases
   - CYD14 (n=101)
   - CYD15 (n=60)

EFFICACY and 95% CI

VE in severe dengue cases:
- CYD14 (n=32)
- CYD15 (n=12)

VE in DHF dengue cases:
- CYD14 (n=28)
- CYD15 (n=11)

VE* in hospitalized dengue cases:
- CYD14 (n=101)
- CYD15 (n=60)
TWO PHASE III EFFICACY TRIALS DEMONSTRATED A CONSISTENT EFFICACY AND SAFETY PROFILE DURING THE 25 MONTHS

<table>
<thead>
<tr>
<th></th>
<th>ASIA-CYD14¹</th>
<th>LatAm-CYD15²</th>
<th>Pool results in the targeted age indication (9-16 yrs)³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-14 yo</td>
<td>9-16 yo</td>
<td></td>
</tr>
<tr>
<td>Efficacy against symptomatic dengue*</td>
<td>56.5% (95% CI: 43.8-66.4)</td>
<td>60.8% (95% CI: 52.0-68.0)</td>
<td>65.6% (95% CI: 60.7-69.9)</td>
</tr>
<tr>
<td>Reduction in hospitalized dengue‡</td>
<td>67.2% (95% CI: 50.3-78.6)</td>
<td>80.3% (95% CI: 64.7-89.5)</td>
<td>80.8% (95% CI: 70.1-87.7)</td>
</tr>
<tr>
<td>Efficacy against severe dengue† ‡</td>
<td>80.0% (95% CI: 52.7-92.4)</td>
<td>95.0% (95% CI: 64.9-99.9)</td>
<td>92.9% (95% CI: 76.1-97.9)</td>
</tr>
</tbody>
</table>

*Per protocol, 12 months post-dose 3 ; †Dengue hemorrhagic fever, World Health Organization (WHO) 1997 criteria, intent to treat; ‡Intent to treat, 25 months postdose 1.

### Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease (CYD 14, CYD 15: up to 3 years; CYD 23 (57): year 3-4)

**Table 1. Annual Incidence of Hospitalization for Virologically Confirmed Dengue, According to Trial, Age Group, and Study Period.**

<table>
<thead>
<tr>
<th>Trial, Age Group, and Study Period</th>
<th>Vaccine Group</th>
<th></th>
<th>Control Group</th>
<th></th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases of Dengue</td>
<td>Total Participants</td>
<td>Annual Incidence Rate (95% CI)</td>
<td>Cases of Dengue</td>
<td>Total Participants</td>
</tr>
<tr>
<td>All participants§</td>
<td>27</td>
<td>6,778</td>
<td>0.4 (0.3–0.6)</td>
<td>13</td>
<td>3,387</td>
</tr>
<tr>
<td>2–5 yr</td>
<td>15</td>
<td>1,636</td>
<td>1.0 (0.6–1.6)</td>
<td>1</td>
<td>813</td>
</tr>
<tr>
<td>6–11 yr</td>
<td>10</td>
<td>3,598</td>
<td>0.3 (0.1–0.6)</td>
<td>8</td>
<td>1,806</td>
</tr>
<tr>
<td>12–14 yr</td>
<td>2</td>
<td>1,544</td>
<td>0.1 (0.0–0.5)</td>
<td>4</td>
<td>768</td>
</tr>
<tr>
<td>&lt;9 yr</td>
<td>19</td>
<td>3,493</td>
<td>0.6 (0.4–0.9)</td>
<td>6</td>
<td>1,741</td>
</tr>
<tr>
<td>≥9 yr</td>
<td>8</td>
<td>3,285</td>
<td>0.3 (0.1–0.5)</td>
<td>7</td>
<td>1,646</td>
</tr>
<tr>
<td>CYD15</td>
<td>16</td>
<td>13,268</td>
<td>0.1 (0.1–0.2)</td>
<td>15</td>
<td>6,630</td>
</tr>
<tr>
<td>9–11 yr</td>
<td>10</td>
<td>6,029</td>
<td>0.2 (0.1–0.3)</td>
<td>9</td>
<td>3,005</td>
</tr>
<tr>
<td>12–16 yr</td>
<td>6</td>
<td>7,239</td>
<td>&lt;0.1 (0.0–0.2)</td>
<td>6</td>
<td>3,625</td>
</tr>
</tbody>
</table>

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease: Efficacy wane over the time esp. in youngers (CYD 14, CYD 15: up to 3 years; CYD 23 (57): year 3-4)

Table 1. Annual Incidence of Hospitalization for Virologically Confirmed Dengue, According to Trial, Age Group, and Study Period.*

| Trial, Age Group, and Study Period | Vaccine Group | | | Control Group | | | | Relative Risk (95% CI) |
|-----------------------------------|--------------|---|---|--------------|---|---|---|
| Cases of Dengue | Total Participants† | Annual Incidence Rate‡ | no. | % (95% CI) | Cases of Dengue | Total Participants† | Annual Incidence Rate‡ | no. | % (95% CI) | |
| CYD57 | | | | | | | | | | |
| All participants | | | | | | | | | | |
| Year 3 | 22 | 2,131 | 1.1 (0.7–1.7) | 11 | 1072 | 1.1 (0.6–2.0) | 1.01 (0.47–2.30) |
| Year 4 | 16 | 2,131 | 0.8 (0.4–1.2) | 17 | 1072 | 1.6 (0.9–2.5) | 0.47 (0.22–1.00) |
| 4 or 5 yr | | | | | | | | | | |
| Year 3 | 5 | 393 | 1.4 (0.5–3.2) | 1 | 192 | 0.6 (0.0–3.1) | 2.44 (0.27–115.54) |
| Year 4 | 5 | 393 | 1.3 (0.4–2.9) | 3 | 192 | 1.6 (0.3–4.5) | 0.81 (0.16–5.24) |
| 6–11 yr | | | | | | | | | | |
| Year 3 | 17 | 1,738 | 1.1 (0.6–1.7) | 10 | 880 | 1.2 (0.6–2.3) | 0.86 (0.37–2.10) |
| Year 4 | 11 | 1,738 | 0.6 (0.3–1.1) | 14 | 880 | 1.6 (0.9–2.7) | 0.40 (0.16–0.94) |
| <9 yr | | | | | | | | | | |
| Year 3 | 19 | 1,338 | 1.5 (0.9–2.4) | 6 | 665 | 1.0 (0.4–2.1) | 1.57 (0.60–4.80) |
| Year 4 | 13 | 1,338 | 1.0 (0.5–1.7) | 12 | 665 | 1.8 (0.9–3.1) | 0.54 (0.23–1.29) |
| ≥9 yr | | | | | | | | | | |
| Year 3 | 3 | 793 | 0.4 (0.1–1.2) | 5 | 407 | 1.3 (0.4–3.1) | 0.31 (0.05–1.58) |
| Year 4 | 3 | 793 | 0.4 (0.1–1.1) | 5 | 407 | 1.2 (0.4–2.8) | 0.31 (0.05–1.58) |

Study Cumulative RR (%) and 95% CI

All ages

CYD14

CYD15

CYD23/57

<9 years of age

CYD14

CYD23/57

≥9 years of age

CYD14

CYD15

CYD23/57


RR=relative risk; VCD=virologically confirmed dengue.
REDUCTION IN HOSPITALIZED VCD (ANY SEVERITY) IN SUBJECTS 9-16 YEARS OF AGE IN POOLED RRs AT YEAR 3

<table>
<thead>
<tr>
<th>Age Group</th>
<th>RR (%) and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages (2-16 y)</td>
<td>0.56 - 1.24</td>
</tr>
<tr>
<td>&lt;9 years of age</td>
<td>0.83 - 1.58</td>
</tr>
<tr>
<td>9-16 years of age</td>
<td>0.29 - 0.86</td>
</tr>
</tbody>
</table>

RR=relative risk; VCD=virologically confirmed dengue.

Hadinegoro, 2015, N Engl J Med,
The Protective Efficacy of CYD vaccine in 25 months

Against mild/moderate disease

Against all disease

<table>
<thead>
<tr>
<th>CYD trial</th>
<th>Sero-status</th>
<th>Sero-</th>
<th>Sero+</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>All ages</td>
<td>32%</td>
<td>68%</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Halstead SB. Vaccine 2016;34:1643-7.
A SUITABLE deployment of this vaccine might be the use among seropositive individuals.
Immunogenicity data in adults aged 46-60 yo and 18-60 yo in CYD17, Australia, at baseline and 28 days post-dose 3

- Good immunogenicity in adults
  It is expected that the efficacy in adults should not be less than children

Torresi, et.al. 2015 Vaccine

<table>
<thead>
<tr>
<th></th>
<th>Pre-inj 1</th>
<th>Post-inj 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>46-60 yo</td>
<td>54.2</td>
<td>144</td>
</tr>
<tr>
<td>18-60 yo</td>
<td>45.3</td>
<td>74.9</td>
</tr>
</tbody>
</table>

N=241 N=655
Licensure of CYD-TDV in endemic countries

- CYD-TDV is a prophylactic, tetravalent, live attenuated viral vaccine. The schedule consists of 3 injections of 0.5 mL administered at 6-month intervals.

- The indication from the 1st licenses is for prevention of dengue illness caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9–45 years or 9–60 years of age (depending on the license), living in dengue endemic areas.

- In December 2015, CYD-TDV (Dengvaxia®) was licensed in Mexico, Philippines, and Brazil for use in 9-45 year olds in endemic areas.
Contraindication

- History of severe allergic reaction to any component of the dengue vaccine or after prior administration
- Congenital or acquired immune deficiency that impairs cell-mediated immunity
- Symptomatic HIV infection or asymptomatic HIV infection accompanied by evidence of impaired immune function
- Pregnant or breastfeeding women
Some important issues about CYD – TDV (1)

• Vaccine efficacy varied by country, ranging from 31.3% (95% CI 1.3%–51.9%) in Mexico to 79.0% (95% CI 52.3%–91.5%) in Malaysia.

• This reflects that baseline seropositivity and circulating serotypes may contribute to the vaccine efficacy.

• Vaccine may theoretically increase the future risk of hospitalized or severe dengue illness in those who are seronegative at the time of first vaccination regardless of age.

• RR of severe dengue illness was lower during the first 2 years of the trials than during the later years. These may reflect potential waning of protection among all age groups.
Some important issues about CYD – TDV (2)

• Active surveillance is currently ongoing, so need to wait for the result to see the duration of protection.

• With an assumed vaccine coverage of 80% for the 3-dose series and vaccination at 9 yrs of age, all models found CYD-TDV would result in an overall reduction in dengue illness in settings with moderate to high transmission intensity (seroprevalence ≥50% at 9 yrs).

• The impact of vaccination was greatest in high transmission intensity settings (seroprevalence ≥70% at 9 years),
WHO position (1)

• Countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease.

• Seroprevalence should be approximately 70% or greater in the age group targeted for vaccination.

• Vaccination of populations with seroprevalence between 50% and 70% is acceptable but the impact of the vaccination programme may be lower.

• The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination (low efficacy and potential longer-term risks of severe dengue in vaccinated seronegative individuals).
WHO position (2)

- **Age-stratified serosurveys** are currently the best method for selecting populations suitable for vaccination.

- With the increase in false-positive results from serological testing of CYD-TDV vaccinated individuals, diagnostic testing should move to *virological confirmation* whenever possible.
HOW ABOUT OTHER DENGUE VACCINE CANDIDATES?
TDV (Takeda) & TV003/TV005 (NIH)

3 most clinically advanced dengue vaccine candidates

<table>
<thead>
<tr>
<th>Structural</th>
<th>Non-structural</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>prM</td>
</tr>
<tr>
<td>5’</td>
<td></td>
</tr>
<tr>
<td>Sanofi Pasteur CYD-TDV:</td>
<td>Unique DENV proteins 8</td>
</tr>
<tr>
<td>Takeda TDV:</td>
<td>Chimeric</td>
</tr>
<tr>
<td>NIH TV003/TV005:</td>
<td>Full-length 32</td>
</tr>
</tbody>
</table>

Asia Dengue Summit 2016. www.adva.asia
Dengue virus NS1 triggers endothelial permeability and vascular leak that is prevented by NS1 vaccination

P. Robert Beatty, Henry Puerta-Guardo, Sarah S. Killingbeck, Dustin R. Glasner, Kaycie Hopkins, Eva Harris

The four dengue virus serotypes (DENV1 to DENV4) are mosquito-borne flaviviruses that cause up to ~100 million cases of dengue annually worldwide. Severe disease is thought to result from immunopathogenic processes involving serotype cross-reactive antibodies and T cells that together induce vasoactive cytokines, causing vascular leakage that leads to shock. However, no viral proteins have been directly implicated in triggering endothelial permeability, which results in vascular leakage. DENV nonstructural protein 1 (NS1) is secreted and circulates in patients’ blood during acute infection; high levels of NS1 are associated with severe disease. We show that inoculation of mice with DENV NS1 alone induces both vascular leakage and production of key inflammatory cytokines. Furthermore, simultaneous administration of NS1 with a sublethal dose of DENV2 results in a lethal vascular leak syndrome. We also demonstrate that NS1 from DENV1, DENV2, DENV3, and DENV4 triggers endothelial barrier dysfunction, causing increased permeability of human endothelial cell monolayers in vitro. These pathogenic effects of physiologically relevant amounts of NS1 in vivo and in vitro were blocked by NS1-immune polyclonal mouse serum or monoclonal antibodies to NS1, and immunization of mice with NS1 from DENV1 to DENV4 protected against lethal DENV2 challenge. These findings add an important and previously overlooked component to the causes of dengue vascular leak, identify a new potential target for dengue therapeutics, and support inclusion of NS1 in dengue vaccines.
### Other Dengue candidate vaccines which have promising immunogenicity and safety data

<table>
<thead>
<tr>
<th></th>
<th>Current phase</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Takeda</strong></td>
<td>3 (start Q3 2016)</td>
<td>เคยคิดจะฉีดเข็มเดียว เพราะภูมิคุ้มกันขึ้นดีทั้ง DEN1,2,3 แต่สุดท้ายวางแผนใหม่จะฉีด 2 เข็ม เพื่อให้ภูมิคุ้มกันขึ้นตั้งแต่ตัว*</td>
</tr>
<tr>
<td><strong>NIAID</strong></td>
<td>2 (enroll ครับ กำลัง follow up ปีที่ 2 ต่อ 3) (plan F/U 5 ปีตามคำแนะนำใหม่ของ WHO)  -กำลังวางแผนทำ phase 3 อยู่  -กำลังหาประเทศที่อยากผลิตวัคซีนนี้ (บรรยากาศ เรียดนำมาทดลองแล้ว)</td>
<td>เปลี่ยนจากวัคซีน TV003 เป็น TV005 (อย่างหลังเพิ่ม DEN4 1 Log) ทำให้ภูมิคุ้มกันขึ้นตั้งแต่ตัว* จากการฉีดเพียงเข็มเดียว  -พบผื่นได้ประมาณ 18% แต่เป็นผื่นบางๆ (ไม่ใช่แบบโรคตามธรรมชาติ) หายเองทั้งหมด</td>
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A recombinant, chimeric tetravalent dengue vaccine candidate based on a dengue virus serotype 2 backbone

Jorge E. Osorio, Derek Wallace & Dan T. Stinchcomb

ABSTRACT
Dengue fever is caused by infection with one of four dengue virus (DENV) serotypes (DENV-1–4), necessitating tetravalent dengue vaccines that can induce protection against all four DENV. Takeda’s live attenuated tetravalent dengue vaccine candidate (TDV) comprises an attenuated DENV-2 strain plus chimeric viruses containing the prM and E genes of DENV-1, -3 and -4 cloned into the attenuated DENV-2 ‘backbone’. In Phase 1 and 2 studies, TDV was well tolerated by children and adults aged 1.5–45 years, irrespective of prior dengue exposure; mild injection-site symptoms were the most common adverse events. TDV induced neutralizing antibody responses and seroconversion to all four DENV as well as cross-reactive T cell-mediated responses that may be necessary for broad protection against dengue fever.
A single dose of either TV003 or TV005 induced seroconversion to four DENV serotypes in 74–92% (TV003) and 90% (TV005) of flavivirus seronegative adults.
ข้อควรพิจารณาสำหรับประเทศไทย

ข้อดี

• อาจช่วยลดอัตราการป่วยด้วยเชื้อเดงกี่ที่ต้องนอนรพ.ในเด็กอายุ 9 ปีขึ้นไปที่ได้รับวัคซีน

ข้อพึงระวัง

• รายที่ไม่เคยมีภูมิคุ้มกันมาก่อนอาจเกิดอันตราย เมื่อติดเชื้อภายหลัง

• ไม่ได้ผลดีต่อพื้นที่ที่มีความชุกของการเกิดโรคต่ำ

• อาจไม่ได้ผลต่อการป้องกัน DENV 2

• อาจต้องมีการ booster เมื่อเวลาผ่านไป

• อาจมีผลให้ละเลยมาตรการควบคุมโรคอื่น ๆ ที่จำเป็นต้องดำเนินการต่อไป

คณะทํางานทบทวนข้อมูลเพื่อการพิจารณา wannavich kengkham kachana ที่มีใช้เป็นเครื่องมือในการป้องกันควบคุมโรค กรมควบคุมโรค กันยายน 2559
ข้อแนะนำ

• การศึกษาทางระบาดวิทยาเพื่อค้นหาความชุกของการติดเชื้อเดงกี่ในประชากรกลุ่มเด็กอายุ 9 ปี และการกระจายของเชื้อเดงกี่ทั่ว 4 สายพันธุ์
• ติดตามการศึกษาความปลอดภัยระยะยาวของ Dengvaxia®
• ติดตามการศึกษาวัคซีนรุ่นใหม่ที่อยู่ใน pipeline อย่างใกล้ชิด
• เร่งรัดมาตรการป้องกันควบคุมโรคต่อไป โดยเฉพาะมาตรการควบคุมยุงพาหะโดยชุมชน

คณะที่ว่าการทบทวนข้อมูลเพื่อการพิจารณาวัคซีนเดงกี่มาใช้เป็นเครื่องมือในการป้องกันควบคุมโรค
กรมควบคุมโรค กันยายน 2559
THANK YOU