Where are we with dengue vaccines?

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President, ISTM
Senior Advisor, Dengue Vaccine Initiative
Scientific Coordinator, DengueTools (funded by EU)
Dengue infections
Dengue Virus Infection

Infection Incidence
~ 5% / year

Asymptomatic
75%

Symptomatic
25%

Dengue Fever
98-99%

Severe Dengue
DHF/DSS
1-2%

Survive

Death
0.5 - 5%

Risk factors:
↑ Viral titer
2° Infection

• A major cause of febrile illness in endemic areas

High morbidity, relatively low mortality disease

• 98-99% symptomatic
  • 75% asymptomatic
Dengue Hemorrhagic Fever

DCVMN
Time course

Days of illness

Temperature

Potential clinical issues

Dehydration

Shock bleeding

Reabsorption fluid overload

Organ impairment

Laboratory changes

Hematocrit

Platelet

Serology and virology

Viraemia

IgM/IgG

Course of dengue illness:

Febrile

Critical

Recovery phases

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Dengue Virus

- Flavivirus (YF, JE, TBE, WN)
- RNA Virus: 3 structural proteins & 7 non-structural proteins

- 4 close but genetically different serotypes
  - DEN-1
  - DEN-2
  - DEN-3
  - DEN-4

Zhang et al., 2003,
Antibodies can be protective or destructive

Protection

Illness

Strong, specific response to the infecting serotype

Cross-reactive antibodies rise in response to infection and wane to varying degrees over time

1st infection, serotype 1

Time (months)

Serotype 1

Serotype 2

Serotype 3

Serotype 4

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Immunity

- Monotypic immunity
- Heterotypic immunity
- Multitypic immunity
Additional hurdles

• Animal model
• True correlate of protection
  – Neutralizing antibody appears to be poor predictor
• Overcoming viral interference with a tetravalent vaccine (live)
• Role of cellular immunity
Dengue Vaccine

- High level country interest in a vaccine
- 30 year of development
- Robust vaccine pipeline
- First Phase 3 efficacy results in 2014
- First vaccine licensed in 2015
Competitive landscape, different stages

**Preclinical**
- GSK – TDEN-VPIV
  - *Inactivated vaccine*
  - Inactivated virus
- Butantan – TV003
  - *Live attenuated*
  - Dengue chimeras and gene deletion
- Merck – DEN4-80E
  - *Recombinant subunit*
  - Subunit vaccine
- NIAID – TetraVax-DV
  - *Live attenuated*
  - Dengue chimeras and gene deletion

**Phase I**
- Panacea Biotec
- Serum Institute of India

**Phase II**
- Sanofi Pasteur – CYT-TDV
  - *Live attenuated*
  - Yellow fever – Dengue chimera
- Takeda – DENVax
  - *Live attenuated*
  - Dengue chimeras

**DCVMN**
Live chimeric vaccine (SP)

Live attenuated CYD vaccinal viruses express the pre-membrane (prM) and envelope (E) proteins of each dengue serotype, which genes have been inserted in place of the corresponding genes of the YF 17D vaccine.

The surface phenotype of these vaccines is thus no longer a YF-17D one, and their tropism is first linked to their dengue envelope.

Envelope is the immunizing Ag from an heterologous virus

RNA replication engine is from YF17D
Phase II randomized controlled trial in Singapore

Figure 3. Seropositivity rates (percentage of participants PRNT$_{50}$ titer ≥ 10 1/dil) against each of the four dengue virus serotypes (1, 2, 3 and 4) at baseline and 28 d after the third vaccination in all participants and in each of the three age groups.
Sites of Phase 3 trials

DCVMN
Study design: Randomized, observer-masked, placebo-controlled, multicenter, phase III trials\(^1,\!\!^2,\!\!^3\)

**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**
- Ratio 2:1

**Vaccination with CYD-TDV**
- Months:
  - 0
  - 6
  - 12
  - 13
  - 18
  - 25

**Vaccination with placebo**
- N=10,275 CYD14
- N=20,869 CYD15

**Active phase**

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

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ClinicalTrials.gov, 2014, NCT01374516.
3 Villar, 2014, N Engl J Med (Supplementary Appendix)
## Vaccine efficacy

<table>
<thead>
<tr>
<th></th>
<th>Latin American Trial (N = 20869)</th>
<th>Asian Trial (N = 10275)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Per Protocol</td>
<td>60.8% (52.0-68.0)</td>
<td>56.5 (43.8-66.4)</td>
</tr>
<tr>
<td><strong>Serotype Specific Efficacy (Per Protocol)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• DEN-1</td>
<td>50.3 (29.1-65.2)</td>
<td>50.0 (24.6-66.8)</td>
</tr>
<tr>
<td>• DEN-2</td>
<td>42.3 (14.0-61.1)</td>
<td>35.0 (-9.2-61.0)</td>
</tr>
<tr>
<td>• DEN-3</td>
<td>74.0 (61.9-82.4)</td>
<td>78.4 (52.9-90.8)</td>
</tr>
<tr>
<td>• DEN-4</td>
<td>77.7 (60.2-88.0)</td>
<td>75.3 (54.5-87.0)</td>
</tr>
</tbody>
</table>
Efficacy by flavivirus baseline status

1. Dengue status + at baseline
   - CYD 14
     - N: 52
   - CYD 15
     - N: 31

2. Dengue Status** - at baseline
   - CYD 14
     - N: 41
   - CYD 15
     - N: 18

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Efficacy by Age

CYD14 efficacy against VCD by age (active phase)
Vaccine efficacy against severe disease

<table>
<thead>
<tr>
<th>Efficacy against</th>
<th>Latin American Trial (N= 20869)</th>
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<tr>
<td>Hospitalization</td>
<td>80.3 (64.7-89.5)</td>
<td>67.2 (50.3-78.6)</td>
</tr>
<tr>
<td>Severe Dengue</td>
<td>91.7 (31.4-99.8)</td>
<td>80.8 (42.7–94.7)</td>
</tr>
<tr>
<td>DHF</td>
<td>90 (10.7-99.8)</td>
<td>88.5 (58.2–97.9)</td>
</tr>
</tbody>
</table>
Vaccine efficacy-intermediate summary

- Age
- Seropositivity
- Serotype

- Efficacy against severity of disease > against incidence
Study design: Randomized, observer-masked, placebo-controlled, multicenter, phase III trials\textsuperscript{1,2,3}

Inclusion criteria:
- Children
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Randomization:
- 2:1
- N=10,275 CYD14
- N=20,869 CYD15

Vaccination with CYD-TDV:
- Months: 0, 6, 12, 13, 18, 25

Vaccination with placebo:
- Active phase

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

\textsuperscript{1} Capeding, 2014, Lancet.
ClinicalTrials.gov, 2014, NCT01374516.
HOSPITALIZED VCD (ANY SEVERITY) IN SUBJECTS 4–11 YEARS OF AGE BY AGE GROUP (CYD23/57)¹*

25-Month Active Phase + Year 3 and 4

Subjects <9 Years of Age

Annual Incidence Rate (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td>Year 1</td>
<td>0.50 (0.11, 2.15)</td>
<td>0.76 (0.09, 0.98)</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.75 (0.36, 1.59)</td>
<td>0.17 (0.03, 0.68)</td>
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<tr>
<td>Year 3</td>
<td>1.57 (0.60, 4.80)</td>
<td>0.31 (0.05, 1.58)</td>
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<tr>
<td>Year 4</td>
<td>0.54 (0.23, 1.29)</td>
<td>0.31 (0.09, 0.93)</td>
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<td>Cumulative Results up to Year 3</td>
<td>0.89 (0.54, 1.52)</td>
<td>0.29 (0.11, 0.69)</td>
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Subjects ≥9 Years of Age

Annual Incidence Rate (%)

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<td>Year 2</td>
<td>1.2 (0.36, 1.59)</td>
<td>0.4 (0.3, 0.68)</td>
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<tr>
<td>Year 3</td>
<td>1.7 (0.60, 4.80)</td>
<td>0.4 (0.05, 1.58)</td>
</tr>
<tr>
<td>Year 4</td>
<td>1 (0.23, 1.29)</td>
<td>0.4 (0.09, 0.93)</td>
</tr>
<tr>
<td>Cumulative Results up to Year 3</td>
<td>1.1 (0.54, 1.52)</td>
<td>0.3 (0.11, 0.69)</td>
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Efficacy Surveillance Phase

RR (%) (95% CI)

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3 main interconnected hypotheses to explain the CYD14 observations in the younger age group

Waning
- Abs waning below protective threshold
- More rapid waning below protective levels in SNeg

Cluster effect
- Clustered « primary infection » (vaccination)
- Then clustered « secondary infection » (1st wt infection), potentially more symptomatic/severe, before this takes place in placebos
- This would then be only temporary

Serostatus
- Primary infection-like vaccination in SNeg
- Low responses in SNeg, thus waning more rapidly below protective levels

Age
In the younger age group:
- More chance of being Sneg
- More chance of getting severe disease
- More immature immune system

Hospital Phase / CYD14
Hypotheses to explain the observations in the younger age group
Licensure filed for age 9 and above
SUMMARY OF POOLED EFFICACY: VE WAS CONSISTENTLY DEMONSTRATED FOR THE CANDIDATE DENGUE VACCINE IN SUBJECTS AGED 9–16 YEARS IN THE 25-MONTH ACTIVE PHASE

<table>
<thead>
<tr>
<th>Pooled results (CYD14+CYD15; ITT)</th>
<th>VE (%) and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serotype</td>
<td></td>
</tr>
<tr>
<td>DENV-1</td>
<td>60.7 - 65.6</td>
</tr>
<tr>
<td>DENV-2</td>
<td>47.7 - 58.4</td>
</tr>
<tr>
<td>DENV-3</td>
<td>31.3 - 59.2</td>
</tr>
<tr>
<td>DENV-4</td>
<td>64.4 - 73.6</td>
</tr>
</tbody>
</table>

| Severe dengue                     |                   |
| DENV-1                            | 77.3 - 93.2       |
| DENV-2                            | 76.1 - 92.9       |
| DENV-3                            | 70.1 - 80.8       |

| Hospitalized cases                |                   |
| DENV-1                            | 67.2 - 81.9       |
| DENV-2                            | 52.5 - 76.1       |

DENV=dengue virus; DHF=dengue hemorrhagic fever; ITT=intent to treat; VE=vaccine efficacy; WHO=World Health Organization.
Do we use a vaccine with moderate efficacy, limited to age group 9 and above, with little efficacy in seronegatives subjects?
Vaccine preventable disease incidence (VPDI) = Incidence[unvaccinated] \times VE

Number needed to vaccinate = NNV - 1/ARR

<table>
<thead>
<tr>
<th>Dengue (5)*</th>
<th>Vaccine efficacy (95% CI)</th>
<th>VPDI</th>
<th>NNV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All virologically confirmed clinical cases</td>
<td>65% (59, 70)</td>
<td>1778</td>
<td>28</td>
</tr>
<tr>
<td>All virologically confirmed hospitalized cases</td>
<td>80% (65, 89)</td>
<td>204</td>
<td>245</td>
</tr>
</tbody>
</table>
Immunization, Vaccines and Biologicals

SAGE Working Group on Dengue Vaccines and Vaccination (established March 2015)

Terms of Reference
The Working Group will be asked to review the evidence, identify the information gaps, and formulate proposed recommendations on the use of a licensed dengue vaccine for a SAGE review. This review is tentatively scheduled for April 2016. This will lead to the publication of a WHO position paper on the use of a dengue vaccine.

The Working Group will specifically be asked to review data relating to:

- the global prevalence and burden of disease caused by dengue
- the safety, efficacy, and immunogenicity profile of a licensed dengue vaccine
- the schedule, age of administration, and potential vaccination strategies for a dengue vaccine, including setting-specific attributes that may be important for designing immunization programs
- the disease impact and cost-effectiveness of dengue immunization programs
- identification of key data gaps that may be important for decisions about immunization programs, and recommendations for data collection related to key issues such as long-term safety, duration of protection, etc.
- additional critical issues that need to be considered in drafting proposed recommendations

MEMBERSHIP
- Terry Nolan (Co-Chair), Australia
- Jeremy Farrar (Co-Chair), UK
- Ananda Amarasinghe, Sri Lanka (until 1.3.2016)
- Alan Barrett, USA
- Anna Durbin, USA (until 31.12.2015)
- Elizabeth Ferdinand, Barbados
- Maria Guzman, Cuba
- Maria Novaes, Brazil
- Lee Ching Ng, Singapore
- Amadou Sall, Senegal
- Peter Smith, UK
- Wellington Sun, USA (until 1.2.2016)
- Piyanit Tharmaphornphilas, Thailand
- Stephen Thomas, USA

DCVMN
Key sources for WHO global policy on dengue vaccine

- WHO Vaccine Position Paper (published: 29 July 2016)
  http://www.who.int/wer/2016/wer9130.pdf

Spanish circulated, to be posted online soon
Summary of Vaccine Efficacy Estimates
(from M0-M25, ITT ≥1 dose, post-hoc, pooled analyses)

- Vaccine efficacy amongst 9-16 year-olds was 65.6% (CI 60.7-69.9) (any severity)

- Vaccine efficacy varied by:
  - **serotype** of dengue
    - DENV-1 58.4%, DENV-2 47.1%, DENV-3 73.6%, DENV-4 83.2%
  - **serostatus** at time of vaccination
    - dengue-exposed 81.9%, dengue-naive 52.5%
  - **severity** of disease
    - severe dengue 93.2%, hospitalised dengue 80.8%
Number of hospitalized and/or severe VCD cases by age group and dengue immune status at baseline

<table>
<thead>
<tr>
<th>Age group</th>
<th>Serostatus</th>
<th>Active phase cases/N (%)</th>
<th>Hospital phase-SEP† cases/N (%)</th>
<th>Cumulative cases/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CYD group</td>
<td>Control group</td>
<td>CYD group</td>
</tr>
<tr>
<td>2-8 years</td>
<td>Seropositive*</td>
<td>2/493 (0.4)</td>
<td>8/240 (3.3)</td>
<td>7/476 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Seronegative*</td>
<td>2/337 (0.6)</td>
<td>2/178 (1.1)</td>
<td>15/326 (4.6)</td>
</tr>
<tr>
<td>9-16 years</td>
<td>Seropositive*</td>
<td>0/1605 (0.0)</td>
<td>6/777 (0.8)</td>
<td>7/1508 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Seronegative*</td>
<td>0/398 (0.0)</td>
<td>2/214 (0.9)</td>
<td>7/372 (1.9)</td>
</tr>
</tbody>
</table>

Pool of CYD14, CYD15, and CYD57. *Includes only subjects from the Full Analysis Set for Immunogenicity; † Includes all subjects from the Safety Analysis Set for Efficacy; SEP: Surveillance Expansion Phase
WHO recommendations (1)

- Countries should consider introduction of 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.

- The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination.
WHO recommendations (2)

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

- Decisions about introduction require careful assessment at the country level, including consideration of local priorities, national and subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific inputs, affordability and budget impact.
WHO recommendations (3)

- The target age for routine vaccination should be defined by each country based on maximizing program impact and programmatic feasibility of targeting particular ages.
  - Modelling predicts vaccinating at different age groups depending on endemicity will maximize the number of cases averted
  - Programmatic factors such as school attendance, co-administration, etc., may also guide decisions about age groups to target

- If CYD-TDV is introduced it should be administered as a 3-dose series given as a 0/6/12 month schedule.
Summary

- The CYD-TDV vaccine profile is complex
- SAGE/WHO recommendations are conditional, recommending consideration only in select areas meeting seroprevalence criteria
- Vaccination should be considered as part of a comprehensive dengue control strategy
- If used as recommended in settings fitting the criteria recommended by SAGE, the vaccine could have a substantial public health impact on dengue
- Global recommendations are meant to inform national decision-making for national programs, which should always be done with consideration of the national context
Recombinant live attenuated DENV vaccine strategies

Sanofi-Pasteur:
- Chimeric
- Chimeric
- Chimeric
- Chimeric

Takeda:
- Chimeric
- Full-length
- Chimeric
- Chimeric

NIH:
- Full-length
- Chimeric
- Full-length
- Full-length

Unique DENV proteins:
- Sanofi-Pasteur: 8
- Takeda: 16
- NIH: 32
RESEARCH ARTICLE | INFECTIOUS DISEASE

The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model

Beth D. Kirkpatrick¹*, Stephen S. Whitehead²*, Kristen K. Pierce¹, Cecilia M. Tibery³, Palmtama L. Grier³, Noreen A. Hynes⁴, Catherine J. Larsson¹, Beulah P. Sabundayoh⁵, Kawsar R. Talaat⁶, Anna Janiak³, Marya P. Carmolli¹, Catherine J. Luke⁴, Sean A. Diehl¹ and Anna P. Durbin³†
Summary

- First dengue vaccine (SP) licensed in a few countries

- Efficacy is only partial

- Given the high burden of dengue, even a vaccine with partial efficacy will have a public health impact

- Long-term data on duration of efficacy and safety are needed

- Many other dengue vaccine candidates in the pipeline
Thank you!