DENGUE: PREVENTION & CONTROL

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DENGUE IS A PUBLIC HEALTH PRIORITY

WHO Estimates

- 3.9 billion people live in dengue-endemic countries (about half of the world’s population).
- 390 million people infected per year.
- 96 million symptomatic infections per year.
- 500,000 people with severe dengue require hospitalization each year.
- 2.5% of people with severe dengue die.

WHO objective:
- Mortality by ≥50%
- Morbidity by ≥25%

WHO=World Health Organization.

DENGUE DISEASE COSTS MORE THAN US$6 BILLION ANNUALLY WORLDWIDE

- Nearly US$ 40B* considering the number of cases estimated in 2011
  
- US$ 6.25B* in total on average per year are spent for dengue disease
  
- Nearly US$ 40B* considering the number of cases estimated in 2011

Can be compared to the cost of damages caused by:
- The 2010 earthquake in Haiti: $14B
- Hurricane Irene in 2011: $7-$10B

* Incl. medical and non medical costs, loss of productivity, and cost of premature deaths (no vector control considered).

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3. Shepard, ASTMH poster 2014
DENGUE

• Most common global vector-borne viral infection
• Increasing global burden driven by
  - population growth
  - urbanization
  - globalization
  - ecological changes
• World needs dengue vaccine as part of an integrated approach to dengue prevention and control
DENGUE VIRUS

- RdRP; methyltransferase
- Inhibition of IFN singal transduction
- NS3 serine protease cofactor
- Signal transduction
- Non-structural protein
- C prM E
  - Structural protein
  - vRNA packing
  - Prevention of mature fusion
  - Receptor binding
# RECEPTORS AND TARGET CELL OF DENGUE

<table>
<thead>
<tr>
<th>RECEPTORS</th>
<th>TARGET CELLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin sulfate</td>
<td>Liver cells; VERO; BHK21; C636</td>
</tr>
<tr>
<td>Hsp 70/90</td>
<td>Monocyte derived Macrophage; human; Neuroblastoma cells</td>
</tr>
<tr>
<td>GRP78/BiP</td>
<td>Liver cells</td>
</tr>
<tr>
<td>37/67 Kda high affinity Lamina receptor</td>
<td>Liver cells</td>
</tr>
<tr>
<td>CD14</td>
<td>Monocyte derived Macrophage</td>
</tr>
<tr>
<td>DC-SIGN</td>
<td>Dendritic cells, Langerhans cells</td>
</tr>
<tr>
<td>L-SIGN</td>
<td>Liver cell; LN; Spleen</td>
</tr>
</tbody>
</table>
PATHOGENESIS OF DENGUE DISEASES

• Dengue NS1 protein
• Dengue virus genome
• Antibody-Dependent Enhancement
• T cell
• Endothelial cell
• Dendritic cell
Global strategy for dengue prevention & control, 2012-2020

GOAL:
TO REDUCE THE BURDEN OF DENGUE

OBJECTIVES:
• To reduce dengue mortality by at least 50% by 2020*
• To reduce dengue morbidity by at least 25% by 2020*
• To estimate the true burden of the disease by 2015

* The year 2010 is used as the baseline.

ENABLING FACTORS FOR EFFECTIVE IMPLEMENTATION OF THE GLOBAL STRATEGY:
• advocacy and resource mobilization
• partnership, coordination and collaboration
• communication to achieve behavioural outcomes
• capacity building
• monitoring and evaluation
WHO OBJECTIVES

- Reduce dengue mortality by ≥50% by 2020*
- Reduce dengue morbidity by ≥25% by 2020*
- Estimate true burden of disease by 2015

TECHNICAL ELEMENTS

- Diagnosis & case management
- Integrated surveillance & outbreak preparedness
- Sustainable vector control
- Future vaccine implementation
- Basic operational & implementational research
DENGUE: PITFALLS IN DIAGNOSIS AND MANAGEMENT

- Communications to parents and caregivers
- Diagnostic tests
- Medications
- DDx with other acute febrile illnesses
- Fluid therapy
- Bleeding tendency
- Organopathy

WHO OBJECTIVES

- Reduce dengue mortality by ≥50% by 2020*
- Reduce dengue morbidity by ≥25% by 2020*
- Estimate true burden of disease by 2015

TECHNICAL ELEMENTS

- Diagnosis & case management
- Integrated surveillance & outbreak preparedness
- Sustainable vector control
- Future vaccine implementation
- Basic operational & implementational research
Age distribution of dengue patients in King Chulalongkorn Memorial Hospital between 1987-2007

CHANGING EPIDEMIOLOGY OF DENGUE PATIENTS IN BANGKOK METROPOLITAN THAILAND

Wongvat Lielak*, Chinnan Sonthichai*, Sirinya Saeam*, Usa Thisyakorn**

*Communicable Disease Control Division, Health Department, Bangkok Metropolitan
**Chulalongkorn University Bangkok, Thailand

BACKGROUND

Dengue is the most common mosquito-borne virus causing disease in several countries. In Thailand, dengue patient was first seen in Bangkok, Thailand in 1958 and was then appeared to other part of the country.

OBJECTIVE

This study describes the changes in the epidemiological pattern of dengue patients in Bangkok, Thailand.

METHODS

Analysis of dengue patients data reporting to Communicable Disease Control Division, Health Department, Bangkok Metropolitan Administration, Thailand from January 1991 to June 2010 was done.

The diagnosis of dengue patients adhered to clinical and laboratory criteria for the diagnosis of dengue patients as established by the World Health organization.

RESULTS

During the past 20 years, the rate of dengue patients in Bangkok, Thailand varied from 27.99 per 100,000 in 1992 to 292.24 per 100,000 population in 2001 (Fig.1).

The case fatality rate was less than 0.21% throughout the period of study (Fig.2).

The incidence by age group has shown that rates in older children and adults have increased dramatically during the last decade (Fig.3).

DISCUSSION

These data show that dengue patients are common in Bangkok, Thailand causing heavy burden on the health system during the past 20 years.

The case fatality rate was less than 0.21% throughout the period of study which indicates early recognition and improved management of dengue patients.

The trend towards higher age in dengue patients during the past decade is a problem of concern and need further clarification.

CONCLUSION

Dengue infection is a significant problem in Bangkok, Thailand.

The trend of increasing age in dengue patients has been evident.
**Introduction**

Dengue, one of the most devastating mosquito-borne viral diseases in humans, is now a significant problem globally. The disease, caused by the four dengue virus serotypes, ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF) and severe dengue hemorrhagic fever (DHF) with or without shock. In Thailand, dengue patient was first seen in Bangkok in 1958 and then appeared to other part of the country.

**Objective**

This study describes the changes in the epidemiological pattern of dengue patients in Ratchaburi, Thailand.

**Materials and Methods**

Analysis of dengue patients data reported to Ratchaburi provincial health office, Ministry of Public Health from 2000 to 2010 was done. The diagnosis of dengue patients adhered to clinical and laboratory criteria for the diagnosis of dengue patients as established by the World Health Organization.

**Conclusion**

Dengue is a significant problem in Ratchaburi, Thailand. The trend of increasing age in dengue patients has been evident.
Thailand, number of dengue cases per age group from 2010 to 2015

Dengue serotype in Thailand from 2000-2016

Source: NIH, MOPH, 2000-2016
DENGUE IN BANGKOK

• First outbreak: 1958
• Rate of patients: 27.99-292.24 per 100,000 population
• Case fatality rate: 0-0.21%
• Serotype: all 4 serotypes circulate continuously with predominant serotype emerging as the cause of each epidemic
• Changing epidemiology: a trend towards higher ages

Dengue in Bangkok 2015

[Bar chart showing the number of dengue cases by age group. The x-axis represents age groups in years, and the y-axis represents the number of cases. The chart indicates the distribution of cases across different age groups.]
Dengue serotype in Bangkok 2015-2016

DON'T MAKE DR USA WORRY!
The King’s announcement about the prioritization of dengue in 1999

- Major impact on the surveillance for dengue and increased in number of DF reports seen from 2003 to 2011, after the electronic system was in place.

- In 1999, MOPH initiated a dengue prevention and control program
  - Aim is to reduce incidence of dengue to < 50 cases per 100,000 population
  - *A. aegypti* larval source reduction through an integrated, community-based approach
INTEGRATED VECTOR MANAGEMENT

• Advocacy, social mobilization and legislation
• Collaboration within the health sector and with other sectors
• Integrated approach to disease control
• Evidence-based decision-making
• Capacity-building

DENGUE VECTOR CONTROL: ASSESSING WHAT WORKS?

• Vector control can be effective, implementation remains an issue
• Single interventions are probably not useful, efficacy varies, with little sustainability
• Combinations of interventions have mixed results
• Interventions are often applied in outbreaks with questionable effectiveness
• Key elements for more effective vector control: timely alerts of outbreaks followed by immediate vector control and health promotional campaigns
• Careful implementation may be most important

The candidates dengue vaccine could help meet WHO objectives of decreasing dengue-related mortality by ≥50% and morbidity by ≥25% by 2020.¹

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

Clinical Dengue Vaccine Development Pipeline

Phase I
- DPIV
- GlaxoSmithKline, Biomanguinhos
- WRAIR

Phase II
- TV003/TV005
- US National Institutes of Health,¹
- Butantan
- DEN-80E
- Merck
- DENVax2
- Takeda

Phase IIb

Phase III
- TV003/TV005
- US National Institutes of Health,¹
- Butantan
- DENVax2
- Takeda

Registration
- CYD-TDV
- Sanofi Pasteur

Live attenuated (recombinant)
DNA
Inactivated
Heterologous Prime-Boost
Subunit

¹Licensing agreements also with Merck, Panacea, SII, Vabiotech
Phase 3 study approved for Butantan

World Health Organization
Recombinant live attenuated DENV vaccine strategies

Structural: 5' C prM E NS1 NS2A NS2B NS3 NS4A NS4B NS5 3'

Sanofi-Pasteur

Inviragen

NIAID / LID

Legend:
- DENV-1
- DENV-2
- DENV-3
- DENV-4
- YFV
OBJECTIVE OF THE PUBLICATION: GLOBAL VIEW OF CLINICAL PROFILE OF SANOFI PASTEUR VACCINE CANDIDATE BASED ON EFFICACY AND LTFU INTERIM ANALYSES DATA


LTFU=long-term follow-up.
KEY RESULTS OF CYD14 & CYD15

• Variable efficacy for all serotypes
• Increased efficacy in people with prior dengue infection
• High efficacy in protecting against severe dengue
• Good efficacy in decreasing hospitalization
• Prevented asymptomatic dengue infection
• Safe
The WHO SAGE recommends countries consider introduction of CYD-TDV in geographic settings where dengue is highly prevalent.

Integrated vaccination strategy with a communication strategy, vector control, clinical care, surveillance.

Introduction requires careful assessment by each country.

15 April 2016

WHO position
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.

In defining populations to be targeted for vaccination, prior infection with dengue virus of any serotype, as measured by seroprevalence, should be approximately 70% or greater in the age group targeted for vaccination in order to maximize public health impact and cost-effectiveness. 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.

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. Vaccine introduction must be accompanied by a targeted communication strategy. 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. At the time of introduction, countries are encouraged to have a functional pharmacovigilance system with at least minimal capacity to monitor and manage adverse events following immunization. Countries considering vaccination should also have a dengue surveillance system able to detect and report hospitalized and severe dengue cases consistently over time.
DENGUE VACCINE: WHO POSITION PAPER

• Countries should consider introduction of CYD-TDV in geographic settings where dengue is high burden.

• A combination of seroprevalence data, and programmatic factors should define the target population.

• Integrated vaccination strategy with vector control, clinical care, surveillance, communication strategy.

• Introduction requires careful assessment by each country.

29 July 2016
WHO estimates

3.9 billion people live in dengue-endemic countries (about half of the world’s population).

390 million people are infected per year.

96 million symptomatic infections per year.

500,000 people with severe dengue require hospitalization each year.

2.5% of people with severe dengue die.

Symptomatic : Asymptomatic = 1 : 4

SILENT INFECTION: 300M/Year

SYMPTOMATIC INFECTION: 96M/Year

WHO=World Health Organization.

# Studies That Assessed Relative Incidence of Asymptomatic Dengue Virus Infection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Age, y</th>
<th>Subjects, No.</th>
<th>Study Period</th>
<th>Incidence Ratio (Symptomatic:Asymptomatic)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3,563</td>
<td>2006–2007</td>
<td>1:16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3,676</td>
<td>2007–2008</td>
<td>1:3</td>
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<tr>
<td>Katzelnick et al [34]</td>
<td>Managua, Nicaragua</td>
<td>2–14</td>
<td>7,547</td>
<td>2004–2014</td>
<td>1:2.6</td>
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<tr>
<td>Burke et al [27]</td>
<td>Bangkok, Thailand</td>
<td>4–16</td>
<td>1,752</td>
<td>1980–2001</td>
<td>1:5.6</td>
</tr>
<tr>
<td>Mammen et al [46]</td>
<td>Kamphaeng Phet, Thailand</td>
<td>0.5–15</td>
<td>556</td>
<td>2004–2005</td>
<td>1:0.9</td>
</tr>
<tr>
<td>Present study</td>
<td>32 cities in 10 countries (Asia and Latin America)</td>
<td>2–16</td>
<td>3,669</td>
<td>2011–2013</td>
<td>1:3.9</td>
</tr>
</tbody>
</table>
Tetravalent Dengue Vaccine Reduces Symptomatic and Asymptomatic Dengue Virus Infections in Healthy Children and Adolescents Aged 2–16 Years in Asia and Latin America

Gustavo Olivera-Botello,1 Laurent Coudeville,1 Karen Fanouillere,2 Bruno Guy,1 Laurent Chambonneau,3 Fernando Noriega,4 and Nicholas Jackson; for the CYD-TDV Vaccine Trial Group

1Sanofi Pasteur, Lyon, 2Sanofi, Chilly-Mazarin Codex, and 3Sanofi Pasteur, Marcy l’Étoile, France; and 4Sanofi Pasteur, Swiftwater, Pennsylvania

Background. Asymptomatic dengue virus–infected individuals are thought to play a major role in dengue virus transmission. The efficacy of the recently approved quadrivalent CYD-TDV dengue vaccine against asymptomatic dengue virus infection has not been previously assessed.

Methods. We pooled data for 3736 individuals who received either CYD-TDV or placebo at 0, 6, and 12 months in the immunogenicity subsets of 2 phase 3 trials (clinical trials registration NCT01373281 and NCT01374516). We defined a seroconversion algorithm (i.e., a ≥4-fold increase in the neutralizing antibody titer and a titer of ≥40 from month 13 to month 25) as a surrogate marker of asymptomatic infection in the vaccine and placebo groups.

Results. The algorithm detected seroconversion in 94% of individuals with a diagnosis of virologically confirmed dengue between months 13 and 25, validating its discriminatory power. Among those without virologically confirmed dengue (n = 3 669), 219 of 2 485 in the vaccine group and 157 of 1 184 in the placebo group seroconverted between months 13 and 25, giving a vaccine efficacy of 33.5% (95% confidence interval [CI], 17.9%–46.1%) against asymptomatic infection. Vaccine efficacy was marginally higher in subjects aged 9–16 years (38.6%; 95% CI, 22.1%–51.5%). The annual incidence of asymptomatic dengue virus infection in this age group was 14.8%, which was 4.4 times higher than the incidence for symptomatic dengue (3.4%).

Conclusions. The observed vaccine efficacy against asymptomatic dengue virus infections is expected to translate into reduced dengue virus transmission if sufficient individuals are vaccinated in dengue-endemic areas.
CYD-TDV Prevented Asymptomatic Infections in the Pivotal Phase III Efficacy Trials

- CYD-TDV was efficacious against both symptomatic and asymptomatic dengue infections in individuals* aged 9–16 years in CYD14 and CYD15

<table>
<thead>
<tr>
<th>Symptomatic Infections</th>
<th>Asymptomatic Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>n=2747</em></td>
<td><em>n=2699</em></td>
</tr>
</tbody>
</table>

Vaccine Efficacy

<table>
<thead>
<tr>
<th>Symptomatic Infections</th>
<th>Asymptomatic Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>72.8%</strong></td>
<td><strong>38.6%</strong></td>
</tr>
</tbody>
</table>

*Individuals in the immunogenicity subset.

Conclusion

• Dengue is one disease entity with different clinical manifestations, often with unpredictable clinical evolutions and outcomes

• The human and economic cost of dengue are significant and likely to be even higher than estimated

• Disease prevention is a key to public health
THANK YOU