Zika, Dengue, and Chikungunya Viruses in the Americas—Oh My!

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Outline
• A bit of virology and epidemiology
• Infection and Disease from the "Old" Arboviruses
  • Dengue [DEN]
  • Chikungunya [CHIKV]
• Zika virus [ZIKAV] Infection and Disease
  • What is it?
  • Why & what should we know about it?
  • Mothers and children and ZIKAV
  • What should we advise our patients?

Some Mosquito-Borne Arboviruses

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunyaviridae</td>
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<td>CEE, LaCrosse, Jamestown Canyon, Rift Valley Fever</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td></td>
<td>Dengue, YF, WNV, SLE, JEV, Murray Valley, Omsk HF, Kyassnu Forest, Sepik, Spondweni, Zika</td>
</tr>
<tr>
<td>Togaviridae</td>
<td>Alphavirus</td>
<td>EEE, VEE, WEE, Ross River, Sindbis, Semliki Forest, O’nyong-nyong, CHIKV</td>
</tr>
</tbody>
</table>
Transmission Cycles:  
--Direct or Vector-borne  
--Anthroponotic or Zoonotic

Arboviruses:  
Vector-borne, but can be anthroponotic or zoonotic

YF, WNV, ZIKAV:  
Zoonotic in wild [sylvatic cycle]  
Anthroponotic in urban settings [urban cycle]

Major Mode of Transmission—*Aedes* spp. Mosquitos

Mosquito vectors:  
- *Aedes aegypti*  
- *Aedes albopictus*

Same vectors transmit DEN, CHIKV, ZIKAV

Widely distributed throughout the tropics  
Aggressive daytime biters, multiple feeds
Dengue Fever Virus

Dengue infection:
Often asymptomatic, but if with symptoms, may be severe!
**DENV Clinical course**

- Asymptomatic or mild febrile illness—most!
- "Breakbone fever"
- DHF
- DSS

**Dengue Warning Signs**

- Sunburn Rash
- Tourniquet sign
CHIKV activity, 2013—late 2015

CHIKV
- Majority (72%–97%) of infected people develop clinical symptoms
- Between 3% and 28% of persons with antibodies to CHIKV have asymptomatic infections.
- Incubation period usually 3–7 days (range 1–12 days)
- Primary clinical symptoms are fever and polyarthralgia; some joint findings persist [“bending over fever”]

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<th>Clinical and laboratory features</th>
<th>Chikungunya virus infection</th>
<th>Dengue virus infection</th>
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<tbody>
<tr>
<td>Fever (≥102°F or ≥39°C)</td>
<td>***</td>
<td>++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>***</td>
<td>±/±</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Rash</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Breathing dysnesia</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>

*When frequency of symptoms from studies where the two diseases were directly compared among patient seeking care: *** = 70–100% of patients; ++ = 40–70%; ±/± = 10–40%; ± = 5–10%; - = 0–5%.
Zika Virus--History

• April 1947: Rockefeller Foundation jungle YF Research Program in Zika Forest, Uganda [near Entebbe]--caged rhesus monkey #766 becomes ill with a transmissible non-YF agent, later named Zika virus [GW Dick et al]

• 1964: 1st well-described human case [DI Simpson's own case]

• 1951-1981: serostudies in East, West Afr & Asia show 10% to 40% of population in some areas Aby, but <20 cases known in people!

• April 2007: Major outbreak [66% of pop. of 7,500] in Yap, Fed States of Micronesia

• 2013-2014: Even bigger outbreak, French Polynesia [66% of pop. of 270,000]

• 2015-2016: South America [esp. Brazil]; between 440,000 and 1.3 million est. cases!

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Yap, Micronesia Outbreak 2007

• 11,241 inhabitants across several islands; 7391 on Yap itself; ~5,000 likely infected
• Household survey: 74% IgM positive, but likely only 20% of them attributable clinical illness recalled
• No deaths, mild illness of several days' duration
• 90% rash; 65% fever; 55% non-purulent conjunctivitis; 40-50% each with myalgia, ha, retro-orbital pain
• Too few pregnant women to detect neonatal effects!
Zika: Clinical Illness

- Only about 20% of infected symptomatic
- Fever, rash (pruritic), conjunctivitis, arthralgia
- “Dengue-like”
- GBS...
- Fetal effects...

Reported Clinical Symptoms Among Confirmed Zika Virus Disease Cases

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosquito or popular rash</td>
<td>20</td>
<td>90%</td>
</tr>
<tr>
<td>Subjective fever</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20</td>
<td>65%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>17</td>
<td>50%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16</td>
<td>49%</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>45%</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>12</td>
<td>39%</td>
</tr>
<tr>
<td>Edema</td>
<td>6</td>
<td>19%</td>
</tr>
<tr>
<td>Ulcerating</td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>

Adapted from Calvet, et al. and from the Yap State Department of Health Services presentation.

Calvet GA et al., Curr Opin Infect Dis 2016, 29:439-446
DOI: 10.1097/QCO.0000000000003301

FIGURE 1. Nonpurulent conjunctivitis and facial edema.
FIGURE 2. Mosquito/arthralgia on the trunk.
What else is different about ZIKAV?
Other Modes of Transmission

- Maternal-fetal
  - Intrauterine
  - Perinatal
- Other
  - Sexual
  - Blood transfusion
  - Laboratory exposure
- Theoretical
  - Organ or tissue transplantation
  - Breast milk
Wherever it cam from, it’s here…but early reports overestimated microcephaly...

<table>
<thead>
<tr>
<th>Country</th>
<th>Specificity</th>
<th>Sensitivity</th>
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<tr>
<td>Brazil (1)</td>
<td>70%</td>
<td>90%</td>
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Wherever it cam from, it’s here…but early reports overestimated microcephaly...

França GVA et al

Medicine of the Highest Order

Figure 1: Intra- and interobserver variability of ultrasound at birth, showing the estimated number of fatal or high-probability, moderate- or low-probability, and unclassifiable cases.

França GVA et al

Medicine of the Highest Order

Figure 2: Prevalence overlap between Zika virus infection during pregnancy, reported cases, and microcephaly in newborns.

França GVA et al

Medicine of the Highest Order

Figure 3: Prevalence overlap between Zika virus infection during pregnancy, reported cases, and microcephaly in newborns.
Can we estimate risks/rates?
Retrospective data, French Polynesia 2013-2014

Guillain-Barre Syndrome

- ~100% of 42 cases pos. for ZIKAV antibodies, vs. ~50% of controls
- 88% of cases with ZIKAV-like illness 1 wk earlier
- Rate 0.24/1,000 ZIKAV infections, ~= to that following Campylobacter infections (~10X bg rate)

Neonatal Microcephaly

Zika Virus and Pregnancy

- Limited information is available
- Existing data show:
  - No evidence of increased susceptibility
  - Infection can occur in any trimester
  - Incidence of Zika virus in this population is not known
  - No evidence of more severe disease

Maternal-Fetal Transmission of Zika Virus

- Evidence of maternal-fetal transmission
  - Zika virus infection confirmed in infants with microcephaly in Brazil and in infants whose mothers have traveled to Brazil but delivered in the US
  - Zika virus RNA identified in specimens of fetal losses
  - Zika virus detected prenatally in amniotic fluid
    - Two women at ~30 weeks gestation with a history of symptoms consistent with Zika infection
    - Fetal microcephaly and intracranial calcifications detected on ultrasound
    - Amniotic fluid testing positive for Zika virus RNA by RT-PCR
- Evidence of perinatal transmission (during time of delivery)
  - Zika outbreak in French Polynesia 2013-2014
    - Two pregnant women with signs and symptoms consistent with Zika infection around the time of delivery
    - Both mothers tested positive for Zika virus RNA by RT-PCR
    - Zika virus infection was confirmed in the neonates, 1-3 days after delivery
    - Unlikely that neonates were exposed to mosquitoes
    - Outcomes regarding microcephaly was not reported
What is Microcephaly?
- Clinical finding of a small head when compared to infants of same sex and age
- Measured by head circumference (HC) or occipitofrontal circumference (OFC)
- Reliable assessment of intracranial brain volume
- Often leads to cognitive and/or neurologic issues
- Mechanisms
  - Primary due to abnormal development (often with a genetic etiology)
  - Secondary due to arrest or destruction of normally-forming brain tissue (by infection, vascular disruption)
- Difficult birth defect to monitor because of inconsistent definition and use of terminology

Infants with Microcephaly

Fetal Brain Disruption Sequence
- First described in 1984 but noted in earlier literature
- Brain destruction resulting in collapse of the fetal skull, microcephaly, scalp rugae and neurologic impairment
- Images below from 1990 series; phenotype appears to be present in some affected babies in Brazil (2015—present)

[Also joint abnormalities such as arthrogryposis]
CDC Recommendations:
Pregnant Women Considering Travel

- Pregnant women in any trimester should consider postponing travel to areas where Zika is present.
- Pregnant women who do travel to one of these areas should talk to their healthcare provider and strictly follow steps to avoid mosquito bites during the trip.
- Avoid mosquito bites:
  - Use EPA-registered insect repellent
    - DEET is considered safe to use in pregnant and lactating women.
  - Wear long-sleeved shirts and long pants to cover exposed skin.
  - Use Permethrin-treated clothes.
  - Stay and sleep in screened-in or air-conditioned rooms.
- Avoid mosquito bites mostly during the daytime.
- Practice mosquito prevention strategies throughout the entire day.

**UPDATED INTERIM PREGNANCY GUIDANCE:**

**Testing and interpretation recommendations:**

- Culture: Newborn infants with possible exposure to Zika virus.
- Enzyme-linked immunosorbent assay (ELISA): IgM, IgG.
- Real-time RT-PCR: Zika virus RNA.
- Zika virus IgM capture EIA: IgM.
- Zika virus IgG capture EIA: IgG.

**Clinical management of a pregnant woman with diagnosed Zika virus infection:**

**Presentation of Laboratory Results:**

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<th>Medical Management</th>
<th>Potential Management</th>
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<tbody>
<tr>
<td>Zika virus RNA detected</td>
<td>Live virus testing</td>
<td></td>
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<tr>
<td>Zika virus IgM detected</td>
<td>Live virus testing</td>
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</tr>
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**Potential management:**

- Live virus testing:
  - Prenatal care and monitoring
  - Palliative care for advanced disease

- No evidence of Zika virus detected:
  - Supportive care for advanced disease
  - Palliative care for advanced disease

**Potential management:**

- Supportive care for advanced disease
  - Palliative care for advanced disease
  - Symptomatic treatment for mild disease

**Live virus testing:**

- Prenatal care and monitoring
  - Palliative care for advanced disease
  - Symptomatic treatment for mild disease

**Zika virus IgM antibody detected:**

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  - Palliative care for advanced disease

**Zika virus IgG antibody detected:**

- Live virus testing
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  - Prenatal care and monitoring
  - Palliative care for advanced disease
**COC's Response to Zika**

**Counseling Travelers**

**When and Where**: Independence Day and any other stretching event.

**Guidelines**:

1. **Travelers should**:
   - Wear long sleeves and long pants, use insect repellent with a DENV-2 concentration of 20%, and cover open wounds.
   - Wash hands frequently and avoid touching their face.
   - Take antibiotics to prevent infections.
   - Use oral hygiene products to prevent infections.
   - Avoid contact with infected skin or mucous membranes.
   - Seek medical attention if symptoms persist.

2. **Travellers should not**:
   - Travel to areas where dengue is prevalent.
   - Visit health care facilities for care.
   - Seek medical attention if symptoms persist.

**www.cdc.gov/zika**

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**Figure**: Initial clinical evaluation and management of infants with laboratory evidence of Zika virus infection and associated neurodevelopmental abnormalities in the setting of congenital Zika syndrome.

- **Neurologists** should evaluate infants with primary care providers should receive monthly for at least 1 year of age.
- **Follow-up patients**: monitor developmental delay and growth milestones.
- **Psychological support**: provide emotional support, anticipatory guidance, and developmental services.
- **Orthopedics** and physical therapy for infants with orthopedic conditions.
- **Neurologists** or neurotherapists for infants with seizures.
- **Lactation consultants** and neonatologists for infants with feeding difficulties.
- **Pediatricians** and neurologists for infants with feeding difficulties.
- **Psychologists** and developmental specialists for emotional engagement.
- **Respiratory therapists** and developmental specialists for emotional engagement.

**Table**: Summary of guidelines for newborns with congenital Zika syndrome.

- **Vaccination**: Rubella, varicella, hepatitis B, and pneumococcal vaccines.
- **Follow-up**: monthly for at least 1 year of age.
- **Physical therapy**: for infants with orthopedic conditions.
- **Psychological support**: for infants with developmental delays.
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FIGURE 1. Number of confirmed and probable Zika virus disease cases reported from U.S. states and the District of Columbia — January 1–July 31, 2016

FIGURE 2. Number of confirmed and probable Zika virus disease cases reported from U.S. states and the District of Columbia, by month of illness onset and source of infection — January 1–July 31, 2016
Overall Summary

- Arbovirus infections [DEN, CHIKV, ZIKAV] have arrived and are likely to stay for a long while
- ZIKA has important different characteristics—fetal effects, sexual transmission, Guillain-Barre syndrome
- Information rapidly updating—see CDC publications, website for most recent:
  