What's Lurking Out There??????

Dave Warshauer, PhD, D(ABMM)
Deputy Director, Communicable Diseases
Wisconsin State Laboratory of Hygiene
david.warshauer@slh.wisc.edu
The Patient

- 33-year-old woman
- 11 weeks pregnant
- Presented with
  - Ocular pain
  - Myalgia
  - Mild fever which lasted for 5 days
  - Rash developed second day of fever
- Husband reported similar symptoms
History

- Travel
- Had been traveling the week before
- Guatemala
- Belize
- Mexico
- Onset 1 day after return home
- Reported mosquito bites, particularly in Guatemala
- Vaccinated against yellow fever virus 10 years earlier
Serology

- Serology----4 weeks after onset
- **Dengue** virus
  - IgG Pos, IgM Neg
- **Chikungunya** virus
  - IgG Neg, IgM Neg
- **Zika** virus
  - IgG Pos, IgM Pos
    - Acute or recent Zika virus infection
What about the fetus?

- Ultrasound at 16 and 17 weeks
- No evidence of microcephaly or intracranial calcifications.
- During 16 to 20 weeks
  - Decrease in head circumference
  - From 47th percentile at 16 weeks to 24th percentile at 20 weeks
- Zika virus detected in mother’s serum at 16 weeks gestation
  - Closely related to Guatemalan strain
The Fetus

- Ultrasound at 19 weeks gestation
  - Abnormal intracranial anatomy
- MRI at 20 weeks gestation
  - Diffuse atrophy of the cerebral mantle with other abnormalities
- Pregnancy terminated at 21 weeks
- Maternal serum positive for Zika RNA on the day before termination
  - $2.1 \times 10^3$ copies/ml
- Mother also positive at 4 weeks and 10 weeks after clinical onset
- PCR negative one day after termination
Zika Virus

- First identified in Uganda in 1947
- From the blood of a sentinel rhesus monkey during a study of sylvan cycle of yellow fever virus
  - Febrile illness
- Isolated from mosquitoes in 1948
  - *Aedes africanus*
Zika Virus

- Mosquito-borne single-stranded RNA flavivirus
  - 10,794 bases
  - Closely related to dengue, yellow fever, Japanese encephalitis and West Nile viruses.
  - 40 nm diameter
  - Icosahedral
  - Lipid enveloped
  - Neurotropic
Zika Virus Epidemiology

- Prior to 2007, only sporadic human cases reported from Africa and southeast Asia
  - Many cases and outbreaks likely not recognized
- 2007, first outbreak reported on Yap Island, Federated States of Micronesia
- 2013-2014, >28,000 suspected cases reported from French Polynesia
- May 2015, locally-acquired cases reported in Brazil
Countries and Territories with Active Zika Virus Transmission

Zika Virus in the USA

- Local transmission not yet reported in the continental US
- Zika is a nationally notifiable disease
- As of April 13, ≈350 travel-associated cases reported to CDC
- 32 pregnant
  - Of the first 9 reported
    - 2 early pregnancy losses
    - 2 elective terminations
    - 1 infant with severe microcephaly
    - 2 healthy infants
Zika Vectors

Aedes aegypti

Aedes albopictus
Aedes spp. Distribution

A. aegypti

A. albopictus

Revised map March 30, 2016
Other Modes of Transmission

Maternal-fetal: during pregnancy and time of birth. Other documented modes of transmission: rare?

- **Sexual**
  - Male to female
  - One report of virus detected in semen at 62 days after onset

- **Blood transfusion**
  - Reports in Brazil being investigated
  - Deferral for 4 weeks in US
    - Suspension of blood donations in Puerto Rico
  - Roche Zika PCR assay approved for screening March 30th

- **Laboratory exposure**

Theoretical concerns:

- Organ or tissue transplantation
  - Reports in Brazil being investigated

- Breast milk
  - Infectious virus has been detected
Clinical Disease Course

- Incubation several days to a week
- 80% asymptomatic
- Usually mild disease
  - Lasting several days to a week
- Hospitalization uncommon
- Fatalities rare
- Guillain-Barré syndrome reported following suspected Zika virus infection
## Clinical Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N (n=31)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or papular rash</td>
<td>28</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>55%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15</td>
<td>48%</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>Vomiting</td>
<td>3</td>
<td>10%</td>
</tr>
</tbody>
</table>

Yap Island, 2007
Zika and Microcephaly in Brazil

- Zika virus infections may be associated with microcephaly:
  - Increase in number of infants born with microcephaly during the outbreak
  - Zika virus RNA detected from several babies born with microcephaly and from fetal losses among women infected during pregnancy.

- CDC concludes Zika is a cause of microcephaly and other severe fetal brain defects
  - NEJM April 13, 2016
Zika and Associated Birth Defects

- Microcephaly
- Brain atrophy
- Cerebral and intraocular calcifications
- Abnormal formed or absent brain structures
- Cataracts

Tip of iceberg? Developmental problems and other effects on the brain?
Diagnostic Testing

- Real-time PCR
- IgM Serology
- Immunohistochemical staining
Need to Distinguish Zika from Dengue and Chikungunya

- All transmitted by the same mosquitoes with similar ecology
- Dengue and chikungunya can circulate in same area and rarely cause co-infections
- All have similar clinical features
- Important to rule out dengue, as proper clinical management can improve outcome
IgM Capture ELISA

- CDC EUA Zika IgM Capture assay
- Serum and CSF
  - CSF must be accompanied by a serum specimen
  - IgM detectable ≥4 days after illness onset
    - Detectable up to 12 weeks
IgM Capture ELISA

- Difficult to distinguish infecting virus in people previously infected or vaccinated against a related flavivirus
- Anti-dengue virus IgM antibodies cross-react, so positive Zika IgM ELISA specimens must be confirmed
  - Plaque reduction neutralization assay (PRNT) performed at CDC
Reverse Transcriptase Real-Time PCR

- CDC EUA Triplex RT-PCR
  - Zika
  - Dengue 1-4
  - Chikungunya

- Approved specimen types
  - Serum
  - CSF
  - Urine-----Zika Only
  - Amniotic fluid-----Zika Only

- Must be collected within 7 days of illness onset
Diagnosis and Testing, Wisconsin

- All requests for fee-exempt Zika virus testing must be approved by the DPH. Phone 608-267-9003

- **Criteria for testing**
  - History of travel to an area with localized Zika virus transmission
  - Signs and symptoms within 2 weeks after returning. (Males or Females)
  - Asymptomatic pregnant females who are within 2-12 weeks of return from travel to an area with localized Zika virus transmission
# Zika Testing Performed

**History of Travel to area of Zika virus transmission AND Symptomatic**

<table>
<thead>
<tr>
<th>Specimen collected within</th>
<th>PCR</th>
<th>IGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days of onset</td>
<td>Zika, Chik, Dengue</td>
<td></td>
</tr>
<tr>
<td>4-7 days of onset</td>
<td>Zika, Chik, Dengue</td>
<td>Zika, Chik, Dengue</td>
</tr>
<tr>
<td>1-12 weeks of onset</td>
<td></td>
<td>Zika, Chik, Dengue</td>
</tr>
</tbody>
</table>
References and Resources

- CDC COCA. Zika Virus — What Clinicians Need to Know: http://emergency.cdc.gov/coca/calls/2016/callinfo_012616.asp
- CDC MMWR. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016: http://www.cdc.gov/mmwr/volumes/65/wr/mm6502e1.htm
Thank You