CDC Provides Interim Guidance on Congenital Zika Virus CME/CE

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Faculty and Disclosures

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Clinical Context

The Zika virus has received large amounts of attention in the lay media and medical press, and patients and clinicians are both concerned about this public health threat. There has been a confirmed case of infection with the Zika virus in the United States. This case involved a woman who was most likely infected during a trip to El Salvador and was subsequently diagnosed with the Zika virus in Texas.

The characteristic symptoms of infection with the Zika virus include fever, maculopapular rash, myalgia, and conjunctivitis, although up to 80% of patients infected with the Zika virus may remain asymptomatic. In a recent poll of clinicians published in *Medscape Medical News*,[1] more than 90% correctly ascertained the symptoms of Zika virus infection.

Infection with the Zika virus is particularly concerning for potential cranial and cerebral malformations among the offspring of women infected with the virus during pregnancy. The Centers for Disease Control and Prevention (CDC) recommends that pregnant women avoid travel to areas active for infection in the first place, and the agency advocates for the aggressive use of measures to prevent mosquito bites for individuals who must go to these areas. The CDC also recommends testing for the Zika virus among pregnant women with symptoms and a history of travel to countries associated with the Zika virus outbreak within the past 2 weeks. More than 70% of clinicians identified these measures in the *Medscape Medical News* clinician survey.

Overall, 70% of clinicians in the survey had heard of the Zika virus case in the United States. However, only 6% of clinicians stated that they felt "very prepared" to diagnose and manage someone with the Zika virus. To that end, the CDC offers new recommendations for the evaluation and management of infants with suspected Zika virus infection, which are summarized in Study Highlights.

Synopsis and Perspective

The CDC has issued interim guidelines for the evaluation, testing, and management of infants with possible congenital Zika virus infection.

Developed in conjunction with the American Academy of Pediatrics, the guidelines address the care of infants with microcephaly or intracranial calcifications detected prenatally or at birth, as well as infants without these findings whose risk is based on maternal exposure and testing for Zika virus infection.

The guidelines are published in the January 26 early-release issue of the *Morbidity and Mortality Weekly Report*.[2]

The CDC advises pediatric healthcare providers to work with obstetric providers to identify infants whose mothers were potentially infected with Zika virus during pregnancy (based on travel to or residence in an area with Zika virus transmission) and to review fetal ultrasounds and maternal testing for Zika virus infection.

The guidelines recommend Zika virus testing for infants with microcephaly or intracranial calcifications who were born to women who traveled to or resided in an area with Zika virus transmission while pregnant and for infants born to mothers with positive or inconclusive test results for Zika virus infection. In these situations, the CDC recommends the following:

- Infant serum should be tested for Zika virus RNA, Zika virus immunoglobulin M (IgM) and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies. The initial sample should be collected either from the umbilical cord or directly from the infant within 2 days of birth, if possible.
- If cerebrospinal fluid is obtained for other studies, it should also be tested for Zika virus RNA, Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.
- Histopathologic evaluation of the placenta and umbilical cord with Zika virus immunohistochemical staining on fixed tissue and Zika virus reverse transcription-polymerase chain reaction (RT-PCR) on fixed and frozen tissue may also be considered.
- If not already performed during pregnancy, the mother's serum should be tested for Zika virus IgM and neutralizing antibodies and dengue virus IgM and neutralizing antibodies.

For infants with possible congenital Zika virus infection, the CDC recommends the following:

- Comprehensive physical examination, including careful measurement of the occipitofrontal circumference, length, weight, and assessment of gestational age.
- Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions. Full-body photographs and any rash, skin lesions, or dysmorphic features should be documented. If an abnormality is noted, an appropriate specialist should be consulted.
- Cranial ultrasound, unless prenatal ultrasound results from the third trimester demonstrated no abnormalities of the brain.

- Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, before hospital discharge or within 1 month after birth. Infants with abnormal initial hearing screening results should be referred to an audiologist.
- Ophthalmologic evaluation, including examination of the retina, before hospital discharge or within 1 month after birth. Infants with abnormal initial eye evaluation results should be referred to a pediatric ophthalmologist.
- Other evaluations specific to the infant's clinical presentation.

For infants with microcephaly or intracranial calcifications, the CDC recommends the following additional actions:

- Consultation with a clinical geneticist or dysmorphologist.
- Consultation with a pediatric neurologist to determine appropriate brain imaging and additional evaluation.
- Testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infections. Clinicians should consider consulting a pediatric infectious disease specialist.
- Complete blood count, platelet count, and liver function and enzyme tests, including alanine aminotransferase, aspartate aminotransferase, and bilirubin.
- Consideration of genetic and other teratogenic causes based on additional congenital anomalies that are identified through clinical examination and imaging studies.

The CDC also recommends long-term follow-up for infants with possible congenital Zika virus infection:

- Clinicians should conduct additional hearing screen at age 6 months, plus any appropriate follow-up of hearing abnormalities detected through newborn hearing screening.
- Clinicians should carefully evaluate occipitofrontal circumference and developmental characteristics and milestones throughout the first year of life, with use of appropriate consultations with medical specialists (eg, pediatric neurology, developmental and behavioral pediatrics, physical and speech therapy).

The CDC encourages health providers to report cases of possible congenital Zika virus infection to their state, territorial or local health departments, and monitor for additional guidance as it is released. "As an arboviral disease, Zika virus disease is a nationally notifiable condition," the CDC notes.

"No specific antiviral treatment is available for Zika virus infections and no vaccine against Zika virus is available," the CDC states. "Treatment of congenital Zika virus infection is supportive and should address specific medical and neurodevelopmental issues for the infant's particular needs; investigations are ongoing to better understand what services will be most effective for these children as they grow," the agency adds.

More information on the Zika virus can be found on the CDC's website.[3]

Study Highlights

- There are 2 principal groups of infants who should receive testing for the Zika virus:
    - Children with microcephaly or intracranial calcifications whose mothers resided in or traveled to an area with active Zika virus transmission.
    - Children born to mothers with positive or inconclusive testing results for the Zika virus.
- Microcephaly is defined by an occipitofrontal circumference less than the third percentile, based on standard growth charts. Neurologic deficits may also prompt testing for the Zika virus, even if the occipitofrontal circumference is slightly higher.
- Infants with suspected Zika virus infection should also have an ophthalmologic examination in the first month of life, as this infection may promote abnormal eye findings.
- Clinicians should report cases of positive or inconclusive findings for Zika virus infection to state or local health departments. Children who fit these criteria should complete a second formal hearing test at 6 months, as the Zika virus is associated with sensorineural hearing loss.
- Children with possible Zika virus infection after testing should receive a cranial ultrasound examination. Children with microcephaly or intracranial calcifications should receive a consultation with a geneticist or dysmorphologist.
- These children should also be considered for consultation with an infectious disease specialist, and testing should be performed for other congenital infections such as rubella, cytomegalovirus, syphilis, toxoplasmosis, herpes simplex virus, and choriomeningitis virus infection.
- Infants with normal findings and whose mothers tested negative for the Zika virus infection may receive routine newborn care only.
- There are no commercially available tests for the Zika virus. Testing is completed at the CDC and at some state public health laboratories.
- When indicated, children should be tested for the Zika virus using RT-PCR as well as serologic testing for Zika virus IgM. Clinicians may also consider immunohistochemical staining to identify the Zika virus antigen.
- Testing should be performed on the placenta and umbilical cord of suspicious cases for the Zika virus. The infant's serum may also be tested within 2 days of birth. The child's cerebrospinal fluid should also be tested with RT-PCR for the Zika virus.
- There is cross-reactivity between the Zika virus and dengue, but serum IgM testing can be useful to differentiate between the 2 infections.
- There is no specific antiviral treatment of infection with the Zika virus. Care is primarily supportive. Women are encouraged to breastfeed infants in areas of Zika virus infection, as the benefits of breastfeeding are thought to outweigh those of potential vertical transmission of the virus via breastfeeding.

Clinical Implications

- A recent survey revealed that most clinicians appear to have heard about the diagnosis of a case of Zika virus in the United States, but only 6% feel very prepared to diagnose and manage a case of this infection. Most clinicians could

identify the key symptomatic criteria of fever, maculopapular rash, myalgia, and conjunctivitis associated with the Zika virus infection, as well as measures to prevent and diagnose the infection.

- The current CDC recommendations advocate testing for the Zika virus among infants born with microcephaly or intracranial calcifications, as long as their mothers have a history of recent travel to an area of Zika virus infection. Children born to mothers with positive or inconclusive testing results for the Zika virus should also be tested. Testing for infants suspected of having Zika virus infection should include RT-PCR and serologic testing.
- Implications for the Healthcare Team: Emerging infections with potentially devastating consequences require a high level of vigilance by the healthcare team. All pregnant women should be queried regarding any history of travel to areas with active Zika virus infection, and there should be proactive efforts to counsel pregnant women to avoid travel to these areas. The healthcare team should also cooperate by testing for newborns with possible Zika virus infection, as well as counseling and follow-up testing for infants with inconclusive or positive results.

CME Test

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

You hear about an infant being considered for evaluation for the Zika virus infection on her first day of life. The infant was a full-term normal spontaneous vaginal delivery from an uncomplicated pregnancy, and the estimated gestational age is 37 weeks. The mother returned from travel to Brazil 2 weeks ago, but she is asymptomatic. A fetal ultrasound result 1 week ago was normal, and all neonatal measurements are normal as well. According to the recent survey from *Medscape Medical News*, what should you consider regarding clinicians' confidence in caring for patients with possible Zika virus infection?

- Only 10% of clinicians have heard of the Zika virus
- Most clinicians feel confident in the diagnosis and management of Zika virus infection
- Most clinicians identify intractable abdominal pain and diarrhea as the key symptoms of Zika virus infection
- Most clinicians identify appropriate means to prevent and diagnose Zika virus infection

According to the current recommendations from the CDC, what might you recommend regarding Zika virus testing for this infant?

- Assessment with RT-PCR and serologic testing
- Assessment with RT-PCR only
- Assessment with serologic testing only
- No testing for the Zika virus

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