Interim Guidance for the Diagnosis, Evaluation, and Management of Infants with Possible Congenital Zika Virus Infection (CDC Agency Guidance)

Brief Authors
Kelly Todd, JD/MA Candidate [5]

Brief Editors

The Policy

Synopsis

On October 20, 2017, the Centers for Disease Control and Prevention (CDC) issued an updated interim clinical guidance [10] for healthcare providers caring for infants with possible congenital Zika virus infection. According to the CDC [11], the updated guidance emphasizes the importance of healthcare
providers properly assessing the risk of congenital Zika virus infection, communicating with obstetrical providers, and remaining alert for problems that may develop later on in infants without birth defects born to mothers with possible Zika virus exposure during pregnancy.

The CDC's guidance suggests that a physician’s first step in caring for an infant with possible Zika exposure should be to determine whether the infant presents clinical findings consistent with congenital Zika syndrome [12]. Congenital Zika syndrome is a unique pattern of birth defects marked by the following features:

- Severe microcephaly involving a partially collapsed skull;
- Decreased brain tissue arising from a specific amount and pattern of brain damage;
- Eye damage (i.e., scarring, pigment changes);
- A limited range of motion in joints, such as clubfoot; and
- Restricted body movement arising from too much muscle tone soon after birth.

The updated guidance goes on to provide specific directions for healthcare providers in three clinical scenarios:

1. Infants with clinical findings consistent with congenital Zika syndrome regardless of maternal testing results;
2. Infants without clinical findings consistent with congenital Zika syndrome who were born to mothers with laboratory evidence of possible Zika virus infection; and
3. Infants without clinical findings consistent with congenital Zika syndrome who were born to mothers without laboratory evidence of possible Zika virus infection.

Laboratory evidence of Zika virus infection requires a determination of clinical levels of Zika virus RNA or immunoglobulin M [13] (“IgM”) present in a body fluid sample. For infants falling within the third group, the CDC does not recommend further testing or clinical evaluation. For the first and second groups, the CDC offers specific guidance.

The standard evaluation recommended by the CDC involves the following components:

- Comprehensive physical exam, including growth parameters;
- Developmental monitoring and screening using validated screening tools [14] recommended by the American Academy of Pediatrics [15];
- Vision screening as recommended by the American Academy of Pediatrics Policy Statement Visual System Assessment in Infants, Children, and Young Adults by Pediatricians [16]; and
- Newborn hearing screen at birth, preferably with automated auditory brainstem response.

The recommendations for infants with clinical findings consistent with congenital Zika syndrome born to mothers with possible Zika virus exposure in pregnancy (Category 1) include:

- Initial evaluation:
  - Standard evaluation (see above for more detail);
  - Zika virus RNA nucleic acid testing [17] (NAT) and IgM testing;
  - Consider Zika virus NAT and IgM testing on cerebrospinal fluid (CSF);
  - Head ultrasound by one month of age;
  - Comprehensive ophthalmologic exam by one month of age;
Automated auditory brainstem response (ABR) testing by one month of age; and
Evaluate for other causes of congenital anomalies.

- Referral to developmental specialist and early intervention services;
- Provide family support services;
- Consider additional consultations with:
  - Infectious disease specialist – for evaluation for other congenital infections and assistance with Zika virus management;
  - Clinical geneticist – for confirmation of clinical phenotype and evaluation for other causes of microcephaly or congenital anomalies;
  - Neurologist – by one month of age for comprehensive neurologic examination;
  - Ophthalmologist – by one month of age for comprehensive eye exam; and
  - Other clinical specialists based on clinical findings of infant.

The recommendations for infants without clinical findings consistent with congenital Zika syndrome born to mothers with laboratory evidence of possible Zika virus infection during pregnancy (Category 2):

- Initial evaluation:
  - Standard evaluation (see above for more detail);
  - Zika virus NAT and IgM testing;
  - Head ultrasound by one month old;
  - Comprehensive ophthalmologic exam by age 1 month; and
  - Automated ABR by one month old.

- If initial evaluation is abnormal or there is laboratory evidence of congenital Zika virus infection, proceed with further testing and referrals recommended for infants with findings consistent with Congenital Zika Syndrome;
- If initial evaluation is normal and there is no laboratory evidence of congenital Zika virus infection, infection is unlikely and infants should continue to receive routine care; and
- Health care providers should remain alert for any new findings of congenital Zika virus infection.

Finally, the guidance addressed the methods used for the prenatal diagnosis of congenital Zika virus infection. Citing a lack of evidence on the reliability of using ultrasound or amniocentesis [18] to diagnose Zika virus infection before delivery and the absence of effective interventions to treat congenital Zika virus infection, the CDC recommends a shared decision-making model.

**Context**

In updating this guidance, the CDC incorporated new laboratory evidence of Zika virus infection, including evidence on eye findings, post-natal onset microcephaly, post-natal onset hydrocephalus, sleep abnormalities, and diaphragmatic paralysis. The guidance also accounted for the updated guidance for health care providers caring for pregnant women with possible Zika virus exposure and the uncertainty regarding the sensitivity and specificity of currently available diagnostic tests for congenital Zika virus infection.

Prior to publishing this guidance, the CDC convened the **Forum on the Diagnosis, Evaluation, and Management of Zika Virus Infection Among Infants** [19] to obtain expert opinions and to identify strategies to enhance communication and coordination of care of mothers and infants affected by Zika virus.
Policy History

This guidance updates the CDC’s August 2016 interim guidance [20] on the same issue.

The Science

Science Synopsis

**Zika virus** [21] is a viral infection that is mainly spread through the bite of an infected mosquito. The symptoms [22] associated with Zika virus infection are generally mild, and include mild fever, rash, and joint or muscle pain for individuals with a healthy immune system. One meta-analysis found that 82% [23] of individuals infected with Zika virus showed no symptoms, and may not even know that they have been infected. Zika virus can also be transmitted through unprotected sexual intercourse [24]; the CDC released the “Clinical Guidance for Healthcare Providers for Prevention of Sexual Transmission of Zika Virus” [25] to address this mode of transmission.

The limitations of current diagnostic tests are largely due to the transience of Zika virus RNA in body fluids. The level of Zika virus IgM that is present in a given sample is affected by the timing of sample collection. False-negative results can be caused by sample collection before the development of IgM antibodies, or after the antibodies have waned. False-positive results may occur when IgM antibodies remain detectable for months after the initial infection, or due to the cross-reactivity of Zika virus IgM antibody tests with other flaviviruses. In drafting its updated guidance, the CDC considered the limitations of these tests, as well as the declining prevalence of Zika virus infection in the Americas. The lower prevalence of Zika infection translates to a lower pretest probability of infection and a higher probability of false-positive test results.

Though Zika symptoms are generally mild and nonirritating, Zika virus has obtained notoriety as a public health threat due to the serious complications linked to Zika infections during pregnancy. Recent studies have confirmed links between Zika virus infection during pregnancy to miscarriage [26] and other serious birth defects [27], including serious damage to the brain and microcephaly [28]. About one in ten [29] children in the United States who are exposed to Zika virus in utero are born with birth defects.

A child born with microcephaly has a head size much smaller than other babies of the same age and sex, and will likely experience a number of problems including seizures, developmental delays, intellectual disabilities, feeding problems, hearing loss, and vision problems. Zika infection during pregnancy can also lead to congenital Zika syndrome [29], “a pattern of birth defects that includes brain abnormalities, vision problems, hearing loss, and problems moving limbs.” Though the mechanisms by which Zika virus causes microcephaly and other birth defects are still not completely understood, studies have suggested that the virus may attack stem cells [30] during early brain development.

In adults, there is some evidence linking Zika virus infection with certain neurological diseases [31], including Guillain-Barré syndrome.
Zika virus infection currently has no treatment or vaccine [22], and prevention efforts mainly focus on reducing the risk of mosquito bites.

**Relevant Experts**

**Sallie Permar** [32], MD/PhD, is a Professor of Pediatrics, Immunology, and Molecular Genetics and Microbiology at Duke University Medical Center. *Her research* [33] focuses on the development of immunologic strategies to eliminate neonatal pathogens.

**Relevant publications:**


**The Debate**

**Endorsements & Opposition**

At present, there have not been any publicly reported endorsements of or opposition to this action.

**Status**

The guidance was published by the Centers for Disease Control and Prevention on October 20, 2017, in Volume 66, Issue 41 of the *Morbidity and Mortality Weekly Report* [36]. The CDC expects to update this guidance further as more information on Zika virus diagnosis, evaluation, and management becomes available.

The CDC issued this updated guidance in part as a follow-up to its *July 2017 updated interim guidance* [37] for health care providers caring for pregnant women with possible Zika virus exposure. The July 2017 guidance recommended a shared decision-making model for testing and screening pregnant women.

**Recommended Citation**


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