Tropical Troubleshooting: What You Need to Know About Dengue, Ebola, and Zika
Target Audience: Pharmacists
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Activity Type: Knowledge-based
Disclosures

Jeff Goad, Pharm.D., MPH is on advisory boards with Merck, GSK and Sanofi-Pasteur and on the speakers bureau for Merck.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Explain the routes of transmission, clinical features, and available treatment options for selected tropical diseases, including dengue, Ebola, and Zika.
2. Identify resources to educate patients about current recommendations for preventing the transmission of dengue, Ebola, and Zika viruses.
3. Discuss the status of vaccine development for the prevention of dengue, Ebola, and Zika.
1. Assessment Question

Which disease is spread by blood contact primarily

A. Dengue
B. Chikungunya
C. Ebola
D. Zika
2. Assessment Question

What is the best way to prevent Dengue infection in travelers?
A. Dengue vaccine
B. Insect repellant
C. Avoiding nighttime exposure
D. Chemoprophylaxis
3. Assessment Question

Which mosquito borne disease can have a hemorrhagic presentation?
A. Ebola  
B. Dengue  
C. Chikungunya  
D. Zika
4. Assessment Question

Which of the following diseases have a vaccine licensed for use outside of the U.S.?
A. Zika  
B. Dengue  
C. Chikungunya  
D. Ebola
Tropical Disease by Route of Transmission

- **Vector**: Dengue, CHK, Zika
- **Food/Water**: Ebola
- **Blood**: Ebola
- **Zoonotic**: Ebola
- **Respiratory**: Ebola
Mosquito Borne Diseases in Travelers

- Malaria
- Yellow Fever
- Dengue
- CHK
- Zika

- Anopheles spp
- Aedes spp

Vaccine Preventable
Dengue Fever and Chikungunya

- Genus *flavivirus*

- Dengue – “Break-bone fever”
  - 40% of world's population at risk
  - 50-100 million cases/year

- Chikungunya – “That which bends up”
  - An African virus + an Asian mosquito = outbreak in India
  - Impact of the global village

- Viral disease

<table>
<thead>
<tr>
<th>Dengue</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-limiting</td>
<td>Similar</td>
</tr>
<tr>
<td>Fever, joint/muscle pain</td>
<td>Similar</td>
</tr>
<tr>
<td>2-3 weeks</td>
<td>Weeks to yrs</td>
</tr>
<tr>
<td>DHF (30% mortality)</td>
<td>Not fatal</td>
</tr>
</tbody>
</table>

- Mosquito borne, daytime biter, urban primarily
- NO U.S. Vaccine
- NO specific treatment, use DEET and/or permethrin

*Aedes aegypti, CDC 2005*
Aedes aegypti and Aedes albopictus are two highly efficient vectors for dengue.

**Dengue transmission cycle**

1. **First infection (one serotype)**
   - Human infects mosquito
   - Mosquito infects human

2. **Second infection (different serotype)**
   - Human infects mosquito
   - Mosquito infects human

**Co-infection with multiple dengue**

- Mosquitos can harbor multiple serotypes
- Simultaneous transmission of >1 serotype may occur, however there are currently no conclusive data
- Individuals can be co-infected with >1 serotype
- Disease outcomes may be altered but it is currently unknown if this leads to more severe disease

**Co-infection with other**

- Co-infection with two other diseases transmitted by Aedes mosquitos, chikungunya and Zika, has been observed
- The number of reported co-infections is limited
- Data are inconclusive on whether the severity of illness is increased

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**DENGUE ± WARNING SIGNS**

- **WHO, 2016**

**SEVERE DENGUE**

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

**CRITERIA FOR DENGUE ± WARNING SIGNS**

**Probable dengue**
- live in / travel to dengue endemic area.
- Fever and 2 of the following criteria:
  - Nausea, vomiting
  - Rash
  - Aches and pains
  - Tourniquet test positive
  - Leukopenia
  - Any warning sign

**Laboratory-confirmed dengue**
(important when no sign of plasma leakage)

**Warning signs***
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count
* (requiring strict observation and medical intervention)

**CRITERIA FOR SEVERE DENGUE**

- **Severe plasma leakage**
  - leading to:
    - Shock (DSS)
    - Fluid accumulation with respiratory distress

- **Severe bleeding**
  - as evaluated by clinician

- **Severe organ involvement**
  - Liver: AST or ALT ≥ 1000
  - CNS: Impaired consciousness
  - Heart and other organs
Dengue throughout Latin America

Dengue incidence rates in the Americas in 2015
(per 100,000 population)
Incidence rate is based on probable cases of dengue and severe dengue reported to the authorities.

In 2014 → 1,176,529 cases of dengue, 16,238 severe dengue cases and 761 deaths

Although dengue affects people of all ages, the majority of cases occur in pre-adolescence through to adulthood.

In the past 5 years, >75% of dengue cases in Brazil, Mexico and Thailand occurred in those aged ≥10 years\(^1,3,4\)*

*Proportion of dengue cases by age and country based on epidemiological surveillance data on dengue. Data available from Ministries of Health. Data retrieved 7 October 2015.

**CYD-TDV (Dengvaxia)**

- Not licensed in the U.S.
  - 19 countries have licensed in SE Asia and South America
- Live attenuated, tetravalent
  - Develops immunity to all 4 types of DENV
  - Uses a Yellow Fever virus backbone
  - 0, 6 and 12 months for ≥ 9 years old
  - VE 59.2% for dengue and 79.1% severe dengue
- Not likely to be useful for the U.S.
  - Most effective when given to seropositive DENV recipients
  - May increase the risk of severe dz in seronegative
    - “Philippines gripped by dengue vaccine fears” – Feb 2018, BBC

The virus occurs as four distinct serotypes (DENV-1–4), all of which can cause disease.

[Diagram showing the progression of infections and vaccine effectiveness]
Zika Virus (Zika)

- Genus *flavivirus*

- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses

- Primarily transmitted through the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*)
  - City dwelling mosquito
  - Day time biter
## Symptoms of Tropical Mosquito-related Viral Infections

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Zika, n=31</th>
<th>Dengue, n=127</th>
<th>Chikungunya, n&gt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>90%</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>Fever</td>
<td>65% (low)</td>
<td>72% (high)</td>
<td></td>
</tr>
<tr>
<td>Arthritis or arthralgia</td>
<td>65%</td>
<td>89%</td>
<td>90%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>55%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>48%</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>39%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>10%</td>
<td>78%</td>
<td>45%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0%</td>
<td>68%</td>
<td>5%</td>
</tr>
</tbody>
</table>

NEJM 2009;360:2536-43  
J Clin Vir 2014; 61: 365–370  
Incubation and viremia

- Incubation period for Zika virus disease is 3–14 days
- Zika viremia ranges from a few days to 1 week
- Some infected pregnant women can have prolonged viremia
- Virus remains in semen and urine longer than in blood
### Men and women with possible Zika exposure

Possible exposure via recent travel or sex without a condom with a partner infected with Zika

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use condoms for at least</strong></td>
<td>Use condoms for at least 8 weeks after travel or start of symptoms (or diagnosis)</td>
<td>Use condoms for at least 6 months after travel or start of symptoms (or diagnosis)</td>
</tr>
</tbody>
</table>
Pregnant women

- Should not travel to areas with Zika
- Should consider postponing nonessential travel to Southeast Asia, where Zika is endemic
- If they must travel to areas with Zika, pregnant women should protect themselves from mosquito bites and take steps to prevent sexual transmission during and after travel
Congenital Zika syndrome

**Congenital Zika syndrome** is associated with five types of birth defects that are either not seen or occur rarely with other infections during pregnancy:

- **Severe microcephaly** (small head size) resulting in a partially collapsed skull
- **Decreased brain tissue** with brain damage (as indicated by a specific pattern of calcium deposits)
- **Damage to the back of the eye** with a specific pattern of scarring and increased pigment
- **Limited range of joint motion**, such as clubfoot
- **Too much muscle tone** restricting body movement soon after birth
Mosquito bite protection

- Insect repellents
  - DEET (30-35%)
  - Picaridin (20%)
  - IR3535 (20%)
  - oil of lemon eucalyptus (30%) or PMD
  - 2-undecanone
- All safe in pregnancy with proper use
- Do not spray repellent on the skin under clothing
- Wash off when not needed
- If you are also using sunscreen, apply sunscreen before applying insect repellent
- Apply permethrin (0.5%) to clothing for extra protection
Ebola
Ecology

**Animal-to-Animal Transmission**
Evidence suggests that bats are the reservoir hosts for the Ebola virus. Bats carrying the virus can transmit it to other animals, like apes, monkeys, and duikers (antelopes), as well as to humans.

**Spillover Event**
A “spillover event” occurs when an animal (bat, ape, monkey, duiker) or human becomes infected with Ebola virus through contact with the reservoir host. This contact could occur through hunting or preparing the animal’s meat for eating.

**Human-to-Human Transmission**
Once the Ebola virus has infected the first human, transmission of the virus from one human to another can occur through contact with the blood and body fluids of sick people or with the bodies of those who have died of Ebola.

**Survivor**
Ebola survivors face new challenges after recovery. Some survivors report effects such as tiredness and muscle aches, and can face stigma as they re-enter their communities.
### Ebola Outbreaks

**Guinea, Liberia and Sierra Leone (40%)**

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Country</th>
<th>Ebola subtype</th>
<th>Reported number of human cases</th>
<th>Reported number (%) of deaths among cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>May – July 2017</td>
<td>Democratic Republic of the Congo</td>
<td>Ebola virus</td>
<td>8</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>August-November 2014</td>
<td>Democratic Republic of the Congo</td>
<td>Ebola virus</td>
<td>66</td>
<td>49 (74%)</td>
</tr>
<tr>
<td>March 2014-2016</td>
<td>Multiple countries</td>
<td>Ebola virus</td>
<td>28,616</td>
<td>11,310 (40%)</td>
</tr>
</tbody>
</table>

https://www.cdc.gov/vhf/ebola/index.html
Ebola Presentation

- 5 known species of Ebola (a Filovirus)
- Transmission
  - blood or body fluids
  - objects (like needles and syringes)
  - infected fruit bats or primates
  - possibly from contact with semen from a man who has recovered from Ebola
- Symptoms appear 2 to 21 days after exposure to Ebola
  - Fever, nausea, vomiting, bleeding

When is someone able to spread the disease to others?

A person is only contagious after Ebola symptoms begin.

After 21 days, if an exposed person does not develop symptoms, they will not become sick with Ebola.

It is possible that Ebola can be spread through semen from men who have survived.

cdc.gov/ebola
Ebola Vaccines

- 15 Ebola vaccines in development
- rVSV-ZEBOV
  - recombinant Vesicular Stomatitis Virus *Zaire ebolavirus* vaccine
  - Cannot transmit Ebola
  - 100% effective (1 outbreak, no control group), Phase 3 trial
  - 1 dose IM
  - Not approved in the U.S.
- ChAd3-ZEBOV
  - Recombinant chimpanzee adenovirus expressing Ebola glycoprotein
  - Cannot transmit Ebola
  - In Phase I/II trials, uses a prime then boost strategy

https://www.cdc.gov/vhf/ebola/strive/qa.html
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Question and Answer Session