Clinical Policy Title: Zika virus

Clinical Policy Number: 17.01.04

Effective Date: October 1, 2016
Initial Review Date: May 18, 2016
Most Recent Review Date: May 18, 2016
Next Review Date: May 2017

Related policies:

CP# 12.01.02 Prenatal obstetrical ultrasound

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

Care management of persons with Zika virus exposure or illness is a rapidly developing area. In instances where AmeriHealth Caritas Pennsylvania policies and Centers for Disease Control and Prevention (CDC) guidelines conflict, CDC guidance will govern.

A. AmeriHealth Caritas Pennsylvania considers the following preventive services to be medically necessary up to plan limit in at-risk areas:

- Over-the-counter (OTC) Environmental Protection Agency (EPA)-registered insect repellents when used as directed. EPA-registered insect repellents contain one of the following active ingredients: DEET, picaridin, IR3535, oil of lemon eucalyptus, or para-menthane dol. They are known as safe and effective when used as directed, even for pregnant and breast-feeding women. See searchable database of EPA-registered insect repellents:
• Family planning counseling to help members make informed and responsible decisions about family planning and reproductive health, as well as learn safe sexual practices to reduce Zika transmission.
• Contraception to prevent the transmission of the Zika virus (e.g., condoms) and other methods of contraception that prevent or delay pregnancy including oral contraceptives, condoms, diaphragms, foams, gels, patches, rings, injections, tablets, emergency contraceptives, and long-acting reversible contraception (LARC). LARC includes both intrauterine devices and contraceptive implants. Insertion and removal of LARC are considered medically necessary.

B. AmeriHealth Caritas Pennsylvania considers the use of Zika virus testing to be clinically proven and, therefore, medically necessary when performed in accordance with CDC guidelines (See CDC Clinical Guidance: http://www.cdc.gov/zika/hc-providers/clinical-guidance.html) and the following criteria are met:

**Indications for Zika virus testing:**

• Members of any age who traveled to or resided in an affected area within the previous two weeks and present with two or more of the following symptoms consistent with Zika virus disease: fever, rash, conjunctivitis or arthralgia.
• Any pregnant woman with possible Zika virus exposure regardless of the presence of clinical illness (see Appendices A and B).
  - Possible Zika virus exposure includes travel to an area with active Zika virus transmission, or sex (oral, anal or vaginal intercourse) without a condom with a man who traveled to, or resided in, an area with active Zika virus transmission.
  - Repeat Zika virus testing during pregnancy is medically necessary if clinical illness consistent with Zika virus disease develops later in pregnancy.
• Any person attempting conception who presents with one or more symptoms consistent with Zika virus disease within two weeks of possible Zika virus exposure. Exposure includes:
  - Travel to an area with active Zika virus transmission.
  - Sexual exposure with a man without a condom who either:
    ▪ Travelled to, or resided in, an area with active Zika virus transmission either during pregnancy or the eight weeks before conception (six weeks before the last menstrual period).
    ▪ Is diagnosed with Zika virus disease or has a clinical illness consistent with Zika virus disease.
• A newborn who meets any of the following criteria (see Appendix C):
  - Born to a mother with a positive or inconclusive test result for Zika virus infection.
  - Presents with symptoms of Zika virus disease in the first two weeks of life and born to a mother who traveled to or resided in an affected area within two weeks of delivery.
- With evidence of microcephaly or intracranial calcifications and born to a mother who was exposed to Zika virus while she was pregnant.
  - If not already performed during pregnancy. Testing of the mother’s serum for Zika virus, dengue virus and neutralizing antibodies is considered medically necessary.

**Zika virus testing consists of:**

- Reverse transcriptase-polymerase chain reaction (RT-PCR) for individuals meeting CDC Zika virus clinical criteria and/or CDC Zika virus epidemiological criteria when performed during the first seven days of the onset of illness using one of the following Food and Drug Administration (FDA)-authorized tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>Acceptable specimen</th>
<th>Testing for:</th>
<th>Laboratory requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC Trioplex Real-time RT-PCR</td>
<td>Serum or CSF¹²</td>
<td>Zika, Chikungunya, dengue viral RNA</td>
<td>CDC-approved</td>
</tr>
<tr>
<td></td>
<td>Urine¹ or amniotic fluid¹</td>
<td>Zika viral RNA</td>
<td></td>
</tr>
<tr>
<td>Focus Diagnostics Zika Virus RNA Qualitative Real-Time RT-PCR</td>
<td>Serum</td>
<td>Zika viral RNA</td>
<td>Designated by Focus Diagnostics and CLIA³-certified to perform high complexity tests</td>
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<tr>
<td>RealStar® Zika Virus RT-PCR Kit U.S. (Altona Diagnostics, Germany)</td>
<td>Serum or urine¹</td>
<td>Zika viral RNA</td>
<td>CLIA¹-certified to perform high complexity tests</td>
</tr>
</tbody>
</table>

¹Collected alongside a patient-matched serum specimen.
²In infants and children, testing can be performed in CSF if obtained for other reasons.
³Clinical Laboratory Improvement Amendments (CLIA) of 1988.

- Antibody testing:
  - Anti-Zika Virus Enzyme-Linked Immunosorbent Assay (ELISA):
    - Immunoglobulin M [IgM] performed within two to 12 weeks of the onset of illness.
    - Immunoglobulin G [IgG] testing for past Zika infection.
  - On blood serum or CSF specimens only, or semen for research purposes only.
  - Performed in CDC-approved laboratories.
  - Plaque-reduction neutralization testing (PRNT) when results of Zika IgM Antibody Capture (MAC) ELISA are positive or inconclusive.
  - In infants and children, Zika MAC-ELISA testing and PRNT can be performed in CSF if obtained for other reasons.

**Additional considerations for pregnant women:**

- For pregnant women who do not reside in a Zika-affected area, see CDC testing algorithm in Appendix A.
• For pregnant women who reside in a Zika-affected area, see CDC testing algorithm in Appendix B.
• Testing for dengue or chikungunya virus infection should also be performed.
• For women with possible exposure to Zika virus, prenatal obstetrical ultrasound is medically necessary to detect the presence of fetal abnormalities associated with Zika virus disease. Prenatal obstetrical ultrasound may not detect symptoms until the late second or early third trimester of pregnancy.
  - When laboratory evidence of Zika virus infection is positive or inconclusive, serial prenatal obstetrical ultrasounds should be considered with no upper limit on number of tests.
  - When laboratory evidence is negative, one prenatal obstetrical ultrasound should be performed. A negative IgM test result obtained two to 12 weeks after known exposure suggests a recent Zika virus infection did not occur and could obviate the need for serial prenatal obstetrical ultrasounds.
• When laboratory evidence of Zika virus infection is positive and prenatal obstetrical ultrasound is abnormal, computed tomography/magnetic resonance imaging (CT/MRI) may be considered to ensure the health of the mother and fetus.
• Amniocentesis may be considered on a case-by-case basis, taking into account the risks and benefits of the procedure.

Additional considerations for infants and children age <18 years (see Appendix C):
• For possible congenital infection:
  - The initial serum sample should be collected either from the umbilical cord or directly from the infant within two days of birth, if possible. CSF can be used if obtained for other studies.
  - 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.
• For possible non-congenital, acute Zika virus infection:
  - If Zika virus RNA is not detected and symptoms have been present for ≥ 4 days, testing for Zika virus IgM and neutralizing antibodies and dengue virus IgM and neutralizing antibodies should be performed.

Limitations:

• All other uses of Zika virus testing are not medically necessary including, but not limited to:
  - Serum or semen testing of men for assessing the risk for sexual transmission, because current understanding of the duration and pattern of shedding of Zika virus in the male genitourinary tract is limited.
  - Routine Zika virus testing for women or men who are attempting conception who have possible exposure to Zika virus but no clinical illness.
Pregnant women with possible sexual exposure to Zika virus who do not reside in a Zika-affected area if both partners are asymptomatic.

Alternative covered services:

- Testing for flavivirus infection.
- Support measures for treating symptoms.

Background

Zika virus is a single-stranded ribonucleic acid (RNA) virus of the genus *Flavivirus*. It is related to other mosquito-borne viruses such as dengue, yellow fever, Japanese B encephalitis and West Nile fever viruses (Centers for Disease Control and Prevention [CDC], 2016a). Prior to 2015, Zika virus outbreaks occurred in areas of Africa, Southeast Asia and the Pacific Islands. In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infection in Brazil. On February 1, 2016, the World Health Organization (WHO) declared Zika virus a public health emergency of international concern (PHEIC) based on clusters of congenital microcephaly and Guillain-Barré syndrome in areas affected by Zika virus (CDC, 2016a). However, a causal relationship between Zika virus and these and other potential clinical outcomes awaits scientific confirmation (Check Hayden, 2016).

As of June 6, 2016, there were 618 cases of travel-associated Zika virus disease in the United States: 146 (23 percent) were pregnant, 11 (two percent) were sexually transmitted and one case of Guillain-Barré syndrome was reported. No locally acquired vector-borne cases have been reported. However, in the U.S. territories of Puerto Rico, American Samoa and the U.S. Virgin Islands, 1,110 cases have been reported and all but four were locally acquired (CDC, 2016b).

Zika virus is transmitted to humans primarily through the bite of an infected *Aedes* genus mosquito (CDC, 2016a). Perinatal, intrauterine and possible sexual and transfusion transmission events have also been reported. Transmission of Zika to the fetus has been documented in all trimesters; Zika virus RNA has been detected in fetal tissue and the placenta. However, uncertainties remain about Zika virus in pregnancy such as timing, likelihood and relevance of symptomatic versus asymptomatic infection.

There is no evidence that prior Zika virus infection poses a risk of birth defects in future pregnancies. Detection of Zika virus infection in the mother does not provide any definitive information about the state of health of the fetus, making clinical management in the setting of potential Zika virus exposure (i.e., travel to endemic areas) or maternal infection difficult. Therefore, disease transmission is often difficult to determine and likely to change over time. Death from Zika virus infection appears to be rare in persons of all ages.

Approximately one in five people infected with Zika virus become symptomatic, and most symptoms are mild and self-limiting. Characteristic clinical findings are acute onset of fever with maculopapular rash,
arthralgia and conjunctivitis. Other common symptoms include myalgia and headache. The symptoms of Zika overlap with those of dengue and chikungunya diseases spread through the same mosquitoes that transmit Zika.

The incubation period (the time from exposure to symptoms) for Zika virus disease is not known, but is likely to be a few days to a week. Once infected, a person is likely to be protected from future infections. No specific vaccine or antiviral treatment is available for Zika virus disease. Disease management includes supportive treatment (e.g., rest, fluids, analgesics and antipyretics) and prevention of local transmission (CDC, 2016c). As an arboviral disease, Zika virus disease is a nationally notifiable condition.

**Prevention:**

There is no vaccine available for Zika virus. The major means of prevention currently available are mosquito control, protection against mosquito bites and contraception for women of childbearing age who do not wish to become pregnant. Family planning counseling can help individuals make informed and responsible decisions about family planning and reproductive health, as well as learn safe sexual practices to reduce Zika transmission.

**Diagnosis:**

The differential diagnosis for Zika virus infection is broad and may include dengue, leptospirosis, malaria, rickettsia, group A streptococcus, rubella, measles and infections caused by parvovirus, enterovirus, adenovirus and alphavirus. Preliminary diagnosis is based on the patient’s clinical signs and symptoms, epidemiological information and travel history. The laboratory diagnosis of Zika virus infection is made through molecular and serologic testing for viral isolation, RT-PCR to detect virus or viral nucleic acid, virus-specific IgM antibodies and PRNT for neutralizing antibodies.

Each test has limitations that must be considered for appropriate interpretation of test results (CDC, 2016d). Zika virus produces a viremia of sufficient magnitude and duration to allow isolation of viruses during the acute phase of illness during seven days following onset of symptoms. Persistence of viral RNA in CSF, amniotic fluid and urine is not well characterized but may be longer than in serum. Antibodies in blood sera of a person infected with Zika virus typically appear four to five days after the onset of illness and last for about 12 weeks.

False positive results may occur in patients with a history of exposure to other flaviviruses, (e.g., dengue infection, yellow fever or Japanese encephalitis vaccination) that produce cross-reactivity and could result in the impaired ability to detect and receive appropriate medical care for the true infection causing the symptoms, an unnecessary increase in the monitoring of a woman's pregnancy or other unintended adverse effects. False negative results may occur if testing takes place outside the windows of optimal detection (e.g., if RT-PCR testing was conducted more than seven days after onset of symptoms) or if clinical presentation indicates Zika virus infection and diagnostic tests for other causes of illness are negative.
The FDA has not approved any commercially available diagnostic tests specifically for Zika virus detection. The FDA has authorized four Zika virus tests under an Emergency Use Authorization (EUA) for the qualitative detection of Zika virus (FDA, 2016). The four tests are (FDA, 2016; CDC, 2016e):

- CDC Trioplex rRT-PCR for the qualitative detection and differentiation of RNA from Zika virus, dengue virus and chikungunya virus in human serum or CSF (collected alongside a patient-matched serum specimen), and for the qualitative detection of Zika virus RNA in urine and amniotic fluid (each collected alongside a patient-matched serum specimen). The Trioplex rRT-PCR has been designed to minimize the likelihood of false positive test results caused by cross-reactivity of any of the test’s components. If there is doubt about the accuracy of the symptom onset date or if the patient lacks symptoms, serological testing of negative serum specimens may be appropriate to look for evidence of infection.
- Focus Diagnostics, Inc.’s, Zika Virus RNA Qualitative Real-Time RT-PCR test for the qualitative detection of RNA from Zika virus in human serum specimens from individuals meeting CDC Zika virus clinical criteria and/or CDC Zika virus epidemiological criteria.
- Altona Diagnostics GmbH’s RealStar® Zika Virus RT-PCR Kit U.S. for the qualitative detection of RNA from Zika virus in human serum and urine (collected alongside a patient-matched serum specimen) specimens.
- CDC Zika MAC-ELISA for the qualitative detection of IgM antibodies (or IgG) in blood samples or CSF (submitted alongside a patient-matched serum specimen) and other authorized specimen types. Compared to RT-PCR, Zika MAC-ELISA can be performed over a longer time period after the start of illness, is faster and cheaper and requires less training to perform. Confirmation of Zika MAC-ELISA positive or equivocal results requires additional testing by CDC or CDC-designated laboratories.

In addition, PRNT may be performed to measure virus-specific neutralizing antibodies both to confirm primary flavivirus infections (e.g., a positive Zika MAC-ELISA) and to differentiate from other viral illnesses. Testing is considered positive if neutralizing antibody titers are at least four-fold higher than dengue virus neutralizing antibody titers in serum. Testing is considered inconclusive if Zika virus neutralizing antibody titers are less than four-fold higher than dengue virus neutralizing antibody titer. Because PRNT is expensive and takes at least a week longer to do than the Zika MAC-ELISA, the ELISA test is widely considered the more practical option in many cases (CDC, 2016d).

Searches

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).
We conducted searches on March 9-10, 2016. Search terms were: "Zika Virus" [Mesh], "Zika Virus Infection" [Mesh], “zika” and "Zika MAC-ELISA."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

We identified no systematic reviews or economic analyses for this policy. We identified several guidance documents from CDC that provide the basis for this policy. Several professional organizations such as the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (AAP) and the American Medical Association (AMA) have issued practice advisories in accordance with these guidelines (ACOG, 2016; AAFP, 2016; AAP, 2016; AMA, 2016).

CDC recommends Zika virus testing for potentially exposed persons with signs or symptoms consistent with Zika virus disease. The signs and symptoms consistent with Zika virus disease are two or more of the following: acute onset of fever, maculopapular rash, arthralgia or conjunctivitis. Exposure consists of (Oster, 2016, Petersen, 2016):

- Travel to or living in a Zika-affected area.

- Recent sexual contact with a male not using a condom who had recent exposure to Zika virus or has a diagnosis of or symptoms consistent with Zika virus disease, as Zika virus can be transmitted in sperm from males to other sexual partners. For women attempting to conceive, recent exposure includes during pregnancy or the eight weeks before conception (six weeks before the last menstrual period).

Zika virus testing is currently not recommended for either:

- Assessment of risk for sexual transmission in men, because current understanding of the duration and pattern of shedding of Zika virus in the male genitourinary tract is limited (Oster, 2016).

- Pregnant women not residing in Zika-affected areas and possible sexual exposure to Zika virus if both partners are asymptomatic (Petersen, 2016).
The type of testing will depend on time since acute onset of symptoms and exposure to other viruses that are endemic to the same areas. In general, RT-PCR can be performed on serum and CSF collected within the first week of illness and for the qualitative detection of Zika virus RNA in urine and amniotic fluid (each collected alongside a patient-matched serum specimen. CDC has made no recommendations related to the use of saliva or semen samples. Zika MAC-ELISA testing can be performed after the period of viremia has passed (usually two weeks after the onset of symptoms) and up to 12 weeks. PRNT can be used to measure virus-specific neutralizing antibodies to Zika virus and confirm positive Zika MAC-ELISA results. Other testing may include amniocentesis, histopathologic examination and immunohistochemical staining of the placenta and umbilical cord, Zika virus testing of frozen placental tissue and cord tissue and Zika MAC-ELISA and neutralizing antibody testing of cord blood.

Special considerations for pregnant women, infants and children:

Zika virus testing is recommended in pregnant women with possible exposure to Zika virus during pregnancy regardless of the presence of clinical illness. For persons attempting conception, Zika virus testing of serum should be performed in persons with clinical symptoms of infection within two weeks of possible exposure; routine testing is not currently recommended for women or men who are attempting conception and have possible exposure to Zika virus but no clinical illness. Perinatal infection may also be suspected in a woman who had sexual exposure to a male with possible Zika virus exposure (Petersen, 2016).

In symptomatic pregnant women, RT-PCR and Zika MAC-ELISA and PRNT can be performed on serum within two weeks of travel. In asymptomatic pregnant women, Zika MAC-ELISA antibody testing should be conducted two to 12 weeks after travel; if the Zika MAC-ELISA test result is positive or indeterminate, PRNT on serum specimens should be performed. Testing for dengue or chikungunya virus infection is also recommended, as cross-reaction with related flaviviruses is common and may be difficult to discern on other testing.

Laboratory evidence of maternal Zika virus infection includes: 1) Zika virus RNA detected by RT-PCR in any clinical specimen; or 2) positive Zika virus Zika MAC-ELISA with confirmatory PRNT titers that are ≥ four-fold higher than dengue virus neutralizing antibody titers in serum. Testing is considered inconclusive if Zika virus PRNT titers are < four-fold higher than dengue virus neutralizing antibody titer.

Diagnostic imaging may be indicated to assess maternal and fetal health. Prenatal obstetrical ultrasound is recommended to detect the presence of fetal abnormalities associated with Zika virus disease: microcephaly; intracranial calcifications; and brain and eye abnormalities. Serial testing should be considered to monitor fetal growth and anatomy in pregnant women with laboratory evidence of Zika virus infection. A negative IgM test result obtained two to 12 weeks after known exposure suggests that a recent Zika virus infection did not occur and could obviate the need for serial ultrasounds. CT/MRI may be needed to further monitor fetal health in the presence of Zika positive testing and an abnormal prenatal obstetrical ultrasound. Zika virus testing of amniotic fluid may be considered on an individual basis for each clinical circumstance.
Testing of infants with possible congenital Zika virus infection who were born to mothers who traveled to or resided in areas affected by Zika virus during pregnancy should be guided by the presence of microcephaly, intracranial calcifications, and brain and eye abnormalities detected prenatally or at birth along with the mother’s Zika virus testing results. The results of previous prenatal ultrasounds and maternal Zika virus testing should be reviewed, and a thorough newborn physical examination, with assessment of head (occipitofrontal) circumference, length and weight should be performed (Staples, 2016).

Acute Zika virus disease should be suspected in an infant or child <18 years of age who traveled to or resided in an affected area within the previous two weeks and presents with two or more of the following symptoms: fever, rash, conjunctivitis, or arthralgia. Acute Zika virus disease should also be suspected in an infant in the first two weeks of life whose mother traveled to or resided in an affected area within two weeks of delivery and who presents with two or more of the following manifestations: fever, rash, conjunctivitis or arthralgia. Perinatal infection may also be suspected in women who had sexual contact with a person who has traveled to or resided in an area affected by Zika virus (Fleming-Dutra, 2016).

**Summary of CDC guidelines: For pregnant women, infants and children**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Testing population</th>
<th>Testing recommendations</th>
</tr>
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</table>
| Petersen (2016) For CDC Women of Reproductive Age with Possible Zika Virus Exposure* | Pregnant women not residing in an area with active Zika virus transmission (Appendix A) | - If symptomatic within two weeks of exposure, testing includes Zika virus RT-PCR, MAC-ELISA and neutralizing antibodies on serum.  
- If asymptomatic, perform Zika virus MAC-ELISA.  
  - If IgM test result is positive or indeterminate, perform neutralizing antibody testing on serum specimens. Testing should be performed 2–12 weeks after travel.  
- If Zika virus testing is negative, perform fetal ultrasound to detect abnormalities consistent with Zika virus disease. Fetal ultrasound may not detect symptoms until the late second or early third trimester of pregnancy.  
- Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluation for dengue or chikungunya virus infection is also recommended.  
- Repeat Zika virus testing during pregnancy if clinical illness consistent with Zika virus disease develops later in pregnancy.  
- Pregnant women with possible sexual exposure to Zika virus should have Zika virus testing if the woman develops at least one sign or symptom of Zika virus disease or if her male partner has been diagnosed Zika virus disease or becomes symptomatic.  
- Testing is not currently recommended for pregnant women with possible sexual exposure to Zika virus if both partners are asymptomatic.  
- Consideration of amniocentesis should be individualized for each clinical circumstance. Sensitivity, specificity, |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Testing population</th>
<th>Testing recommendations</th>
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<tbody>
<tr>
<td></td>
<td><strong>Who is diagnosed with Zika virus disease or has a clinical illness consistent with Zika virus disease.</strong></td>
<td><strong>predictive values and timing of RT-PCR testing of amniotic fluid for congenital Zika virus infection are unknown.</strong></td>
</tr>
</tbody>
</table>
| | All pregnant women living in a Zika affected area regardless of the presence of clinical illness *(Appendix B)* | • **If symptomatic, RT-PCR should be performed on serum collected within 7 days of symptom onset. A negative RT-PCR result from serum collected 5–7 days after symptom onset does not exclude Zika virus infection, and serologic testing should be performed.**  
• **If asymptomatic, MAC-ELISA testing upon initiation of prenatal care; if negative Zika MAC-ELISA results, consider repeat testing in the mid-second trimester because of the ongoing risk for Zika virus exposure and infection throughout pregnancy.**  
• **Fetal ultrasound performed after Zika virus testing.**  
  - **If positive findings, repeat maternal Zika MAC-ELISA testing and consider serial fetal ultrasound.** |
| | **Persons attempting contraception *(Appendix A).*** | • **Perform Zika virus testing of serum in persons with possible exposure to Zika virus who have one or more of the following signs or symptoms within two weeks of possible exposure: acute onset of fever, rash, arthralgia, or conjunctivitis.** |
| **Staples (2016)**  
**For CDC**  
**Infants with Possible Congenital Zika Virus Infection** | Infant whose mother traveled to or resided in an area with Zika virus transmission while pregnant and one of the following *(Appendix C)*:  
• Evidence of microcephaly or intracranial calcifications detected prenatally or at birth.  
• Positive or inconclusive test results for Zika virus infection in mother. | • **RT-PCR testing for Zika virus RNA and Zika virus and dengue virus IgM and neutralizing antibodies on serum collected from the umbilical cord or directly from infant within two days of birth, if possible.**  
• **If CSF is obtained for other reasons, test for Zika virus RNA, Zika virus MAC-ELISA and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.**  
• **Consider histopathologic evaluation of the placenta and umbilical cord with Zika virus immune-histochemical staining on fixed tissue and Zika virus RT-PCR on fixed and frozen tissue.**  
• **For infants with laboratory evidence of a possible congenital Zika virus infection, additional clinical evaluation and follow-up is recommended.** |
| **Fleming-Dutra (2016)**  
*(Updates Staples, 2016)*  
**For CDC**  
**Infants and Children with** | Infant or child age <18 years with the following criteria:  
• Traveled to or resided in an affected area within the past two weeks.  
• Has at least two of the following: | • **RT-PCR testing for Zika virus RNA on serum (and, if obtained for other reasons, CSF) if symptoms have been present for fewer than seven days.**  
• **Test serum (and, if obtained for other reasons, CSF) for Zika virus MAC-ELISA and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies if Zika virus RNA is detected or if symptoms are consistent with congenital Zika virus infection.**  
• **Recommended laboratory testing for infants with possible congenital Zika virus infection includes RT-PCR testing for Zika virus RNA on serum and CSF.**  
• **Consider repeating Zika MAC-ELISA and neutralizing antibodies testing and serologic testing if symptoms persist.**  
• **Consider repeat MRI of the head if abnormalities are detected on initial neuroimaging.**  
• **Infants with laboratory evidence of a possible congenital Zika virus infection should receive comprehensive clinical, developmental, and neurologic evaluation.** |
Possible Acute Zika Virus Infection

<table>
<thead>
<tr>
<th>Testing population</th>
<th>Testing recommendations</th>
</tr>
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</table>
| following manifestations: fever, rash, conjunctivitis or arthralgia. Infant during the first two weeks of life with the following criteria:  
  - Whose mother traveled to or resided in an affected area within two weeks of delivery.  
  - Who has at least two of the following manifestations: fever, rash, conjunctivitis or arthralgia. | virus RNA is not detected and symptoms have been present for four or more days.  
  - Routine care is recommended for infants without microcephaly or intracranial calcifications whose mothers traveled to or resided in areas with Zika virus transmission during pregnancy but did not receive Zika virus testing. |

Glossary

**Arbovirus** — A class of viruses transmitted to humans by arthropods such as mosquitoes and ticks.

**Chikungunya** — An arboviral disease that causes fever and severe, often debilitating joint pain. Derives from a word in the Kimakonde language, meaning “to become contorted,” and describes the stooped appearance of sufferers with joint pain.

**Dengue** — An arboviral infection of sudden onset that usually follows a benign course with flu-like symptoms and rash. Occasionally develops into a potentially lethal complication called severe dengue.

**Guillain-Barré syndrome** — A rare autoimmune disorder characterized by progressive symmetrical paralysis and loss of reflexes, usually beginning in the legs.

**Microcephaly** — An occipitofrontal circumference less than the third percentile for gestational age and sex based on standard growth curves, not explained by other etiologies.

**Viral isolation** — The process of separating the virus from the patient specimen during the acute stage of the disease.

References

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Clinical trials:**

Searched clinicaltrials.gov on March 15, 2016, using terms Zika | Open Studies. One study found, one relevant.


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
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<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<td>87798</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism</td>
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<table>
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<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comments</th>
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<td>Z11.5</td>
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<td>Z20.89</td>
<td>Contact with and (suspected) exposure to other viral communicable diseases</td>
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Appendix A

Updated interim guidance: Testing algorithm for a pregnant woman with possible Zika virus exposure, not residing in an area with active Zika virus transmission.

Testing is recommended for pregnant women with clinical illness consistent with Zika virus disease, including one or more of the following signs or symptoms: acute onset of fever, rash, arthralgia, or conjunctivitis during or within two weeks of travel or possible sexual exposure. Testing includes Zika virus RT-PCR and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. More information is available at http://www.aphl.org/Materials/CDCMemo_Zika_Chik_Deng_Testing_011916.pdf. Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection.

Testing can be offered to pregnant women without clinical illness consistent with Zika virus disease. If performed, testing should include Zika virus IgM, and if IgM test result is positive or indeterminate, neutralizing antibodies on serum specimens. Testing should be performed 2–12 weeks after travel.
Laboratory evidence of maternal Zika virus infection: 1) Zika virus RNA detected by RT-PCR 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. Testing is considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasound might not detect abnormalities until late second or early third trimester of pregnancy.

Possible exposure to Zika virus includes travel to an area with active Zika virus transmission (http://wwwnc.cdc.gov/travel/notices/), or sex (vaginal intercourse, anal intercourse, or fellatio) without a condom with a man who traveled to, or resided in, an area with active Zika virus transmission. Testing is not currently recommended for pregnant women with possible sexual exposure to Zika virus if both partners are asymptomatic.

Adapted from Petersen (2016).

Appendix B

CDC interim guidance: For a pregnant women residing in an area with ongoing Zika virus transmission, with or without clinical illness consistent with Zika virus disease.
Tests for pregnant women with clinical illness consistent with Zika virus disease include Zika virus reverse transcription-polymerase chain reaction (RT-PCR), and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection. If chikungunya or dengue virus RNA is detected, treat in accordance with existing guidelines. Timely recognition and supportive treatment for dengue virus infections can substantially lower the risk of medical complications and death. Repeat Zika virus testing during pregnancy is warranted if clinical illness consistent with Zika virus disease develops later in pregnancy.

Testing can be offered to pregnant women without clinical illness consistent with Zika virus disease. If performed, testing should include Zika virus IgM, and if IgM test result is positive or indeterminate, neutralizing antibodies on serum specimens. Results from serologic testing are challenging to interpret in areas where residents have had previous exposure to other flaviviruses (e.g., dengue, yellow fever) because of cross-reactivity with other flaviviruses.

Laboratory evidence of maternal Zika virus infection: 1) Zika virus RNA detected by RT-PCR in any clinical specimen; or 2) positive Zika virus IgM with confirmatory neutralizing antibody titers that are 24-fold higher than dengue virus neutralizing antibody titers in serum. Testing would be considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titer.

Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasound might not detect abnormalities until late second or early third trimester of pregnancy.

Local health officials should determine when to implement testing of asymptomatic pregnant women based on information about levels of Zika virus transmission and laboratory capacity.

Clinical illness is consistent with Zika virus disease if one or more signs or symptoms (acute onset of fever, rash, arthralgia, or conjunctivitis) are present.

Adapted from Petersen (2016).

Appendix C

CDC interim guidelines for the evaluation and testing of infants whose mothers traveled to or resided in an area with ongoing Zika virus transmission during pregnancy.
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 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, 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 dengue virus IgM and neutralizing antibodies.

For possible acute Zika virus disease:

If symptoms have been present for <7 days, test serum (and, if obtained for other reasons, cerebrospinal fluid) for Zika virus RNA by RT-PCR.
If Zika virus RNA is not detected and symptoms have been present for ≥4 days, test serum (and, if obtained for other reasons, cerebrospinal fluid) for Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.


*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 2) an infant born to a mother with a positive or inconclusive test result for Zika virus infection.

†Indications for testing during acute disease include: Infants and children aged <18 years who 1) traveled to or resided in an affected area within the past two weeks and 2) have ≥2 of the following manifestations: fever, rash, conjunctivitis or arthralgia. Infants in the first two weeks of life 1) whose mothers have traveled to or resided in an affected area within two weeks of delivery and 2) have ≥2 of the following manifestations: fever, rash, conjunctivitis or arthralgia.


**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 one 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 one 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.