

CDC Issues Guidelines for Zika Virus in Pregnancy CME/CE

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Clinical Context

An outbreak of infections with the Zika virus has caught the nation's attention, especially following reports of fetal microcephaly associated with the infection. The Zika virus is a flavivirus, like dengue and chikungunya, and it can be challenging to separate infections with these different viruses based on their initial clinical presentation and laboratory testing. The Zika virus is spread by *Aedes aegypti* mosquitoes, which are primarily found in Latin America but also can be encountered in the United States.

Approximately 80% of individuals infected with the Zika virus are asymptomatic, and the infection is mild for most patients in whom clinical symptoms develop. Symptoms of Zika virus infection include fever, arthralgia, maculopapular rash, and conjunctivitis. The duration of symptoms is usually less than 1 week, and hospitalization and mortality are rare.

The data regarding infection with Zika virus during pregnancy are very limited. There is no evidence to suggest that pregnancy predisposes women to infection with the Zika virus, or that the course of illness is more severe during pregnancy. However, it is clear that vertical transmission of the Zika virus can occur throughout pregnancy, and there have been a number of case reports of microcephaly among infants whose mothers were infected with the Zika virus. Therefore, the US Centers for Disease Control and Prevention (CDC) has put together guidelines for the care of pregnant women during the current Zika virus outbreak.

Synopsis and Perspective

On January 19, the CDC issued interim guidance for obstetricians and other healthcare providers caring for pregnant women returning to the United States from areas affected by the Zika virus.

The new guidance, published online on January 19 and appearing in the January 22nd issue of *Morbidity and Mortality Weekly Report*,^[1] follows a travel alert issued by the agency. In that advisory,^[2] the CDC advised women who are or might become pregnant not to travel to 14 countries and territories in Central and South America and the Caribbean where the Zika virus is spreading.

OB/GYNs Asked to Screen, Test for Zika in Pregnancy

Working in consultation with the American Congress of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, the CDC advised clinicians to ask all pregnant women about recent travel to areas where Zika virus transmission is ongoing. Those who report such travel and experience fever, rash, muscle aches, or conjunctivitis during or within 2 weeks of travel should be tested for Zika virus infection, and positive test results for Zika should be reported to the appropriate local or state health department.

Maternal serum from symptomatic women can be tested using reverse-transcription polymerase chain reaction (RT-PCR) within 1 week of symptom onset. Antibody testing is not recommended 4 or more days after symptom onset, as there can be cross-reactivity to other flaviviruses (eg, dengue or yellow fever). Amniotic fluid can also be tested using RT-PCR, but the sensitivity and specificity are unknown at this time.

The agency notes that no test is currently commercially available, but testing can be done at the CDC and several state departments of health. Detailed instructions on Zika clinical evaluation^[3] and on Zika diagnostic testing,^[4] including detailed instructions for preparing and sending specimens, are provided in the CDC.gov website.

The CDC guidance recommends that clinicians who care for Zika-positive pregnant women consider scheduling regular ultrasound examinations to monitor the growth of the fetus, as Zika has been linked to microcephaly.

There is as yet no effective antiviral treatment of Zika. The CDC recommends symptomatic treatment, including acetaminophen for pregnant women who have fever.

First Confirmed Zika Microcephaly Case in US

The first confirmed case of Zika-related microcephaly in the United States was reported on January 15^[5] and involved a mother who had lived in Brazil in May 2015 before moving to Hawaii.

In addition, public health officials have recently confirmed several cases of Zika in adults in the continental United States, including a woman in Harris County, Texas,^[6] who had traveled to El Salvador. Also, 3 cases were confirmed in Florida:^[7] 2 in Miami-Dade County, in residents who had traveled to Colombia in December, and 1 in a Hillsborough County resident who had traveled to Venezuela in December.

All US Zika Cases From Travel to Other Countries -- So Far

CDC press officer Candice Burns Hoffmann, from the National Center for Emerging and Zoonotic Infectious Diseases, emphasized to *Medscape Medical News* that so far there have been no cases of locally transmitted Zika in the United States.

Hoffmann said, "The first travel-associated Zika virus disease case among U.S. travelers was reported in 2007. From 2007-2014, a total of 14 returning U.S. travelers had positive Zika virus testing performed at CDC. In 2015 and 2016, at least 12 U.S. travelers have had positive Zika virus testing performed at CDC. However, CDC is still receiving specimens for Zika virus testing from returning U.S. travellers who became ill in 2015 or 2016."

The CDC expects to see more cases of Zika virus among travelers visiting or returning to the United States, which is likely to increase the risk for localized spread in areas such as the Gulf Coast, where there are mosquitoes capable of spreading the virus.

"CDC has been monitoring outbreaks in the Americas and is prepared to address cases imported into the United States and cases transmitted locally," Hoffmann said. She also noted that experience with recent chikungunya and dengue outbreaks in the United States, vectored by the same mosquito species as the Zika virus, suggest that Zika outbreaks in the US mainland will likely be small and focal.

Increased Cases of Babies Born With Microcephaly in Brazil

Zika is a relatively mild problem for adults -- only 1 in 5 of whom becomes symptomatic with fever, rash, arthralgia, or conjunctivitis -- but represents a major risk for the developing fetus.

According to the CDC, "During the current outbreak in Brazil, Zika virus RNA has been identified in tissues from several infants with microcephaly and from fetal losses in women infected during pregnancy.^[8] The Brazil Ministry of Health has reported a marked increase in the number of babies born with microcephaly. However, it is not known how many of the microcephaly cases are associated with Zika virus infection and what factors increase risk to the unborn baby. Additional studies are planned to learn more about the risks of Zika virus infection during pregnancy. Guillain-Barré syndrome also has been reported in patients following suspected Zika virus infection."

Experts Warn of Brazil Summer Olympic Games Zika Risk

Kamran Khan, MD, and colleagues in the Division of Infectious Diseases at the University of Toronto, Ontario, Canada, modeled the anticipated international spread of Zika virus from Brazil and reported in the *Lancet*^[9] that from September 2014 to August 2015, a total of 9.9 million travelers departed for international destinations from Brazilian airports in areas conducive to year-round Zika transmission. Of these, 65% traveled to the Americas, 27% to Europe, and 5% to Asia. In their study, published online January 14 in the *Lancet*, the authors note that more than 60% of the populations of Argentina, Italy, and the United States live in areas conducive to seasonal Zika transmission.

With no vaccine or antiviral therapy available, the main tools for fighting Zika remain personal protection such as insect repellents, community-level mosquito-control

measures, and disrupting the human-mosquito-human transmission chain by helping Zika-infected patients avoid being bitten by other mosquitoes.

"The summer Olympic Games in Brazil in August, 2016, heighten the need for awareness of this emerging virus" Khan and colleagues concluded.

Dr Khan is founder of BlueDot, a social benefit corporation that models global infectious disease threats.

Highlights

- The CDC recommends that all pregnant women consider postponing travel to areas in which the transmission of the Zika virus remains active. The infection is currently most prevalent in Central America and South America.
- *A aegypti* mosquitoes bite mostly during the daytime. Persons who must travel to areas of active Zika infections should practice advanced mosquito prevention strategies. The authors note that insect repellents containing DEET, picaridin, and IR3535 are safe to use during pregnancy.
- Healthcare providers should query all pregnant women about recent travel. However, only symptomatic women with symptoms within 2 weeks of travel should be tested for infection with the Zika virus. These women should be evaluated for dengue and chikungunya virus as well.
- There are no commercially available tests for the Zika virus infection. Available tests use RT-PCR technology as well as antibody testing. State and local health departments may be necessary to help interpret test results.
- Fetal ultrasonography should be ordered regardless whether the test result for the Zika virus is positive among symptomatic women. Ultrasonography should also be performed among asymptomatic women with a history of travel to areas of active Zika virus infection.
- If microcephaly or intracranial calcifications are present on fetal ultrasound, women should have the option to undergo amniocentesis and counseling. The Zika virus can be isolated from amniotic fluid, but the sensitivity and specificity of this testing are unknown.
- If results on fetal ultrasonography are normal in a woman with a positive test result for the Zika virus, the clinician and patient should consider serial fetal ultrasounds every 3 to 4 weeks to monitor fetal anatomy and growth.
- Any positive test result for the Zika virus should prompt a referral to a maternal-fetal medicine specialist or an infectious disease specialist with expertise in pregnancy.
- After delivery in a case of maternal Zika virus infection, the placental and cord tissue and cord serum should be tested for the Zika virus. The CDC is developing guidelines for the management of infants infected with the Zika virus.
- There is no treatment for infection with the Zika virus beyond supportive care.

Clinical Implications

- The Zika virus is usually acquired via mosquito bites, but approximately 80% of individuals infected with the Zika virus remain asymptomatic. The duration of

symptoms is usually less than 1 week in the remainder of infected patients, and hospitalization and mortality are rare with Zika infection.

- The current guidelines by the CDC suggest that pregnant women avoid travel to areas of active Zika virus infection. For those individuals who must travel to such areas, insect repellents can be safe during pregnancy. Women who return from areas of active Zika virus infection should undergo fetal ultrasonography to detect cranial abnormalities, but only symptomatic women and women with abnormal ultrasound findings should undergo serologic testing for the Zika virus.
- Implications for the Healthcare Team: Travel history is not typically at the forefront of issues in completing the history of prenatal patients, but the potentially devastating effects of the Zika virus infection mean that the healthcare team should be actively searching for at-risk patients. Moreover, the team can spread the message among pregnant women to avoid travel to areas with active Zika virus infection.

CME Test

To receive *AMA PRA Category 1 Credit™*, you must receive a minimum score of 75% on the post-test.

You are seeing a woman in prenatal care for her first pregnancy. She is currently at 18 weeks' estimated gestational age and just returned from a vacation in Costa Rica. She is asymptomatic, but you consider whether she might have an infection with the Zika virus. Which of the following statements regarding the epidemiology and clinical presentation of Zika virus infection is *most* accurate?

- It is transferred person to person via droplets or aerosols
- Most individuals with infection remain asymptomatic
- The duration of illness is at least 2 weeks

Approximately 60% of patients with Zika virus infection require hospitalization

According to the current guidelines from the CDC, what is the *best* course of action for this patient with potential exposure to the Zika virus?

- No special treatment
- Fetal ultrasonography only
- Maternal serum testing for the Zika virus only
- Maternal serum testing for the Zika virus, ultrasonography, and consideration of amniocentesis

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