Zika Virus Update for Clinicians

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Topics to be covered

- Brief overview of Zika virus disease
- Clinical presentation, diagnosis, management, and prevention
- Zika virus and pregnancy
  - CDC Guidance for Pregnant Women
  - US Zika Pregnancy Registry
Zika virus

Zika Virus Transmission and Current Domestic and International Situation

Susan Hills
Medical Epidemiologist
Arboviral Diseases Branch
What is Zika virus disease?

- Disease spread primarily through the bite of an *Aedes* mosquito infected with Zika virus
  - Aggressive daytime biters,
  - Live in and around households
  - Lay eggs in domestic water-holding containers
  - Also transmit dengue and chikungunya viruses

*Aedes aegypti* mosquito
Transmission of Zika virus

- Non-vector modes of transmission
  - Intrauterine and perinatal transmission
  - Sexual transmission
  - Laboratory exposure

- Theoretical modes of transmission
  - Blood transfusion
  - Organ or tissue transplantation
  - Breast milk
  - Fertility treatment

Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. NEJM DOI: 10.1056/NEJMra1602113

CDC: All Countries and Territories with Active Zika Virus Transmission Link to Areas with Active Zika (accessed 4/11/16)
Where is Zika now?

35 countries and territories in the Americas and 43 countries worldwide reporting active Zika virus transmission (as of 4/20/16)
Status of Zika Virus in the United States

- Local vector-borne transmission of Zika virus has not been reported in the continental United States
Estimated Range of *Aedes aegypti* and *Aedes albopictus* Mosquitoes in the United States

*Aedes aegypti*

*Aedes albopictus*

*Maps have been updated from a variety of sources. These maps represent CDC's best estimate of the potential range of *Aedes aegypti* and *Aedes albopictus* in the United States. Map is not meant to represent risk for spread of disease.*
Zika Virus

Zika Virus Presentation, Diagnosis, Management and Prevention

Maleeka Glover
Clinical Inquiries, Medical Investigations Team
April 26, 2016
Clinical Presentation

- Most people infected with Zika virus won’t even know they have the disease because they won’t have symptoms.

- Symptoms are mild and last for several days to a week:
  - Fever, maculopapular rash, arthralgia, conjunctivitis
  - Myalgia, headache
  - Severe disease requiring hospitalization is uncommon

- Once a person has been infected, he or she is likely to be protected from future infections.
Diagnosis

- Preliminary diagnosis is based on the patient’s clinical features, places and dates of travel, and activities

- Reverse transcription-polymerase chain reaction (RT-PCR) for viral RNA in serum collected ≤7 days after symptom onset

- Serology for immunoglobulin M (IgM) in serum collected ≥4 days after illness onset

- HCPs should contact their state or local health department to facilitate testing

Reporting

- Zika virus is a nationally notifiable condition
- State, local, and territorial health departments are encouraged to report laboratory-confirmed cases to CDC through ArboNET, the national surveillance system for arboviral diseases.
- Healthcare providers should report suspected Zika cases to their state, local, or territorial health department according to the laws or regulations for reportable diseases in their jurisdiction
Clinical Management

- No vaccine or specific antiviral treatment; supportive care
- Treat the symptoms:
  - Get plenty of rest
  - Drink fluids to prevent dehydration
  - Take medicine such as acetaminophen to reduce fever and pain
  - Avoid aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS) until dengue can be ruled out to reduce the risk of bleeding
  - Avoid aspirin in children due to the association with Reye’s syndrome
  - If you are taking medicine for another medical condition, talk to your healthcare provider before taking additional medication.
Prevention of Zika Virus Infection

- Mosquito prevention
  - Air conditioning or window and door screens when indoors
  - Long-sleeves and long pants
  - Use permethrin-treated clothing and gear
  - When use as directed on the product label, most EPA*-registered insect repellants can be used in children ≥ 2 months
  - Oil of lemon eucalyptus should not be used in children < 3 years old
  - Mosquito netting for carriers, strollers, or cribs for infants

*N= Environmental Protection Agency
Nasci, RS et al. Protection against Mosquitoes, Ticks, & Other Arthropods in Chapter 2: The Pre-Travel Consultation: Counseling & Advice for Travelers
Does Zika cause Guillain-Barré Syndrome (GBS)?

- GBS is an uncommon sickness of the nervous system in which a person’s own immune system damages the nerve cells.
- GBS symptoms include weakness of the arms and legs that is usually the same on both sides of the body.
- These symptoms can last a few weeks or several months. Although most people fully recover from GBS, some people have permanent damage.
- GBS is very likely triggered by Zika in a small proportion of infections, much as it is after a variety of other infections.
- CDC is investigating the link between Zika and GBS.

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On March 25, 2016, this report was posted as an MMWR Early Release on the MMWR website (http://www.cdc.gov/mmwr). CDC issued interim guidance for the prevention of sexual transmission of Zika virus on February 5, 2016 (1). The following recommendations apply to men who have traveled to or reside in areas with active Zika virus transmission* and their female or male sex partners. These recommendations replace the previously issued recommendations and are updated to

onset; RT-PCR of blood at that time was negative (7). Because serial semen specimens were not collected for these three cases, the duration of persistence of infectious Zika virus in semen remains unknown.

All reported cases of sexual transmission involved vaginal or anal sex with men during, shortly before onset of, or shortly after resolution of symptomatic illness consistent with Zika virus disease. It is not known whether infected men who never
Sexual Transmission of Zika Virus: CDC Recommendations for Men Who Live in or Traveled to an Area of Active Zika Virus Transmission

Couples in which a woman is pregnant

- Use condoms consistently and correctly or abstain from sex for the duration of the pregnancy

Other couples concerned about sexual transmission

- If man had confirmed Zika virus infection or clinical illness consistent with Zika virus disease
  - Should consider using condoms or abstaining from sex for at least 6 months after illness onset
- If man traveled to an area with active Zika virus transmission but did not develop symptoms
  - Should consider using condoms or abstaining from sex for at least 8 weeks after departure from the area
- If man resides in an area with active Zika virus transmission but has not developed symptoms
  - Might consider using condoms or abstaining from sex while active transmission persists

Zika Virus

Implications for Pregnant Women

Dana Meaney-Delman MD MPH, FACOG
Clinical Team, Pregnancy and Birth Defects Task Force

April 26, 2016
First time in history...

"Never before in history has there been a situation where a bite from a mosquito could result in a devastating malformation," Frieden said. –April 13, 2016

“...the last time an infectious pathogen (rubella virus) caused an epidemic of congenital defects was more than 50 years ago...”  

“[Zika] became the first major infectious disease linked to human birth defects to be discovered in more than half a century and created such global alarm that the World Health Organization (WHO) would declare a Public Health Emergency of International Concern.”  
– Petersen et al. March 30, 2016
Zika Virus Infection in Pregnant Women

- Pregnant women can be infected
  - Through a mosquito bite
  - Through sex with an infected male partner
- If infected around conception,
  - Zika might present risk to fetus
- If infected during pregnancy,
  - Zika can be passed to the fetus during pregnancy or around the time of birth
Zika Virus in Pregnancy

- Limited information demonstrates:
  - No evidence of increased susceptibility
  - Infection can occur in any trimester
  - Incidence of Zika virus infection in pregnant women is not known
  - No evidence of more severe disease compared with non-pregnant people
CDC Lab Confirms Zika In Fetal Tissues

- Zika virus RNA and/or antigen has been identified in:
  - Amniotic fluid
  - Placenta
  - Brain
  - Products of conception
Brain Abnormalities Associated with Congenital Zika Virus Infection

- Intracranial calcifications
- Hydrocephalus ex-vacuo
- Hydranencephaly
- Pachygyria, lissencephaly
- Agyria
- Brain atrophy and asymmetry
- Enlargement of posterior fossa
- Ventriculomegaly
- Restricted middle cerebral artery flow

- Abnormally formed or absent structures
  - Corpus callosum
  - Thalami
  - Cerebellar vermis
  - Brainstem

Infants with Microcephaly

AP Photos/Felipe Dana

Note scattered intracranial calcifications

Note large ventricles and volume loss
**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
- Photos and x-ray from 1990 series*; phenotype appears to be present in affected babies in Brazil

Zika Virus – Fetal Brain Abnormalities

- 2016 Brazil study: 42 women with laboratory-confirmed Zika virus infection with prenatal ultrasound
  - 12 (29%) abnormalities detected, including 2 intrauterine fetal deaths
  - 7 (17%) structural brain anomalies (microcephaly, calcifications, cerebellar atrophy, ventriculomegaly)

- 2013-14 outbreak in French Polynesia
  - 8 cases of microcephaly identified
  - Modeling estimated infection with Zika during 1st trimester of pregnancy resulted in microcephaly risk of ≈1%


Fetal Brain Abnormalities and Prolonged Viremia

2016 case report: pregnant woman with symptom onset 12 weeks’ gestation

- Prenatal ultrasound
  - No prenatal diagnosis of microcephaly
  - Decrease in head circumference from 47th to 24th percentile 16-20 weeks
  - Abnormal intracranial anatomy at 19 weeks
  - Fetal MRI at 20 weeks: brain abnormalities, including diffuse cerebral atrophy

- Postmortem evaluation
  - Diffuse cerebral cortical thinning
  - High levels of Zika virus RNA; positive viral culture

Reviewing the evidence for causality
Zika is a cause of microcephaly
Adverse Outcomes and Zika Virus

- A range of problems related to CNS injury have been detected among fetuses and infants with known or suspected congenital infection with Zika virus
  - Eye abnormalities
  - Hearing impairment
  - Seizures
  - Swallowing impairment
  - Hypertonicity and posturing
  - Contractures including club foot and arthrogryposis
  - Severe irritability
  - Developmental delay
  - Growth abnormalities include IUGR and disproportionate growth (head size alone affected)
Pregnancy Outcomes and Zika Virus

- Zika virus has been linked to spontaneous abortion and fetal demise but evidence is insufficient at this point in time to determine causality.
- Researchers are collecting data to better understand the clinical spectrum of congenital Zika virus disease.
  - US
  - Brazil
  - Colombia
Many Questions Remain

- What is the level of risk from a Zika virus infection during pregnancy?
- What is the level of risk when a woman has symptoms of Zika as compared to when she does not have symptoms?
- When during pregnancy Zika virus infection poses the highest risk to the fetus?
- What is the full range of potential health problems that Zika virus infection may cause?
- What are other factors (e.g., co-occurring infection) that might affect the risk for birth defects?
What CDC is Doing to Learn More

Collecting data for action

US Zika Pregnancy Registry

Zika Active Pregnancy Surveillance System (Puerto Rico)

Proyecto Vigilancia de Embarazadas con Zika (Colombia)
What CDC is Doing to Share Information

- Providing updated clinical guidelines
- Sharing up-to-date information
- Responding to your inquiries (24/7 hotline)
Clinical Inquiries Hotline

- Call the CDC Emergency Operations Center Watch Desk at 770-488-7100 and ask for the Zika Pregnancy Hotline
- Email ZikaMCH@cdc.gov.
Tools for Healthcare Providers

Update: Interim Guidance for Health Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016

PRECONCEPTION COUNSELING
For Women and Men Living in Areas with Ongoing Spread of Zika Virus Who Are Interested in Conceiving

Recommendation Key Issue Questions to Ask Sample Script
Assess pregnancy intention Introduce importance of pregnancy planning Have you ever thought about having a baby? Would you like to become pregnant in the next year? Are you currently using any form of birth control?
Assess risk of Zika virus exposure Environment Do you have air conditioning in your home? At work? Do you have windows and doors screens in your home? Are you at work? Do you have a bed? If so, you feel comfortable sleeping in bed? Do you live in an area with a lot of mosquitoes? Are you willing to wear clothes that cover your skin, like long pants and long-sleeved shirts?
Personal measures to prevent mosquito bite

What CDC knows about Zika virus and pregnancy
• Zika virus can spread from mother to fetus during pregnancy and around the time of birth.
• What CDC doesn’t know about Zika virus and pregnancy and is researching quickly to find out
• How the virus will affect the fetus.
• How often the virus is passed to fetuses.
• When in pregnancy the infection might lead to birth defects or other pregnancy complications.
• When in pregnancy the infection might lead to your health effects for the fetus.

How can I find out if I have Zika?
If you get infected with Zika, the virus will be in your blood for about 4 months. If you get sick with a fever, joint pain, rash, or eye pain, doctors or other healthcare providers can take a small amount of your blood and test for Zika virus.

www.cdc.gov/zika

CDC's Response to Zika
ZIKA Virus Testing for Pregnant Women Living in an Area with ZIKA

CDC understands that pregnant women may be worried and have questions about Zika virus infection during pregnancy. Learn more about Zika virus testing for pregnant women and what you might expect if you have Zika virus during your pregnancy.
CDC Guidance for Healthcare Providers Caring for Pregnant Women
CDC Recommendations:
Testing Asymptomatic Pregnant Women with Possible Exposure

- Serologic (IgM) testing can be offered to asymptomatic pregnant women
- Negative IgM result within 2-12 weeks after exposure could suggest a recent infection did not occur and obviate serial ultrasounds
- Information about performance of testing of asymptomatic persons limited
CDC Recommendations:

Testing Pregnant Women Travelers with Possible Exposure

- If one or more signs/symptoms of Zika virus disease within 2 weeks of travel, serum testing should be performed.
- Testing can be offered to asymptomatic pregnant women with possible exposure:
  - History of travel to an area with active Zika virus transmission or
  - Sex without a condom with a symptomatic male.
- Testing is not currently recommended for pregnant women with possible sexual exposure to Zika virus if both partners are asymptomatic.
CDC's Response to Zika
Updated Interim Guidance:
Testing Algorithm for a Pregnant Woman with Possible Exposure to Zika Virus\(^1,\)\(^2\), Not Residing in an Area with Active Zika Virus Transmission\(^3\)

1. Pregnant woman with possible exposure to Zika virus
   - Test for Zika virus infection
     - Positive or inconclusive for Zika virus infection
       - Consider serial fetal ultrasounds
     - Negative for Zika virus infection
       - Fetal ultrasound to detect abnormalities consistent with Zika virus disease\(^4\)
         - Fetal abnormalities consistent with Zika virus disease present
           - Retest pregnant woman for Zika virus infection
         - Fetal abnormalities consistent with Zika virus disease not present
           - Routine prenatal care

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\(^1\) Possible exposure to Zika virus includes travel to an area with active transmission of Zika virus (http://wwwnc.cdc.gov/travel/e/zika), or sex without a condom with a man who traveled to, or resided in, an area with ongoing transmission of Zika virus.

\(^2\) Testing is not currently recommended for pregnant women with possible sexual exposure to Zika virus if both partners are asymptomatic.


\(^4\) Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasounds might not detect abnormalities until the second or early third trimester of pregnancy.
**CDC Recommendations:**

**Testing Pregnant Women Who Reside in an Area with Zika**

- If one or more signs/symptoms of Zika virus disease, testing should be performed at presentation
- If the woman does not report one or more signs/symptoms of Zika virus disease, serum IgM testing for Zika virus can be offered:
  - Upon initiation of prenatal care, and (if negative)
  - In mid-second trimester
- Repeat testing if develops symptoms
- Pregnant women with male partners who have or are at risk of Zika virus infection should use condoms or abstain from sexual activity for the duration of pregnancy
CDC’s Response to Zika
Updated Interim Guidance:
Testing Algorithm for a Pregnant Woman Residing in an Area with Active Zika Virus Transmission¹, with or without Clinical Illness² Consistent with Zika Virus Disease³

Pregnant woman residing in an area with local Zika virus transmission

Pregnant woman reports clinical illness consistent with Zika virus disease

Test for Zika virus infection

Positive or inconclusive for Zika virus infection

Consider serial fetal ultrasounds

Negative for Zika virus infection

Fetal ultrasound

Fetal abnormalities consistent with Zika virus disease⁴ present

Retest pregnant woman for Zika virus infection

Fetal abnormalities consistent with Zika virus disease not present

Routine prenatal care
  - Test for Zika virus infection mid-2nd trimester
  - Consider an additional fetal ultrasound

Pregnant woman does not report clinical illness consistent with Zika virus disease

Test for Zika virus infection upon initiation of prenatal care

Positive or inconclusive for Zika virus infection

Consider serial fetal ultrasounds

Fetal ultrasound at 18–20 weeks of gestation
  - Test for Zika virus infection mid-2nd trimester

Negative for Zika virus infection

No fetal abnormalities consistent with Zika virus disease⁴, consider retest for Zika virus infection

Fetal abnormalities consistent with Zika virus disease⁴

Routine prenatal care
  - Consider an additional fetal ultrasound

¹Local health officials determine when to implement testing of asymptomatic pregnant women based on information about levels of Zika virus transmission and laboratory capacity.

²Clinical illness is consistent with Zika virus disease if one or more signs/symptoms (acute onset of fever, rash, arthralgia, or conjunctivitis) are present:


⁴Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasounds might not detect abnormalities until late second or early third trimester of pregnancy.
Zika Virus Infection and Pregnancy: Clinical Management

- Positive or inconclusive Zika virus testing results
  - Antepartum
    - Consider serial ultrasounds every 3–4 weeks
    - Referral to maternal-fetal medicine specialist is recommended
  - Postpartum
    - Histopathologic examination of the placenta and umbilical cord
    - Testing of frozen placental tissue and cord tissue for Zika virus RNA
    - Testing of cord serum for Zika and dengue virus IgM and neutralizing antibodies
US Zika Pregnancy Registry
U.S. Zika Pregnancy Registry

- **Purpose of registry:** To monitor pregnancy and infant outcomes following Zika virus infection during pregnancy and to inform clinical guidance and public health response.

- **How it works:** The registry is a supplemental surveillance effort coordinated by CDC and dependent on the voluntary collaboration of the state, tribal, local, and territorial health departments.
U.S. Zika Pregnancy Registry

- **Who is included**: Pregnant women with laboratory evidence of Zika virus infection and exposed infants born to these women; infants with laboratory evidence of congenital Zika virus infection and their mothers

- **How can you support the registry?** Spread the word about the US Zika Pregnancy Registry and assist with health department follow-up for pregnant women and infants who are part of the registry
# U.S. Zika Pregnancy Registry Forms

**Mother’s Zika virus infection (ADB follow-up)**

<table>
<thead>
<tr>
<th>Mother’s name:</th>
<th>Last</th>
<th>First</th>
<th>MI</th>
<th>State/Territory ID:</th>
<th>DOB:</th>
<th>State/Territory of residence:</th>
<th>Maiden name (if applicable)</th>
</tr>
</thead>
<tbody>
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<thead>
<tr>
<th>County of residence:</th>
<th>Ethnicity:</th>
<th>□ Hispanic or Latino</th>
<th>□ Not Hispanic</th>
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**Race (check all that apply):** □ American Indian or Alaska Native □ Asian □ Black or African American □ Native Hawaiian or other Pacific Islander □ White

**Indication for maternal Zika virus testing:** □ Exposure history, no known fetal concerns □ Exposure history and fetal concerns

**Date of Zika virus symptom onset:** ___/____/____  OR- □ Asymptomatic

**Neonate Assessment**

<table>
<thead>
<tr>
<th>Infant’s name:</th>
<th>Last</th>
<th>First</th>
<th>MI</th>
<th>Sex: □ Male □ Female □ Ambiguous/undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s State/Territory ID</td>
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<tr>
<td>DOB:</td>
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**Gestational age at delivery:** weeks days

<table>
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<tr>
<th>State/Territory of residence:</th>
<th>County of residence:</th>
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**Infant follow up: □ 2 months □ 6 months □ 12 months**

<table>
<thead>
<tr>
<th>Infant’s State/Territory ID</th>
<th>Mother’s State/Territory ID</th>
<th>DOB:</th>
<th>Sex: □ Male □ Female □ Ambiguous/undetermined</th>
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**Infant Death:** □ No □ Yes, date ___/____/____ □ Unknown

Weight: □ grams □ lbs/oz

Length: □ cm □ in

Head circumference □ cm □ in

**Infant findings for corrected age at examination:** (For infants born preterm, please account for corrected age: chronological age minus weeks born before 40 weeks gestation)

- Vaginal □ Caesarean section
- Arterial Cord blood pH if performed
- Venous Cord blood pH if performed

**Based on (check all that apply):** □ LMP □ U/S (1st trimester) □ U/S (2nd trimester) □ U/S (3rd trimester) □ Other
More information about Zika

- More information is available on the U.S. Zika Pregnancy Registry website at [Registry website](https://www.cdc.gov/zika/pregnancy/registry.html). 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](mailto:ZIKApregnancy@cdc.gov).

- More information on caring for pregnant women, infants, or children with Zika virus infection is available at [CDC's Zika website](https://www.cdc.gov/zika/).
Thanks to our many collaborators and partners!

For clinical questions, please contact

ZikaMCH@cdc.gov

For U.S. Zika Pregnancy Registry questions, please contact

ZikaPregnancy@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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.
Additional slides
Special Considerations –
Pregnant Women Living Along the U.S.-Mexico Border

- HCPs should assess patients’ travel histories
  - Frequency of cross-border travel and destinations
  - Include discussion of sexual partners’ travel

- Local health officials to determine when to implement testing of asymptomatic pregnant women based on
  - Information about local levels of transmission
  - Lab capacity
Updated Recommendations:

Testing for Persons with Possible Zika Virus Exposure Who Are Attempting Conception

- Testing of serum should be performed in persons with possible exposure to Zika virus who have one or more Zika-related symptoms

- Routine testing is not currently recommended for women or men who are attempting conception who have possible exposure to Zika virus but have NO symptoms
Updated CDC Recommendations:

Women and Men Interested in Conceiving

Background: viremia

- No current evidence that Zika virus will cause congenital infection in pregnancies conceived after resolution of maternal Zika viremia
- Incubation period for Zika virus disease 3-14 days
- Viremia range from a few days to 1 week (longest documented 11 days)
Interpretation of Prenatal and Postnatal Findings

- If postnatal findings differ from prenatal, clinical judgment is needed
- Example: Newborn with
  1) A prenatal diagnosis of microcephaly
  2) A normal head circumference after birth and normal examination
     - Newborn likely considered to NOT have abnormality consistent with congenital Zika virus disease
     - Newborn would qualify for right side of algorithm
     - Newborn’s testing dependent on mother’s testing