The DENGUE Vaccine

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GLOBAL DENGUE FACTS

• 2.5 billion people, or 40% of the world’s population, live in areas where there is a risk of dengue transmission.

• Dengue is endemic in at least 100 countries in Asia, the Pacific, the Americas, Africa, and the Caribbean.

• Estimated Global Burden
  • 390 million infections annually
    o 93 million clinical infections
    o 2 million severe dengue cases

https://www.cdc.gov/dengue/epidemiology/index.html
Dengue in the U.S.

https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=3314069_6_BouriFigure1.jpg
Global estimated cost of dengue

$752 million
nonmedical cases (8%)

$4,093 million
hospitalized nonfatal cases (46%)

$1,055 million
fatal cases (11%)

$2,987 million
ambulatory nonfatal cases (33%)

$8 billion
Total annual global cost of dengue
Estimated cost per individual dengue case

$84,000
for fatal cases
($80,414 for children and
$75,000, for adults)*

$70
hospitalized cases

$12
cases outside the health care sector

$151
Average cost across all types of cases

$51
ambulatory cases

Note: Each child dengue death represented 28 expected years lost, and each adult death meant 18 expected years lost.

Reduce mortality by ≥50% by 2020

Reduce morbidity by ≥25% by 2020

Estimate true burden of disease by 2015

TECHNICAL ELEMENTS

Diagnosis and case management

Integrated surveillance and outbreak preparedness

Sustainable vector control

Future vaccine implementation

Basic operational and implementational research

*The baseline year is 2010.
WHO=World Health Organization.

TRUTH ABOUT DENGUE CONTROL

PRIMARY PREVENTION
– Vector control

SECONDARY PREVENTION
– Medical management

– Vaccination is a critical pillar of the WHO’s strategy towards effectively fighting dengue
IDEAL DENGUE VACCINE

**Formulation:** tetravalent protection (DENV 1,2,3,4)

**Administration:** delivery over 4-6 months and during established vaccination visits

**Immunogenicity:** High with ≤ 3 doses

**Protection:** > 85% against dengue virus infection
: long term protection, no booster doses

Acknowledgement: Slide taken from Dengue Epidemiology and Vaccine Development, ACIP, February 23, 2017 by Steve Waterman, MD, MPH.
## Dengue Vaccine Candidates

<table>
<thead>
<tr>
<th>DEVELOPER</th>
<th>VACCINE TYPE</th>
<th>CLINICAL TRIAL</th>
<th></th>
<th></th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur</td>
<td>Live attenuated - chimera 17D YF+DENV</td>
<td>PHASE 1</td>
<td>PHASE 2</td>
<td>PHASE 3</td>
<td></td>
</tr>
<tr>
<td>TAKEDA</td>
<td>Live attenuated - chimera DENV2 + DENV 1,3,4</td>
<td></td>
<td>PHASE 2</td>
<td>PHASE 3</td>
<td></td>
</tr>
<tr>
<td>BUTANTAN</td>
<td>DENV attenuated - mutations+ DENV/DENV CHIMERA</td>
<td></td>
<td>PHASE 2</td>
<td>PHASE 3</td>
<td></td>
</tr>
<tr>
<td>GSK</td>
<td>Cell culture derived, inactivated</td>
<td>PHASE 1</td>
<td>PHASE 2</td>
<td>PHASE 3</td>
<td></td>
</tr>
<tr>
<td>MERCK</td>
<td>Envelop subunits of DENVS</td>
<td>PHASE 1</td>
<td>PHASE 2</td>
<td>PHASE 3</td>
<td></td>
</tr>
</tbody>
</table>

[https://www.breakdengue.org/dengue-vaccine-pipeline-2017/]
Dengue Vaccine Development

1992 ➢ 2014

➢ 1994
➢ Partnership with University of Mahidol, Thailand

➢ 2001
➢ Clinical evaluation of live, attenuated dengue vaccine

➢ 2004
➢ Recombinant, live attenuated vaccine adapted

➢ 2007
➢ Positive results in Phase II clinical studies

➢ 2009
➢ First pediatric clinical efficacy study

➢ 2010
➢ Fast track status granted from the US FDA
➢ First Phase III clinical study

➢ 2012
➢ Results of the Phase IIb clinical efficacy study, published

➢ 2014
➢ Results of Phase III efficacy studies

1. sanofi pasteur, 2015, Dengue fact sheet.
5. Sagonowsky, 2015, FiercePharma.
Vaccine Efficacy Studies


CYD14 efficacy study in Asia\(^1\)
2-14 years (N=10,275)

CYD15 efficacy study in Latin America and the Caribbean\(^2\)
9-16 years (N=20,869)
# Vaccine Efficacy Studies

<table>
<thead>
<tr>
<th></th>
<th>CYD 57</th>
<th>CYD 14</th>
<th>CYD 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>IIb</td>
<td>111</td>
<td>III</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td>South East Asia</td>
<td></td>
<td>Latin America</td>
</tr>
<tr>
<td><strong>Countries</strong></td>
<td>Thailand</td>
<td>Indonesia, Malaysia, Philippines, Thailand and Vietnam</td>
<td>Brazil, Colombia, Honduras, Mexico and Puerto Rico</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>4 years</td>
<td>6 years</td>
<td>6 years</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>3203</td>
<td>10,275</td>
<td>20,869</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td>4-11 years</td>
<td>2-14 years</td>
<td>9-16 years</td>
</tr>
</tbody>
</table>

## Vaccine Trial Design

<table>
<thead>
<tr>
<th>YEAR 1</th>
<th>YEAR 2</th>
<th>YEAR 3</th>
<th>YEAR 4</th>
<th>YEAR 5</th>
<th>YEAR 6</th>
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<tbody>
<tr>
<td><strong>ACTIVE SURVEILLANCE PHASE</strong></td>
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<tr>
<td>Investigates: Vaccine efficacy and safety for the first 25 months from the 1st injection of the vaccine</td>
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<tr>
<td>TRIAL: CYD 14 &amp; CYD 15</td>
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<tr>
<td><strong>LONG TERM FOLLOW-UP FOR SAFETY (HOSPITAL PHASE)</strong></td>
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<tr>
<td>Investigates: Long term safety from Year 3 up to Year 6 from the first injection of the vaccine</td>
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<tr>
<td>TRIAL: CYD 57, CYD 14, &amp; CYD 15</td>
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<tr>
<td><strong>LTFU: EXPANSION EFFICACY PHASE</strong></td>
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</tr>
<tr>
<td>Investigates: Long term efficacy from Year 4 to Year 6 from first injection</td>
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</tr>
<tr>
<td>TRIAL: CYD 57, CYD 14, &amp; CYD 15</td>
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### 1997 WHO Criteria

**Fever** (lasting 2-7 days), **PLUS ≥1 of the following:**

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hemorrhagic tendencies, at least one of the ff:</td>
</tr>
<tr>
<td></td>
<td>a. Positive tourniquet test</td>
</tr>
<tr>
<td></td>
<td>b. Petechiae, ecchymoses or purpura</td>
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<tr>
<td></td>
<td>c. Bleeding from mucosa, GIT, injection sites</td>
</tr>
<tr>
<td></td>
<td>d. Hematemesis or melena</td>
</tr>
<tr>
<td>2.</td>
<td>Thrombocytopenia (platelet count ≤ 100,000)</td>
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<tr>
<td>3.</td>
<td>Evidence of plasma leakage, manifested by at least one of the ff:</td>
</tr>
<tr>
<td></td>
<td>a. Rise in Hct ≥ 20% above ave for age, sex and population</td>
</tr>
<tr>
<td></td>
<td>b. Drop in Hct after volume replacement treatment ≥ 20% of baseline</td>
</tr>
<tr>
<td></td>
<td>c. Signs of plasma leakage (pleural effusion, ascites, hypoproteinemia)</td>
</tr>
</tbody>
</table>

### Independent Data Monitoring Committee (IDMC)

**Virologically confirmed dengue fever** (i.e. Temperature ≥ 38°C on ≥ 2 consecutive days and virological confirmation) **PLUS ≥1 of the following:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Platelet count ≤ 100,000 and bleeding (any) and plasma leakage (effusion on CXR, ascites, hematocrit &gt;20% above baseline recovery level or standard for age)</td>
</tr>
<tr>
<td>2.</td>
<td>Shock</td>
</tr>
<tr>
<td></td>
<td>a. Pulse pressure ≤ 20mmHg in child</td>
</tr>
<tr>
<td></td>
<td>b. Hypotension with tachycardia, weak pulse and poor perfusion</td>
</tr>
<tr>
<td>3.</td>
<td>Bleeding requiring transfusion</td>
</tr>
<tr>
<td>4.</td>
<td>Encephalopathy or convulsions not attributable to simple febrile convolution or focal neurological signs</td>
</tr>
<tr>
<td>5.</td>
<td>Liver Impairment (AST &gt; 1000U/L or Prothrombin time, INR &gt; 1.5)</td>
</tr>
<tr>
<td>6.</td>
<td>Impaired kidney function (creatinine ≥ 1.5 mg/dL)</td>
</tr>
<tr>
<td>7.</td>
<td>Myocarditis, pericarditis or heart failure</td>
</tr>
</tbody>
</table>
Dengue vaccine, a technological advance*

- A tetravalent recombinant, live, attenuated vaccine.  
  1,2
  - Four genetic constructs with 1 for each serotype.
  - Genes encoding prM/E structural proteins from each dengue serotype combined with genes encoding capsid (C) and nonstructural (NS) proteins from YFV 17D vaccine strain.

- Combination into a single vaccine.  
  3
  - Freeze-dried.
  - Without adjuvant or preservatives.

*Vaccine referred to in the literature as Chimeric Yellow Fever 17D-Tetravalent Dengue Vaccine (CYD-TDV).
C=capsid; DENV=dengue virus; E=envelope; NS=nonstructural; prM=precursor membrane; YFV 17D=yellow fever vaccine 17D.

**Dengue Vaccine Information**

### Indication
- prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9-45 years of age living in endemic areas

### Administration
- Dengvaxia® should be completely reconstituted using the solvent provided and administered by subcutaneous injection (recommended injection site is the deltoid region)
- The need for a booster dose after primary vaccination with Dengvaxia® has not yet been established
- Three doses (0.5 mL) at 0, 6, 12 months
  - If flexibility in the vaccination schedule is necessary, a time window of +/- 20 days is acceptable

### Dosing

### Special precautions
- Separate syringes/needles and injection sites (preferably separate limbs) must be used if any other vaccines or medicinal products are concomitantly administered*

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*Specific studies on concomitant administration of Dengvaxia® with other medicinal products have not been performed.

Dengvaxia® Generic Labeling Document.
Dengue Vaccine Information

**Contraindication**

- a history of severe allergic reaction to any component of the dengue vaccine or after prior administration of dengue vaccine or a vaccine containing the same components
- moderate to severe febrile or acute disease
- congenital or acquired immune deficiency
- immunosuppressive therapies: chemotherapy or high doses of systemic corticosteroids generally given for 2 weeks or more
- symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function
- pregnant women or to breastfeeding women
Dengue vaccine is efficacious

- In 25,826 subjects aged 9-16 years from 10 countries in Latin America and South East Asia:

65.6% reduction in symptomatic dengue cases
93.2% reduction in cases of severe dengue
80.8% reduction in hospitalization due to dengue

81.9% protection in seropositive subjects
52.5% protection in seronegative subjects

*Pooled data from trials CYD14 and CYD15; †Confirmed virologically; ‡Severe dengue was defined according to criteria of the independent data monitoring committee.
Dengue vaccine efficacious against all dengue serotypes

- In 25,826 subjects aged 9-16 years from 10 countries in Latin America and South East Asia, the efficacy of dengue vaccine against each dengue serotype was:

<table>
<thead>
<tr>
<th>Dengue Serotype</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DENV-1</td>
<td>58.4%</td>
</tr>
<tr>
<td>DENV-2</td>
<td>47.1%</td>
</tr>
<tr>
<td>DENV-3</td>
<td>73.6%</td>
</tr>
<tr>
<td>DENV-4</td>
<td>83.2%</td>
</tr>
</tbody>
</table>

Pooled data from trials CYD14 and CYD15.

Long-Term Safety (Year 5) of the Recombinant Live-Attenuated Chimeric-Yellow Fever-Dengue Virus Tetravalent Dengue Vaccine (CYD-TDV) in Asian Phase III Efficacy Trial

Maria Rosario Capading¹, Caiuna Fragoso², Ngoc Huu Tran³, Edith Langervin⁴, Kusnandri Rusmila⁵, Thelma Lao⁶, Sri Rezeki Hadinegoro⁷, Jeliani Sanchez⁸, Mary Norean Chua⁹, Mhasaia Tila⁹, Dewa Nyoman Wirawan¹⁰, Alain Bouckenooghe²

¹Research Institute for Tropical Medicine, Alabang, Muntinlupa City, Philippines; ²Battelle Tropical Institute, Bacolod, Negros, Philippines; ³Regional Institute of Health, Ho Chi Minh City, Vietnam; ⁴Regional Pasteur Institute, Ho Chi Minh City, Vietnam; ⁵Centre for Research and Training, Nanyang Technological University, Singapore, Singapore; ⁶Centre for Research and Training, Ho Chi Minh City, Vietnam; ⁷Centre for Research and Training, Ho Chi Minh City, Vietnam; ⁸Regional Institute of Health, Papeete, Tahiti, French Polynesia; ⁹Regional Institute of Health, Bogor, Indonesia; ¹⁰Regional Institute of Health, Yogyakarta, Indonesia.

Overall results by study year - Hospitalized VCD (any severity) in subjects < 9 YOA

25-Month Active Phase + Year 3 + Year 4 + Year 5
Subjects < 9 Years of Age (yoa)

25-Month Active Phase + Year 3 + Year 4 + Year 5
Subjects ≥ 9 Years of Age (yoa)

Vaccine Group
Control Group

20th Annual Conference on Vaccine Research – Bethesda, MD, USA – April 24-25, 2017
Immunological extrapolation support registration for adults up to 45 years of age in endemic areas

- Immunogenicity data suggest that subjects 17 years of age and above in endemic areas respond well to the vaccine.
  - **GMTs after the third injection were generally higher.**

- It is anticipated that individuals 17-45 years of age in endemic areas will have similar or higher levels of protection.

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**GMTs in CYD14, CYD15, CYD22, and CYD47<sup>1-4</sup>**

- **CYD14**
  - N=1323
  - (2–14 yo)

- **CYD15**
  - N=1301
  - (9–16 yo)

- **CYD22**
  - N=20
  - (18–45 yo)

- **CYD47**
  - N=126
  - (18–45 yo)

**GMT=geometric mean titer.**

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2. Capeding, et.al. 2014, Lancet
4. Dubey, et.al. 2015. Human Vaccines Immunother
Registration dossier supported by large integrated safety analysis in individuals up to 60 years of age

- Integrated safety analysis performed in the 9- to 60-year-old population creates significant size of safety database.
- 20,667 subjects 9-60 years of age receiving at least 1 dose of vaccine.
  - ~19,700 received all 3 doses
- Allows detection of very common, common, and uncommon AEs in accordance with WHO guidelines.

No safety concerns related to the nature and frequency of unsolicited AEs

Comparable safety results
- Between vaccine and control groups aged 9-60 years
- Across populations (age group, sex, region)

*Integrated safety analysis pooling data from 13 studies that used the final formulation and final vaccination schedule (CYD12, 13, 22, 24, 28, 30, 47, 23, 17, 32, 14, 15, 51).
AE=adverse event; AR=adverse reaction; WHO=World Health Organization.

1. Chuenkitmongkol, 2015, JITMM.
TRUTH ABOUT DENGUE CONTROL

PRIMARY PREVENTION
– Vector control

SECONDARY PREVENTION
– Medical management

– Vaccination is a critical pillar of the WHO’s strategy towards effectively fighting dengue
Dengue Vaccine Application

✓ Public health priority
✓ Disease burden
✓ Disease epidemiology
✓ Ineffective disease control measures
✓ Vaccine scientific data availability
✓ Comprehensive National program feasibility

“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.”

“Dengue vaccine introduction should be a part of a comprehensive dengue control strategy, including well-executed and sustained vector control, evidence-based best practices for clinical care for all patients with dengue illness, and strong dengue surveillance.”
Many countries have taken control

For the public immunization program being launched today, we have used our extensive dengue surveillance data to ensure that we are targeting people at highest risk of disease. We will vaccinate all individuals 15-27 years of age in 28 municipalities and 9-44 years of age in the two municipalities with the top dengue burden in our State over the next three weeks,” said Michele Caputo Neto, Paraná Health Secretary.

“Paraná has a good track record in vaccination coverage in general and successful implementation of this dengue immunization strategy could result in 74% reduction in disease burden in these highly impacted municipalities within 5 years, according to a dengue vaccine impact study published in the Brazilian Journal of Health Economics¹,” Secretary Neto noted.
In the Philippine setting:

- Highly-endemic for Dengue
  - ranked 7th worldwide with the highest average number of Dengue cases reported to WHO
  - 4th overall for the Asia Pacific region (2008 to 2012)
  - increasing trend of explosive Dengue epidemics for the past 10 years
- 64.8% increase in suspect dengue cases in 2015
- Seroprevalence = 82.1 - 100% in ≥ 9 years and above

- PhP16B (USD 345M): Estimated Direct Medical Cost of clinically-diagnosed Dengue infections in the Philippines


WHO Dengue Fact Sheet 117
PIDSR 2015
Trend in the Philippines

Suspect Dengue Disease from January 1, 2015 - May 6, 2017

Dengue Cases

- 2015
- 2016
- 2017

http://www.doh.gov.ph/statistics

DOH Epidemiological Bureau Morbidity Week 52
Geographic Distribution

Suspect Dengue Cases by Region
Philippines, 2015 vs 2016 vs *2017
* as of May 6, 2017
Deaths in 2016 increased by 373 cases (36.60%) compared to 2015.
A total of 33,760 reported dengue cases were reported nationwide from January 1 to May 6, 2017. This is 31.9% lower compared to the same time period last year (49,565).
Geographic Distribution

Most of the cases were from the following regions: Region VII (15.8%), Region III (13.4%), NCR (12.4%), Region IVA (11.4%) and Region XII (10.6%).

Fig. 3 Reported Dengue Cases by Region
Philippines, 2017* vs 2016 (N=33,760)

http://www.doh.gov.ph/statistics
Case Profile

Profile of Cases

Ages of cases ranged from less than 1 month to 98 years old (median = 13 years). Majority of cases were male (54%). Most (21.5%) of the cases belonged to the 5 - 9 years age group.

Fig. 4 Reported Dengue Cases by Age Group and Sex
Philippines, as of May 6, 2017* (N= 33,760)

http://www.doh.gov.ph/statistics
Strengthening Dengue Control and Prevention

Health Advisory
DENGUE
Mag4S Laban sa Dengue

Search and destroy mosquito breeding places.
* "Our first line of defense is prevention," the spokesperson noted, adding that mosquitoes usually lay their eggs in stagnant water.

Self-protection measures are a must.
These include the use of insect repellents, mosquito nets, installation of protective screens at homes, and air-conditioning.

Seek early consultation.
Consult a doctor if fever lasts for more than two days. Check your temperature and use a thermometer. A person has fever when the body temperature is 38.0°C or higher. Symptoms of dengue include a quick rise in temperature to 40°C with skin rashes, severe headache, pain behind the eyes, joint pains, and vomiting. When this happens, the patient should be brought to the hospital immediately.

Dr. Tayag also stressed that one should take paracetamol instead of aspirin or ibuprofen, which could worsen the bleeding when the dengue is already severe.

Say yes to fogging.
Fogging in communities aims to eradicate mosquitoes thriving in their breeding sites. However, Dr. Tayag noted that this procedure should be done properly.

Dr. Tayag warned against the harmful chemical used in fogging and encouraged residents to get results done for them. "Solve your own water problems by keeping garbage away from your homes. Avoid stagnant water, pags, and plastic bags, dispose properly your garbage. If you have to come back, do it in 30 minutes or 1 hour later. Disposing of empty containers properly is the key," he added.

When using commercially-bought medicines, Tayag reminded the public to read instructions carefully.
Philippines: Move to control Dengue

491,990 have received the first dose in Central Luzon, Calabarzon, and the National Capital Region

Minor AE: fever, dizziness, headache, rash, vomiting, abdominal pain, colds, cough, LBM, fainting

415,565 have received the second dose in Central Luzon, Calabarzon, and the National Capital Region

Minor AE: similar of lesser frequency

Third dose is scheduled for April–June 2017

An additional fourth region is planned in 2017

Acknowledgement: Data gathered from poster presented by Dr. Lecciones in the 2017 ASVAC
Top 10 AEFI
** rates experienced among minor AEFI cases
Dengue SBI Round1

Acknowledgment: Data as presented by Dr Julius Lecciones, PCMC, 2nd ADS, March 2017, Manila
Top 10 AEFI
** rates experienced among minor AEFI cases
Dengue SBI Round2, as of February 2, 2017

Acknowledgment: Data as presented by Dr Julius Lecciones, PCMC, 2nd ADS, March 2017, Manila
AEFI rates experienced among serious AEFI cases
Dengue SBI Round2, as of February 2, 2017

Acknowledgment: Data as presented by Dr Julius Lecciones, PCMC, 2nd ADS, March 2017, Manila
Dengue vaccine... now part of routine childhood immunization