Dengue in the United States

The Causes and Impacts of
Neglected Tropical and Zoonotic Diseases

Forum on Microbial Threats
Institute of Medicine
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Centers for Disease Control and Prevention
San Juan, Puerto Rico, USA
Dengue
An Emerging Infectious Disease
Dengue Virus (DENV)

- Long-term protection to infecting virus-type
- No long-term cross protective immunity
- Can be infected up to 4 times during ones lifetime
DENV: Humans the Primary Host

Mosquito acquires virus during feeding, virus replicates in mosquito

Mosquito infects susceptible person

Mosquito acquires virus during feeding, virus replicates in mosquito

Mosquito infects humans – virus in lymph nodes, other organs, blood
Global Increase in Dengue Cases and Countries Reporting Dengue

Disease Burden Estimates

3.61 billion people living in at-risk areas

36 million dengue fever cases / yr

2.1 million severe dengue cases / yr

21,000 deaths / year

Mark Beatty, PDVI, unpublished
Dengue in the United States
Dengue in the United States

Dengue-endemic areas = 4+ million Americans
- Puerto Rico and Virgin Islands
- Pacific Islands – American Samoa, Federated States of Micronesia, Guam, Northern Marianas, Republic of Palau, Republic of the Marshal Islands
Sporadic Dengue

**Locally-acquired outbreaks**
- Texas: 7 since 1980 (1st since 1940)
- Hawaii: 2001 (1st since 1945)
- Florida: 2009 (1st since 1935)

**International travel**
- Tourist travel ~22 million Americans travel to dengue endemic countries in Asia and the Americas each year
- Dengue is the leading cause of febrile illness in returning travelers from these areas
- Immigrant populations with ties to country of origin
- 2006-08: >1000 travel-associated cases
Distribution of Dengue Virus Vectors, United States, 2005

Aedes aegypti

Aedes albopictus

Source: Chester G. Moore, Ph.D., Colorado State University
Dengue – A Reportable Disease
United States, 2010

- Added by Council of State and Territorial Epidemiologists (CSTE) – June 2009
- Endemic and imported cases (travelers)
- Case Classification
  - **Confirmed** – clinically compatible DF, DHF, DSS + confirmatory laboratory results
  - **Probable** – Clinically compatible DF, DHF, DSS + laboratory results indicative of presumptive infection
  - **Suspect** - Clinically compatible DF, DHF, DSS that is epidemiologically linked to a confirmed case
  - **Asymptomatic Blood or Tissue Donor** – viral antigen or NAT demonstrated in blood or organs during screening and confirmatory testing in absence of compatible illness in donor
Dengue Outbreak
Key West, Florida, 2009
Index Case

September 1, 2009
- New York resident with fever, rash, headache after travel to Key West, Florida
- 3x physician visit + MRI + spinal tap
- Eventually dengue suspected

September 10, 2009
- DENV-1 detected by RT-PCR from CSF
Outbreak Investigation

- Alert issued to Key West physicians
  - September 16, 2009 - suspected case, IgM anti-DENV +
  - spouse recently ill, IgM anti-DENV +
- Serologic survey of residents living within 1 km of cases
  - 170 households participated, 240 people
  - PCR, NS1, IgM anti-DENV
  - 13 positives = 5% (95% CI – 2%- 7%)
- Retrospective chart review of febrile illnesses
- Ongoing case identification
Dengue Cases by Source of Identification, Key West, 2009

<table>
<thead>
<tr>
<th>Week of Illness Onset</th>
<th>Number of Cases</th>
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<tbody>
<tr>
<td>July</td>
<td></td>
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<tr>
<td>August</td>
<td></td>
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<tr>
<td>September</td>
<td></td>
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<tr>
<td>October</td>
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</table>

- Household survey (n=13)
- Record Review (n=6)
- Physician identified (n=11)

Index case
Is DENV Transmission Endemic In Key West, FL?

- 2010 = ~44 cases to date
- All DENV -1
- Same phylogenetic relationship
- Dominant vector = *Aedes aegypti*
- “Intensive” vector control efforts
Dengue in Puerto Rico
Follows Global Patterns of Dengue Epidemiology

- Incidence: high endemic + periodic epidemics
- Highly seasonal
- Peak age incidence differs from Asia and Central America
- Co-circulation of multiple DENV types (serotypes)
- Significantly under-identified and reported
<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Cases</th>
<th>Incidence per 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>5,000</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>15,000</td>
<td></td>
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<tr>
<td>1996</td>
<td>20,000</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>25,000</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>40</td>
<td></td>
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</table>
Seasonal Distribution of Dengue Cases
Puerto Rico, 2007

Source: CDC Dengue Branch
Fuente: Sistema de vigilancia para dengue, CDC y DSPR

The graph shows the seasonal distribution of dengue cases in Puerto Rico during 2007. The y-axis represents the number of cases, while the x-axis represents the months from January to December. The peak of cases is observed in October.
Distribution of Dengue Virus Types*

*As percent of positive patient isolates

DENV-1
DENV-2
DENV-3
DENV-4

1986 (20)
1987 (104)
1988 (438)
1989 (161)
1990 (151)
1991 (68)
1992 (643)
1993 (243)
1994 (228)
1995 (110)
1996 (144)
1997 (8)
1998 (8)
1999 (61)
2000 (8)
2001 (22)
2002 (7)
2003 (63)
2004 (166)
2005 (533)
2006 (260)

Jorge Munoz-Jordan
Age-Specific Incidence of Reported Dengue, Puerto Rico
Reported Dengue Cases, Puerto Rico 1998 and 2010

Week of Onset: 2010 vs 1998

Epidemic Threshold

Cases vs Week of Onset

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51

Epidemic Threshold
Dengue
An Under-Recognized Disease
Dengue Virus Infection

Infection Incidence
~ 5% / year

- Asymptomatic 75%
- Symptomatic 25%

Dengue Fever 98-99%
DHF/DSS 1-2%

Survive
Death 0.5 - 5%

A major cause of febrile illness in endemic areas

Adapted from Vaccine 2002; 3043-3046
Dengue Cases among Persons with Febrile Illness
Active Surveillance, Ratchaburi Province, Thailand
2006-2008

Total dengue cases = 317/2,620 = 11.98%

Source: Arunee Sabchareon, Mahidol University
## Under Identification and Reporting of Dengue

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Design</th>
<th>Age Group</th>
<th>Incidence</th>
<th>Incidence (National Surveillance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patillas, Puerto Rico</td>
<td>Enhanced Surveillance</td>
<td>All</td>
<td>0.8%</td>
<td>0.07% (10)</td>
</tr>
<tr>
<td>Managua, Nicaragua</td>
<td>Cohort</td>
<td>4-16 years</td>
<td>0.9%</td>
<td>0.026% (34)</td>
</tr>
<tr>
<td>Kolkata, India</td>
<td>Cohort</td>
<td>All</td>
<td>0.5%</td>
<td>0.002% (250)</td>
</tr>
<tr>
<td>Ratchaburi, Thailand</td>
<td>Cohort</td>
<td>3-13 years</td>
<td>1.7%</td>
<td>0.075% (23)</td>
</tr>
<tr>
<td>Kampong Cham, Cambodia</td>
<td>Active Surveillance</td>
<td>0-15 years</td>
<td>1.0%</td>
<td>0.028% (33)</td>
</tr>
</tbody>
</table>

Laboratory confirmed dengue fever in study sites compared to reported national incidence

PDVI Field Site Consortium data
**Dengue Deaths in Puerto Rico**

**2007 – case review**
- Few death certificates with ‘dengue’ as 1° or 2° cause of death
- 30 + suspect cases identified by searching on symptoms of viral syndrome, acute febrile illness, pleural effusion, ascites, thrombocytopenia, hemorrhage, shock. 19 = DENV (+)

**2010 – case review to date**
- 47 suspect dengue deaths based on identification by symptoms, all have serum or tissue specimens
- < 10% of cases coded as “dengue”
- 22 DENV (+), 8 DENV (-) remainder = pending testing
Tools for Prevention and Control of Dengue
The Tool Box

Integrated Vector Control (1° prevention)
- Sustained vector control programs have NOT successfully prevented or stopped endemic or epidemic dengue
- Future: genetically modified sterile mosquitoes?

Case Management (2° prevention)
- good case management has been shown to reduce case-fatality rates from ~ 5% to <0.3%

Diagnostics (2° prevention)
- An adjunct to case management

Dengue Vaccines (1° prevention)
- 5 vaccines in clinical trials
- 1 in efficacy trial

Antivirals (2° prevention)
- A number under development
2009 - Review of deaths showed
- Low rate (<30%) of laboratory diagnosis
- Late referral for hospital care
- Significant errors in clinical management

2009 – Publication of WHO Proposed Guidelines for Classification and Management of Dengue

2010 – development of postgraduate course on dengue case management
- Physicians (English) and nurses (Spanish)
- 50 master trainers for each group
- Has become a requirement for renewal of medical license
Dengue Diagnostics – Past

- **Complicated**
  - has required 2 samples for IgM anti-DENV testing (acute and convalescent)

- **Difficult to Interpret**
  - second sample often not obtained

- **Slow**
  - not useful for clinical diagnosis, not commercialized

- **Expensive**
  - used investigational reagents
‘Acute’ Dengue – A Diagnostic Challenge

Primary Infection

Secondary Infection

Incubation

Fever Day

0 1 2 3 4 5 6 7 8 9 10

Fever Day

0 1 2 3 4 5 6 7 8 9 10

‘Window’

IgM

NS1

Virus

IgM

NS1

Virus
Significantly improved in last 2-3 years
  - Combination of virus detection (molecular or NS1 and IgM anti-DENV) circumvent need for paired samples

Not widely commercialized
  - No kits FDA approved in the US
  - Limited availability worldwide, especially in low-income countries
Sensitivity of Dengue Diagnostic Tests

Days after onset of symptoms

Based on CDC surveillance data & validations of commercial kits
Dengue Diagnostics – Future

- Commercially available, FDA registered tests (US)
- Wider use for clinical case management
- Establish dengue diagnostic testing (2 tests) at hospitals and qualified laboratories in disease endemic areas
- Establish dengue diagnostic testing (2 tests) in State / Territorial (US) or national reference laboratories
Dengue Vaccines
<table>
<thead>
<tr>
<th>Producer</th>
<th>Approach</th>
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<tbody>
<tr>
<td>Sanofi Pasteur</td>
<td>Live attenuated chimeric vaccine 17D yellow fever virus non-structural genes + respective DENV 1,2,3 or 4 envelope genes</td>
</tr>
<tr>
<td>GSK</td>
<td>Switching from cell culture derived live attenuated vaccine to cell culture derived inactivated vaccine</td>
</tr>
<tr>
<td>InViragen (developed by CDC)</td>
<td>Live attenuated chimeric vaccine Attenuated DENV-2 + chimeras of DENV-2 non-structural genes + DENV 1,3, or 4 envelope genes</td>
</tr>
<tr>
<td>NIAID</td>
<td>Engineered mutations in 3’ NTR and non-structural genes of DENV-1, 2, 4 &amp; DENV-4/DEN-3 chimera</td>
</tr>
<tr>
<td>Hawaii Biotech/ Merck</td>
<td>Subunits of DENV 1,2,3,4 envelope protein expressed in Drosophila S2 cell lines + alum adjuvant</td>
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</table>
Status of Dengue Vaccines

<table>
<thead>
<tr>
<th>Producer / Developer</th>
<th>Process Devel</th>
<th>Evaluation</th>
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<tr>
<td>Sanofi Pasteur</td>
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<td>2009</td>
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<tr>
<td>GSK</td>
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<td>Q3 2010</td>
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<tr>
<td>NIAID</td>
<td></td>
<td>2010</td>
</tr>
<tr>
<td>Butantan (NIAID)</td>
<td></td>
<td>Q3-2010</td>
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<tr>
<td>InViragen (CDC)</td>
<td></td>
<td>Q3-2010</td>
</tr>
<tr>
<td>Hawaii Biotech / Merck</td>
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<td>Q3-2010</td>
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Dengue Vaccine (sanofi pasteur)
Efficacy Trial, 2009 - 2012
Ratchaburi, Thailand

- Double-blind, placebo controlled
- 4000 children 4-11 years of age
- WHO Guidelines *Vaccine* 2008;26:4113-4119

Status:
All children have received dose #1
All children have received dose #2
peak of ‘dengue season’ in Thailand is Aug-Sept
Dengue Vaccines – Challenges

**Interference**
- Multi-valent formulations of live, attenuated vaccines result in decreased immunogenicity and increased number of vaccine doses

**Efficacy and safety**
- Protection against multiple DENV types
- Safety - theoretical potential for immune enhanced disease in previously vaccinated persons

**Access**
- Vaccine financing and delivery
ACKNOWLEDGMENTS

- Pediatric Dengue Vaccine Initiative (PDVI) staff and members
- Dengue Branch, CDC, San Juan, PR
- Arboviral Diseases Branch, CDC, Ft. Collins, CO
- Initiative for Vaccine Research (IVR), WHO, Geneva

To all the experts in the field who have taught me so much about this complex disease