Zika Virus Infection: An Emerging Infectious Disease

Disclosures
I, Dennis A. Conrad, M.D., disclose the following relationships with commercial companies:
Member of Speaker Bureau for Merck Vaccines and SanofiPasteur Vaccines

I, Dennis A. Conrad, M.D., will not discuss the use of any drug or device for an indication currently unapproved by the Food and Drug Administration

Learning Objectives
At the end of this presentation the participant will be able to:
1. Discuss the virology and epidemiology of Zika virus
2. List the current recommendation for the diagnosis and management of Zika virus infection
3. Cite current strategies to prevent Zika virus infection

Arboviruses of Family Flaviviridae
- Dengue
- Japanese encephalitis
- West Nile
- St. Louis encephalitis
- Yellow Fever
- Zika
Zika Virus: First Isolation

- First reported in April 1947 by the Zika Forest Uganda Virus Research Institute occurring in a Rhesus monkey sentinel for yellow fever who developed fever of 40°C
- “New” virus isolated from this monkey
- First human case in 1952 occurred in southeastern Nigeria in a 10-year-old girl who had fever and headache
- First human outbreak in 2007 occurred on Yap Island, Micronesia

Zika Virus: Human Transmission

- Zika virus is primarily transmitted to humans through the bite of Aedes species mosquitoes, most commonly Aedes aegypti and possibly Aedes albopictus
- Aedes is an aggressive daytime biter and also feeds at night
- During outbreaks: Aedes → Human → Aedes → Human

The Aedes Mosquito Vector

Aedes in the United States

Approximate distribution of Aedes aegypti in the United States*

Approximate distribution of Aedes albopictus in the United States*

Probable range of Aedes aegypti (below 2,000 meters altitude)
Climate change could expose an additional 2 billion people to dengue transmission by 2080

Source: WHO. http://www.who.int/mediacentre/factsheets/fs266/en/

Locally Acquired Zika Virus Infections in Puerto Rico

- On December 31, 2015, Puerto Rico Department of Health reported the first locally acquired (index) case of Zika virus disease in a jurisdiction of the United States
- *Aedes aegypti*, the most common mosquito vector of Zika virus worldwide, is present throughout Puerto Rico
- Zika virus is expected to continue to spread throughout the territory, and the 3.5 million residents of Puerto Rico, including approximately 43,000 pregnant women per year, are at risk for Zika virus infection

Zika Virus Infection: Clinical Presentation

- 80% of infections are asymptomatic; 20% are symptomatic:
  - Acute onset fever
  - Maculopapular (pruritic) rash
  - Arthralgia
  - Nonpurulent conjunctivitis
- Recovery within one week
- Death very rare
  - Attributed to Guillain-Barré

### Zika Virus: Symptoms and Signs

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or papular rash</td>
<td>28 (90)</td>
</tr>
<tr>
<td>Fever (objective or subjective)</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>

Zika Virus Infection: Clinical Presentation

- Although the exact incubation period of Zika virus disease has yet to be determined, evidence from case reports and experience from related flavivirus infections indicate that the incubation period likely is 3 days to 2 weeks
- Symptomatic disease is generally mild
- Duration of illness and viremia usually less than one week
A Brief History of Zika Virus and Disease

1947 - Discovered in Rhesus Monkey in the Zika Forest of Uganda
1952 - First Human Case (Nigeria)
2007 - First Outbreak (Yap)

The March of Zika Virus

Countries and Territories in the Americas with Active Zika Virus Transmission [As of 29 February 2016]

Zika Epidemic: New World Beginnings

• Zika virus first detected in the Region of the Americas in Brazil during Spring 2015
• In October 2015, a marked increase in the number of infants with microcephaly was reported in Brazil
• A possible association with prenatal Zika virus infection was postulated
• Laboratory evidence from a limited number of cases with microcephaly has supported this potential association
• Zika declared a Public Health Emergency of International Concern by the World Health Organization 1 February 2016 due to concerns for Zika-associated microcephaly and Guillain-Barré syndrome
Microcephaly cases in Brazil
By state (as of 13 February 2016)

Possible 10
100
1,000
Confirmed


The Face (and Head) of Microcephaly

Zika Virus Crosses the Placenta

Evidence of Zika Virus Infection in Fetus and Newborns

- In December 2015, tissues samples from two newborns (born at 36 and 38 weeks gestation) with microcephaly dying within 20 hours of birth and two miscarriages (fetal losses at 11 and 13 weeks) from Brazil were submitted to CDC for histopathologic evaluation and laboratory testing for suspected Zika virus infection
- All four mothers had clinical signs of Zika virus infection, including fever and rash, during the first trimester of pregnancy
  - None had clinical signs of active infection at the time of delivery or miscarriage

Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses — Brazil, 2015; MMWR / February 19, 2016 / 65(06);159–160

Evidence of Zika Virus Infection in Fetus and Newborns

- Tissues were tested for Zika virus by:
  - Reverse transcription-polymerase chain reaction (RT-PCR)
  - Immunohistochemistry
- Specimens from all four cases were positive by RT-PCR
- In the two newborns, only brain tissue was positive by RT-PCR assays
- For both newborns, significant brain histopathologic changes noted:
  - Parenchymal calcification; microglial nodules; gliosis; cell degeneration and necrosis
- Established link between Zika virus infection and microcephaly and early fetal demise

Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses — Brazil, 2015; MMWR / February 19, 2016 / 65(06);159–160

Zika Virus Infection in United States: Pregnant Travelers

- As of February 17, CDC had received reports of nine pregnant travelers with laboratory-confirmed Zika virus disease and 10 currently under investigation.
- Pregnancy outcomes among the nine confirmed cases included two early pregnancy losses, two elective terminations, and three live births (two apparently healthy infants and one infant with severe microcephaly).
- Two pregnancies (approximately 18 and 34 weeks gestation) continue without known complications.

Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus: Travel

- Offer serologic testing to asymptomatic pregnant women (women who do not report clinical illness consistent with Zika virus disease) who have traveled to areas with ongoing Zika virus transmission.
- Testing can be offered 2–12 weeks after pregnant women return from travel.

Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure: Initial Testing

- Zika virus testing of maternal serum:
  - Reverse transcription-polymerase chain reaction (RT-PCR) testing for symptomatic patients with onset of symptoms during the previous week.
  - Negative RT-PCR result from serum collected 5–7 days after symptom onset does not exclude Zika virus infection.
  - Immunoglobulin M (IgM) and plaque-reduction neutralizing antibody testing should be performed on specimens collected 24 days after onset of symptoms.

Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure: Serologic Testing/Retesting

- Serologic testing for Zika virus can be offered to asymptomatic pregnant women who traveled to an area with ongoing Zika virus transmission.
- Interpretation of a positive IgM results complex because of cross-reactivity among related flaviviruses (dengue; yellow fever; West Nile).
- A negative IgM result obtained 2–12 weeks after travel suggests that a recent Zika virus infection did not occur.
- A negative IgM result can be retested during the mid-second trimester for pregnant women living in areas of active transmission.

Zika Virus Infection In United States: Pregnant Travelers

- Six pregnant women with Zika virus disease reported symptoms during the first trimester:
  - Two early pregnancy losses.
  - Two elective pregnancy terminations.
  - Delivery of a live-born infant with microcephaly.
  - One pregnancy continuing.
- Two pregnant women with Zika virus infection reported symptoms during the second trimester:
  - One apparently healthy infant delivered.
  - One pregnancy is continuing.
- One pregnant woman reported symptoms of Zika virus infection during the third trimester:
  - One apparently healthy infant delivered.

Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure: Symptoms

- For pregnant women with clinical illness consistent with Zika virus disease, testing is recommended during the first week of illness.
- For asymptomatic pregnant women residing in areas with ongoing Zika virus transmission, testing is recommended at the initiation of prenatal care with follow-up testing during mid-second trimester.
### Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure: Prenatal Care

- Pregnant women with negative Zika virus IgM testing should receive routine prenatal care that includes:
  - Assessment of gestational age
  - Fetal ultrasound at 18–20 weeks of gestation
  - Optional additional fetal ultrasound later in pregnancy (fetal microcephaly is most easily detected in the late second and early third trimesters)

### Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure: Abnormal Ultrasound

- If findings of fetal microcephaly or intracranial calcifications observed on prenatal ultrasound:
  - Repeat maternal serum IgM testing
  - Consider amniocentesis (depending on gestational age)
- Zika virus testing can be performed on amniotic fluid using RT-PCR to inform clinical management

### Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure: Suspected Zika Virus Infection

- Serial fetal ultrasounds should be considered to monitor fetal anatomy and growth every 3–4 weeks in pregnant women with positive or inconclusive Zika virus test results
- Zika virus testing is recommended at the time of delivery:
  - Histopathologic examination of the placenta and umbilical cord
  - Testing placental tissue, cord tissue, and cord serum for Zika virus RNA
- If a pregnant woman with Zika virus disease experiences a fetal loss, Zika virus RT-PCR and immunohistochemical staining should be performed on fetal tissues including umbilical cord and placenta

### Guidelines for Prevention of Sexual Transmission of Zika Virus: Prevention by Male Partner

- Men who reside in or have traveled to an area of active Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for the duration of the pregnancy
- Men who reside in or have traveled to an area of active Zika virus transmission who are concerned about sexual transmission of Zika virus to a non-pregnant partner might consider abstaining from sexual activity or using condoms consistently and correctly during sex

### Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission: Risk

- During 6-22 February 2016 communications from multiple states reported 14 instances of suspected sexual transmission of Zika virus
- Two laboratory-confirmed cases and four probable cases of Zika virus disease were identified among these women
- Only identified risk factor was sexual contact (including condomless vaginal intercourse) with a symptomatic or recently symptomatic male partner with recent travel to an area with ongoing Zika virus transmission
Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission: Observations

- Sexual transmission of Zika virus more common than previously reported
- All reported cases of sexual transmission of Zika virus to date have been from symptomatic male partners
- Zika virus has been found in semen two months following resolution of clinical disease
- Sexual transmission of Zika virus from infected women to their sex partners and from persons who are asymptomatically infected has not been reported
- Prevention of infection during pregnancy is particularly important because of the growing evidence linking maternal Zika virus infection with congenital microcephaly, fetal loss, and other adverse reproductive health outcomes

Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure: Vector Control

- Strategies to prevent mosquito bites should be emphasized for women wishing to become pregnant who live in areas with ongoing Zika virus transmission:
  - Wear pants and long-sleeved shirts
  - Use FDA-approved insect repellents
  - Ensure that windows and doors have screens
  - Stay inside air-conditioned spaces whenever possible

Guidelines for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure: Counseling

- Women of reproductive age with current or previous laboratory-confirmed Zika virus infection should be counseled that there is no evidence that prior Zika virus infection poses a risk for birth defects in future pregnancies
- No current evidence suggests that a fetus conceived after maternal viremia has resolved (duration approximately 1 week) would be at risk for fetal infection
Guidelines for Infants and Children with Possible Zika Virus Infection: Post-natal Infection

- Acute Zika virus disease should be suspected in an infant or child aged less than 18 years who:
  - Traveled to or resided in an affected area within the past 2 weeks
  - Has ≥2 of the following manifestations:
    - Fever
    - Rash
    - Conjunctivitis
    - Arthralgia

Guidelines for Infants and Children with Possible Zika Virus Infection: Perinatal Infection

- The spectrum of Zika virus disease in neonates infected in the perinatal period is unknown
- Perinatal transmission of Zika virus infection to infants from mothers infected near the time of delivery has been reported in two cases:
  - One infant was asymptomatic
  - Second infant had thrombocytopenia and a diffuse rash

Guidelines for Infants and Children with Possible Zika Virus Infection: Pediatric Morbidity

- The spectrum of Zika virus disease in infants and children who are infected through mosquito bites indicates that most children are asymptomatic or have mild illness similar to that seen in adults
- Children aged 0–19 years had lower attack rates of confirmed and probable Zika virus disease than did adults aged 20–59 years in a 2007 outbreak on Yap Island, Micronesia

Guidelines for Infants and Children with Possible Zika Virus Infection: Which Infants Should Be Screened?

- Infants with microcephaly or intracranial calcifications born to women who traveled to or resided in an area with Zika virus while pregnant
- Infants whose mothers had symptoms consistent with Zika virus whose testing was positive or inconclusive, even if infant does not have microcephaly
- Infants who have no signs of microcephaly and whose mothers were asymptomatic do not require screening
### Guidelines for Infants and Children with Possible Zika Virus Infection: Pediatric Mortality

- Deaths from Zika virus infection appear to be rare in persons of all ages
- One death reported in a female aged 15 years with sickle cell disease (hemoglobin SC) who experienced 4 days of fever, myalgia, abdominal pain and jaundice; death was attributed to complications of sickle cell disease
- A second death was reported in a female aged 16 years whose symptoms included headache, nausea, and petechiae; no other information available

Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016; MMWR Early Release / February 19, 2016 / 65(7);1–6

### Guidelines for Infants and Children with Possible Zika Virus Infection: Selective Testing of Infants

- Testing of infants with possible congenital Zika virus infection who were born to mothers who traveled to or resided in areas affected by Zika virus during pregnancy should be guided by:
  - Whether the infant had microcephaly or intracranial calcifications detected prenatally or at birth
  - Maternal Zika virus testing results

Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016; MMWR Early Release / February 19, 2016 / 65(7);1–6

### Guidelines for Infants and Children with Possible Zika Virus Infection: Pediatric Guillain-Barré

- In French Polynesia, among 38 reported cases of Guillain-Barré syndrome after Zika virus infection, no case occurred in children
- In Brazil, six patients aged 2–57 year had neurologic syndromes following Zika virus infection:
  - Four had Guillain-Barré syndrome
  - Two had acute disseminated encephalomyelitis

Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016; MMWR Early Release / February 19, 2016 / 65(7);1–6

### Guidelines for Infants and Children with Possible Zika Virus Infection: Selective Testing of Infants

- Infants with microcephaly or intracranial calcifications or infants whose mothers have positive or inconclusive test results for Zika virus infection should be evaluated
- Infants without microcephaly or intracranial calcifications whose mothers have negative Zika virus test results or who were not tested for Zika virus should receive routine care

Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016; MMWR Early Release / February 19, 2016 / 65(7);1–6

### Guidelines for Infants and Children with Possible Zika Virus Infection: Virologic/Serologic Evaluation

- Evaluation of infants and children for acute Zika virus infection (symptom onset within the past 7 days) should include testing of serum and, if obtained for other reasons, cerebrospinal fluid (CSF) for Zika virus RNA using RT-PCR
- If Zika virus RNA is not detected and symptoms have been present for 24 days, serum should be tested for Zika virus immunoglobulin M (IgM) and neutralizing antibodies and dengue virus IgM and neutralizing antibodies

Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016; MMWR Early Release / February 19, 2016 / 65(7);1–6
**Guidelines for Infants and Children with Possible Zika Virus Infection: Confirmation of Infection**

- Laboratory evidence of Zika virus infection in an infant or child:
  - Detectable Zika virus in culture
  - Zika-virus RNA or antigen
  - Detection of Zika-virus IgM with confirmatory neutralizing antibody titers ≥4-fold higher than dengue virus neutralizing antibody titers
  - If Zika-virus antibody titers are <4-fold higher than dengue virus neutralizing antibody titers, test results for Zika virus are considered inconclusive

**Evaluation of infants with possible congenital Zika virus infection: Neurologic Examination**

- Comprehensive physical examination, including careful measurement of occipitofrontal circumference, length, weight, and assessment of gestational age
- Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions
- Cranial ultrasound unless prenatal ultrasound results from third trimester demonstrated no abnormalities of the brain

**Evaluation of infants with possible congenital Zika virus infection: Sensory Examination**

- Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 month after birth
- Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within 1 month after birth
- Other evaluations specific to the infant’s clinical presentation

**Further evaluations for infants with microcephaly or intracranial calcifications**

- Consultation with a clinical geneticist or dysmorphologist
- Consultation with a pediatric neurologist to determine appropriate brain imaging and additional evaluation
- Testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infections

**Recommended long-term follow-up for all infants with possible congenital Zika virus infection**

- Report case to state, territorial, or local health department and monitor for additional guidance as released
- Carefully evaluate occipitofrontal circumference and developmental characteristics and milestones throughout the first year of life
Guidelines for Infants and Children with Possible Zika Virus Infection: Reporting for Testing and Vector Control

- Health care providers should notify their local, state, or territorial health department of suspected Zika cases to arrange testing
- Report so that corrective action can be taken to decrease the risk for local transmission in areas with Aedes species mosquitoes

Guidelines for Infants and Children with Possible Zika Virus Infection: Treatment

- Treatment of Zika virus infection is supportive care
- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue virus is ruled out as the cause of illness, because of the potential for hemorrhagic complications of dengue fever
- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in all children aged <6 months
- Aspirin should not be used in children with acute viral illnesses because of its association with Reye’s syndrome

Guidelines for Infants and Children with Possible Zika Virus Infection: Breastfeeding

- Zika virus RNA has been identified in breast milk, but attempts to culture the virus have been unsuccessful
- No cases of Zika virus infection associated with breastfeeding have been reported
- Mothers with Zika virus infection and living in areas with ongoing Zika virus transmission should breastfeed their infants
- Benefits of breastfeeding outweigh the theoretical risks of Zika virus transmission through breast milk

Guidelines for Infants and Children with Possible Zika Virus Infection: Prevention

- Prevention of mosquito bites is the primary means of preventing Zika virus infection in persons of all ages traveling to or residing in areas with local Zika virus transmission
- Preventions measures include:
  - Using air conditioning or window and door screens
  - Wearing long-sleeved shirts and long pants
  - Using permethrin-treated clothing and gear
  - Using insect repellents
  - Mosquito netting

Mosquito Repellants

- Products with one of the following active ingredients can help prevent mosquito bites; higher percentages of active ingredient provide longer protection:
  - DEET (ages ≥2-months)
    - Products containing DEET include Off!, Cutter, Sawyer, and Ultrathon
  - Picaridin (also known as KBR 3023, Bayrepel, and Icaridin)
    - Products containing picaridin include Cutter Advanced, Skin So Soft Bug Guard Plus, and Autan (outside the US)
  - Oil of lemon eucalyptus (OLE) or PMD (ages ≥3-years)
    - Products containing OLE include Repel and Off! Botanicals
  - IR3535
    - Products containing IR3535 include Skin So Soft Bug Guard Plus Expedition and SkinSmart