Congenital Zika Virus Infection:
Interim Guidance for Clinical Evaluation

I. INTRODUCTION

Congenital Zika virus infections result from intrauterine transmission of the virus from mother to fetus during pregnancy. Zika causes a wide range of adverse perinatal outcomes, including intrauterine fetal demise, microcephaly, other central nervous system (CNS) abnormalities, intrauterine growth retardation, and abnormal amniotic fluid volume.[1] Adverse fetal outcomes have been shown to occur following maternal infection in all trimesters, however risk for adverse outcomes by trimester of infection remains unknown.[2,3]

Infants with possible congenital Zika virus infection include those born to mothers who, while pregnant, became infected through a mosquito bite while traveling or living in a Zika-affected area*, OR through condomless sex with a partner who traveled to or resided in an area with ongoing Zika virus transmission.

Infants with possible congenital Zika virus infection who meet either of the following clinical criteria require Zika virus testing within 48 hours of birth, if possible:

i. Infants with microcephaly, intracranial calcifications, or other abnormalities detected prenatally or at birth

ii. Infants born to mothers with positive or inconclusive Zika virus test results

See the **Figure** for more information on which infants require evaluation and testing.

Care for infants with possible congenital Zika virus infection should include review of previous prenatal ultrasounds and maternal Zika virus testing, and a thorough newborn physical examination, with assessment of head (occipitofrontal) circumference, length, and weight (CDC has provided a brief video on the best way to measure head circumference: https://www.youtube.com/watch?v=LW38bgQ9vVY.)

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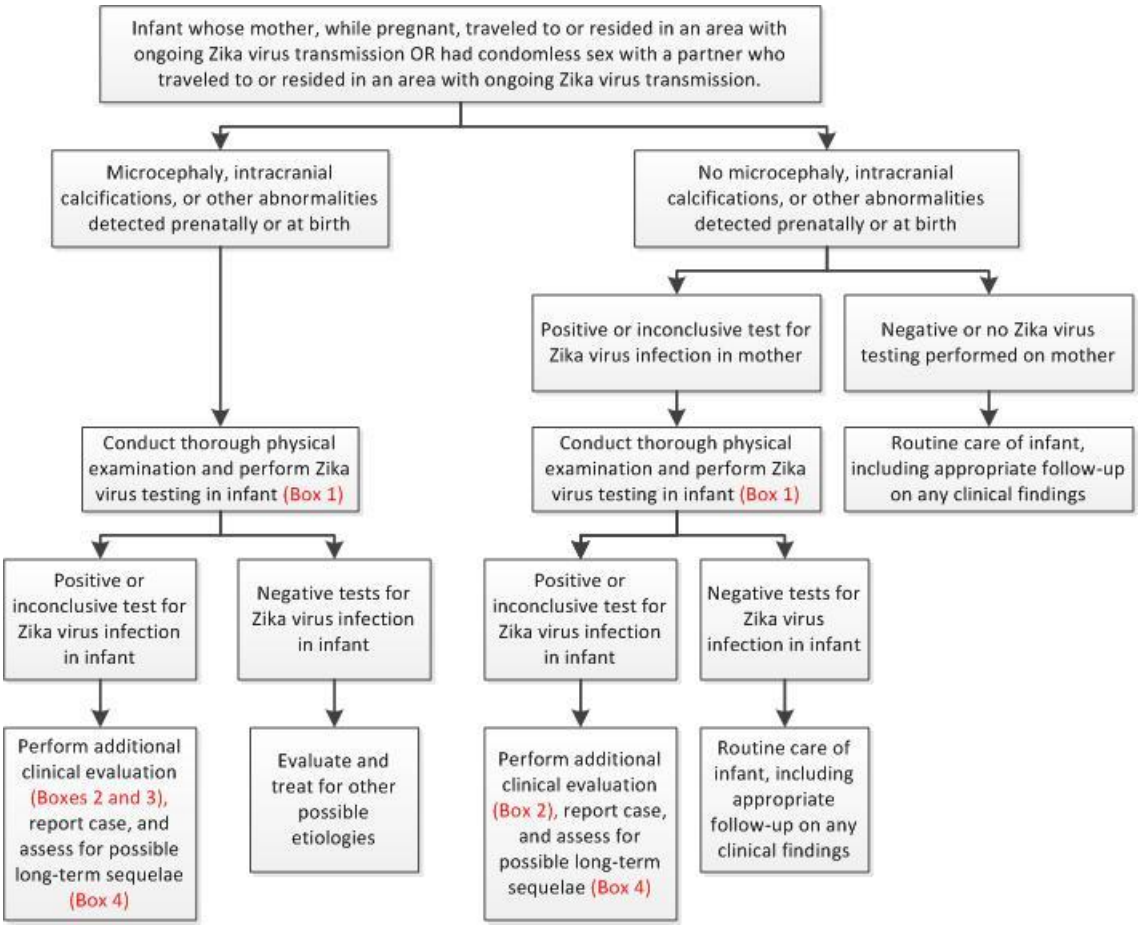
[1] Rasmussen, S. et al., NEJM Apr 13, 2016 http://www.nejm.org/doi/full/10.1056/NEJMsr1604338
[2] Mlakar, J. et al. Zika Virus Associated with Microcephaly. NEJM Mar 10, 2016 http://www.nejm.org/doi/full/10.1056/NEJMoa1600651
[3] Brasil, P. et al., Zika Virus Infection in Pregnant Women in Rio de Janeiro - Preliminary Report. NEJM Mar 4, 2016. http://www.nejm.org/doi/full/10.1056/NEJMoa1602412

*Areas with Zika virus transmission are listed on the CDC website at http://wwwnc.cdc.gov/travel/page/zika-travel-information.

Figure. Interim guidelines for evaluating infants with possible congenital Zika virus infection. [†§¶]



[†]Microcephaly defined as occipitofrontal circumference less than the third percentile for gestational age and sex based on standard growth curves not explained by other etiologies.

[§]Laboratory evidence of Zika virus infection includes 1) detectable Zika virus, Zika virus RNA, or Zika virus antigen in any clinical specimen; or 2) positive Zika virus IgM with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum or cerebrospinal fluid. Testing is considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

[¶]For infants, perform reverse transcription–polymerase chain reaction (RT-PCR) testing for Zika virus RNA and Zika virus IgM and neutralizing antibodies on serum collected from the umbilical cord or directly from infant within 2 days of birth, if possible. If cerebrospinal fluid is obtained for other reasons, test for Zika virus RNA, Zika virus IgM and neutralizing antibodies. Consider histopathologic evaluation of the placenta and umbilical cord with Zika virus immunohistochemical staining on fixed tissue and Zika virus RT-PCR on fixed and frozen tissue. More information on laboratory testing for Zika virus infection is available at http://www.cdc.gov/zika/state-labs/index.html.

Adapted from: Fleming-Dutra, K. et al., MMWR Feb 26, 2016 (http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm)

Because information on the effects of congenital Zika virus infection is limited, health care providers should exercise clinical judgment in the assessment of newborns with abnormalities other than microcephaly who were born to mothers exposed to Zika virus during pregnancy. For these infants, health care providers should consider testing the mother before testing the infant. Further clinical evaluation may also be indicated for infants born to Zika-exposed but untested mothers as well as for infants who test negative for Zika but are born to Zika-positive mothers.

These guidelines will be updated as additional information becomes available.

II. DIAGNOSTIC EVALUATION: Frequently Asked Questions

1. What are the current recommendations for laboratory testing of newborns and infants with possible congenital Zika virus infection?

Get Pre-Approval of Lab Testing from DOHMH. To test patients who are NYC residents, including newborns and infants with possible congenital Zika virus infection, providers must obtain pre-approval from DOHMH. To do so, providers must call 866-692-3641 (the DOHMH Provider Access Line), Monday to Friday, 9 a.m. to 5 p.m. Staff at this number can assist with determination of whom to test and which specimens are required. The Provider Access Line is available during non-business hours for urgent or emergent consultation with a DOHMH physician. For more information on this process, including links to relevant forms, please refer to the quick reference guide and DOHMH Health Alert #7.

BOX 1. Recommended Zika virus laboratory testing for newborns and infants with possible congenital Zika virus infection:

- Test serum for Zika virus RNA, Zika virus immunoglobulin M (IgM), and neutralizing antibodies. Collect the initial sample either from the umbilical cord or directly from the infant within two days of birth, if possible.
- If cerebrospinal fluid is obtained for other studies, test for Zika virus RNA, Zika virus IgM and neutralizing antibodies.
- Consider 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.
- If not already performed during pregnancy, test mother's serum for Zika virus IgM and neutralizing antibodies.

Adapted from: Staples, JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR 2016; 65:63–7. http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm

*Find more information on laboratory testing for Zika virus infection at cdc.gov/zika/state-labs

2. What does "laboratory evidence of Zika virus infection" include?

1) Detectable Zika virus, Zika virus RNA, or Zika virus antigen in any clinical specimen.

   OR

2) Positive results of serologic testing consisting of IgM and neutralizing antibodies in serum or cerebrospinal fluid

III. CLINICAL EVALUATION: Frequently Asked Questions

1. How do I evaluate newborns and infants with positive or inconclusive Zika virus test results?

BOX 2. Recommended clinical evaluation for newborns and infants with positive or inconclusive Zika virus test results:

- Perform a comprehensive physical examination, including careful measurement of head circumference, length, weight and assessment of gestational age.
- Evaluate for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly and rash or other skin lesions. Perform full-body photographs and photographic documentation of any rash, skin lesions or dysmorphic features. If an abnormality is noted, consult with an appropriate specialist.
- Perform a cranial ultrasound, unless prenatal ultrasound results from the third trimester demonstrated no abnormalities of the brain.
- Evaluate hearing by evoked oto-acoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 month after birth. Refer infants with abnormal initial hearing screens to an audiologist for further evaluation.
- Perform an ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within 1 month after birth. Refer infants with an abnormal initial eye evaluation to a pediatric ophthalmologist for further evaluation.
- Perform other evaluations specific to the infant's clinical presentation.

Adapted from: Staples, JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR 2016; 65:63–7. http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm

2. What additional evaluation is recommended for newborns and infants with possible congenital Zika virus infection and microcephaly, intracranial calcifications, or other abnormalities?

Box 3. For Zika-exposed infants with microcephaly, intracranial calcifications or abnormal neurologic findings, additional evaluation includes:

- Consult with a clinical geneticist or dysmorphologist.
- Consult with a pediatric neurologist to determine appropriate brain imaging and additional evaluation (e.g., ultrasound, computerized tomography scan, magnetic resonance imaging or electroencephalogram).
- Test for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection and herpes simplex virus infections. Consider consulting a pediatric infectious disease specialist.
- Perform a complete blood count with platelet count and liver function and enzyme tests, including alanine aminotransferase, aspartate aminotransferase and bilirubin.
- Consider genetic and other teratogenic causes based on additional congenital anomalies that are identified through clinical examination and imaging studies.

Adapted from: Staples, JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR 2016; 65:63–7. http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm

3. How is microcephaly diagnosed?

Microcephaly is diagnosed when an infant's head is smaller than expected as compared to infants of the same age (or gestational age) and sex. Microcephaly, as defined by CDC in the setting of evaluating for possible congenital Zika virus infection, is a **head circumference less than the third percentile**, based on standard growth charts (e.g., Fenton, Olsen, CDC, or WHO growth curves) for sex, age and gestational age at birth. For a diagnosis of microcephaly, the head circumference should be disproportionately small in comparison with the length of the infant and not explained by other etiologies (e.g., other congenital disorders).

4. When should head circumference (HC) be measured?

The optimal time to measure HC is 24 to 36 hours after birth, when molding of the head by the birth canal has subsided. Measuring the HC earlier may not accurately reflect brain volume.

5. What is the recommended long-term follow up for infants with possible congenital Zika virus infection (as defined on page 1)?

Box 4: For all infants with possible congenital Zika virus infection, recommended long-term follow-up:

- Report case to DOHMH and monitor for additional guidance. To report, call DOHMH's Provider Access Line at 1-866-692-3641.
- Consider conducting **additional hearing screen at age 6 months**. Refer any child with developmental delay for an audiologic evaluation. Ensure that appropriate follow-up of abnormal newborn hearing screening has occurred.
- Carefully evaluate head circumference and developmental characteristics and milestones throughout the first year of life, in consultation with appropriate medical specialists (e.g., pediatric neurology, developmental-behavioral pediatrics, physical and speech therapy).

Adapted from: Staples, JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR 2016; 65:63–7. http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm

6. If a mother had Zika virus infection during pregnancy but her newborn tests negative for Zika virus, what is recommended for additional follow-up?

In the absence of abnormal findings on examination, the infant should receive routine pediatric care, including measurement of growth and development and appropriate evaluation and follow-up for any clinical findings that arise. If the newborn has abnormal findings on examination, perform diagnostic testing for other causes of the newborn's conditions, including testing for other congenital viral infections if indicated. Guidance for following infants born to Zika virus-infected mothers is below (Table).

Table. Congenital Zika Virus Infection Monitoring Assessments.

Assessments	Age 0-28 days		Age ≥28 days		
	No microcephaly, intracranial calcifications, or other abnormalities	Microcephaly, intracranial calcifications, or other abnormalities	**2 months**	**6 months**	**12 months**
Measurements					
Weight	+	+	+	+	+
Length	+	+	+	+	+
Head Circumference	+	+	+	+	+
Gestational Age Assessment	+	+	+	+	+
Physical Exam	+	+	+	+	+
Neurological	+	+			
Dysmorphisms*	+	+			
Hepatosplenomegaly	+	+			
Rash/Skin Lesions*	+	+			
Cranial Ultrasound§	+	+			
Hearing Evaluation (OAE or ABR)	+	+		+	
Ophthalmology	+	+			
Genetics Consultation		+			
Pediatric Neurology Consultation		+			
Pediatric Infectious Disease Consultation		+			
Tests					
CBC with Platelets		+			
Liver Functions		+			
Other Congenital Infections/TORCH		+			
Developmental Assessment	+	+	+	+	+

*Photographs should be obtained.
§Unless third trimester ultrasound showed no abnormality.

Adapted from: Fleming-Dutra, K. et al., MMWR Feb 26, 2016 (http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm) and Staples, J.E. et al., MMWR Jan 29, 2016 (http://www.cdc.gov/mmwr/volumes/65/wr/mm6503e3.htm).

IV. OUTCOME/PROGNOSIS: Frequently Asked Questions

1. What is the prognosis for newborns/infants with congenital Zika virus infection?
The prognosis for newborns/infants with congenital Zika virus infection is not known.

2. What is the link between Zika virus and microcephaly?
Zika causes microcephaly and other serious brain anomalies.[4]

3. If a mother infected with Zika virus near the time of delivery passes the virus to her newborn at birth, can the baby develop microcephaly?
We do not know whether a newborn who acquires Zika virus at birth will develop microcephaly after birth. There have been no reports of Zika virus infection around the time of birth leading to microcephaly in infants.

We do know that babies can develop microcephaly after birth, if their head growth slows or their brain fails to develop after birth. Such cases of microcephaly may not be linked to Zika.

4. Is there any information on neurocognitive outcomes in neonates if they are exposed to Zika virus during labor and delivery or after birth?
There is currently no information on neurocognitive outcomes in neonates exposed to Zika virus peripartum, such as during labor and delivery or after birth. Based on evidence from other flaviviruses, such as West Nile virus and dengue virus, a range of poor outcomes have been observed[7].

5. What birth defects have been reported in infants with *confirmed* congenital Zika virus infection?
Brain abnormalities reported in infants with laboratory-confirmed congenital Zika infection include microcephaly and disrupted brain growth. Two recent publications of maternal Zika cases from French Polynesia[5] and Brazil[6] indicate a wide range of risk for abnormal perinatal outcomes, including intrauterine growth restriction, cerebral calcifications, abnormal cerebral and umbilical arterial blood flow, oligohydramnios, anhydramnios, and third-trimester fetal death.

6. What birth defects have been reported in infants with *suspected* congenital Zika virus infection?
A report of 35 infants with microcephaly who were born during a 2015 outbreak of Zika virus infection in Brazil described the following brain abnormalities: intracranial calcifications, ventriculomegaly and neuronal migration disorders (lissencephaly and pachygyria). Other anomalies included congenital contractures and clubfoot. Some infants with possible Zika virus infection have been found to have intracranial calcifications and abnormal eye findings. An important distinction is that neither these infants nor their mothers had laboratory-confirmed Zika virus; however, 75 percent of the mothers reported symptoms consistent with Zika virus[7].

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[4] Rasmussen, S. et al., NEJM Apr 13, 2016 http://www.nejm.org/doi/full/10.1056/NEJMsr1604338
[5] Cauchemez, S et al., Lancet Mar 12 2016 http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)00651-6.pdf
[6] Brasil P., et al NEJM Mar 4, 2016 http://www.nejm.org/doi/full/10.1056/NEJMoa1602412
[7] Schuler-Faccini L, et al. MMWR; 65:59-62

7. What is the CDC Pregnancy Registry?

The CDC's **U.S. Zika Pregnancy Registry** collects information on Zika-infected pregnant women and their infants to better understand the range of pregnancy and infant outcomes. DOHMH will participate in this effort by collecting information about women infected during pregnancy and will follow up with the women through pregnancy outcome and the first 12 months of their infants' lives. DOHMH will collect this information from obstetric and pediatric healthcare providers and submit these data, without identifying information, to CDC. To report cases of suspected congenital Zika infection to DOHMH, call the Provider Access Line at 1-866-692-3641. Information on the registry can be found at www.cdc.gov/zika/hc-providers/registry.