Children’s Hospitals and Preparedness

Caring for Children with Congenital Zika Virus: Building Community Support

Monday, November 14, 2016
3:00pm ET/2:00pm CT

A collaboration of the American Academy of Pediatrics and the Centers for Disease Control and Prevention
Objectives

• Describe Zika virus and update participants about what is known.

• Share strategies for preparedness used at one children’s hospital in the US.

• Discuss key questions children’s hospitals may have while thinking about preparing for seeing infants with congenital Zika virus syndrome.

• Share experiences from other hospitals who have been through the preparedness process.
Welcome Remarks

Centers for Disease Control and Prevention
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Zika Update

American Academy of Pediatrics
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Zika Virus and its Vectors

- Flavivirus related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- *Aedes aegypti* mosquito primary vector (humans)
- *Aedes albopictus* mosquito also competent vector
- Same vectors transmit dengue and chikungunya viruses
- Lay eggs in water containers for household use
- Live in and around households; can feed all day

Other Modes of Transmission

- **Documented**
  - Intrauterine resulting in congenital infection
  - Perinatal
  - Sexual
  - Laboratory exposure

- **Possible***
  - Blood transfusion
  - Organ or tissue transplantation

* Breastmilk: while the virus can be present in breastmilk, to date there are no reports of infants getting Zika virus through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed even in areas where Zika virus is found.

Zika Virus Disease Clinical Course and Outcomes

- Most infections asymptomatic
- When symptomatic, clinical illness usually mild
  - Characterized by fever, rash, arthralgia, or conjunctivitis
  - Severe disease requiring hospitalization uncommon
- Symptoms last several days to a week
- Fatalities rare

Clinical Manifestations

- Microcephaly and other congenital anomalies
- Guillain-Barré syndrome and other neurologic syndromes
- Thrombocytopenia


Photo Credit: Cynthia Goldsmith, 2016 (PHIL 20538)
How Does Congenital Zika Affect Fetuses and Infants?

- Full spectrum of clinical effects and secondary outcomes of Zika virus during pregnancy not yet known
- Includes microcephaly, intracranial calcifications or other brain anomalies, eye anomalies, hearing loss, limb abnormalities
- On exam, some infants have neurologic findings apparent at time of birth
  - Hypertonia, hypotonia, spasticity, hyperreflexia, severe irritability, seizures

Source: http://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_e
5 Features of Congenital Zika Virus Syndrome Rarely Seen with Other Congenital Infections or Unique to Congenital Zika Virus Infection

- Severe microcephaly with partially collapsed skull
- Thin cerebral cortices with subcortical calcifications
- Macular scarring and focal pigmentary retinal mottling
- Congenital contractures
- Marked early hypertonia and symptoms of extrapyramidal involvement

Updated Guidance: Congenital Infection

August 19, 2016

CDC MMWR


CDC has updated its interim guidance for U.S. health care providers caring for infants born to mothers with possible Zika virus infection during pregnancy (1). Laboratory testing is recommended for (1) infants born to mothers with laboratory evidence of Zika virus infection during pregnancy and (2) infants who have abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link suggesting possible transmission, regardless of maternal Zika virus test results. Congenital Zika syndrome is a recently recognized pattern of congenital anomalies associated with Zika virus infection during pregnancy that includes microcephaly, intracranial calcifications or other brain anomalies, or eye anomalies, among others (2). Recommended infant laboratory evaluation includes both molecular (real-time reverse transcription–polymerase chain reaction [RT-PCR]) and serologic (immunoglobulin M [IgM]) testing. Initial samples should be collected directly from the infants in the first 2 days of life. If possible, testing ofcord blood is not recommended. A positive infant serum or urine RT-PCR test result confirms congenital Zika virus infection. Positive Zika virus IgM testing, with a negative RT-PCR result, indicates probable congenital Zika virus infection. In addition to these, infants with laboratory evidence of Zika virus infection during pregnancy should include a comprehensive physical examination, including a neurologic examination, prenatal head ultrasound, and standard newborn hearing screen. Infants with laboratory evidence of congenital Zika virus infection should have a comprehensive ophthalmologic exam and hearing assessment by auditory brainstem response (ABR) testing before 1 month of age. Recommendations for follow-up of infants with laboratory evidence of congenital Zika virus infection depend on whether abnormalities consistent with congenital Zika syndrome are present. Infants with abnormalities consistent with congenital Zika syndrome should have a coordinated evaluation by multiple specialists within the first month of life; additional evaluations will be needed within the first year of life, including assessments of vision, hearing, feeding, growth, and neurodevelopmental and endocrine function. Families and caregivers will also need ongoing psychosocial support and assistance with coordination of care. Infants with laboratory evidence of congenital Zika virus infection without apparent abnormalities should have ongoing developmental monitoring and screening by the primary care provider; repeat hearing testing is recommended. This guidance will be updated when additional information becomes available.

Zika virus infections during pregnancy is a cause of microcephaly and other serious brain anomalies (3); however, the clinical spectrum of the effects of Zika virus infection during pregnancy is not yet known. A wide range of neurologic abnormalities, in addition to microcephaly, has been observed among infants with presumed or confirmed congenital Zika virus infection (2,4). Reported neuroimaging findings include intracranial calcifications; ventriculomegaly and extra-axial fluid; abnormal gyral patterns (e.g., polymicrogyria); decreased brain parenchymal volume; cortical atrophy; and microcephaly; hypoplasia of the cerebellum, cerebellar vermis or brainstem; delayed myelination; and thinning or hypoplasia of the corpus callosum (2,5). Neurologic abnormalities apparent on exami-

Source: https://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w
Updated Guidance: Congenital Infection

Source: https://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w
Many Questions Remain

- What is the full range of potential health problems that Zika virus infection may cause?
- What is the level of risk from a Zika virus infection during pregnancy?
- When during pregnancy does Zika virus infection pose the highest risk to the fetus?
- What are other factors (e.g., co-occurring infection) that might affect the risk for birth defects?
- Does exposure to Zika virus or having symptoms lead to improved immunity? Future risks of any kind (e.g., on fertility)?
Current Surveillance

Collecting data for action

- US Zika Pregnancy Registry
- Zika Active Pregnancy Surveillance System (Puerto Rico)
- Proyecto Vigilancia de Embarazadas con Zika (Colombia)
Cases in the United States as of November 2, 2016

Role of Children’s Hospitals

• Respond to questions from families
• Understand the testing situation in your state (i.e. whether state or commercial labs are doing the testing)
• Inform clinicians about the CDC Zika Pregnancy Registry and the need to ensure infants are included:
  • Infants born to women with laboratory evidence of Zika virus infection.
  • Infants with congenital Zika virus infection.
• Coordinate information sharing and assist in promoting a continuum of care within the community (among obstetricians, primary care providers, early intervention, subspecialists).
Select Resources

CDC Resources:
Pocket guide

Zika webpages
For healthcare providers:
For families:

AAP Zika virus resources:
AAP Zika webpage
For healthcare providers:
www.aap.org/zika
For families:
www.healthychildren.org/zika
Meeting the Need:
The Congenital Zika Virus Program at Children’s National Health System

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Case Presentation

- 33 yo G1PO Washington, DC resident vacationed for one week in Belize, Guatemala, and Cancun at 11 weeks gestation
- 2 days after return to US, developed illness lasting 5 days:
  - Low-grade fever
  - Erythematous maculopapular rash
  - Myalgia
  - Mild photophobia
  - No joint symptoms
- Husband (also on trip) developed identical symptoms within same time frame
Case Presentation (continued)

- Obstetrical Evaluation:
  - 13 weeks gestation (1 week post-symptoms)
    - Fetal ultrasound normal
  - 16/17 weeks gestation (4/5 weeks post-symptoms)
    - Repeat fetal ultrasounds normal
    - Zika testing (serum PCR and IgM) – **positive**
  - 19 weeks gestation (7 weeks post-symptoms)
    - Repeat fetal ultrasound – **abnormal**
    - Referred to CNHS Fetal Medicine Institute for multidisciplinary evaluation
    - **Fetal MRI: Multiple CNS abnormalities detected**
    - Amniotic fluid Zika PCR – **positive**
The New England Journal of Medicine

Brief Report

Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities


Epub ahead of print: March 30, 2016
Published June 2, 2016;374(22):2142-51
Fetal MRI at 20 Weeks Gestation: Severe Atrophy of Cortical Mantle

- Normal lamination pattern absent
- Subplate zone largely undetectable
Zika Cases in the U.S. and U.S. Territories, as of November 2, 2016

U.S. States
- Locally acquired mosquito-borne cases reported: 139
- Travel-associated cases reported: 3,988
- Laboratory-acquired cases reported: 1
- Total: 4,128
  - Pregnant: 1,005
  - Sexually transmitted: 34
  - Guillain-Barré syndrome: 13

U.S. Territories
- Locally acquired cases reported: 30,074
- Travel-associated cases reported: 104
- Total: 30,178*
  - Pregnant: 2,263
  - Guillain-Barré syndrome: 45
Estimated Vector Range in the United States

**A. aegypti**
Originated in sub-Saharan Africa, spread throughout tropics centuries ago.

**A. albopictus**
Originated in Asia, spread to Americas, Africa, Europe as of 1985.
Responding to the Need

Children's National Launches New Congenital Zika Virus Program

May 16, 2016

Washington, DC – Each week, as temperatures rise, the likelihood increases that the United States will experience domestic Zika virus transmission. Indeed, such domestic Zika transmission already is occurring in Puerto Rico and the U.S. Virgin Islands. The Children's National Health System Fetal Medicine Institute and Division of Pediatric Infectious Disease announced today the formation of a Congenital Zika Virus Program to serve as a dedicated resource for referring clinicians and for pregnant women to receive counseling and science-driven answers about the impact of the Zika virus on their pregnancies.
Children’s National Congenital Zika Virus Program

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CNHS Congenital Zika Virus Program Core Components

- Clinical Care Delivery
  - Prenatal: Pregnant mother/fetus
  - Postnatal: Infants
- Advocacy/Policy
- Research
  - Domestic
  - International
CNHS Congenital Zika Virus Program –
Clinical Care Delivery

– Single visit coordinated multidisciplinary care
– Counseling and up-to-date guidance regarding Zika exposure and infection
– Coordination of testing with all state Health Departments
– **Advanced Fetal Imaging**
  • Fetal US (Screening technique)
  • **Fetal MRI (Neurodiagnostic technique)**
    – Detection of more subtle/earlier evidence of impaired fetal brain growth/development
– Coordination with obstetricians, MFM, pediatrician for subsequent monitoring
– Coordination of multidisciplinary care for affected infants
Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States, July 2016

Testing and interpretation recommendations for a pregnant woman with possible exposure to Zika virus — United States (including U.S. territories)

**A**
- Assess for possible Zika virus exposure
  - Evaluate for signs and symptoms of Zika virus disease

  - Symptomatic: <2 weeks after symptom onset, or
  - Asymptomatic and NOT living in an area with active Zika virus transmission: <2 weeks after possible exposure

  **Zika virus RT-PCR on serum and urine**

  **Positive Zika virus RT-PCR on serum or urine**

  Recent Zika virus infection

  **Negative Zika virus RT-PCR on serum and urine**

  Zika virus IgM and dengue virus IgM negative
  - No recent Zika virus infection

**B**
- Symptomatic: 2–12 weeks after symptom onset, or
- Asymptomatic and NOT living in an area with active Zika virus transmission: 2–12 weeks after possible exposure, or
- Asymptomatic and living in an area with active Zika virus transmission: 1st and 2nd trimester

  **Zika virus IgM and dengue virus IgM on serum**

  **Positive Zika virus IgM and dengue virus IgM**

  - Recent Zika virus infection

  **Negative Zika virus IgM and dengue virus IgM**

  **Zika virus IgM positive or equivocal and Zika virus IgM negative**

  Presumptive dengue virus infection

  **Zika virus IgM positive or equivocal and any result on dengue virus IgM**

  Presumptive recent Zika virus or flavivirus infection

  **Zika virus IgM negative**

  No recent Zika virus infection

  **Rapid Zika virus RT-PCR on serum and urine**

  **Positive Zika virus RT-PCR on serum or urine**

  Recent Zika virus infection

  **Negative Zika virus RT-PCR on serum and urine**

  **Zika virus PRINT s10 and dengue virus PRINT s10**

  Recent flavivirus infection, specific virus cannot be identified

  **Zika virus PRINT <10**

  Recent Zika virus infection

  **Abbreviations:** IgM = Immunoglobulin M; PRINT = plaque reduction neutralization test; RT-PCR = real-time reverse transcription-polymerase chain reaction.

  1. Dengue IgM antibody testing is recommended only for symptomatic pregnant women.
  2. If Zika virus RT-PCR testing is requested from laboratories without IgM antibody testing capacity or a process to forward specimens to another testing laboratory, testing of additional serum samples is recommended for IgM antibody testing in the event of a RT-PCR negative result.
  3. Possible exposures to Zika virus include travel to or residence in an area with active Zika virus transmission (http://www.cdc.gov/travel/dengue.html), or sex (vaginal sex, perineal sex, or oral-genital sex) with a man who traveled to an area with active Zika virus transmission.

  1. Testing includes Zika virus RT-PCR on serum and urine samples, Zika virus and dengue virus immunoglobulin M (IgM) and IgM negative results should be interpreted in the context of the patient’s clinical history and if the test result is discordant with clinical presentation, as Zika virus disease is reported whereas a pregnant woman is considered asymptomatic if symptoms are NOT reported.
Laboratory Diagnosis of Zika Virus Infection

- Distinguishing Zika IgM from other flavivirus (e.g., Yellow Fever, dengue) infections may be difficult due to cross-reactivity.
- Requires Plaque Reduction Neutralization assay (PRNT)
Pregnancy Outcomes in Setting of Zika Infection

- **Brazilian Study:** (Nielsen, *NEJM* 2016)
  - Up to 29% of affected pregnancies with birth defect or fetal loss
- **Colombian Study:** (Hohman, *NEJM* 2016)
  - 12,000 Zika-infected pregnancies being followed
    - 3rd trimester infections – few with overt neuro abnormalities
    - 1st and 2nd trimester infection data still pending
- **US:** CDC Pregnancy and Infant Registry
  - 26 liveborn infants with birth defects
  - 6 pregnancy losses with birth defects
    - Microcephaly
    - Calcium deposits in the brain
    - Excess fluid in the brain cavities and surrounding brain
    - Absent or poorly formed brain structures
    - Abnormal eye development
    - Clubfoot or inflexible joint
    - Hearing loss
Monitoring the Fetus Exposed to Zika Virus
Maternal ZIKV Positive: Studies at 19 Weeks GA

Cranial circumference

Fetal ultrasound

Fetal MRI
Fetal MRI at 20 Weeks: Small Corpus Callosum
Fetal MRI at 20 Weeks Gestation: Severe Atrophy of Cortical Mantle
ZIKV Encephalopathy Cerebral Calcifications

Heron Werner, Clinic for Diagnostic Imaging, Rio de Janeiro
Fetal ZIKV Encephalopathy With Arthrogryposis
ZIKV Encephalopathy Cerebral Disruption

Heron Werner, Clinic for Diagnostic Imaging, Rio de Janeiro
Managing the Newborn Exposed to Zika Virus
Laboratory Diagnosis for Infants When Indicated

- **Which Infants Need Testing?**
  - Asymptomatic or Symptomatic infants born to mom with positive/inconclusive Zika testing or exposure/not tested
  - Infants with microcephaly, calcifications or other CNS abnormalities born to woman who traveled to or resided in affected area during pregnancy

- **What Should Be Tested?**
  - Infant serum (not cord blood) within 2 days of life:
    - Zika PCR; Zika and Dengue IgM and neutralizing Abs
  - Infant urine within 2 days of Life: Zika PCR
  - Placenta and umbilical cord:
    - Histopathologic examination
    - Immunohistochemical staining on fixed tissue
    - Zika PCR on frozen tissue
  - If CSF obtained for other studies:
    - Zika PCR; Zika and Dengue IgM and neutralizing Abs
Infants With Possible Congenital Zika Virus Infection (Maternal Probable or Proven, or Exposure/Untested)

Recommended clinical evaluation and laboratory testing for:

- Comprehensive physical examination
- Lab testing: PCR and IgM within 2 days of birth
- Cranial ultrasound
- Hearing evaluation within one month

Infants Testing Positive for Zika Virus Infection

Without abnormalities consistent with Zika infection:

**2 weeks:** Ophthalmology and audiology

**4-6 months:** Consider repeat audiology (ABR)
Ophthalmology

**9 months:** Developmental screening
Behavioral audiology - if no ABR at 4-6 months

Infants Testing Positive for Zika Virus Infection

With abnormalities consistent with Zika infection:

2 weeks: Thyroid screen (TSH/free T₄)
1 month: Neurology exam
2 months: Neurology exam
3 months: Thyroid screen (TSH/free T₄)
           Ophthalmology
4-6 months: Repeat audiology (ABR)
9 months: Developmental screening

Multidisciplinary Management of Infants With Zika-Positive Lab Testing and Consistent Abnormalities

Multidisciplinary Team should include:
• Neurology
• Infectious Diseases
• Endocrinology
• Genetics
• Orthopedics or PT
• Pulmonologist/ENT: Aspiration
• OT/Speech therapy: Feeding
• Family support services
CNHS Congenital Zika Virus Program – Advocacy & Policy

- Education of Practitioners and Community
  - Regional
  - National
    - Referral guidelines
    - Zika website
    - Zika hotline
    - Community lectures and Grand Rounds to hospitals and professional societies
    - In-person visits to obstetrical and MFM practices
- Institutional Awareness and Education
  - Infection control policy
CNHS Congenital Zika Virus Program – Advocacy & Policy

- Emergency Response Planning in Conjunction With Institutional, Regional, and Federal Agencies
  - CNHS disaster preparedness
  - Children’s Hospital Infectious Emergency Task Force
  - Regional authorities
    - DC Department of Health
    - MD Department of Health
    - VA Department of Health
  - National Authorities
    - AAP
    - CDC
CNHS Congenital Zika Virus Program - Research
IRB-approved protocol enrolling in the United States and Colombia

- Serial fetal MRI
- Serial quantitative virologic studies
- Genetics
Questions Without Clear Answers…Yet:

- Can we predict the risk to a fetus/infant if a woman is infected with Zika virus while she is pregnant?
  - Is the fetus at higher risk of infection and/or neurologic injury during certain windows of pregnancy?

- What are the mechanism(s) of damage to fetal brain:
  - Developmental arrest, direct brain injury or both?
  - What cell types are targeted?
  - What are the factors determining breach of the placental barrier and the blood/brain barrier that allows virus to reach the fetal brain?
Questions Without Clear Answers…Yet:

• Risk Factors and Biomarkers for Fetal Infection:
  • Is duration or amount of viremia predictive of likelihood of injury to the fetus?
  • Early fetal MRI findings
    • Are specific demographic groups at higher risk for infection or severe sequelae?
    • Does co-infection or prior infection with other flaviviruses or other factors play a role in the severity of Zika infection?

• What are the long-term neurodevelopmental and neuropsychological outcome of survivors (both symptomatic and asymptomatic)?
  • Are there more subtle, prevalent effects of ZIKV on the developing brain?
The Congenital Zika Virus Program at
Children’s National

CONTACT INFORMATION
• Phone number: 202-476-7409
• Email: fetalmedicine@childrensnational.org
• Web: www.childrensnational.org/zika
Experiences from Other Children’s Hospitals
Questions?

• Dial *1 on your phone to ask a live question.
• Phone: 844-216-1726
• Conference ID: 12231928

• You may also ask a question through the chat box in the lower left hand corner. The AAP staff or presenters will address unanswered questions via e-mail after the call.

• Please e-mail DisasterReady@aap.org to follow-up as needed.
Thank You!

Questions? E-mail DisasterReady@aap.org