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To:	Local health departments and health care providers
From:	Shereen Semple, MS Vectorborne Disease & Ebola Team Lead New Jersey Department of Health (NJDOH) Infectious & Zoonotic Disease Program
Date:	January 29, 2016
Subject:	Zika Virus Update: Guidelines for the testing and evaluation of infants with possible congenital Zika

Zika virus disease (Zika) is a mosquito-borne disease that typically occurs in tropical Africa and southeast Asia. In May 2015, the Pan American Health Organization/World Health Organization (PAHO/WHO) reported the first autochthonous (local) transmission of Zika in the Americas. Local transmission is now being reported in at least twenty-four countries and territories.

The NJDOH is sending this message to local health departments (LHDs) and health care providers to provide updated guidelines for the testing and evaluation of infants born to mothers who traveled to or resided in an area with Zika virus transmission during pregnancy and to share the attached Centers for Disease Control and Prevention (CDC) Interim Guidelines for The Evaluation and Testing of Infants with Possible Congenital Zika Virus Outbreak.

As of January 28, 2016, twenty-four countries or territories are reporting current autochthonous transmission, including Barbados, Bolivia, Brazil, Cape Verde (Africa), Colombia, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Samoa (Oceania/Pacific Islands), Suriname, U.S. Virgin Islands, and Venezuela. This list may increase if more countries confirm transmission. Please visit the CDC's Zika-affected Areas webpage at http://www.cdc.gov/zika/geo/ for the most updated list of countries and territories with current Zika transmission.

For more information on Zika virus, including guidelines for testing pregnant women and non-pregnant individuals, please refer to the following:

- LINCS message #103033-1-15-2016-PHIN: *Zika Virus Disease: Guidelines for Reporting, Testing and Preventing Infection in Travelers* (sent January 15, 2016). Includes background on Zika virus, travel recommendations and prevention measures for minimizing exposure to mosquitoes.

- LINCS message #103037-1-22-2016-PHUP: *Zika virus: Updated Guidelines for Diagnostic Testing for Zika Virus* (sent January 22, 2016). Includes criteria for diagnostic testing and CDC Interim Guidelines for Pregnant Women During a Zika Virus Outbreak.
- LINCS message #103039-1-22-2016-PHAD: *Zika virus—public phone script* (sent January 22, 2016). Includes phone script for assisting local health departments with answering public calls on Zika virus.

As a reminder, clinicians and laboratories must report confirmed cases of all arboviral diseases (e.g. Zika, chikungunya, West Nile, and dengue) to the LHD where the person resides. A list of LHD can be found at http://localhealth.nj.gov As more information becomes available, additional guidance will be provided to our public health partners.

Zika Testing

Updated Testing Criteria Guidance (as of January 28, 2016):

Health care providers may consult with their local health department or the NJDOH during regular business hours to discuss laboratory testing of pregnant women or infants in the following circumstances:

- Pregnant women, or women who recently delivered, who were pregnant during or within two weeks of travel to a country with current Zika transmission and who report during that time period two or more of the following symptoms:
    - Acute onset of fever
    - Rash
    - Arthralgia
    - Conjunctivitis

- Asymptomatic pregnant women with travel to a country with current Zika transmission who have a fetal ultrasound suggestive of microcephaly or intracranial calcifications

- Infants with microcephaly or intracranial calcifications detected prenatally or at birth, and whose mother traveled to or resided in an area with Zika transmission while pregnant

- Infants born to mothers who have a confirmed positive or inconclusive test result for Zika following travel to, or residence in, an area with Zika while pregnant and reported at least two symptoms during that time period.

Requests for Testing:

Clinicians considering testing a pregnant woman or infant for Zika based on the testing considerations above should contact their LHD or the NJDOH Vectorborne Disease Program during normal business hours at (609) 826-5964. The CDC will not accept specimens sent without pre-approval from state health departments. Availability of testing may increase in the

future, and criteria for approval may change. Individuals who are approved for a Zika test should be entered into the online, secure NJDOH Communicable Disease Reporting and Surveillance System (CDRSS).

Clinicians and LHDs seeking approval for Zika testing should be prepared to provide the following information when consulting with the NJDOH: symptom onset date; list of clinical signs and symptoms (including, but not limited to rash and distribution and type of rash, fever, arthralgia, conjunctivitis, headache, myalgia, vomiting, and diarrhea); travel history including dates and location; gestational week(s) at travel and at symptom onset and duration; co-morbidities; history and year of Japanese encephalitis, tickborne encephalitis, and/or yellow fever vaccination; history of past flavivirus infection (e.g., Dengue, West Nile, St. Louis encephalitis virus); and relevant prenatal and/or laboratory testing.

Zika Testing and Testing Limitations:

Laboratory tests for Zika diagnosis are of limited availability, but include:

- Reverse transcription-polymerase chain reaction (RT-PCR) for Zika RNA
    - $\leq$7 days of symptom onset,
- Immunoglobulin M (IgM) ELISA and plaque reduction neutralization test (PRNT) for Zika virus antibodies on serum specimens
    - $\geq$ 4 days after symptom onset.

Given the overlap of symptoms and endemic areas with other viral illnesses, patients should also be evaluated for possible dengue or chikungunya virus infection.

Testing has multiple limitations:

- There are no commercial tests; testing is only available at the CDC through approval from state health departments.
- There is substantial serological cross-reactivity among the flaviviruses, including among those who have been immunized against yellow fever or Japanese encephalitis virus or who have been infected with another flavivirus (e.g., West Nile, St. Louis encephalitis virus) in the past.
- Current IgM antibody assays cannot reliably distinguish between Zika and dengue virus infections. Therefore, an IgM positive result in a dengue or Zika ELISA test should be considered indicative of a recent flavivirus infection.
- It is unknown which test is more reliable for confirming congenital infection.
- RT-PCR tests may not detect Zika virus RNA in a newborn who had Zika virus infection in utero if the period of viremia has passed.

Specimen Collection Guidance:

If testing is approved, the NJDOH or LHD will provide guidelines for sample collection and shipment to the CDC. Follow Table 1 as a guide to collecting samples from infants who meet the above testing criteria.

Table 1. Sample collection and testing guidelines for infants with suspected congenital Zika virus		
Sample	**Considerations**	**Type of Test(s)**
Serum sample from: • Umbilical cord or • Directly from infant	Within 2 Days of birth	• RT-PCR • Zika IgM and neutralizing antibodies • Dengue IgM and neutralizing antibodies
Cerebrospinal fluid (CSF)	IF obtained for other studies	• RT-PCR • Zika IgM and neutralizing antibodies • Dengue IgM and neutralizing antibodies
Frozen tissue sample from: • Placenta • Umbilical cord	N/A	• RT-PCR
Fixed tissue sample from: • Placenta • Umbilical cord	Histopathologic evaluation	• Zika immunohistochemical staining • RT-PCR
Note: Since it has not been established which test is most reliable for a diagnosis in infants, both RT-PCR and IgM tests should be performed.		

Collect serum (≥ 3 mL) in a large, red top tube. Refrigerate serum at 4°C or maintain on ice for no longer than 24 hrs. Samples collected and shipped with expected arrival the same day, can be shipped on cold packs (4°C). If storage/transport will exceed 24 hrs., serum should be frozen at -20°C or lower. These samples should be shipped on dry ice. Follow packing and shipping instructions for Category B, Biological Substances.

Acute serum (≥ 3 mL) collected within the first 7 days following symptom onset can be tested by RT-PCR. IgM antibodies may be detectable by day 4 of illness but are more reliably identified later on in the course of infection; convalescent specimens, collected 2-3 weeks later, may be necessary to confirm or rule-out infection.

Interpretation of Zika Test Results:

Results are considered positive for Zika if:

- Zika RNA or viral antigen is identified in any of the samples (including amniotic fluid, placenta, and/or umbilical cord), or
- Zika IgM antibodies with confirmatory neutralizing antibody titers are ≥4-fold higher than dengue neutralizing antibody titers.

Results are considered inconclusive for Zika if:

- Zika neutralizing antibody titers are <4-fold higher than dengue.

Evaluating Infants for Possible Congenital Zika:

The following clinical evaluation recommendations are summarized directly from the CDC's Morbidity and Mortality Weekly (MMWR) *Interim Guidelines for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection — United States, 2016* (http://www.cdc.gov/mmwr/volumes/65/wr/mm6503e3er.htm?s_cid=mm6503e3er_e) and the CDC's *Q & A's for Obstetrical Healthcare Providers: Pregnant women and Zika Virus Infection* (http://www.cdc.gov/zika/pdfs/questions-answers-clinicians.pdf). For more details, please refer to those resources.

Definition: microcephaly:
CDC defines microcephaly as occipitofrontal 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, occipitofrontal circumference disproportionately small in comparison with the length of the infant, and not explained by other etiologies (e.g., other congenital disorders).

If an infant's occipitofrontal circumference is equal to or greater than the third percentile but is notably disproportionate to the length of the infant, or if the infant has deficits that are related to the central nervous system, additional evaluation for Zika virus infection might be considered.

Clinical Evaluation Recommendations for Infants with Possible Congenital Zika

The following infants should be clinically evaluated for possible congenital Zika:

- Infants who present with microcephaly or intracranial calcifications (detected prenatally or at birth) and whose mother traveled to or resided in a location with Zika transmission during pregnancy (while awaiting results of infant Zika test), or

- Infants where both the mother (prior to delivery or soon after delivery) and subsequently the infant, test positive or inconclusive for Zika.

It is recommended that the initial clinical evaluation includes:

- Comprehensive physical examination (including measurement of the occipitofrontal circumference, length, weight, and assessment of gestational age)

- Evaluation of neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions
    - Full body photographs of any visual rash or features should be documented
    - If abnormalities are detected, the appropriate specialty should be consulted

- Cranial ultrasound (unless prenatal ultrasound results from the third trimester already demonstrate no abnormalities of the brain)

- Evaluation of hearing by evoked optoacoustic emissions testing or auditory brainstem response testing, either before discharge or within one month after birth
    - Infants with abnormal initial hearing screens should be referred to an audiologist

- Ophthalmologic evaluation, including examination of the retina, either before discharge or within one month after birth
    - Infants with abnormal initial eye evaluation should be referred to a pediatric ophthalmologist

- Other evaluations specific to the infant's clinical presentation.

<u>For infants with microcephaly or intracranial calcifications, these additional evaluations are recommended:</u>

- 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.

<u>For infants with a confirmed positive or inconclusive test for Zika:</u>

- Report case to local health department where the mother resides.

- Monitor for additional guidance as it is released.

- Conduct additional hearing screen at age 6 months, in addition to any appropriate follow-up of hearing abnormalities detected through newborn hearing screenings.

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

For infants whose mothers test positive or inconclusive for Zika during pregnancy, but the newborn tests negative for Zika:

- If the newborn does not have 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, diagnostic testing for other causes of the newborn's conditions should be performed including testing for other congenital viral infections if indicated.

Based on available evidence, women who have had Zika during pregnancy should still be able to breastfeed. Although Zika virus RNA has been detected in breast milk, transmission of Zika infection through breastfeeding has not been documented. Based on available evidence, the benefits of breastfeeding infants outweigh any theoretical risk related to Zika virus infection.

For More Information

- Contact the NJDOH Vectorborne Disease Program during regular business hours at (609) 826-5964
- CDC Zika virus website: http://www.cdc.gov/zika/
- CDC's Current Zika-affected Areas: http://www.cdc.gov/zika/geo/
- CDC's Interim Guidelines for Pregnant Women During a Zika Virus Outbreak: http://www.cdc.gov/mmwr/volumes/65/wr/mm6502e1er.htm
- CDC's Interim Guidelines for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection — United States, 2016: http://www.cdc.gov/mmwr/volumes/65/wr/mm6503e3er.htm?s_cid=mm6503e3er_e
- CDC's Q & A's for Obstetrical Healthcare Providers: Pregnant women and Zika Virus Infection: http://www.cdc.gov/zika/pdfs/questions-answers-clinicians.pdf
- CDC health advisories on Zika and other travel-related health risks: http://wwwnc.cdc.gov/travel/notices
- Protection against mosquitoes for travelers: http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-2-the-pre-travel-consultation/protection-against-mosquitoes-ticks-and-other-insects-and-arthropods
- CDC's Clinician Outreach and Communication Activity (COCA): http://emergency.cdc.gov/coca/calls/
- Pan American Health Organization: http://www.paho.org/