LECTURE

Dengue Fever

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Objectives

• Describe the epidemiology of dengue fever in Brazil and globally
• Describe the consequences of infection
• Review transmission cycles
• Define factors that influence vector populations
  – (e.g., location, abundance, extrinsic incubation)
• Describe approaches to dengue control
• Review receptivity of region to other vector-borne viruses

References

• Key references
References: General


Questions for Discussion

- Why is dengue causing larger and more severe epidemics?
- Where is the virus between epidemics?
- Where do new serotypes come from?
- Explain the seasonality and the year-to-year changes in the epidemiology.
- Why does mortality vary by region?

Dengue

- Mosquito-transmitted flavivirus
- Single-stranded RNA virus
- Four major serotypes (DENV 1, DENV 2, DENV 3, DENV 4)
- >3.6 bil persons live in at-risk areas
- Present in tropical and subtropical areas worldwide
The increasing dengue problem, 1955–2007

More cases, more places

Average Incidence of Dengue per 100,000, 1980-2007

Dengue in the Americas
Disease Burden Estimates
2010 data

- 390 million infections/year
- 96 million with symptoms
- Global burden:
  - Asia 70% (half in India)
  - Africa 16%
  - Americas 14% (>half in Brazil and Mexico) [13.3m sx; 40.5m inapparent]
  - Oceania 0.2%
  

Dengue Virus (DENV)

- Ticks
- Flaviviruses
- West Nile Virus
- Murray Valley Encephalitis Virus
- Japanese Encephalitis Virus
- St. Louis Encephalitis Virus
- DENV 1
- DENV 2
- DENV 3
- DENV 4
- Yellow Fever Virus

- Long-term protection to infecting virus-type
- No long-term cross protective immunity
- Can be infected up to 4 times during one's lifetime

Dengue Infections

- Incubation 4-7 days (3-14)
- Infection
  - Asymptomatic or mild
    - Ratio of asymptomatic to symptomatic: 2:1 to 10:1
  - Acute febrile illness (dengue fever)
  - Dengue hemorrhagic fever (DHF)
  - Dengue shock syndrome (DSS)
  - No chronic carrier state
Clinical Findings

- Headache, fever, myalgia
- Nausea, vomiting
- Rash (50%)
- Laboratory
  - Low WBC
  - Low platelets
  - Abnormal liver function

Clinical Course

- Initial febrile phase
  - Lasts 3-7 days
  - Most recover without complications
- Critical phase (at defervescence)
  - Small percent develop vascular leak syndrome
  - Can develop shock, hemorrhage
- Spontaneous recovery phase

Dengue Hemorrhagic Fever/Shock Syndrome

Seventy

- Viremia
- Fever
- Petechiae
- HA / Pain
- Rash

Day post-infection
WHO Classification
Dengue or Severe Dengue

- Dengue: recover, no major complications
- Severe dengue:
  - Plasma leakage resulting in shock and/or
  - Accumulation of serosal fluid -> respiratory distress
  - Severe bleeding
  - Severe organ impairment

Laboratory Diagnostic Options in a Patient with Suspected Dengue Infection

Sensitivity of dengue diagnostic tests.
Hemorrhagic Manifestations of Dengue Infection

Risk Factors for Severe Disease
- Young age
- Female sex
- High body mass index
- Virus strain
- Host genetic make-up
- Second infection with different serotype
  - Antibody-dependent enhancement of virus

Severe & Complicated Dengue
- Mortality > 20% (<1% with good care)
- Risk for DHF increased ~100x with 2nd infection (different serotype)
- Thailand, 2 cohort studies
  - DHF rate 0 in primary infection
  - 1.8% and 12.5% with 2nd
- Virulence may also vary by genotype
  Am J Epidemiol 1984;120:653
  AJTMH 1988;38:172
Dengue Virus Infection

Infection Incidence ~ 5% / year

- Asymptomatic 75%
- Symptomatic 25%
- Dengue Fever 98-99%
- DHF/DSS 1-2%
- Death 0.5 - 5%

A major cause of febrile illness in endemic areas

Adapted from Vaccine 2002; 3043-3046

Treatment

- Current: close observation; judicious use of parenteral fluids
- Clinical trials
  - Chloroquine
  - Prednisolone
  - Balapiravir
  - Statins, other antiviral

Vaccines

- Multiple vaccines are in development
- Vaccine trials are ongoing
  - Will provide better understanding of the immunology of dengue
  - Several are in phase 2 and 3 clinical trials
- Vaccines will not solve dengue problem
**Aedes aegypti**

- Wide distribution in urban areas
  - Well adapted to contemporary urban life
- Breeding sites
  - Discarded plastic containers, cans
  - Used tires, flowerpots, tree holes
  - Construction sites
- Enters homes; prefers human blood
- Nervous feeder; multiple hosts

**Aedes Aegypti**

- Usually do not disperse beyond 100 m
- Most movement of dengue viruses occurs via movement of viremic hosts
- Females typically distribute eggs among multiple sites
**Vertical Transmission of Dengue Virus**

- Transovarial (vertical) transmission of virus can occur (female MQ to eggs)
- *Ae aegypti* eggs subjected to adverse hatching conditions can remain viable in the environment >100 days
- Resistant to desiccation

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**Vector Dispersal**

**Horizontal and Vertical**

- Study site: Singapore
- *Ae aegypti* & *Ae albopictus* fed rubidium-laced blood; female offspring released
- Female movement traced (oviposition sites)
- Findings:
  - Horizontal: radius of 320 m
  - Vertical: release on level 12 of 21-story apt; dispersed to top and bottom


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**Environmental Influences on Vector**

- Presence or absence
- Abundance; longevity of adult
- Time for development
- Frequency of biting
  - Blood feeding frequency increases with higher temperatures
- Extrinsic incubation period (time for virus to disseminate in mosquito)
- Seasonality of pathogen transmission
Extrinsic Incubation Period

- Time between entry of organism into vector and time when vector can transmit pathogen
- Sensitive to environmental conditions
- If extrinsic incubation period exceeds lifespan of vector, it cannot transmit infection

Extrinsic Incubation and Dengue

- Temperature: inverse relationship with EI period (<20 C Ae aegypti eggs do not hatch)
  - 12 days for mosquitoes at 30 C
  - 7 days at 32 and 35 C
- Temperature required for effective transmission depends on virus & vector


Dengue/Mosquito Interaction

- Aedes aegypti needs viral titer 10^5-10^7 particles/ml of blood to become infected
- Vector serves to select viruses that produce high viremia in humans
Global Dengue Risk

Simmons NEJM 2012;366:1424

Figure 4. Map of all airports included in risk model.


http://www.plosone.org/article/info:doi/10.1371/journal.pone.0072129

Distribution of Dengue Virus Vectors, United States, 2005

Aedes aegypti
Reported distribution of Aedes aegypti in the U.S., 2005

Aedes albopictus
Reported distribution of Aedes albopictus in the U.S., 2005

Source: Chester G. Moore, Ph.D., Colorado State University
WHO: Dengue Risk Areas and Year-round Survival of *Ae. Aegypti*

Dengue, countries or areas at risk, 2011

Cities with one million or more population, 2000

Figure 2. Estimated relative prevalence of the 4 serotypes in Thailand.

http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0001876
Distribution of Dengue Virus Types: 1986-2007*
(number of DENV-2 each year)

*As percent of positive patient isolates

Increase in Dengue Fever

- Travel and migration
  - Dispersal of competent vectors
- Urbanization, especially in tropics
- Growing population
  - More urban areas large enough to sustain ongoing viral circulation
- Poor housing, inadequate water supply
- Poor vector control and resistance
Chronology of Dengue in Brazil

- 1981-1993: localized epidemics
  - 1981 outbreak DENV 1 & DENV 4 in NW
  - 1986 DENV 1 in Rio de Janeiro State
  - 1990 intro DENV 2 Rio State; first confirmed DHF
  - 1994-1999 *Ae aegypti* dispersed countrywide
  - 1999 widespread outbreaks
  - 2000 intro DENV 3 in Rio State
  - 2002 large outbreaks (dengue deaths>malaria deaths)

Siqueira et al. EID 2005;11:48
### Regional Incidence of Dengue per 100,000 population (wk 1-23)

<table>
<thead>
<tr>
<th>Region</th>
<th>2008</th>
<th>2009</th>
<th>Serotype 09</th>
</tr>
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<tbody>
<tr>
<td>North</td>
<td>429</td>
<td>296</td>
<td>DENV 1,2</td>
</tr>
<tr>
<td>Northeast</td>
<td>434</td>
<td>226</td>
<td>DENV 1,2</td>
</tr>
<tr>
<td>Southeast</td>
<td>438</td>
<td>150</td>
<td>DENV 1,2,3</td>
</tr>
<tr>
<td>South</td>
<td>55</td>
<td>27</td>
<td>DENV 3</td>
</tr>
<tr>
<td>Midwest</td>
<td>424</td>
<td>475</td>
<td>DENV 1,2,3</td>
</tr>
<tr>
<td>Bahia</td>
<td>215</td>
<td>631</td>
<td>DENV 2</td>
</tr>
<tr>
<td>Overall</td>
<td>380</td>
<td>189</td>
<td></td>
</tr>
</tbody>
</table>

Ministerio da Saude, 2009

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### Dengue Cases Notified by Week by Region, 2006

secretarias de estado da saude

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### Reported Cases and Hospitalizations DF/DHF by Month, Brasil, 1986 – 2013*

* - until September

Source: FHD Brasil, 1986-2013*
Dengue: Brazil 2012

- Clinical dengue: 565,510 (>1 million, 2010)
- Severe dengue: 4055
- Deaths: 284 (7%)
- Serotypes: DENV 1,2,3,4
- Dengue cases in the Americas: >1.1 million

Aedes Albopictus: Asian Tiger Mosquito

Studies

- Mosquitoes survived better in slum areas (mark, release, recapture study)
  - *Ae. aegypti* home preference (Rio: 98% found near homes)
- *Ae. albopictus* potential role as bridge vector
  - Will feed on wide range of hosts
  - Can survive in rural and forest environments

Maciel-de-Freitas R et al. AJTMH 2007;77:659.
Chikungunya Virus

- Alphavirus, family Togaviridae (first identified in Tanzania, 1953)
- Emerged in Indian Ocean islands 2005
- Has moved to India, other countries in region; explosive outbreaks; high attack rates
- Spread by Aedes aegypti and Ae albopictus
- Will it spread to the Americas?
**Chikungunya Virus**

- Point mutation of virus associated with enhanced replication of virus in mosquito midgut (*Ae. albopictus*)
- More rapid dissemination into mosquito salivary glands
- 100-fold higher virus concentration in mosquito saliva
- Mutation absent initially (Reunion outbreak); later found in >90% isolates


**Shipping: Containerization**

- ~90% of non-bulk cargo worldwide moves by containers stacked on container ships
- >20 million containers make >200 m voyages/yr
- Ships can hold >14,500 units
- Often goes directly from ship to destination, where it is opened

Preparedness and Response for Chikungunya Virus Introduction in the Americas

CDC and PAHO


Vector Control

• Current vector control strategies have not controlled dengue
• Resistance of mosquitoes to pesticides is increasing
• New approaches
  – Sterile mosquitoes
  – Symbiotically infected mosquitoes
  – Novel traps to attract adults

Wolbachia: Biological Control Agent

• *Wolbachia pipientis*: intracellular insect bacterium; maternally-inherited agent
• Embryonic introduction of *Wolbachia* into *Aedes aegypti*
• Can spread rapidly in uninfected host populations by inducing cytoplasmic incompatibility
  – Embryos from uninfected females die when mated with infected males
• Also influence mosquito ability to transmit
  – Reduce life span or reduce viral proliferation
Sterile Insect Technology

- Rear, sterilize, and release large number of disabled insects
- Sterile insects mate with wild insects; decrease reproductive potential of target
- Open field trial of engineered *A. aegypti*
  - Released across 10 hectares for 4-wk period
- Grand Cayman Island (Caribbean)
- Successful mating with wild females and fertilized their eggs

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