Integrated Management Strategies for Dengue: Where are We Today?

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The Problem
Dengue is a Global Problem

Adapted from Bhatt, S et al Nature 2013; 496: 504-507
Dengue Virus Transmission

Mosquito acquires virus during feeding, virus replicates in mosquito

Mosquito infects susceptible person

Mosquito infects humans – virus in lymph nodes, other organs, blood

Mosquito acquires virus during feeding, virus replicates in mosquito
Strategies to Prevent and Control Dengue

PAHO Integrated Management Strategy

- Epidemiology
- Integrated vector management
- Social communication
- Laboratory
- Environment
- Patient care

WHO Global Strategy, 2012-2020

- Communication for behavioral outcomes
- Technical elements
- Monitoring and evaluation
- Capacity building
- Advocacy and resource mobilization
- Partnership, coordination and collaboration

From: State of the Art in the Prevention and Control of Dengue in the Americas, 28-29 May 2014
Dengue Prevention and Control Tools

Integrated Vector Control
Surveillance
Clinical Management
Diagnostics
Vaccines

Primary Prevention
Secondary Prevention

Dengue Incidence in the Americas 1980-2013

Source: Pan American Health Organization (PAHO)
What are the Causes of the Apparent Expansion of Dengue?

- Urbanization and vector expansion due to expansion of vector breeding sites
- Movement of people and viruses – all areas now have all four DENVs circulating
- But how much is due to increased recognition of dengue?
Dengue Surveillance

- **Syndromic**: dengue is an acute febrile illness (AFI) syndrome
  - No signs or symptoms differentiate dengue from other diseases except plasma leakage – but this is a late and relatively uncommon event

- **Diagnostic testing**: required to determine the etiology of the syndrome
‘Suspect Dengue’ in Puerto Rico 1986-2013

M, Johansson, CDC unpublished.
Best practices in diagnostic testing over this period: 2009-present = PCR + IgM; 2000 – 2009 = IgM; 1986 – 2000 = virus culture
Causes of Reported Suspected Dengue Cases Puerto Rico, 2010

T. Sharp, CDC unpublished
Acute febrile illnesses among cohort of 5–13 y.o.

Laboratory case definition = fever + DENV viremia or IgM anti-DENV seroconversion = 394 cases

Clinical case definitions = WHO classifications 1997 or 2009

<table>
<thead>
<tr>
<th>Severity by WHO definitions*</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated fever (UF)</td>
<td>210</td>
<td>53.3</td>
</tr>
<tr>
<td>Dengue fever (DF)</td>
<td>142</td>
<td>36.0</td>
</tr>
<tr>
<td>Dengue hemorrhagic fever (DHF)</td>
<td>42</td>
<td>10.7</td>
</tr>
<tr>
<td>Total</td>
<td>394</td>
<td>100</td>
</tr>
</tbody>
</table>

Vaccine 2002; 3043-3046

From Sabchareon, A et al. PLoS NTD 2012; 6: e1732
Sensitivity of Dengue Diagnostic Tests*

*Sensitivity of Dengue Diagnostic Tests*.

- **DENV rRT-PCR + IgM anti-DENV**
- **DENV rRT-PCR**

**Days Post Illness Onset**

**Sensitivity (%)**

*Comparison to IgM anti-DENV seroconversion*

CDC unpublished, CID in press
## Dengue Diagnostic Testing Algorithm

### Days Post-Onset of Illness (DPO)

<table>
<thead>
<tr>
<th>Day Post Onset of Illness</th>
<th>Diagnostic Tests</th>
<th>Probability to confirm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rRT-PCR NS1</td>
<td>IgM anti-DENV</td>
</tr>
<tr>
<td>0-3</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3-7</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>&gt;7</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Febrile Phase**

**Critical / Convalescent**
Dengue Prevention and Control Tools

- Integrated Vector Control
- Vaccines
- Surveillance
- Diagnostics
- Clinical Management

Vector Control
**Aedes aegypti**

- **Highly domesticated**
  - Abundant mosquito development sites – stored water and non-biodegradable containers – adults rest in houses

- **Population tends to be focal and dynamic**
  - Low population densities
  - Number of mosquitoes per house changes over time/ location of infested houses change over time

- **Adults do not move far**
- **Preferential biting of humans**
- **Day biters - ~ 1 bite / day**
- **Low vector transmission thresholds**
Vector Surveillance

- Major shift from immature phase (larvae, pupae) to surveillance for adults
- Reasons
  - Adults are the DENV transmitters
  - Cryptic sites (e.g., septic tanks, underground water storage containers, storm drains) are major source of mosquitoes
Existing Methods for *Aedes aegypti* Control – Immature Stage

- **Major categories include**
  - Containers
  - Social campaigns (COMBI)
    - Education and source reduction
  - Environmental management
  - Legislation

- **Difficult to achieve and sustain reductions in vector density with larval control**

- **Relative effectiveness = 0.25 (95% CI 0.17–0.37)**

Al-Muhandis N and Hunter PR. PLoS NTD 2011; 5: e1278
Existing Methods for Aedes aegypti Control – Adult Stage

- **Insecticides**
  - Resistance is a major problem

- **Repellents**
  - Personal protection only as long as applied

Adults - Interventions Under Development

### Status of New Approaches to *Aedes aegypti* Control

<table>
<thead>
<tr>
<th>Setting</th>
<th>Outcome</th>
<th>RIDL</th>
<th>Wolb</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cage studies</td>
<td>Reduction in adult mosquitoes</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Community studies</td>
<td>Reduction in adult mosquitoes</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Community studies</td>
<td>Reduction in dengue</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Need for large-scale community studies whose outcome is reduction in disease / infection (Phase III equivalent)

*Vaccine* 2002; 3043-3046
Dengue Vaccines
<table>
<thead>
<tr>
<th>Producer (Developer)</th>
<th>Vaccine Type</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur (Acambis)</td>
<td>Live attenuated - chimera 17D yellow fever + DENV</td>
<td>Phase I, II, III</td>
</tr>
<tr>
<td>Takeda (CDC, Invirogen)</td>
<td>Live attenuated - chimera DENV-2 + DENV 1,3, 4</td>
<td>Phase I, II, III</td>
</tr>
<tr>
<td>Butantan (NIAID)</td>
<td>DENV attenuated - mutations + DENV/DENV chimera</td>
<td>Phase I, II, III</td>
</tr>
<tr>
<td>GSK (WRAIR)</td>
<td>Cell culture derived, inactivated</td>
<td>Phase I, II, III</td>
</tr>
<tr>
<td>MERCK (Hawaii Biotech)</td>
<td>Envelop subunits of DENVs</td>
<td>Phase I, II, III</td>
</tr>
</tbody>
</table>
## Sanofi Dengue Vaccine Efficacy Trials (CYD)

<table>
<thead>
<tr>
<th>Site(s)</th>
<th>Design</th>
<th>N</th>
<th>Ages (yrs)</th>
<th>Pre-existing DENV antibody (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratchaburi, Thailand</td>
<td>Phase 2B</td>
<td>4002</td>
<td>4-11</td>
<td>69.5</td>
</tr>
<tr>
<td>Asia – Indonesia, Malaysia,</td>
<td>Phase 3</td>
<td>10,275</td>
<td>2-14</td>
<td>67.5</td>
</tr>
<tr>
<td>Philippines, Thailand, Vietnam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>Phase 3</td>
<td>20,869</td>
<td>9-16</td>
<td>79.4</td>
</tr>
<tr>
<td>Colombia, Brazil, Mexico,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puerto Rico, Honduras</td>
<td></td>
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Short-term Clinical Outcomes of Efficacy Trials

- No differences between vaccine and placebo groups in clinical features or severity of dengue
- No safety signals observed in short-term
- Serotype – specific differences in observed efficacy: DENV 2 < DENV 1 < DENV 3 / 4
- Poor immunogenicity and protection in children without previous DENV infection

Longer-term Follow-up

- Surveillance for dengue hospitalization among the CYD-14, 15, 23/57 participants - 99, 95, 80% follow-up, respectively.

- In year 3, risk of hospitalization shifted upward among vaccinated children, driven by < 9yo in CYD-14 and CYD-23/57. However, year-to-year variability observed in CYD 23/27 where there was longer follow-up.

- The clinical pattern of cases during long-term follow-up phase was similar to hospitalized children in the efficacy phase - with no differences in clinical severity or viremia.

Efficacy Results – Age Effect
Sanofi Vaccine (pooled analysis CYD14+15)

- Age effect
  - ≥ 9 years - 65.6% (CI_{95} 60.7 - 69.9)
  - <9 years - 44.6% (CI_{95} 31.6 - 55.0)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥9 years</td>
</tr>
<tr>
<td>1</td>
<td>58.4</td>
</tr>
<tr>
<td>2</td>
<td>47.1</td>
</tr>
<tr>
<td>3</td>
<td>73.6</td>
</tr>
<tr>
<td>4</td>
<td>83.1</td>
</tr>
</tbody>
</table>

What’s Next

- Continued Phase 3 trials for candidate dengue vaccines
- Multi-year, long-term follow-up studies of CYD trials
- Development of a better test(s) for neutralizing (protective) anti-DENV
- Vaccine effectiveness / safety studies – large-scale community studies with CYD and vaccines showing efficacy in Phase 3 trials
- Improve dengue surveillance and diagnostics to prepare for vaccine introduction (it will happen)
- Design and implement studies that evaluate use of vaccines and vector control
Dengue – Case Management
Proper Case Management Critical to Survival

- Timely diagnosis improves prognosis
- Recognize severe dengue (WHO, 2009)
  - Plasma leakage results in compensated or decompensated shock
  - Includes a subset of individuals which develop
    - Dengue hemorrhagic fever
    - Dengue shock syndrome
  - Life threatening, requires critical, supportive care
- If properly managed, case fatality rate < 1%
  - Early recognition of plasma-leakage based on presence of “warning signs”
  - Proper fluid management and resuscitation of plasma-leakage

Clinical Course of Dengue

Non-specific signs and symptoms: muscle, joint, and/or bone pain, headache, eye pain, and rash (30-40%)

Mosquito bite
- Range: 3 to 14 days; usually 4 to 7 days

Incubation

Viremia

Febrile Phase
- Range: 2 to 7 days; usually 3 to 5 days

Critical Phase*
- 1 to 3 days; usually <48 hrs

Convalescent Phase
- Usually 3 to 5 days

Differential diagnosis includes malaria, influenza, leptospirosis, meliodosis, hepatitis A, chikungunya, Zika

Severe disease due to plasma leakage at defervescence - warning signs, decreased platelets, hemoconcentration

* Typically uncomplicated DHF/DSS lasts for 10 to 12 days
CDC Dengue Case Management E-Learning Course

- Dengue Case Management Educational tool
  - Designed for healthcare providers
  - Includes case management steps recommended by WHO and incorporated in many dengue endemic countries

Free CME Training: cdc.gov/dengue/training/cme.html
Conclusions

- A number of new tools are being evaluated for primary prevention of dengue
- Need to move from controlled trials to community assessment of promising tools
- Dengue surveillance – syndromic + diagnostic testing – required to determine effectiveness of prevention tools
- An integrated approach using several tools will likely be required to control / prevent dengue