Zika Virus: The Evolving Story
The Latest & What You Need to Know

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• We do not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.
• The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Today’s Presentation

• Zika: The Current Situation
• Epidemiology of Congenital Zika Syndrome
• Clinical Manifestations of Acquired and Congenital Zika Virus Infections
• Zika and the Developing Brain
• CDC Guidance: Infants with Possible Zika Virus Infection
• Testing and Diagnosis
• Prevention
Zika Virus: The Current Situation
What is Zika Virus?

- Single-stranded RNA virus
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- Primarily transmitted by the bite of two *Aedes* species mosquitoes
  - *Aedes aegypti* and *Aedes albopictus* mosquitoes
- Additional modes of transmission
  - Intrauterine and perinatal transmission (mother to fetus)
  - Sexual transmission
  - Laboratory exposure
  - Probable: Blood transfusion
Zika Virus: A Newly Emerging Pathogen

• 1947: First isolated from a macaque, Zika Forest, Uganda

• Before 2007: only 14 sporadic human disease cases reported from Africa and southeast Asia

• In 2007, first outbreak reported on Yap Island, Federated States of Micronesia

• 2013-2014: >30,000 suspected cases reported from French Polynesia and other Pacific Islands

Epidemiology of Congenital Zika Syndrome
Among pregnant women in the United States with laboratory evidence of possible Zika virus infection:

- About 6% of fetuses or infants had potentially-related birth defects
- About 6% of pregnancies with birth defects was similar among symptomatic and asymptomatic pregnant women
- Among women with infection in the first trimester, birth defects were reported in 11% of fetuses or infants
Among pregnant women in the US territories with laboratory evidence of possible Zika virus infection

- Overall about **5%** of fetuses or infants had birth defects potentially related to Zika virus
- Among women with infection during pregnancy, birth defects were reported in
  - **8%** of fetuses or infants in the **first trimester**
  - **5%** of fetuses or infants in the **second trimester**
  - **4%** of fetuses or infants in the **third trimester**
Baseline Prevalence of Birth Defects Observed with Zika Virus

• Used data from birth defects surveillance systems in Massachusetts, North Carolina, and Atlanta, Georgia, during pre-Zika outbreak years (2013-2014)
• Compared with data from US Zika Pregnancy Registry
• Prevalence of Zika-related birth defects before Zika outbreak in the Americas:
  
  3 out of every 1,000 births
• Proportion of infants with birth defects among completed pregnancies with possible Zika infection (2016):
  
  58 out of every 1,000 completed pregnancies

Researchers estimate a 20-fold increase in Zika-related birth defects in pregnancies with possible Zika virus infection compared with pre-Zika outbreak years.
Pregnant women with confirmed Zika virus infection had a fetus or baby with birth defects in 1 in 10 cases. Approximately 44 states reported pregnant women with evidence of Zika virus infection in 2016. Babies with possible congenital Zika infection were reported to have received brain imaging after birth in only 1 in 4 cases.

The Clinical Manifestations of Zika in People
Clinical Manifestations of Zika Virus Infection

• Acquired Infection
  » Fever, usually “low-grade”
  » Rash, erythematous, maculopapular involving the face, neck, trunk, arms
  » Arthralgia
  » Headache

Clinical Manifestations of Zika Virus Infection

- Acquired Infection
  - Conjunctivitis
  - Abdominal pain, nausea, or vomiting (infrequent)
  - Jaundice
  - Symptoms last 3 to 7 days

Clinical Manifestations of Zika Virus Infections

- Congenital Zika Syndrome
  - Microcephaly and other CNS abnormalities
  - Chorioretinitis, optic atrophy
  - Sensorineural hearing loss
  - Arthrogryposis
  - Intrauterine growth restriction
## Comparison: Zika and Cytomegalovirus (CMV)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Zika</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic</strong></td>
<td>IUGR, <strong>Arthrogryposis</strong></td>
<td>IUGR, <strong>jaundice, petechiae, hepatosplenomegaly</strong></td>
</tr>
<tr>
<td><strong>Ophthalmological</strong></td>
<td>Chorioretinitis, optic atrophy</td>
<td>Chorioretinitis, optic atrophy</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td>Microcephaly, Hydrocephalus, Cortical dysplasia, Polymicrogyria (PMG), Lissencephaly, <strong>Fetal brain disruption</strong></td>
<td>Microcephaly, Cortical dysplasia, Polymicrogyria (PMG), Lissencephaly, <strong>Schizencephaly, brain clefting</strong></td>
</tr>
<tr>
<td><strong>Audiological</strong></td>
<td>Sensorineural hearing loss</td>
<td>Sensorineural hearing loss</td>
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Zika and the Nervous System

- Zika virus is neurotropic
  - Acquired Infection
    - Guillain-Barré syndrome (GBS) (axonal)
  - Congenital Infection
    - Microcephaly, intracranial calcifications
    - Cortical dysplasia (PMG), lissencephaly
    - Fetal brain disruption
Zika-associated GBS

- **Onset**: 6 days (median) after signs of Zika infection; rapid clinical progression
- **Clinical features**: Generalized muscle weakness, inability to walk, facial paralysis, areflexia, dysphagia, respiratory failure
- **Neurodiagnostic features**: Elevated CSF protein ("albuminocytologic dissociation"), acute motor axonal neuropathy
- **Treatment**: Intravenous immunoglobulin
- **Outcome**: Generally favorable
# Imaging the Child’s Brain

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Modality</th>
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<tbody>
<tr>
<td><strong>Ultrasound</strong></td>
<td><strong>CT</strong></td>
</tr>
<tr>
<td>Risks</td>
<td>• Negligible</td>
</tr>
</tbody>
</table>
| Strengths       | • Portable, rapid  
|                 | • Images midline structures well 
|                 | • Detects calcifications | • Rapid  
|                 | • Detects calcifications  
| Weaknesses      | • Insensitive imaging of cortex and posterior fossa | • Not portable  
|                 | • Insensitive imaging of cortex and white matter | • Not portable, slow  
|                 | • Insensitive imaging of calcifications |
Imaging the Child’s Brain

Ultrasound

CT
Imaging the Child’s Brain

CT

MRI
Congenital CMV Infection

Ultrasound  CT  MRI
Congenital Zika Syndrome and the Brain

• Congenital Microcephaly

Photos source: Google Images
Congenital Zika Syndrome and the Brain

Calcifications

Cortical Dysplasia

Source: Soares de Oliveira-Szejnfeld, P. Radiology 2016

Congenital Zika Syndrome and the Brain

Fetal Brain disruption
- Rare before Zika
- Severe brain destruction, intracranial calcifications
- Collapse of skull and scalp
- Profound microcephaly
- Chorioretinitis

Pathogenesis of Brain Abnormalities in Congenital Virus Infection

Maternal Viremia

Placental infection

IUGR

Neuronal cell loss
Abnormal cell migration
Calcifications

CNS invasion

Fetal viremia

CDC Guidance: Infants with Possible Congenital Zika Virus Infection
Update Posted April 2017: New Considerations

- **Evaluation and Testing: Congenital Zika Virus Infection**
  - New considerations and clarifying information to update the [August 2016 MMWR](https://www.cdc.gov/zika/pdfs/placental-testing-guidance.pdf)
Infants with Possible Congenital Zika Virus Infection

- Testing of infants with possible congenital Zika virus infection should be guided by
  - Whether the infant has abnormalities consistent with congenital Zika syndrome (CZS)
    - Test without waiting for maternal test results when infant has clinical or neuroimaging findings suggestive of CZS
  - The mother’s Zika virus testing results
    - All infants born to mothers with laboratory evidence of Zika virus infection should receive:
      - A comprehensive physical exam
      - Neurologic assessment
      - Head ultrasound
      - Zika virus testing
      - Hearing screen
  - Test infant before hospital discharge if concerns of loss to follow up

Infants with Possible Congenital Zika Virus Infection

- Congenital Zika virus infection can be diagnosed by RNA nucleic acid testing (NAT) and through serologic testing
- Collect specimens within 2 days of birth when possible
  » Specimens collected outside this period may still be useful

Mother with laboratory evidence of Zika virus infection during pregnancy*

Perform a comprehensive physical exam on infant, head ultrasound, standard newborn hearing assessment and infant Zika virus laboratory testing

Infant with findings consistent with congenital Zika virus syndrome

Infant without findings consistent with congenital Zika virus syndrome

Testing Babies for Zika Virus Infection: New Considerations

- **Testing of cerebrospinal fluid (CSF)**
  - Consider obtaining CSF for Zika virus RNA and IgM antibody testing in infants with clinical findings of possible Congenital Zika Syndrome but whose initial laboratory tests are negative on serum and urine
  - Placental Testing
    - Consider testing of the placenta for Zika virus PCR

Infants with **Possible** Congenital Zika Virus Infection

Recommendations for follow up depend on whether these infants have abnormalities consistent with Congenital Zika Syndrome

Initial Evaluation

Infants with abnormalities consistent with congenital Zika syndrome born to a mother with lab evidence of Zika virus infection

- Before hospital discharge:
  - Routine newborn care: physical exam, including occipitofrontal (head) circumference, weight, length
  - Neurologic exam
  - Universal hearing screen
  - Head ultrasound
  - Testing for congenital Zika virus infection
  - Complete blood count, metabolic panel and liver enzyme testing
  - Consult with multiple subspecialists

- Referral for comprehensive eye exam by an ophthalmologist
- Referral for auditory brainstem response (ABR) hearing evaluation
- Consider advanced cranial imaging (e.g., MRI)
- Consider transfer to hospital with specialty care

- Refer for a comprehensive ophthalmologic exam and evaluation of hearing by ABR testing before 1 month of age

https://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w
Initial Evaluation & Outpatient Management

Infants with lab evidence of Zika and **without** abnormalities consistent with congenital Zika syndrome

- Before hospital discharge infants should receive
  - Routine care including monitoring of occipitofrontal circumference, length, and weight
- **Outpatient management includes routine follow-up care and**
  - Establish medical home
  - Conduct developmental monitoring, encourage caregivers to monitor child’s development.
  - Emphasize anticipatory guidance for families.
  - Perform developmental screening at 9 months, or earlier if parental or provider concerns.
  - Refer to ophthalmology within one month of birth. Perform vision screening at every visit.
  - Evaluate hearing: consider repeat ABR testing at 4–6 months or perform behavioral diagnostic testing at age 9 months if ABR is not done at 4–6 months
  - Refer to appropriate specialists
  - Provide information about family support services

Outpatient Management

Infants with abnormalities consistent with congenital Zika syndrome and lab evidence of Zika

- Establish a medical home to facilitate coordination of care
- Provide routine preventive pediatric health care, including immunizations and monthly primary care visits for at least the first 6 months
- Conduct developmental monitoring at each routine visit
- Complete neurologic exam at age 1 and 2 months, then as needed
- Refer patients to developmental specialist and early intervention services
- Repeat ophthalmology exam with retinal assessment at 3 months
- Repeat ABR hearing assessment at age 4–6 months
- Conduct thyroid screening at age 2 weeks and age 3 months
- Provide family support services
- Provide appropriate referrals
Pediatric Evaluation and Follow-Up Care: New Considerations

**Imaging**

- Perform a head ultrasound before hospital discharge or within 1 month of birth for infants with possible Zika virus infection.
- For infants with a small or absent anterior fontanelle and poor visualization of the intracranial anatomy on ultrasound, other imaging (i.e., magnetic resonance imaging or computed tomography) should be considered.
Consult with Specialists
Infants with abnormalities consistent with CZS and lab evidence of Zika virus infection

- **Neurologist** to determine appropriate neuroimaging and additional evaluation
- **Infectious disease specialist** to evaluate other congenital infections
- **Ophthalmologist** to examine the eye and evaluate for possible cortical visual impairment prior to discharge from hospital or within 1 month of birth
- **Endocrinologist** to evaluate for hypothalamic or pituitary dysfunction
- **Clinical geneticist** to evaluate for other causes of microcephaly or other anomalies if present
Consult with Specialists

Infants with abnormalities consistent with CZS and lab evidence of Zika virus infection

Consultation with the following should also be considered:

- Orthopedist, physiatrist, physical medicine, rehabilitation physician, and physical therapist to manage hypertonia, club foot, or arthrogrypotic-like conditions
- Pulmonologist or otolaryngologist to consult about aspiration
- Lactation specialist, nutritionist, gastroenterologist, or speech or occupational therapist to manage feeding issues
Infants with Possible Postnatal Zika Virus Infection

- **Guidance for testing and clinical management** of infants and children with postnatal Zika virus infection is in line with testing and clinical management recommendations for adults.

- **Symptomatic treatment and supportive care** are appropriate and usually sufficient to treat Zika. Special considerations to treat children with Zika include
  - Aspirin should never be used to treat children with symptoms of acute viral illness because of the risk of Reye’s syndrome.
  - All non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in children <6 months.

- Patients with suspected Zika virus infections should be evaluated and managed for possible dengue or chikungunya virus infection.
  - Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue can be ruled out.
Resources
Pediatric Evaluation and Follow-up Tools

Initial Evaluation and Outpatient Management During the First 12 Months of Life for Infants with Possible Congenital Zika Virus Infection

Developing Tools for Healthcare Providers

Pregnancy & Zika Testing

Select your profession:
- Obstetrician/Gynecologist
- Family Physician
- Nurse
- Nurse-midwife
- Other healthcare provider
- State health department official
- Local health department official
- Other


*Free materials available in English, Spanish, and other languages
More Information about Zika virus

More information on caring for pregnant women, infants, or children with Zika virus infection is available at [CDC's Zika website](http://www.cdc.gov/zika).
Report Cases to US Zika Pregnancy Registry

• Healthcare providers are encouraged to report and actively monitor pregnancies and congenital outcomes among symptomatic and asymptomatic women with laboratory evidence of possible Zika virus infection

• More information
  • To contact CDC Registry staff, call the CDC Emergency Operations Center watch desk at 770-488-7100 and ask for the Zika Pregnancy Hotline or email ZIKApregnancy@cdc.gov
  • For non-urgent requests, call 800-CDC-INFO (800-232-4636)
Zika Care Connect: Improving Access to Clinical Services

• **Referral Network**
  Identify specialty healthcare providers
  » Maternal-fetal medicine, mental health services, audiology, radiology, pediatric ophthalmology, pediatric neurology, developmental pediatrics, infectious disease, and endocrinology
  » Consider joining the network if you are a healthcare professional located within one of the Zika Care Connect focus areas

• **Professional Resources**
  Information for healthcare professionals caring for patients with Zika
  » Links to materials from American Academy of Pediatrics, American College of Obstetricians and Gynecologists, CDC, and March of Dimes
  » Contact information for the CDC Zika Pregnancy Hotline

Website: www.zikacareconnect.org
HelpLine: 1-844-677-0447 (toll-free)
Future directions
Congenital Zika Syndrome: Sequelae

- Developmental delay/cognitive impairment
- Failure to thrive
- Cerebral palsy, arthrogryposis
- Epilepsy
- Hydrocephalus/microcephaly/poor brain growth
- Vision loss
- Sensorineural hearing loss
- Death (especially in fetal brain disruption)
Zika Virus: Vaccine Development

- NIH DNA plasmid vaccine
- Phase 2 trials began March 2017
  - Estimated completion date: 2019
- Other vaccine strategies
  - Inactivated virus
  - Attenuated live virus
  - Gene-based platform: mRNA
  - Genetically engineered version of vesicular stomatitis virus
  - Protection against multiple mosquito-borne diseases

Thank you!