Zika, chikungunya, dengue and the work-related traveler

Emerging and Re-Emerging Occupational and Environmental Exposure and Disease and Updates in Occupational and Environmental Medicine

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Disclosures

• I have nothing to disclose

Arboviral diseases and the traveler

• Arboviruses are RNA viruses that are transmitted to humans and other species primarily through the bites of infected mosquitoes, ticks, sand flies and midges
  • Arbovirus is a general term and reflects transmission routes rather than taxonomy
  • Can also be transmitted through blood transfusion, organ transplantation, perinatally (including through breastfeeding), sexually and through laboratory accidents
• Endemic in most of the tropical and subtropical world, including the United States and California
Arboviral diseases of public health significance

- More than 130 are known to cause human disease
- Most belong to four families:
  - Flaviviridae
  - Togaviridae
  - Bunyaviridae
  - Rhabdoviridae
- Arboviral infections can range from asymptomatic to acute febrile rash illness to encephalopathy and death
- Divided into two forms:
  - Neuroinvasive
  - Non-neuroinvasive
- California serogroup viruses
  - Chikungunya
  - Dengue virus
  - Eastern equine encephalitis
  - Japanese encephalitis
  - Powassan virus
  - St. Louis encephalitis
  - West Nile virus
  - Western equine encephalitis
  - Yellow fever
  - Zika virus

Zika Virus a Global Health Emergency, W.H.O. Says

Short Answers to Hard Questions About Zika Virus

Epidemiology of Zika virus

- Discovered in 1947 in a rhesus monkey at the Uganda Virus Research Institute as part of studies of sylvatic yellow fever
- The first human cases were reported in Nigeria in 1968
- Before 2007, ZIKV was known to exist as a mild viral illness of humans in a broad band from West Africa across South and Southeast Asia to the Philippines and Indonesia corresponding to the Old World distribution of Aedes spp
**Epidemiology of Zika virus infection, 1947-2007**

![Map of Zika virus transmission](image)

**Flaviviridae family**

- Flavivirus
  - West Nile virus
  - Japanese encephalitis virus
  - St. Louis encephalitis virus
  - Dengue virus
  - Yellow fever
  - Zika virus
  - Tick-borne encephalitis virus

- Hepacivirus
  - Hepatitis C virus

- Pegivirus
  - GBV-C (hepatitis G)

- Pestivirus
  - Hog cholera

**Zika virus transmission**

- Single-stranded RNA virus
- Primarily mosquito-borne
  - *Aedes aegypti*, *Ae. africanus*, *Ae. apicoargenteus*, *Ae. vitattus*, *Ae. furcifer*, *Ae. polynesiensis*
- From infected mother to her fetus
- Blood transfusion
- Sexual transmission

*Figure 1. Map of Zika virus transmission in countries with evidence of Zika virus infection in humans prior to 1 April 2016.*

**Aedes aegypti**

- Zika and dengue transmitted by infected female mosquito
- Primarily a daytime feeder
  - *Therefore, bed nets provide no protection*
- Lives in and around human habitation
- Lays eggs and produces larvae preferentially in artificial containers

**Aedes aegypti breeding sites**

**Distribution of Ae. aegypti**

[Map showing distribution of Ae. aegypti]
Zika virus clinical manifestations

• 80 percent of infections are asymptomatic
• When symptomatic, generally mild
  • Fever
  • Rash
  • Arthralgia
  • Conjunctivitis
• Lasts several days to a week
• No specific treatment, avoid aspirin in children
• No NSAIDs until dengue is ruled out to avoid hemorrhagic complications

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**Table 1. Clinical Characteristics of 31 Patients with Confirmed Zika Virus Disease on Yap Island during the Period from April through July 2007.**

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular rash</td>
<td>28 (90)</td>
</tr>
<tr>
<td>Fever*</td>
<td>20 (65)</td>
</tr>
<tr>
<td>Arthritis or arthralgia</td>
<td>20 (65)</td>
</tr>
<tr>
<td>Nonpurulent conjunctivitis</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Edema</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

* Cases of measured and subjective fever are included.

Clinical Manifestations of ZIKV

Images courtesy of Dr. Sáfadi, FCM da Santa Casa de São Paulo

Recent epidemiology of Zika

• The first cases outside of Africa and Asia were described in an outbreak on Yap Island in the Marianas in 2007
• ZIKV spread across the Pacific and reached Easter Island in 2014
• Continuing outbreaks in the Pacific (New Caledonia and American Samoa)
• First cases in Brazil in May 2015
• Spread across almost all of Latin America and the Caribbean including southern Florida, following the range of Aedes
• WHO declared a "Public Health Emergency of International Concern" on 1 February 2016
  • Ended 18 November 2016 as containment moved to longer-term strategy
Comparison of Zika virus outbreaks in Yap, French Polynesia and Brazil

<table>
<thead>
<tr>
<th></th>
<th>Yap World/Polynesia</th>
<th>French Polynesia</th>
<th>Brazil (Maricá and Macaé)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>20k</td>
<td>300k</td>
<td>248,604,000</td>
</tr>
<tr>
<td>Confluent cases</td>
<td>45</td>
<td>106</td>
<td>107</td>
</tr>
<tr>
<td>Estimated attack (% of population)</td>
<td>5% (5%)</td>
<td>30% (30%)</td>
<td>30% (30%)</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Rash, fever, arthritis, conjunctivitis</td>
<td>Rash, fever, arthritis, conjunctivitis</td>
<td>Rash, fever, arthritis, conjunctivitis</td>
</tr>
<tr>
<td>Lab confirmation</td>
<td>2</td>
<td>6</td>
<td>17</td>
</tr>
</tbody>
</table>

Reported complications of Zika virus infection

- Microcephaly
- Guillain-Barré syndrome
- Thrombocytopenic purpura
- Leukopenia

In French Polynesian outbreak in 2013, of 10,000 registered cases, there were 70 (0.7%) severe cases.
Zika virus in pregnancy

- 88 pregnant Brazilian women with new rash of ≤5 days
- 72 positive for ZIKV, 16 negative
- Fetal ultrasonography in 42 ZIKV+ and all ZIKV-
  - 12/42 v 0/16 fetal abnormalities
- Adverse findings
  - 2 fetal deaths (36, 38 wks)
  - 5 IUGR with or without microcephaly
  - 7 ventricular calcifications or other CNS lesions
  - 7 oligohydramnios or decreased umbilical artery flow

Microcephaly

- Abnormally small cranial vault secondary to abnormal brain growth
- Clinical manifestations
  - Seizures, developmental delay, intellectual disability, problems with movement and balance, dysphagia, hearing and vision loss
- Incidence 2-12/10,000 live births in the U.S.
- Causes
  - Infection (rubella, toxoplasmosis, cytomegalovirus)
  - Severe malnutrition
  - Toxic exposures (e.g., alcohol)

Congenital Zika syndrome

1. Severe microcephaly (>3 SD below mean)
   - Fetal brain disruption syndrome
2. Brain anomalies
   - Subcortical calcifications
3. Ocular anomalies
4. Congenital contractions
   - Arthrogryposis
5. Marked early hypotonia and signs of extrapyramidal involvement


Two theories on the genesis of Zika-associated microcephaly and Guillain-Barré syndrome

• Genetic change with greater neurotropism and greater potential for epidemic spread

• Insufficient power in earlier reports to detect rare statistical events

ZIKV phylogeny of African-Asian/Pacific and Latin American virus isolates, including mapping of amino acid substitutions

**Sexual transmission**

- 33 U.S. cases of male-to-female transmission as of 26 October 2016
  - Intercourse few days before onset of symptoms
  - In 2 cases, men were asymptomatic
  - 1 case of female-male transmission
  - 5 cases of replication-competent Zika virus isolated from semen 69 days after illness onset (persisted longer than in blood)
  - CDC recommends abstinence or condoms for men who may have been exposed and their pregnant sexual partners
  - Unknowns:
    - Duration of carriage of replication-competent ZIKV in semen, blood

**Additional preventive measures for Zika virus infection**

- Avoid areas with active transmission
- Avoid or postpone pregnancy in living in an endemic area (five countries)
- Condoms if potential for sexual exposure
- Immunization
  - Three strategies being pursued at NIAID:
    - DNA vaccine (strategy similar to WNV vaccine)
    - Attenuated live virus vaccine (similar to dengue vaccine)
    - Genetically engineered VSV (similar to Ebola vaccine)
- Natural infection to achieve immunity before becoming pregnant
- As far as we know, immunity following infection is life long
- Herd immunity (some evidence from Polynesia)
  - This might happen in some Caribbean islands

**Chikungunya virus**
Chikungunya virus

- Mosquito-borne viral disease characterized by acute onset of fever with severe arthralgias
- Single-stranded RNA virus
- Member of the Togaviridae family and the Alphavirus genus
  - Togaviridae also contain rubella virus
  - Alphaviruses included eastern equine encephalitis, Venezuelan encephalitis and western equine encephalitis
  - Chikungunya is part of the Semliki Forest virus complex
- First isolated in Tanganyika in 1953

Chikungunya epidemiology

- Distribution follows habitat of Ae. aegypti and Ae. albopictus
- Occurs in large outbreaks with high attack rates
  - Large outbreak in the Indian Ocean basin in 2005-2008
    - 1.4 million cases in India alone
    - Hundreds of cases imported to Europe and North America
  - Autochthonous transmission in Italy with 292 cases
  - More recent outbreaks in the Americas
    - First case in December 2013 in Saint Martin
    - 1.5 M cases by June 2015
    - 185 000 reported in 2017

Countries with reported local transmission of chikungunya virus
Chikungunya virus transmission

- Transmitted by *Aedes aegypti* and *Ae. Albopictus*
- Yes, this is the same vector as Zika virus (and, as we’ll see for dengue virus)
- Mosquito feeds in the *daytime*
- Other means of transmission
  - Intrapartum (in utero transmission results in spontaneous abortion)
  - Parenteral (blood transfusion, organ transplantation, needlestick injuries)
  - No evidence of breastmilk transmission
Chikungunya virus clinical symptoms

- Majority (72%–97%) of infected people symptomatic
- Incubation period usually 3–7 days (range 1–12 days)
- Primary clinical symptoms are fever >39º and polyarthralgia
- Arthralgia usually bilateral and symmetric
- Pain can be severe and debilitating
- Other symptoms
  - Headache, myalgia, arthritis, conjunctivitis, nausea/vomiting, or maculopapular rash
- Deaths are rare (consider dengue)

Chikungunya virus clinical course

- Symptoms usually resolve within 7–10 days
- Rare complications can include uveitis, retinitis, myocarditis, hepatitis, nephritis, bullous skin lesions, hemorrhage, meningoencephalitis, myelitis, Guillain-Barré syndrome, and cranial nerve palsies
- Relapsing polyarthralgia, polyarthritis, tenosynovitis (12%)

Dengue, dengue hemorrhagic fever and dengue shock syndrome
**Dengue virus**

- Single-stranded RNA flavivirus
- Has 4 serotypes (DEN-1, 2, 3, 4)
- Transmitted primarily by *Aedes aegypti* and *Ae. albopictus*
- Can also be transmitted by blood transfusion or organ transplantation
- Each serotype provides specific lifetime immunity, and short-term cross-immunity
- All serotypes can cause severe and fatal disease
  - Dengue fever
  - Dengue hemorrhagic fever
- Some genetic variants within each serotype appear to be more virulent or have greater epidemic potential

**Epidemiology of dengue virus**

- Endemic in most of the tropical and sub-tropical world
- Can occur in epidemics during peak mosquito breeding seasons
- Probably originated in Africa and Southeast Asia and emerged after World War II
- WHO estimates 50-100 million cases per year with 500,000 cases of DHF and 22,000 deaths (in children primarily)

**Burden of dengue virus by continent, 2010**

<table>
<thead>
<tr>
<th>Continent</th>
<th>Dengue fever (millions)</th>
<th>Asymptomatic and mildly symptomatic infections (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>15.7</td>
<td>48.4</td>
</tr>
<tr>
<td>Asia</td>
<td>66.8</td>
<td>204.4</td>
</tr>
<tr>
<td>Americas</td>
<td>13.3</td>
<td>40.5</td>
</tr>
<tr>
<td>Oceania</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Global</td>
<td>96</td>
<td>293.9</td>
</tr>
</tbody>
</table>

Dengue and dengue hemorrhagic fever in the Americas, 1980-2007

Since 2014, 6,319,395 cases have been reported from 49 countries in the Americas
- Brazil: 3,989,289
- Columbia: 326,546
- Mexico: 549,208
- Nicaragua: 237,768

Clinical manifestations
- Acute febrile illness – varies in severity over a 5 to 7-day period
- Symptoms appear 2 to 7 days after being bitten
- Characterized by fever with ≥2 other symptoms:
  - Headache and retro-orbital pain
  - Arthralgia
  - Myalgia
  - Rash
  - Mild bleeding (nose or gums)
  - Neutropenia
- Infection with one subtype of dengue virus confers lifelong immunity against that subtype only
- May be partial or temporary cross-immunity to other serotypes but...
- Risk of severe complications increase with infection with other serotypes
- Dengue fever can progress to dengue hemorrhagic fever
- Pathophysiology is plasma leak with thrombocytopenia

Warning signs that may occur at or after onset of illness:
- Persistent vomiting
- Clinical shock (accompanied by hypotension or syncopal event)
- Hemothorax/pleural effusion
- Liver or renal failure
- Convulsions
- Increased intracranial pressure with rapid decrease in platelet count
Clinical manifestations
• Dengue hemorrhagic fever
  • Follows three phases: febrile phase, critical (plasma leak) phase and convalescent (reabsorption) phase
  • Treatment is supportive and designed to avoid hypovolemic shock
• Critical phase occurs at defervesence and lasts 24-48 hours
• Gradual recovery with reabsorption of extravasated fluids
• Can proceed to frank hypovolemic shock and massive gastrointestinal hemorrhage (dengue shock syndrome)
• Treated DHF has case fatality rate of 2-5%, untreated 50%

Prevention of Zika, Chikungunya and dengue virus infections in travelers
• Understand risk of exposure: https://wwwnc.cdc.gov/travel/
• Primary strategy is avoidance of Aedes spp. bites
  • No travel in some cases (e.g., pregnancy)
  • Long-sleeved shirts and pants
  • Permethrin-treated clothing
• Because Aedes spp. bite during the day, sleeping under bed nets is ineffective
• Mosquito repellants
• Other measures
  • Stay in places with air conditioning or window screens
  • If staying long term, clean up environmental water around houses and control mosquitoes in and around housing
• Dengvaxia (CYD-TDV, Sanofi Pasteur) registered in Mexico in 2015 — live recombinant tetravalent dengue vaccine given as a 3-dose series (0/6/12 months)
• Only for use in endemic countries, not yet approved for travelers in the United States

Distribution of *Ae. aegypti*
Mosquito repellents

DEET, picaridin and IR 3535 are safe to use during pregnancy
* EPA search tool for commercially available repellents: https://www.epa.gov/insect‐repellents/find‐repellent‐right‐you

Conclusions

• These three arboviral infections are very common in the tropical and subtropical world
• They are co-circulating in Latin America and the Caribbean
• Infection in travelers is common in U.S. travelers
  • 425 cases of Zika virus in 2017
  • 951 cases of dengue virus in 2015
  • 905 cases of imported Chikungunya
• Primary strategy is avoiding Aedes bites

MOC Questions

• Which of the following is not recommended for preventing Zika, Chikungunya and dengue virus infection in travelers to endemic areas:
  A. Sleeping under insecticide-treated bed nets
  B. DEET
  C. Picardin
  D. Staying in accommodations with window screens or air conditioning

• Which of the following is not a warning sign of possible dengue hemorrhagic fever following defervescence from dengue fever:
  A. Abdominal pain or tenderness
  B. Ascites
  C. Mucosal bleeding
  D. Disorientation

• Which of the following is not a reported complication of Zika virus infection:
  A. Microcephaly
  B. Severe chorioretinopathy and polyneuritis
  C. Guillain–Barré syndrome
  D. Conjunctivitis