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Outline

• Dengue
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  • Vector
  • Clinical Manifestation
  • Immunity
  • Epidemiology
  • Intervention

• Results
  • Dengue Incidence among PCVs
  • Peace Corps vs. WHO data

• Explanation
  • Increased risk among travelers
  • Underreporting
  • Other explanations
The Virus

- Dengue is caused by four serologically related but antigenically distinct viruses, known as DENV-1, DENV-2, DENV-3, and DENV-4.

- Dengue viruses are single-stranded, positive-sense, and composed of RNA.

- DENV-1 was first isolated in 1943 from the blood of a Japanese patient.
The Virus

- The four dengue viruses originated in monkeys and independently jumped to humans between 100 and 800 years ago (9)

- The record of a disease outbreak in Philadelphia in 1780 points to dengue fever

- Dengue was geographically limited until the middle of the 20th Century

- The first known epidemic of severe dengue occurred in the Philippines in 1953
The Vector

- *Aedes aegypti* mosquitoes are the principal vector of dengue
- They can also transmit chikungunya, yellow fever, and zika virus
- Females preferentially feed indoors during the daytime and bite multiple people in a single feeding period
- Eggs are commonly deposited in man-made water containers and can survive drying for up to several months
Transmission

- Female mosquitoes acquire the virus by biting an infected human.
- The virus incubates for 8 to 12 days inside the mosquito before it can be transmitted.
- The virus is introduced into the blood stream of a human from the mosquito salivary glands when the female takes a blood meal.
- Symptoms generally last for 2 to 7 days, during which time the virus can be taken up by mosquitoes.
Clinical Manifestations

• Dengue infections are often asymptomatic in children younger than 15, but symptomatic in adults

• Clinical disease can present as dengue or severe dengue

• Dengue is a milder, generally self-limiting infection

• Severe dengue is characterized by complications such as plasma leakage or severe bleeding
- Chikungunya presents with similar symptoms to dengue fever

- Clinical distinction: severe joint pain accompanies most chikungunya infections but is rare among dengue patients

- Laboratory distinction: elevated hematocrit occurs in 40-69% of dengue patients but does not occur in patients with chikungunya (23)

<table>
<thead>
<tr>
<th>Clinical and laboratory features</th>
<th>Chikungunya virus infection</th>
<th>Dengue virus infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;102°F or 39°C)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Myalgias</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Arthalgias</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>++^b</td>
</tr>
<tr>
<td>Rash</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Bleeding dyscrasias</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Elevated hematocrit</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

^a Mean frequency of symptoms from studies where the two diseases were directly compared among patient seeking care; +++ = 70-100% of patients; ++ = 40-69%; + = 10-39%; +/- = <10%; - = 0% ^b Often retroorbital

PAHO and CDC (2011) Preparedness and Response for Chikungunya Virus Introduction in the Americas
Immunity

- Dengue infection provides long-term immunity to the infecting serotype and 2 to 3 months immunity to the three non-infecting serotypes.

- Secondary infection with a different serotype increases the risk of severe disease:
  - Improved clinical management has resulted in a decline in case fatality among hospitalized severe dengue cases from 20% to less than 0.5%.

- Antibody-dependent enhancement:
  - Explains the increased risk for severe disease among dengue patients with a secondary infection.
INITIAL INFECTION WITH DENGUE VIRUS

1. Dengue virus infects a cell.
2. The virus is engulfed by the cell.
3. The virus is replicated and released.
4. Cytokines and virus are engulfed by a macrophage.
5. Antibodies bind to the virus.
6. The virus is destroyed.

SECOND INFECTION WITH DIFFERENT VIRAL TYPE

5. Infected cells activate memory B cells.
6. Memory B cell (from initial dengue infection) releases antibodies.
7. Antibodies are less effective in binding to virus.
8. Virus replicates and is released from the macrophage.
Epidemiology

- Dengue infections occur in more than 100 countries in the Asia-Pacific region, the Americas, the Middle East and Africa.

- Incidence, distribution, and clinical severity of dengue has increased globally over the last 60 years.

- The WHO currently estimates that there are 390 million dengue infections per year, of which 96 million manifest apparently (24).

- Roughly 2.5 billion people live in areas potentially at risk for dengue transmission.
Dengue, countries or areas at risk, 2013

The contour lines of the January and July isotherms indicate areas at risk, defined by the geographical limits of the northern and southern hemispheres for year-round survival of Aedes aegypti, the principal mosquito vector of dengue viruses.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

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Clinical Interventions

- 5 vaccines are in the clinical stages of development

- CYD-TDV vaccine
  - The only vaccine to enter Phase III clinical trials
  - Tetravalent live-attenuated vaccine developed by Sanofi Pasteur Group
Clinical Interventions

- Asia CYD-TDV Vaccine Phase III Trial
  - 10,275 subjects aged 2 to 14 years old
  - 56.5% overall efficacy
  - 88.5% efficacy against severe dengue

- Latin America CYD-TDV Vaccine Phase III Trial
  - 20,869 subjects aged 9 to 16 years old
  - 60.8% overall efficacy
  - 91.7% efficacy against severe dengue

- December 2015: market approval in Mexico, Brazil, and the Philippines
Environmental Interventions

• Environmental management and modification

• Chemical control interventions

• Biological interventions

• Integrated vector management involves a combination of interventions as well as community education and involvement (11)
Individual-Level Interventions

- Personal protection can be an important barrier to *Aedes aegypti* mosquitoes and other disease-carrying vectors

- Insecticides
  - The CDC recommends using products with 20% to 50% DEET concentration

- Clothing
  - Permethrin-treated clothing repels mosquitoes and kills insects that come in contact with the cloth (28)
United States Peace Corps

- Created by President JFK in 1961
- To help the people of interested countries in meeting their need for trained men and women
- To help promote a better understanding of Americans on the part of the peoples served
- To help promote a better understanding of other peoples on the part of Americans
Peace Corps Demographics

- Americans who have served: nearly 220,000
- Host countries served to date: 141
- Gender: 63% female, 37% male
- Minorities: 28% of Volunteers
- Average age: 28
- Volunteers over 50: 7% of Volunteers
Peace Corps Location of Service

- Percentage of total Volunteers serving, by geographic region, in 2015
  - Africa: 45%
  - Latin America: 22%
  - Eastern Europe/ Central Asia: 10%
  - Asia: 13%
  - The Caribbean: 4%
  - North Africa/ Middle East: 3%
  - Pacific Islands: 3%

*Results may not equal 100 due to rounding*
Peace Corps Volunteers

- Peace Corps Volunteers (PCVs) commit to a 27-month assignment abroad
- Work at the grass-roots level around the world, primarily in low- and middle-income countries
- Generally young and healthy individuals
- PCVs have a unique risk of dengue due to long-term travel to endemic countries as well as in-country living conditions
Methods

• Monthly Epidemiological Surveillance System (ESS) reports submitted to the PC Epidemiology Unit by Peace Corps Medical Officers (PCMOs)

• ESS reports include the number of laboratory confirmed dengue cases

• Peace Corps countries divided into the following regions: Europe and Central Asia, East and South Asia, Africa, Caribbean, Central America, South America, and Pacific Islands
Methods

• Dengue incidence rates calculated using the yearly total of dengue cases and Volunteer/Trainee years (VT years)
  – All rates reported in cases per 1,000 VT Months

• Data analyzed using SAS 9.3 (Cary, NC), OpenEpi 3 (Atlanta, GA), and ArcGIS 10.3.1 (Redlands, CA)
Results

Overall Incidence Rates of Dengue among PCVs, 2000-2014

Cases per 1,000 VT Months

1.2 0.9 0.6 1.2 1.0 1.2 1.2 1.7 0.7 1.2 1.5 0.7 1.4 1.6 0.8
Results

Cumulative Incidence Rates of Dengue Among PCVs by Region, 2000-2014

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases per 1,000 VT Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe and Central Asia</td>
<td>0.03</td>
</tr>
<tr>
<td>Africa</td>
<td>0.12</td>
</tr>
<tr>
<td>South America</td>
<td>1.16</td>
</tr>
<tr>
<td>Pacific Islands</td>
<td>2.30</td>
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<tr>
<td>Central America</td>
<td>2.55</td>
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<tr>
<td>East and South Asia</td>
<td>3.34</td>
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<tr>
<td>Caribbean</td>
<td>5.51</td>
</tr>
</tbody>
</table>
Results

Percentage of Dengue Cases by Region, 2000-2014

- Caribbean: 25.8%
- Central America: 31.6%
- East and South Asia: 19.8%
- South America: 9.8%
- Pacific Islands: 8.2%
- Europe and Central Asia: 0.5%
- Africa: 4.3%
Results

Incidence Rates of Dengue Among PCVs, 2000-2014

Cases per 1,000 VT Months

Caribbean
Results

Incidence Rates of Dengue Among PCVs, 2000-2014

Cases per 1,000 VT Months

Caribbean
East and South Asia
Results

Incidence Rates of Dengue Among PCVs, 2000-2014

Cases per 1,000 VT Months

- Caribbean
- East and South Asia
- Central America
Results

Incidence Rates of Dengue Among PCVs, 2000-2014

- Caribbean
- Central America
- East and South Asia
- Pacific Islands

Cases per 1,000 VT Months
Results

Incidence Rates of Dengue Among PCVs, 2000-2014

Cases per 1,000 VT Months


Caribbean
Pacific Islands
East and South Asia
South America
Central America
### 2000: Number of Reported Cases of Dengue & Dengue Hemorrhagic Fever (DHF), Region of the Americas (by country)

**Provisional figures for confirmed or suspected cases, to week noted by each country**

<table>
<thead>
<tr>
<th>Country</th>
<th>Date of Report</th>
<th>D &amp; DHF</th>
<th>Incidence</th>
<th>Serotype</th>
<th>DHF</th>
<th>Deaths</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>Week 47</td>
<td>1,700</td>
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<td>0</td>
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<td>Bolivia</td>
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<td>73</td>
<td>0.88</td>
<td>Den 1, 2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Brazil</td>
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<td>231,471</td>
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<td>Den 1, 2, 3</td>
<td>59</td>
<td>3</td>
<td>170,115</td>
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<tr>
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<td>Week 52</td>
<td>22,775</td>
<td>53.81</td>
<td></td>
<td>1,819</td>
<td>19</td>
<td>42,321</td>
</tr>
<tr>
<td>Costa Rica**</td>
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<td>4</td>
<td>0</td>
<td>1,129</td>
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<tr>
<td>Cuba</td>
<td>Week 52</td>
<td>138</td>
<td>1.23</td>
<td>Den 3, 4</td>
<td>0</td>
<td>0</td>
<td>11,201</td>
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<tr>
<td>Dominican Republic</td>
<td>Week 52</td>
<td>3,462</td>
<td>40.75</td>
<td>Den 1, 2, 3, 4</td>
<td>58</td>
<td>6</td>
<td>8,495</td>
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<tr>
<td>Ecuador</td>
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<td>22,937</td>
<td>181.38</td>
<td>Den 1, 2, 3, 4</td>
<td>3</td>
<td>1</td>
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<tr>
<td>El Salvador</td>
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<td>51.75</td>
<td>Den 2 (Jam)</td>
<td>411</td>
<td>26</td>
<td>6,276</td>
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<tr>
<td>Guatemala</td>
<td>Week 52</td>
<td>9,006</td>
<td>79.10</td>
<td>Den 2</td>
<td>42</td>
<td>9</td>
<td>11,385</td>
</tr>
<tr>
<td>Haiti</td>
<td>Nil</td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
<td>0</td>
<td>8,222</td>
</tr>
<tr>
<td>Honduras</td>
<td>Week 52</td>
<td>13,642</td>
<td>210.36</td>
<td>Den 2</td>
<td>314</td>
<td>10</td>
<td>6,485</td>
</tr>
</tbody>
</table>
Results

Ratio of Dengue Incidence Among PCVs Compared to WHO Reported Dengue Incidence

- Dominican Republic
- Nicaragua
- Philippines
Risk Among Travelers

- A cohort study of Dutch travelers to Asia in 2002 reported an dengue incidence rate of 30.0 cases per 1,000 person-months (7)

- A study conducted in 2013 among long-term aid workers from New Zealand reported a dengue incidence rate of 3.4 cases per 1,000 person-months (31)
Risk Among Travelers

• Bhatt et al. compiled data from 27 cohort studies and determined a mean dengue incidence rate of 129.7 cases per 1,000 person-years (10.8 per 1,000 person-months) (2)

• Multiple cohort studies involving short-term American missionary trips to the Caribbean have reported dengue infection in 25% or more of travelers (20, 21, 26)
Risk Among Travelers

- The increased risk among PCVs could potentially be explained by their lack of previous exposure.

- A study conducted in 2006 in Nicaragua found that the overall seroprevalence of dengue antibodies among school-aged children was 91% (1).

- A similar study in the Dominican Republic reported that 98% of adults and 56% of children under 10 were positive for dengue IgG antibodies (35).
Underreporting

- Underreporting is a major issue in dengue surveillance.

- In 2010, there were an estimated 96 million clinically apparent dengue cases globally; only 2.2 million cases were reported to the WHO.
Underreporting

• Most dengue surveillance is passive and many countries do not require reporting of dengue cases in adults

• The Nicaraguan Pediatric Dengue Cohort Study identified an average of 21.3 times more dengue cases per 100,000 persons per year than the Nicaraguan Ministry of Health (27)

• Vong et al. estimated that there was as high as a 30-fold degree of under-recognition and underreporting of dengue in Cambodia between 2006 and 2008 (32)
Other Explanations

- Differences in treatment seeking behavior
- Demographic and genetic differences between PCVs and host country nationals
- Differences in use of personal protection to avoid mosquito bites
- Dengue testing may be more readily available to PCVs
- PCMOs may be more inclined to test for dengue than other physicians
Conclusions

- The incidence rate of dengue among PCVs globally appears to follow a 3-year cyclical pattern.

- Each region demonstrated a unique pattern in dengue incidence rates over the 15-year study period.

- Peace Corps Volunteers serving in the Caribbean appear to be at the highest risk for contracting dengue.

- Countries with the highest cumulative incidence rates appear to be geographically clustered within each region.
Conclusions

• The rate of dengue infection among PCVs appears to be higher than the rate reported among host country nationals in high-incidence countries. Explanations:
  – Lack of previous exposure to dengue
  – Underreporting

• The distribution of dengue is ever-changing

• Continued surveillance is critical for understanding transitions in disease patterns and informing public health decision making
Next Steps

• Continued monitoring of dengue incidence among PCVs in order to inform decision making when a vaccine becomes available

• PCMEDICS
  – Information about demographics, comorbidities, and hospitalization of dengue patients

• Education for PCVs
  – Adherence to mosquito control is currently the only way to reduce dengue incidence
  – This data may eventually be available for prospective Peace Corps Volunteers
Questions?
References

References

References


