Clinical Policy Title: Zika virus

Clinical Policy Number: 17.01.04

Effective Date: October 1, 2016
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Most Recent Review Date: June 22, 2017
Next Review Date: June 2018

Related policies:

CP# 12.01.02 Prenatal obstetrical ultrasound
CP# 09.01.06 Brainstem auditory evoked response (BAER)

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’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 Prestige Health Choice 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. Prestige Health Choice’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. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’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 Prestige Health Choice policies and Centers for Disease Control and Prevention (CDC) guidelines conflict, CDC guidance will govern.

Prestige Health Choice considers the following preventive services to be medically necessary up to plan limit in at-risk areas:

- Over-the-counter 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 diol. They are proven 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 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.

Restricting travel to areas with active Zika virus transmission with posted CDC Zika Travel Notices: https://wwwnc.cdc.gov/travel/page/zika-information.


Prestige Health Choice 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/hcp-providers/clinical-guidance.html):

**Indications for Zika virus testing:**

- Members of any age with possible Zika virus exposure¹ within the previous two weeks who present with two or more of the following symptoms consistent with Zika virus infection:
  - Fever.
  - Rash.
  - Conjunctivitis.
  - Arthralgia.

- Pregnant women with possible Zika virus exposure regardless of the presence of clinical symptoms (Appendix A).
  - Repeated Zika virus testing during pregnancy is medically necessary if clinical illness consistent with Zika virus disease develops later in pregnancy, or if her male partner has been diagnosed with Zika virus, or becomes symptomatic (Appendix A).
  - Pregnant women who lived in or traveled to Miami-Dade County between August 1, 2016, and eight weeks after June 2, 2017, and who conceived up to eight weeks after June 2, 2017 (CDC, 2017f).

- Members attempting to conceive who present with one or more symptoms consistent with Zika virus disease within two weeks of possible Zika virus exposure (Petersen, 2016).

- Infant who presents with anomalies consistent with congenital Zika syndrome (Russell, 2016).

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¹ Possible Zika virus exposure includes residence in or travel to an area with active Zika virus transmission, sex (oral, anal, or vaginal intercourse) without a condom with a partner who traveled to, or resided in, an area with active Zika virus transmission with posted CDC Zika Travel Notices, or a sexual partner who tests positive for Zika virus infection.
- Infants who are phenotypically normal and fit one of the following criteria (Russell, 2016):
  - Mother has laboratory evidence of Zika virus infection or recent flavivirus infection, but specific virus cannot be identified.
  - Mother has a presumptive recent Zika virus or flavivirus infection (non-negative Zika IgM and PRNT pending).
  - Mother was not tested.

**Medically necessary Zika virus testing includes:**

- Zika virus ribonucleic acid (RNA) nucleic acid testing (NAT) when performed on serum collected during the first two weeks after symptom onset, on urine samples collected less than 14 days after symptom onset, or on amniocentesis specimens if amniocentesis is performed for other reasons.
  - A positive RNA NAT result on any sample confirms Zika virus infection, and no additional testing is indicated; a negative RNA NAT requires further IgM serologic antibody testing.
  - Reflex RNA NAT testing is included as a subsequent test for women who are IgM positive.

- Triplex reverse transcriptase-polymerase chain reaction (RT-PCR) in individuals meeting CDC Zika virus clinical criteria and/or CDC Zika virus epidemiological criteria when performed during the acute phase of infection and up to 14 days following onset of symptoms.
  - To detect Zika virus, dengue virus, and chikungunya virus RNA in human sera, whole blood, or cerebrospinal fluid (CSF), in situations where there is an increased risk of these viral infections; each collected alongside a patient-matched serum specimen.
  - To detect Zika virus RNA in urine and amniotic fluid (each collected alongside a patient-matched serum specimen).

- Serologic antibody testing for Zika, dengue, and chikungunya virus.
  - Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA) near day four and up to 12 weeks after symptom onset, or at least 14 days after symptom onset with no earlier samples collected.
  - Plaque-reduction neutralization testing (PRNT) when results of Zika 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 (Appendix A; CDC, 2017a):**

- Laboratory antibody testing for dengue or chikungunya virus infection should be performed along with Zika virus to confirm primary flavivirus infection and differentiate from other viral illnesses.
For pregnant women with possible Zika virus exposure, 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 of Zika virus infection 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, neuroimaging (e.g., computed tomography or magnetic resonance imaging) 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.

For asymptomatic pregnant women living in or frequently traveling to areas with posted CDC Zika Travel Notices:

- Zika NAT testing should be considered at least once per trimester in addition to IgM testing, unless a previous test has been positive.
- Pregnant women should receive Zika NAT testing promptly if they become symptomatic during their pregnancy or if a sexual partner tests positive for Zika virus infection.
- Pregnant women should be counseled each trimester on the limitations of IgM and NAT testing.

To help determine whether a positive IgM test result suggest a recent infection, other diagnostic methods, such as NAT testing of amniocentesis specimens or serial ultrasounds, may provide additional information.

Additional considerations for infants and children age <18 years (see Appendices B and C):

- For possible congenital infection, CDC recommends testing for infants with possible congenital Zika virus infection within two days after birth. Additional recommendations for Zika laboratory testing, neuroimaging, and Zika placental testing should be based on infant outcome and maternal Zika virus exposure and laboratory test results.
- Cord blood sampling is not recommended, as it can yield false positive results through contamination with maternal blood and might also yield false negative results. CSF can be used if obtained for other studies.
- For possible noncongenital, acute Zika virus infection, testing for Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies is medically necessary if Zika virus RNA is not detected and symptoms have been present for ≥4 days.
• Routine pediatric care, including supportive treatment, is advised for infants and children who acquire Zika virus infection postnatally.
• CDC encourages breastfeeding by mothers with Zika virus infection and mothers living in areas with ongoing Zika virus transmission.

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of Zika virus testing are not medically necessary, including, but not limited to:
• Serum or semen testing of men to assess 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.
• Zika virus testing of asymptomatic nonpregnant persons who are not planning to attempt conception.
  – Exception: IgM testing may be considered to determine baseline Zika virus IgM levels as part of preconception counseling.

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 (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 issued an alert regarding the first confirmed Zika virus infection in Brazil. On February 1, 2016, the World Health Organization declared Zika virus a public health emergency of international concern 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. The FDA has not approved any commercially available diagnostic tests specifically for Zika virus detection. The FDA has authorized several Zika virus tests under an Emergency Use Authorization for the qualitative detection of Zika virus (FDA, 2016).

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.

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 titers. Because PRNT is expensive and takes at least one week longer to perform than the Zika MAC-ELISA, the ELISA test is widely considered the more practical option (CDC, 2016d).

**Searches**

Prestige Health Choice 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 May 16, 2017. 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, 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 orMRI 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).

**Policy updates:**

In 2017, we found additional information from the CDC. CDC has updated its guidance on performing Zika testing and interpreting Zika test results for several populations at risk of possible Zika exposure that affect recommendations for testing and prevention. The objective of the new guidance is to decrease Zika virus transmission and the risk of potential Zika exposure, and to increase the proportion of persons, particularly pregnant women, with Zika virus infection who receive a definitive diagnosis. The updates are:

- Petersen (2016b) replaces Petersen (2016a), Brooks (2016) and Oster (2016).

New epidemiological data suggested a small potential risk of Zika virus transmission associated with exposure to semen from male residents in the Florida tri-county area of Miami Dade, Palm Beach, and Broward counties since June 15, 2016 (CDC, 2017c). These data raise concerns for potential undiagnosed asymptomatic Zika virus infections, particularly among pregnant women and nonpregnant women who are trying to conceive.

On June 2, 2017, the CDC removed its Zika cautionary (yellow) area designation for Miami-Dade County (CDC, 2017f). Although the level of risk of Zika virus transmission is likely to remain low, CDC recommends that people living in or traveling to Miami-Dade County continue to protect themselves from mosquito-borne illnesses, including Zika virus. CDC continues to recommend Zika virus testing for persons at risk of Zika virus exposure, or with signs and symptoms of Zika virus disease or Zika congenital symptom that may be related to travel to, or living in, Miami-Dade County between August 1, 2016 and June 2, 2017. CDC guidance extents testing to pregnant women who conceived up to eight weeks after June 2, 2017.
On May 5, 2017, CDC issued a health advisory regarding the limitations of IgM antibody testing (CDC, 2017a). Zika virus IgM can persist beyond 12 weeks in a subset of infected people. Therefore, detection of IgM may not always indicate a recent infection. IgM persistence would have the greatest effect on clinical management of pregnant women with a history of living in or traveling to areas with Zika virus transmission before conception. Pregnant women who test positive for IgM antibody may have been infected with Zika virus and developed an IgM response before conception.

Accordingly, CDC has updated its guidance on preconception counseling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure (Petersen, 2016; CDC, 2017c). As part of preconception counseling, IgM testing may be considered to determine baseline Zika virus IgM levels (CDC, 2017c). Prevention strategies include limiting travel of pregnant women to areas with active Zika virus infection risk and offering Zika virus testing for any symptomatic pregnant women with possible Zika exposure, including her partner (male or female) who lives in or has traveled to an area with Zika virus infection risk. Recommendations for asymptomatic pregnant women will differ depending on where they live or traveled. CDC recommends expanding surveillance using NAT in asymptomatic pregnant women who live in or frequently travel to areas with Zika virus transmission with posted CDC Zika Travel Notices (CDC, 2017a).

Emerging data indicate that Zika virus RNA can be detected for prolonged periods in some pregnant women (Oduyebo, 2016). To increase the proportion of pregnant women with Zika virus infection who receive a definitive diagnosis, CDC recommends extending the timeframe for rRT-PCR testing of serum and including rRT-PCR testing for some asymptomatic pregnant women with possible Zika virus exposure based on the circumstances of possible exposure (i.e., ongoing versus limited exposure) and the elapsed interval since the last possible Zika virus exposure (Oduyebo, 2016; Appendix A).

For infants with possible congenital Zika virus infection, laboratory testing is recommended for (Russell, 2016; CDC, 2017b):

- Infants born to mothers with laboratory evidence of Zika virus infection during pregnancy.
- Infants who have abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link suggesting possible transmission, regardless of maternal Zika virus test results.

Congenital Zika syndrome is a recently recognized pattern of congenital anomalies associated with Zika virus infection during pregnancy that includes microcephaly, intracranial calcifications or other brain anomalies, or eye anomalies, among others. Detailed recommendations on clinical care, neuroimaging, and placental testing are reflected in the new guidance in Appendices B and C.

**Summary of CDC guidelines for Zika virus testing in adults, infants, and children**

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<thead>
<tr>
<th>Citation</th>
<th>Testing population</th>
<th>Testing recommendations</th>
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<tr>
<td>CDC (2017a)</td>
<td>Asymptomatic</td>
<td>• Screen pregnant women for risk of Zika exposure and</td>
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<tr>
<td>Citation</td>
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| Prolonged IgM antibody response in people infected with Zika virus: implications for interpreting serologic testing results for pregnant women | pregnant women living in or frequently traveling to areas with Zika virus transmission with posted CDC Zika Travel Notices For symptomatic women, see Oduyebo (2016) | symptoms of Zika. Promptly test pregnant women with NAT if they become symptomatic during their pregnancy or if a sexual partner tests positive for Zika virus infection.  
- Consider NAT testing:  
  - At least once per trimester, unless a previous test has been positive.  
  - Of amniocentesis specimens if amniocentesis is performed for other reasons.  
- Consider IgM testing to determine baseline Zika virus IgM levels as part of preconception counseling.  
- Counsel pregnant women each trimester on the limitations of IgM and NAT testing. |
| CDC (2017b) Implementing CDC guidance for infant neuroimaging and infant and placental Zika virus testing | Infants | Test within two days of birth if either:  
- Infant presents with anomalies consistent with congenital Zika syndrome.  
- Infant is phenotypically normal and either:  
  - Mother has laboratory evidence of Zika virus infection or recent flavivirus infection, but specific virus cannot be identified.  
  - Mother has a presumptive recent Zika virus or flavivirus infection (non-negative Zika IgM and PRNT pending).  
  - Mother not tested.  
- Decision to test the infant can be deferred until maternal test results are available.  
- Consider testing CSF if serum and urine results are negative. |
| Oduyebo (2016) Pregnant women with possible Zika virus exposure | Symptomatic pregnant women | Serum and urine Zika virus rRT-PCR testing if patient presents <2 weeks after symptom onset.  
Zika virus IgM antibody testing if patient presents 2 to 12 weeks after symptom onset; if positive or equivocal, serum and urine rRT-PCR should be performed. |
| | Asymptomatic pregnant women who reside in an area without active Zika virus transmission | Perform rRT-PCR testing if woman is evaluated <2 weeks after last possible exposure. If negative, a Zika virus IgM antibody test should be performed two to 12 weeks after the exposure.  
Perform Zika virus IgM antibody testing if woman is first evaluated two to 12 weeks after last possible exposure; if positive or equivocal, serum and urine rRT-PCR should be performed.  
Perform Zika virus IgM antibody testing as part of routine obstetrical care during the first and second trimesters if woman has an ongoing risk for exposure; if equivocal, immediate rRT-PCR testing should be performed. |
<p>| | Pregnant women with confirmed or possible | This guidance also provides updated recommendations for the clinical management of pregnant women with confirmed |</p>
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| Petersen (2016b) Update: Interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure | Persons with possible Zika virus exposure planning to conceive | - Men should wait to conceive until at least six months after symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic).  
- Women should wait to conceive until at least eight weeks after symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic).  
- Couples with possible Zika virus exposure, who are not pregnant and do not plan to become pregnant, who want to minimize their risk for sexual transmission of Zika virus should use a condom or abstain from sex for the same periods for men and women described above.  
- Women of reproductive age, who have had or anticipate future Zika virus exposure and do not want to become pregnant, should use the most effective contraceptive method that can be used correctly and consistently.  
- Symptomatic persons should receive testing in accordance with CDC interim guidance: “Algorithm for U.S. Testing of Symptomatic Individuals.”  
- Zika virus testing of asymptomatic nonpregnant persons, including persons who are planning to attempt conception, or to assess the risk for sexual transmission of Zika virus is not recommended. |
  - Infants born to mothers with laboratory evidence of Zika virus infection during pregnancy.  
  - Infants who have abnormal clinical or neuroimaging findings suggestive of congenital Zika syndrome and a maternal epidemiologic link suggesting possible transmission, regardless of maternal Zika virus test results.  
  - Infant laboratory evaluation includes both molecular rRT-PCR and IgM testing. Initial samples should be collected directly from the infant in the first two days of life, if possible; testing of cord blood is not recommended.  
  - A positive infant serum or urine rRT-PCR test result confirms congenital Zika virus infection. Positive Zika virus IgM testing with a negative rRT-PCR result indicates probable congenital Zika virus infection.  
  - Initial evaluation should also include a comprehensive physical examination, including a neurologic examination, postnatal head ultrasound, and standard newborn hearing screen.  
  - Infants with laboratory evidence of congenital Zika virus infection should have a comprehensive ophthalmologic |
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<td>exam and hearing assessment by auditory brainstem response (ABR) testing before one month of age.</td>
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**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


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

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**


**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.

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<thead>
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<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tr>
<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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<th>ICD-10 Code</th>
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<tbody>
<tr>
<td>A92.5</td>
<td>Zika virus disease</td>
<td></td>
</tr>
<tr>
<td>Z11.59</td>
<td>Encounter for screening for other viral diseases</td>
<td></td>
</tr>
<tr>
<td>Z20.89</td>
<td>Contact with and (suspected) exposure to other viral communicable diseases</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
</table>

16
Appendix A

Updated interim guidance: testing and interpretation recommendations for a pregnant woman with possible exposure to Zika virus** — United States (including U.S. territories).

Abbreviations: IgM = immunoglobulin M; PRNT = plaque reduction neutralization test; rRT-PCR = real-time reverse transcription–polymerase chain reaction.

Table 1. Clinical management of a pregnant woman with suspected Zika virus infection.
<table>
<thead>
<tr>
<th>Interpretation of laboratory results*</th>
<th>Prenatal management</th>
<th>Postnatal management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Zika virus infection</td>
<td>Consider serial ultrasounds every 3 – 4 weeks to assess fetal anatomy and growth.† Decisions regarding amniocentesis should be individualized for each clinical circumstance.§</td>
<td>Live births: Cord blood and infant serum should be tested for Zika virus by rRT-PCR, and for Zika IgM and dengue virus IgM antibodies. If CSF is obtained for other reasons, it can also be tested. Zika virus rRT-PCR and IHC staining of umbilical cord and placenta are recommended.† Fetal losses: Zika virus rRT-PCR and IHC staining of fetal tissues are recommended.§</td>
</tr>
<tr>
<td>Recent flavivirus infection; specific virus cannot be identified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presumptive recent Zika virus infection**</td>
<td>Consider serial ultrasounds every 3 – 4 weeks to assess fetal anatomy and growth.† Amniocentesis might be considered; decisions should be individualized for each clinical circumstance.</td>
<td>Live births: Cord blood and infant serum should be tested for Zika virus by rRT-PCR, and for Zika virus IgM and dengue virus IgM antibodies. If CSF is obtained for other reasons, it can also be tested. Zika virus rRT-PCR and IHC staining of umbilical cord and placenta should be considered.† Fetal losses: Zika virus rRT-PCR and IHC staining of fetal tissues should be considered.¶</td>
</tr>
<tr>
<td>Presumptive recent flavivirus infection**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent dengue virus infection</td>
<td>Clinical management in accordance with existing guidelines.††</td>
<td></td>
</tr>
<tr>
<td>No evidence of Zika virus or dengue virus infection</td>
<td>Prenatal ultrasound to evaluate for fetal abnormalities consistent with congenital Zika virus syndrome.† Fetal abnormalities present: repeat Zika virus rRT-PCR and IgM test; base clinical management on corresponding laboratory results. Fetal abnormalities absent: base obstetric care on the ongoing risk for Zika virus exposure risk to the pregnant woman.</td>
<td></td>
</tr>
</tbody>
</table>

* Refer to the previously published guidance for testing interpretation: (http://www.cdc.gov/mmwr/volumes/65/wr/mm6521e1.htm).

** rRT-PCR or PRNT should be performed for positive or equivocal IgM results as indicated. PRNT results that indicate recent flavivirus infection should be interpreted in the context of the currently circulating flaviviruses. Refer to the laboratory guidance for updated testing recommendations (http://www.cdc.gov/zika/laboratories/lab-guidance.html). Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection.

† Fetal abnormalities consistent with congenital Zika virus syndrome include microcephaly, intracranial calcifications, and brain and eye abnormalities.

§ Health care providers should discuss risks and benefits of amniocentesis with their patients. It is not known how sensitive or specific rRT-PCR testing of amniotic fluid is for congenital Zika virus infection, whether a positive result is predictive of a subsequent fetal abnormality, and if it is predictive, what proportion of infants born after infection will have abnormalities.

¶ Refer to pathology guidance for collection and submission of fetal tissues for Zika virus testing for detailed information on recommended specimen types (http://www.cdc.gov/zika/laboratories/test-specimens-tissues.html).


Adapted from Oduyebo (2016).
Appendix B.

CDC recommendations for Zika virus testing and evaluation of infants born to mothers with laboratory evidence of Zika virus infection during pregnancy.

Table 2. Interpretation of results of laboratory testing of infant’s blood, urine, or CSF for evidence of congenital Zika virus infection.

<table>
<thead>
<tr>
<th>Infant test results*</th>
<th>Interpretation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>rRT-PCR</td>
<td>IgM</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive or Negative</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

* Infant serum, urine, or CSF.
† Laboratory results should be interpreted in the context of timing of infection during pregnancy, maternal serology results, clinical findings consistent with congenital Zika syndrome, and any confirmatory testing with PRNT.
<table>
<thead>
<tr>
<th>Mother</th>
<th>Infant clinical exam</th>
<th>Before hospital discharge</th>
<th>Infant testing</th>
<th>2 wks.</th>
<th>1 mo.</th>
<th>2 mos.</th>
<th>3 mos.</th>
<th>4–6 mos.</th>
<th>9 mos.</th>
<th>12 mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory evidence of Zika virus infection*</td>
<td>No evidence of abnormalities</td>
<td>Routine newborn care: PE, HC, weight/length, and neurologic exam; Hearing screen; Head US; Infant Zika virus testing</td>
<td>Negative for Zika virus infection</td>
<td>Routine care, including monitoring of OFC and development at every well child visit and age-appropriate developmental screening.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laboratory evidence of Zika virus infection*</td>
<td>Ophthalmology exam</td>
<td>ABR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitoring of OFC and development at every visit and age-appropriate developmental screening</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormalities consistent with congenital Zika syndrome</td>
<td>As above plus: Consider transfer to hospital with subspecialty care; CBC, metabolic panel, LFTs, ophthalmology exam; ABR; Consider advanced neuroimaging.</td>
<td>Negative for Zika virus infection</td>
<td>Evaluate for other causes of congenital anomalies. Further management as clinically indicated.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laboratory evidence of Zika virus infection*</td>
<td>Thyroid screen</td>
<td>Neurologic exam</td>
<td>Neurologic exam</td>
<td>Thyroid screen, ophthalmology exam</td>
<td>Repeat ABR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Routine preventive health care, including monitoring of feeding and growth. Routine and congenital infection-specific anticipatory guidance. Referral to specialists, including evaluation of other causes of congenital anomalies as needed.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not tested, or tested outside of appropriate window†</td>
<td>No evidence of abnormalities</td>
<td>Maternal Zika virus testing† Consider Zika virus placental testing Routine newborn care: PE, HC, weight/length, and neurologic exam. Hearing screen Head US</td>
<td>Perform infant Zika virus testing if evidence of Zika virus infection on maternal testing*†</td>
<td>Outpatient management for appropriate infant clinical exam and test results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormalities</td>
<td>As above, plus: Negative</td>
<td></td>
<td>Evaluate for other causes of congenital anomalies.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Laboratory evidence of Zika virus infection includes positive serology, positive PCR, positive antigen detection, or positive culture.
†Not tested, or tested outside of appropriate window includes infants born after the Zika virus outbreak.

Table 3. Initial evaluation and recommended outpatient management during the first 12 months of life for infants with possible congenital Zika virus infection, based on maternal and infant laboratory tests and infant clinical findings.
Mother Infant clinical exam Before hospital discharge Infant testing 2 wks. 1 mo. 2 mos. 3 mos. 4–6 mos. 9 mos. 12 mos.
consistent with congenital Zika syndrome Consider transfer to hospital with subspecialty care. CBC, metabolic panel, LFTs, ophthalmology exam; ABR. Consider advanced neuroimaging. Infant Zika virus testing. for Zika virus infection Further management as clinically indicated.
Laboratory evidence of Zika virus infection* Refer to outpatient management for infant with abnormalities consistent with congenital Zika syndrome.

**Abbreviations:** CBC = complete blood count; LFTs = liver function tests; HC = head (occipitofrontal) circumference; PE = physical examination; US = ultrasound.

* Laboratory evidence of maternal Zika virus infection includes: 1) Zika virus RNA detected by rRT-PCR in any clinical specimen; or 2) positive Zika virus IgM with confirmatory neutralizing antibody titers. Confirmatory neutralizing antibody titers are needed in addition to IgM for maternal Zika virus infection. † Mothers should be tested by rRT-PCR within 2 weeks of exposure or symptom onset, or by IgM within 2–12 weeks of exposure or symptom onset. Because of the decline in IgM antibody titers and viral RNA levels over time, negative maternal testing 12 weeks after exposure does not rule out maternal infection.

**Initial clinical evaluation and management of infants with laboratory evidence of Zika virus infection and abnormalities consistent with congenital Zika syndrome:**

- Consultation with:
  - Neurologist for determination of appropriate neuroimaging and additional evaluation.
  - Infectious disease specialist for diagnostic evaluation of other congenital infections (e.g., syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infection).
  - Ophthalmologist for comprehensive eye exam and evaluation for possible cortical visual impairment prior to discharge from the hospital or within one month of birth.
  - Endocrinologist for evaluation for hypothalamic or pituitary dysfunction.
  - Clinical geneticist to evaluate for other causes of microcephaly or other anomalies if present.
- Consider consultation with:
- Orthopedist, physiatrist, or physical therapist for the management of hypertonia, club foot or arthrogrypotic-like conditions.
- Pulmonologist or otolaryngologist for concerns about aspiration.
- Lactation specialist, nutritionist, gastroenterologist, or speech or occupational therapist for the management of feeding issues.

- Perform auditory brainstem response to assess hearing.
- Perform complete blood count and metabolic panel, including liver function tests.
- Provide family and supportive services.

Outpatient management of infants with laboratory evidence of Zika virus infection and abnormalities consistent with congenital Zika syndrome:

- A medical home should be established, and visits with primary care provider should occur monthly for at least the first six months of life.
- Follow growth parameters; monitor development; provide routine immunizations, anticipatory guidance, and psychosocial support; and ensure infants receive necessary testing and consultations.
- Neurologic examination by the primary care provider at one and two months of age. Refer to neurology for any abnormalities, or for any parental or provider concerns.
- Refer to developmental specialist and early intervention services.
- Repeat comprehensive ophthalmologic exam at age three months, and refer to ophthalmology for any abnormal findings, or for any parental or provider concerns.
- Repeat auditory brainstem response testing at age 4 – 6 months, and refer to audiology for any abnormal findings, or for any parental or provider concerns.
- Repeat testing for hypothyroidism at age two weeks and three months, even if the initial testing results were normal. Refer to endocrinology for any abnormal findings.
- Provide family and supportive services.

Outpatient management of infants with laboratory evidence of Zika virus infection, but without abnormalities consistent with congenital Zika syndrome:

- A medical home should be established.
- Follow growth parameters, and perform developmental screening at each well child visit.
- Emphasize anticipatory guidance for families regarding developmental milestones, feeding and growth, sleep and irritability, and abnormal movements.
- Use a standardized, validated developmental screening tool at 9 months as currently recommended, or earlier for any parental or provider concerns.
- Referral to ophthalmology for comprehensive eye exam within one month of birth. Perform vision screening and assess visual regard at every well child visit, and refer to ophthalmology for any abnormal findings, or for any parental or provider concerns.
• Perform auditory brainstem response within one month of birth. Consider repeat auditory brainstem response at 4 – 6 months or perform behavioral diagnostic testing at nine months of age and refer to audiology for any abnormal findings, or for any parental or provider concerns.
• Provide family and supportive services.

Adapted from Russell (2016).

Appendix C.

Implementing CDC guidance for infant neuroimaging and infant and placental zika virus testing based on maternal Zika virus exposure and laboratory test results.
Adapted from CDC (2017b).