Evaluation and Follow-Up Procedures for Infants with Suspected Congenital Zika Virus Infection

California Department of Public Health, March 2016

Overview:

The US Centers for Disease Control and Prevention (CDC) recommends infants be evaluated for congenital Zika virus infection and sequelae in two situations: (1) those born to mothers with positive or indeterminate Zika virus testing during pregnancy, and (2) those born with microcephaly or intracranial calcifications to a mother who was potentially exposed to Zika virus while she was pregnant. Exposure can occur through travel to or residence in an area with Zika virus transmission or unprotected sex with a male partner who previously experienced symptoms of Zika virus infection within 2 weeks of traveling to an area with active Zika virus infection. Details of these indications and recommended tests can be found at the following link and in subsequent sections: http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm

This California Department of Public Health (CDPH) document details procedural components of appropriate evaluation, testing, and reporting of such cases. In order for providers and local health jurisdictions to perform the following procedure in a timely manner, **they must be aware in advance of the following information:**

- All pregnant women testing positive for Zika virus infection **or with Zika tests still pending at time of delivery**
- Estimated dates of confinement (EDC) or due dates
- Obstetrics providers and contact information
- Hospitals where deliveries are planned

Specimen collection:

Specimens from infants might include some that can only be gathered at the time of delivery**.** Although Zika virus infection in infants is not a clinical emergency, **urgent communication with the pregnant patient's obstetric and neonatal providers might be necessary**. Potential specimens to collect can include infant serum obtained within 2 days of delivery, cord blood, placenta, umbilical cord, and/or infant cerebrospinal fluid, depending on additional information. See **Figure 1** for indications for testing of infant specimens. **Box 1** describes appropriate specimens for collection from an infant where indicated. **Table 1** includes detailed collection and storage information for each specimen type.

Clinical evaluation:

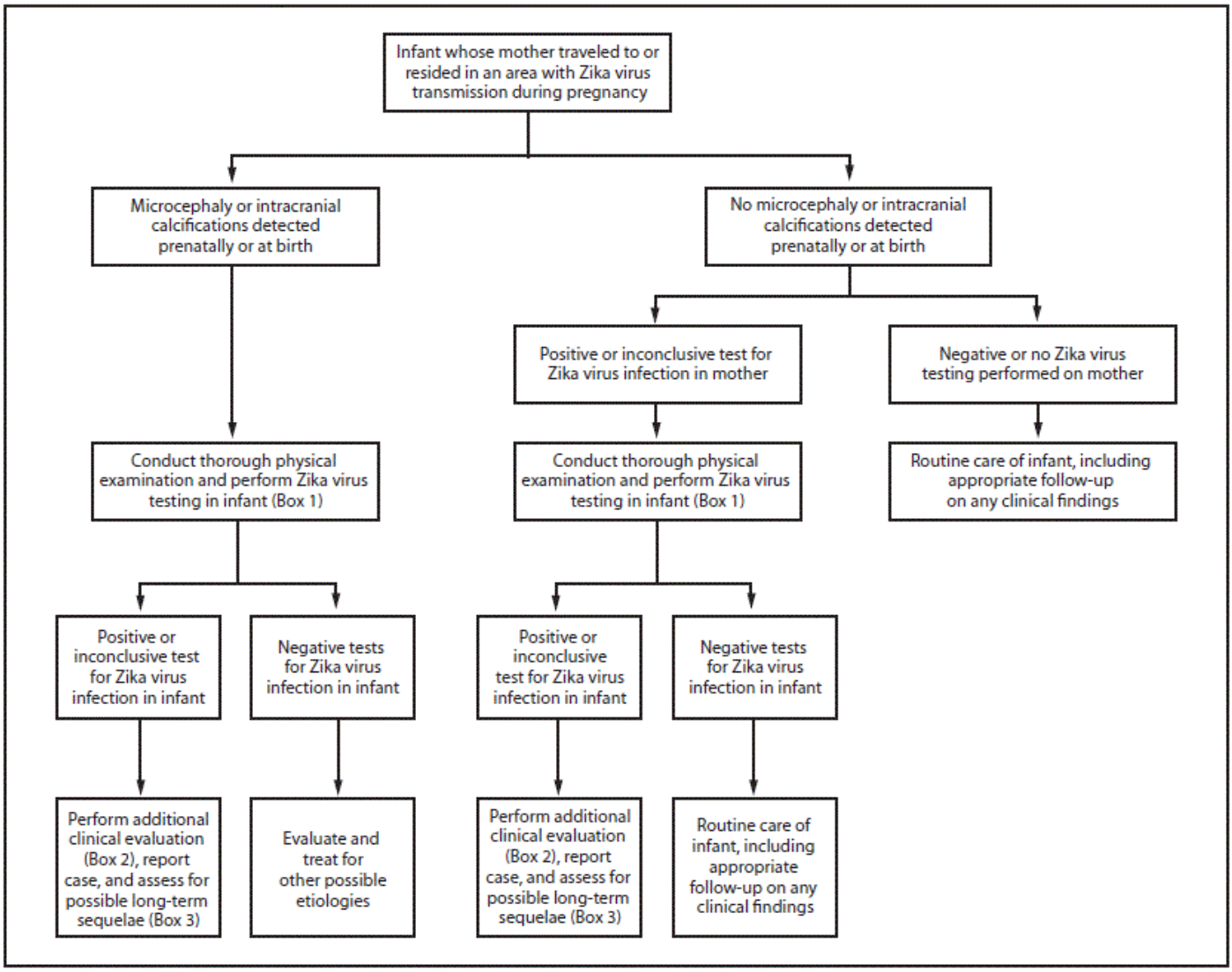
Special clinical evaluation is recommended at birth and in certain cases throughout the first year of life. See **Box 2** for appropriate clinical evaluation and additional testing to be performed at time of delivery. **Box 3** contains additional recommendations for further evaluation in certain circumstances.

Case reporting:

Any infant under evaluation for congenital Zika virus requires his or her own case report form for suspected Zika virus infection, separate from the form created for the mother. Contact your local health department for reporting information.

The information contained in the following pages was originally published in the February 26, 2016 issue of the CDC MMWR (Fleming-Dutra KE, Nelson JM, Fischer M, et al. Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65place_Holder_For_Early_Release:182–187. DOI: http://dx.doi.org/10.15585/mmwr.mm6507e1).

FIGURE 1. Interim guidelines for the evaluation and testing of infants whose mothers were potentially exposed to Zika virus during pregnancy. Note: Since this figure's publication, CDC has expanded their definition of exposure to include EITHER travel to an area with Zika virus transmission OR unprotected sex with a man who experienced symptoms of acute Zika virus infection within 2 weeks of returning to an area with Zika virus transmission.



BOX 1. Recommended Zika virus laboratory testing for infants and children when indicated*

For possible congenital Zika virus infection:

- Test infant serum 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, test for Zika virus RNA, Zika virus IgM and neutralizing antibodies, and dengue 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, and IgM and neutralizing antibodies for other potentially cross-reacting viruses as appropriate.

***Indications for testing for congenital infection include 1) an infant with microcephaly or intracranial calcifications born to a woman who traveled to or resided in an area with Zika virus transmission while she was pregnant or who had unprotected sex during her pregnancy with a man who experienced symptoms of acute Zika virus infection within 2 weeks of returning to an area with Zika virus transmission, or 2) an infant born to a mother with a positive or inconclusive test result for Zika virus infection.

Table 1: Specimen Collection and Storage for Zika virus testing in infants (updated 2/26/16)

Specimen	When to Collect	Preferred Amount	Container	Storage and Shipment Conditions	Tested at CDC	Tested at VRDL
Serum (infant)†	<2 days post onset	≥2 ml (one tube preferred)	red or tiger top tube	cold	serology, PCR	serology, PCR
Serum (mother)	at time of collection of infant serum	≥2 ml (one tube preferred)	red or tiger top tube	cold	serology, PCR	serology, PCR
CSF	if collected for other studies	≥1 ml	sterile cryovial	cold	serology, PCR	N/A
Amniotic Fluid	when available	≥1 ml	sterile cryovial	frozen	PCR	N/A
Cord Blood	when available	0.5-1 ml	sterile cryovial	cold or frozen	PCR	serology, PCR
Placental/Fetal Tissue§	when available	0.5-1.0 cm	sterile container	both a.) cold formalin fixed and b.) frozen tissues	HP, IHC, PCR	N/A

† Infant serum or cord blood are acceptable specimens for serological and PCR testing.

§ For additional information on collecting placental and fetal or infant tissues, see http://www.cdc.gov/zika/hc-providers/tissue-collection-submission.html

BOX 2. Recommended clinical evaluation and laboratory testing for infants with possible congenital Zika virus infection

For all infants with possible congenital Zika virus infection, perform the following:

- Comprehensive physical examination, including careful measurement of 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 photographic documentation of any rash, skin lesions, or dysmorphic features should be performed. If an abnormality is noted, consultation with an appropriate specialist is recommended.
- Cranial ultrasound, unless prenatal ultrasound results from third trimester demonstrated no abnormalities of the brain.
- Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 month after birth. Infants with abnormal initial hearing screens should be referred to an audiologist for further evaluation.
- Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within 1 month after birth. Infants with abnormal initial eye evaluation should be referred to a pediatric ophthalmologist for further evaluation.
- Other evaluations specific to the infant's clinical presentation.

For infants with microcephaly or intracranial calcifications, additional evaluation includes the following:

- Consultation with a clinical geneticist or dysmorphologist.
- Consultation with a pediatric neurologist to determine appropriate brain imaging and additional evaluation (e.g., ultrasound, computerized tomography scan, magnetic resonance imaging, and electroencephalogram).
- Testing 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.
- Complete blood count with 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

BOX 3. Recommended long-term follow-up for infants with possible congenital Zika virus infection

- 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 occipitofrontal circumference and developmental characteristics and milestones throughout the first year of life, in consultation with appropriate medical specialists (e.g., pediatric neurology, developmental and behavioral pediatrics, physical and speech therapy).