



Clinical Evidence Surrounding the Zika Virus

WHAT IS THE CLINICAL EVIDENCE IN THE LITERATURE SURROUNDING THE PRESENTATION, SCREENING, AND TREATING OF THE ZIKA VIRUS?

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LEGEND	
<b>ACOG:</b>	American Congress of Obstetricians and Gynecologists
<b>CDC:</b>	Centers for Disease Control and Prevention
<b>CSF:</b>	Cerebrospinal Fluid
<b>IgM:</b>	Immunoglobulin M
<b>PRNT:</b>	Plaque Reduction Neutralization Testing
<b>RT-PCR:</b>	Reverse Transcriptase-Polymerase Chain Reaction
<b>U/S:</b>	Ultrasound

**PROBLEM STATEMENT**

Zika virus is a single-stranded RNA virus of the *Flaviviridae* family that is transmitted to humans through the bite of an infected *Aedes* species mosquito that rarely results in severe complications or death.<sup>1,2,4,9</sup> Historically confined to Africa and Asia, cases are reported in Central and South America, Mexico, the Caribbean, Puerto Rico and the United States.<sup>3,4,9</sup>

**EVIDENCE SUMMARY**

- Viral transmission primarily occurs via mosquito bites, indoors or out, at any time, but primarily during the day.** Perinatal and *in utero* transmission have been reported, with transmission through sexual intercourse and blood transfusions. Zika virus RNA has been identified in asymptomatic blood donors during an ongoing outbreak.<sup>1,2,5-13</sup> ●
- Anyone living in or traveling to an area where the Zika virus is found is at risk for transmission.** The [CDC](#) advises women who are pregnant or who could become pregnant to delay travel to [specific destinations](#). Women can become infected at any stage of pregnancy, and it is unknown at which stage(s) transmission to the fetus occurs.<sup>2</sup> ●
- Approximately 1 in 5 people infected will become symptomatic.** Clinical symptoms include acute onset fever with maculopapular rash, arthralgia, conjunctivitis, myalgia, and headache. Concurrent cases of Guillain-Barre syndrome have been reported. Presentation of illness is similar in pregnant women, but **reported fetal microcephaly and poor pregnancy outcomes in women infected with Zika virus while pregnant warrant additional caution.**<sup>1,2,4,5,9,14-15</sup> ●
- Diagnosis relies on clinical presentation and recent travel/activities, and lab testing involves analysis of serum, plasma, viral nucleic acid, or immunoglobulin M and neutralizing antibodies specific to the virus. However, there is **no commercially available diagnostic test, with testing limited to CDC and selected state health departments.**<sup>16-17</sup> ●
- With diagnosis, timing is key. Within one week after symptom appearance, **reverse transcriptase-polymerase chain reaction (RT-PCR) of serum or plasma can aid diagnosis although positive results may not necessarily predict fetal infection.** Additional case reports suggest efficacy in performing RT-PCR from urine samples.<sup>18-19</sup> Neutralizing antibodies can be used to differentiate between Zika and *Flavivirus* through plaque-reduction neutralization testing (PRNT), but cross-reaction with flaviviruses such as dengue and yellow fever commonly occur.<sup>20</sup> ●
- The **incubation period** of Zika virus is not known, but **estimated to be a few days to a week.**<sup>2</sup> ●
- CDC guidance suggests pregnant women with risk of or confirmed Zika infection may require one or more of the following: fetal ultrasound, amniocentesis, and/or postnatal histologic examination with RNA testing of placenta and umbilical cord and testing of cord serum for neutralizing antibodies.** Due to symptom similarities, women should be tested for dengue and chikungunya virus infection.<sup>1</sup> For further details, please see [Appendix](#). ●
- There is **no preventive vaccine or medication to treat for Zika virus, and information from the CDC is incomplete.** Additional studies are required to identify effective treatments.<sup>21</sup> **Current treatment is supportive care**, including rest, fluids, and acetaminophen for fever while avoiding aspirin/NSAIDs until dengue fever is ruled out. Patients should avoid further mosquito bites.<sup>2,22</sup> **In pregnant women with laboratory confirmation of Zika virus, serial ultrasounds (U/S) are recommended to monitor fetal development and growth.**<sup>1,23</sup> Serial U/S is also recommended for all pregnant women who travel to endemic regions regardless of symptoms. Based on lab tests, gestational age, and severity of U/S findings, ACOG states pregnancy termination or delivery at a neonatal facility may be warranted.<sup>23</sup> ●

**Strength of Recommendation:** ● C: Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.

## KEY COMMUNICATIONS TO CLINICIANS & FACILITIES<sup>23,24,28</sup>

### *About the Virus*

- The **majority of infection is asymptomatic** and symptomatic disease (1 in 5 patients) is generally mild.
- **No evidence suggests pregnant women are more susceptible to Zika virus** or have more severe disease.
- The true **incidence of microcephaly with Zika infection is unknown**, and diagnosing microcephaly is difficult.
- The **most common symptoms** are fever, rash, joint pain, or conjunctivitis (red eyes); other common symptoms include muscle pain and headache.
- The **incubation period is likely to be a few days to a week**, and usually remains in the blood of an infected person for a few days.

### *Avoiding Risk*

- The primary focus of transmission prevention is **protective measures for mosquito bites throughout the day**.
- **Mosquito prevention strategies** include: wearing long-sleeved shirts and long pants, using U.S. Environmental Protection Agency (EPA)–registered insect repellents (repellents containing DEET, picaridin, and IR3535 are safe in pregnancy), using permethrin-treated clothing and gear, and staying in screened or air-conditioned rooms.
- **Avoid travel** to areas where Zika virus transmission is ongoing if pregnant.
- Partners can protect each other by using **condoms during vaginal, anal and oral sexual activity**. Refer to the CDC for continuing guidance to prevent sexual transmission of the virus.
- **Do not donate blood for 28 days** after returning from an endemic area to avoid risk of transmission to others.

### *Screening At-Risk Patients*

- Introduce recent travel inquiries to **all pregnant women, even if asymptomatic, and any nonpregnant adults, adolescents and pediatric patients with symptoms** into nursing workflow.
- **Symptomatic women who have traveled to an endemic area for Zika virus in last 2 weeks should have RT-PCR Zika virus testing**, and be considered for additional testing for other mosquito-transmitted viruses (such as dengue and chikungunya virus). Testing asymptomatic pregnant women is not recommended.
- **Serial ultrasounds** are recommended for pregnant women with a history of travel to an area with Zika virus transmission to detect microcephaly or intracranial calcifications.

### *Facility Guidance*

- The CDC recommends all **pregnant or symptomatic patients be screened for travel to endemic areas and receive appropriate laboratory evaluation**.
- Screening of pregnant women will most commonly be performed by their provider as an outpatient prior to any obstetric admission; however **screening should be verified upon admission**.
- **In certain facility areas** (e.g. ED, OB triage) where pregnant patients may be evaluated for the first time during the pregnancy, the **facility is responsible for primary screening of the Zika virus**, as well as for providing an **outpatient prenatal care provider referral**.
- Use **Facility Point of Contact Screens for Acute Respiratory Symptoms including recent travel** to any Caribbean Island, South America, Central America, Mexico or Samoa for **all pregnant women, even if asymptomatic**. Please refer to the [CDC travel website](#) for the latest affected areas.
- For **neonates born with suspected microcephaly**, resources or referral options should already be in place to insure proper postnatal follow-up.
- Per CDC guidelines, **outpatient prenatal care providers need to schedule or perform follow-up sonographic surveillance** for intracranial calcifications or microcephaly for all potentially infected pregnant patients, even if asymptomatic, who have traveled to endemic areas.
- Health care providers **must report suspected Zika infection cases to the local and state health departments** who in turn will notify confirmed cases to the CDC.

## EVIDENCE SEARCH DESCRIPTION

Systematic literature search [keywords: zika virus, zika virus treatment, treating zika virus, screening] of PubMed.gov, Medline Complete, CINAHL, Google Scholar, CDC.gov, and society websites through January 27, 2016, was conducted to identify relevant or ongoing trials.

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**Table 1. Screening in Women and Pediatric Patients**<sup>1,6,16-17,20,24,26</sup>

	<b>Pregnant Women</b>	<b>Infants</b>
<b>Which members of this population?</b>	<ul style="list-style-type: none"> <li>Assess travel history of pregnant women to guide decisions regarding tests.</li> <li>Pregnant women with a history of travel to a Zika virus transmission area and who report two or more symptoms consistent with Zika virus disease (including acute onset of fever, maculopapular rash, arthralgia or conjunctivitis) during or within two weeks of travel should be tested.</li> <li>Pregnant women with a history of travel to a Zika virus transmission area and who have abnormal ultrasound findings of fetal microcephaly or intracranial calcifications should also be tested for Zika virus.</li> <li>Testing is not indicated for pregnant women without a travel to Zika virus transmission area, and not recommended for asymptomatic pregnant women with a travel history unless there is an abnormal fetal ultrasound finding.</li> <li>Should also be evaluated for dengue and chikungunya virus infection</li> </ul>	<p>Infants (born to women who traveled to or live in Zika virus transmission area during pregnancy) who were diagnosed with microcephaly or intracranial calcifications or have mothers with positive or inconclusive test results.</p>
<b>How is Zika virus infection diagnosed, and how is testing conducted?</b>	<ul style="list-style-type: none"> <li>Zika virus RNA detected by RT-PCR in any clinical specimen (can be diagnosed by serum RT-PCR within first week of illness)</li> <li>Serology assays can also be used to detect Zika virus-specific IgM and neutralizing antibodies</li> <li>Plaque-reduction neutralization testing (PRNT)</li> <li>Positive Zika virus IgM with confirmatory neutralizing antibody titers that are <math>\geq 4</math>-fold higher than dengue virus neutralizing antibody titers in serum (considered inconclusive if <math>&lt; 4</math>-fold higher). Completed on specimen collection <math>\geq 4</math> days after symptom onset</li> </ul>	<ul style="list-style-type: none"> <li>RT-PCR and Zika virus-specific Immunoglobulin M (IgM) tests</li> <li>PRNT</li> <li>Testing conducted at the CDC Arbovirus Diagnostic Laboratory and select state health departments</li> </ul> <p><u>Congenital infection</u></p> <ul style="list-style-type: none"> <li>Viral RNA is found in any newborn specimen or during amniotic fluid or placenta testing</li> <li>IgM antibodies are found with confirmed neutralizing antibody titers that are <math>\geq 4</math>-fold higher than dengue virus neutralizing antibody titers in infant serum or CSF</li> <li>Considered inconclusive if viral IgM antibodies are found, but neutralizing antibody titers are less than 4-fold higher than dengue virus neutralizing antibody titers</li> </ul>

	Pregnant Women	Infants
<b>What specimens can be collected for testing?</b>	<ul style="list-style-type: none"> <li>• Zika virus RT-PCR and serology assays on maternal serum, plasma, or amniotic fluid.</li> <li>• Histopathologic examination and immunohistochemical staining of the placenta and umbilical cord</li> <li>• Frozen placental tissue and cord tissue</li> <li>• IgM and neutralizing antibody testing of cord blood</li> </ul>	<ul style="list-style-type: none"> <li>• Zika virus RT-PCR and serology assays on infant serum or serum/plasma collected from the umbilical cord</li> <li>• RT-PCR on fixed and frozen tissue</li> <li>• If cerebrospinal fluid (CSF) specimens readily available, conduct RT-PCR; however, CSF should not be obtained solely for testing</li> <li>• Histopathologic examination and immunohistochemical staining of the placenta and umbilical cord</li> </ul>
<b>Challenges to diagnosis</b>	<ul style="list-style-type: none"> <li>• RT-PCR may not detect Zika virus RNA in an infected patient if beyond the “period of viremia”.</li> <li>• Cross-reactivity with related flaviviruses (dengue and yellow fever viruses) complicating differentiation among infections</li> <li>• Neutralizing antibodies may cross-react results in patients with previous <i>Flavivirus</i> infection or yellow fever or Japanese encephalitis vaccination.</li> </ul>	<ul style="list-style-type: none"> <li>• RT-PCR tests may not detect Zika virus RNA in a newborn who was infected in utero beyond the “period of viremia.”</li> <li>• Serologic tests can lead to false-positives due to cross-reaction.</li> <li>• Neutralizing antibodies may cross-react with maternal antibodies transferred to the infant.</li> </ul>
<b>What are other considerations for patient evaluation?</b>	See Table 2	<ul style="list-style-type: none"> <li>• If positive or inconclusive results, comprehensive physical exam (head circumference, length, weight, and gestational age)</li> <li>• Cranial ultrasound (unless conducted during third trimester prenatal screening and no abnormalities were detected)</li> <li>• Ophthalmologic evaluation</li> <li>• Hearing screen at six months</li> <li>• Developmental milestones, through the first year of life (including head circumference)</li> </ul>

**Table 2. Fetal Ultrasound and Amniocentesis in Pregnant Women With Suspected Zika Virus Infection<sup>1,24,27</sup>**

	<b>Fetal Ultrasound</b>	<b>Amniocentesis</b>
<b>Who should undergo this test?</b>	<ul style="list-style-type: none"> <li>Part of routine care of pregnant women at 18-20 weeks of gestation to evaluate fetal anatomy</li> </ul>	<ul style="list-style-type: none"> <li>Offered to pregnant women with recent travel to Zika virus transmission area and a positive or inconclusive maternal serum test.</li> <li>Pregnant women with recent travel to Zika virus transmission area and ultrasound findings of microcephaly or intracranial calcifications.</li> <li>Consultation with a maternal-fetal medicine specialist</li> </ul>
<b>Why should pregnant women consider this test?</b>	<ul style="list-style-type: none"> <li>Microcephaly and intracranial calcifications can be detected during routine ultrasounds, as well as later ultrasounds through progression of pregnancy. Microcephaly and intracranial abnormalities have been reported in pregnant women with confirmed Zika virus infection and have been detected as early as 18-20 weeks.</li> </ul>	<ul style="list-style-type: none"> <li>Amniocentesis can be offered to pregnant women with abnormal ultrasound findings and recent travel to a Zika virus transmission area.</li> <li>Risk vs. benefits of amniocentesis should always be considered.</li> <li>Positive amniotic fluid RT-PCR result suggests intrauterine infection and can guide decisions about delivery timing and the level of neonatal care</li> </ul>
<b>When to consider testing?</b>	<ul style="list-style-type: none"> <li>If a pregnant woman has symptoms consistent with Zika virus disease infection during or within 2 weeks of travel, she should see a healthcare provider.</li> <li>In the absence of clinical symptoms during or within 2 weeks of travel, pregnant women should undergo ultrasound evaluation.</li> <li>Serial ultrasound screening is based on provider discretion and should be considered in pregnant woman with Zika virus in serum or amniotic fluid specimens.</li> <li>Optimal time for ultrasound screening for fetal microcephaly/neurologic abnormalities is unknown.</li> </ul>	<ul style="list-style-type: none"> <li>Timing of amniocentesis is individualized and based on the patient's clinical status.</li> <li>Amniocentesis is not recommended until after 15 weeks of gestation due to decreased complication rate</li> <li>Referral to maternal-fetal medicine/infectious disease specialist with expertise in pregnancy management may be needed.</li> <li>Assess the risks vs. benefits of testing.</li> </ul>

Document Version	1
Last Major Revision	<New Search Date>
Last Minor Revision	<Added Reference Number, Date>
Original Published Date	February 5, 2016
Last Updated	<Month, Year>
Reviewers	Dr. Jon Perlin, Dr. Ravi Chari, Dr. Jane Englebright, Dr. JT Christmas, Dr. Ed Septimus, Julia Moody, Sue Cadwell, 7 Members included in Physician Expert Review