Clinical Policy: Diagnostic Testing for Zika Virus

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See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Zika virus is a flavivirus whose infection causes Zika virus disease. The virus is primarily transmitted by the bite of infected *Aedes* species mosquitoes. However, Zika virus can be sexually transmitted from an infected man to his sexual partners. While Zika virus infection is usually asymptomatic or causes mild illness, a causal relationship exists between prenatal Zika virus and microcephaly, as well as other serious brain anomalies. Diagnostic tests to evaluate Zika virus infection include molecular and serologic testing. This policy describes the medical necessity requirements for these diagnostic tests.

***Note:** All references to travel or residence in the policy/criteria indicate travel within 2 weeks to or residence in an area with ongoing Zika virus transmission.

Policy/Criteria

I. It is the policy of health plans affiliated with Centene Corporation® that real time reverse transcriptase – polymerase chain reaction (rRT-PCR) testing to evaluate Zika virus infection is **medically necessary** for any of the following:
- A. Pregnant women with clinical symptoms consistent with Zika virus disease with exposure due to travel, residence, or sexual contact*:[2,4,6]
  1. Serum testing within 7 days of symptom onset, or
  2. Urine testing within 8 – 14 days of symptom onset;
- B. Neonates with microcephaly or intracranial calcifications born to women with possible exposure to Zika virus through travel, residence, or sexual contact while pregnant, within 2 days of birth*;[9]
- C. Neonates without microcephaly or intracranial calcifications born to women with positive or inconclusive Zika virus testing, within 2 days of birth.

II. It is the policy of health plans affiliated with Centene Corporation® that Zika IgM capture enzyme linked immunosorbent assay (MAC-ELISA) and subsequent plaque-reduction neutralization (PRNT) testing for IgM positive samples is **medically necessary** to evaluate Zika virus infection for any of the following:
- A. Pregnant women with clinical symptoms consistent with Zika virus disease with exposure due to travel, residence, or sexual contact, within 4 days – 12 weeks of symptom onset*;[6, 7]
- B. Asymptomatic pregnant women who may have had Zika virus transmission through travel or sexual contact within 2 – 12 weeks of possible exposure*;[2, 4,6, 7, 11]
- C. Asymptomatic pregnant women residing in areas with ongoing Zika virus transmission at the initiation of prenatal care with follow-up testing mid-second trimester;[6]
- D. Neonates with microcephaly or intracranial calcifications born to women with possible exposure to Zika virus through travel, residence, or sexual encounter while pregnant*;[9]

E. Neonates without microcephaly or intracranial calcifications born to women with positive or inconclusive Zika virus testing.[9]

III. It is the policy of health plans affiliated with Centene Corporation® that evaluation including rRT-PCR, histopathologic examination, and immunohistochemical staining is **medically necessary** for the evaluation of fetal loss and stillbirth if the woman may have had Zika virus transmission during her pregnancy through travel, residence, or sexual contact.[10]

IV. It is the policy of health plans affiliated with Centene Corporation® that the following diagnostic tests to evaluate Zika virus infection are considered **experimental/investigational** under any of the following circumstances:
A. Testing for men for assessing risk for sexual transmission;[4]
B. Routine testing for women and men who are attempting conception who have possible exposure to Zika but no clinical illness;[4]

Background

Zika virus is a flavivirus that was originally discovered from a sentinel rhesus monkey in the Zika Forest in Uganda during a study of yellow fever in 1947.[1] Since its discovery, few cases of the infection had been reported until outbreaks in the State of Yap, Federated States of Micronesia, and French Polynesia in 2007 and 2013, respectively.[1] Zika virus was first identified in the Americas in March 2015 in Brazil.[1] As of March 2016, active Zika virus transmission is occurring in 39 countries and territories in the Americas.[2]

Among recent cases, Zika virus is primarily transmitted by the bite of infected *Aedes* species mosquitoes – most commonly through *Ae. aegypti* and possibly through *Ae. albopictus* mosquitoes.[3] Zika virus can be sexually transmitted from infected males to their sexual partners,[4] and it is possible that the virus can also be transmitted from mother to fetus during pregnancy.[3] Most persons infected with Zika virus are asymptomatic.[2] Yet the most common attributes of Zika virus disease are fever, rash, joint pain, and conjunctivitis, and these symptoms usually last for up to one week.[2] No antiviral medication is available, and supportive care is recommended.

Pregnant women can be infected during any trimester.[3] A causal relationship exists between prenatal Zika virus infection and congenital microcephaly, as well as other serious brain and eye anomalies.[5] Preliminary research has found that the risk of congenital birth defects is greatest with Zika virus infection in the first and second trimesters.[12] However, according to the Centers for Disease Control and Prevention (CDC)'s "Interim Guidance for Health Care Provider's Caring for Women of Reproductive Age with Possible Zika Virus Exposure," there is no evidence that Zika virus will cause congenital infection in pregnancies conceived after the resolution of Zika viremia.[2] Moreover, at the present time testing the risk for sexual transmission of Zika virus is of uncertain value because of the limited understanding of the shedding of the virus in the male genitourinary tract.[4]

Furthermore, a temporal and geographical observation has been made between Zika virus infection and Guillain-Barre syndrome.[1] Continued investigations attempt to understand the link between Zika virus infection and Guillain-Barre syndrome.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization to allow the use of CDC's diagnostic tools to assess Zika virus infection. The diagnostic tests for evaluating Zika virus infection include molecular and serologic testing. Molecular testing is real time reverse transcriptase-polymerase chain reaction (rRT-PCR) for the *in vitro* detection of Zika virus nucleic acids. The CDC's Trioplex rRT-PCR assesses Zika, dengue, and chikungunya. viruses simultaneously. According to "Revised diagnostic testing for Zika, dengue, and chikungunya viruses in US Public Health Laboratories," viral RNA can be identified in serum during the first 7 days of these illnesses,[7] and additional information from the CDC states that urine samples can be collected less than 14 days after the onset of symptoms for rRT-PCR testing.[8]

Serologic testing includes the Zika IgM capture enzyme linked immunosorbent assay (MAC-ELISA) and plaque-reduction neutralization (PRNT) tests for the respective detection of viral specific IgM and neutralizing antibodies to Zika virus. While virus specific IgM antibodies may be detectable ≥ 4 days after onset of illness, serum collected within 7 days of illness onset may not have detectable levels of these antibodies.[7] IgM antibodies remain present for approximately 2-12 weeks.[7] Importantly, an IgM positive result from the MAC-ELISA cannot differentiate between the presence of Zika and dengue viruses, and thus is indicative of the presence of a flavivirus.[7] Therefore, PRNT assays can be used to discriminate between cross reacting antibodies for in situations that are positive for IgM.[7]

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 IgM with confirmatory neutralizing antibody tiers that are ≥4 fold higher than dengue virus neutralizing antibody titers in serum by PRNT.[10] Testing is inconclusive if Zika virus neutralizing antibody tiers are < 4 fold higher than dengue virus neutralizing antibody titers.[10]

Reviews, Revisions, and Approvals	Date	Approval Date
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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of

insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.