

# Clinical Policy: Diagnostic Testing for Zika Virus

Reference Number: CP.MP.111

Last Review Date: 05/19

[Revision Log](#)

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## 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 partner(s). While Zika virus infection is usually asymptomatic or causes mild illness, a causal relationship exists between prenatal Zika virus and microcephaly in the infant, as well as other serious brain anomalies. Diagnostic tests to evaluate for Zika virus infection include molecular and serologic testing. This policy describes the medical necessity requirements for these diagnostic tests.

**\*Note:** All references to possible exposure includes living in, traveling to, or having unprotected sex with someone who lives in or traveled to an area with risk of Zika.

## Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that nucleic acid testing (NAT) using FDA Emergency Use Authorized tests, such as real time reverse transcriptase-polymerase chain reaction (rRT-PCR) testing, to evaluate for Zika virus infection, is **medically necessary** for any of the following:
  - A. Symptomatic non-pregnant individuals with possible Zika virus exposure\*, if < 14 days from symptom onset;
  - B. Pregnant women with clinical symptoms consistent with Zika virus disease, with possible Zika exposure<sup>2,4,6</sup>;
  - C. Asymptomatic pregnant women with ongoing possible Zika virus exposure. Testing at least once per trimester should be considered if living in, or frequently traveling to, areas with active Zika virus transmission, unless a previous rRT-PCR test has been positive;<sup>15</sup>
  - D. Asymptomatic pregnant women with a positive or equivocal MAC-ELISA test for Zika IgM, 2-12 weeks following potential Zika exposure. Testing should be conducted on all appropriate specimen types available;<sup>13</sup>
  - E. Asymptomatic pregnant women who have recent possible Zika virus exposure (i.e., through travel or sexual exposure) but without ongoing possible exposure, if certain jurisdictions recommend testing for epidemiologic considerations such as seasonality;
  - F. Amniocentesis specimens if amniocentesis is conducted for reasons other than Zika testing;
  - G. Pregnant women who have recent possible Zika virus exposure and who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome;
  - H. Infants with birth defects consistent with congenital Zika syndrome, born to women with possible Zika exposure, ideally within 2 days of birth\*;<sup>9</sup>
  - I. Infants without birth defects consistent with congenital Zika syndrome, born to women with positive or inconclusive Zika virus testing, ideally within 2 days of birth;
  - J. Repeat testing if first result is inconclusive or equivocal.<sup>4,9</sup>

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- 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 nonnegative samples is **medically necessary** to evaluate for Zika virus infection for any of the following:
- A. Symptomatic non-pregnant individuals with possible Zika virus exposure, if < 14 days from symptom onset and rRT-PCR is negative, or if ≥ 14 days after symptom onset;
  - B. Symptomatic pregnant women with possible Zika virus exposure, within 4 days – 12 weeks of symptom onset\*;<sup>6, 7</sup>
  - C. Asymptomatic pregnant women who may have had Zika virus transmission through travel or sexual contact, within 2 – 12 weeks of possible exposure, if certain jurisdictions recommend testing for epidemiologic considerations such as seasonality, even if rRT-PCR testing conducted within two weeks of exposure was negative;<sup>2, 4, 6, 7, 11</sup>
  - D. Pregnant women who have recent possible Zika virus exposure and who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome;
  - E. Infants with birth defects consistent with congenital Zika syndrome, born to women with possible exposure to Zika virus, ideally within 2 days of birth\*;<sup>9</sup>
  - F. Infants without birth defects consistent with congenital Zika syndrome, born to women with positive or inconclusive Zika virus testing, ideally within 2 days of birth;
  - G. Repeat testing if first result is inconclusive or equivocal.<sup>4, 9</sup>

\*\*Note: PRNT is not routinely recommended for testing any specimens in Puerto Rico.

- III.** It is the policy of health plans affiliated with Centene Corporation® that PRNT testing is medically necessary to evaluate for Zika virus infection for any of the following:
- A. Infants whose initial sample is IgM nonnegative and rRT-PCR results were negative, if PRNT was not performed on the mother’s sample;
  - B. Infants ≥ 18 months old, whose initial (neonatal) sample was anti-Zika IgM nonnegative, with Zika-specific neutralizing antibodies detected by previous PRNT in either the mother’s or infant’s sample;<sup>13</sup>
  - C. Infants ≥ 18 months old, whose initial (neonatal) sample was negative by both MAC-ELISA and rRT-PCR,<sup>13</sup> or who was not tested at birth, and both (1 and 2):
    1. Infant’s mother had laboratory evidence of possible Zika virus infection during pregnancy;
    2. The infant has clinical findings suggestive of congenital Zika virus syndrome, including any of the following:<sup>13</sup>
      - a. Microcephaly;
      - b. Abnormal neuroimaging findings such as intracranial calcifications, decreased brain parenchymal volume, ventriculomegaly and extra-axial fluid, abnormal gyral patterns, or hypoplasia of brain structures;
      - c. Neurologic abnormalities such as congenital limb contractures, dysphagia, sensorineural hearing loss, epilepsy, abnormal tone or movement, including marked hypertonia and extrapyramidal movement;
      - d. Ocular abnormalities such as microphthalmia, coloboma, intraocular calcifications, optic nerve hypoplasia and atrophy, macular disc scarring, or cortical visual impairment.

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- D. IgM testing for Zika virus is ambiguous (e.g. inconclusive, equivocal, and indeterminate), and retesting has not resolved the ambiguity.<sup>4</sup>

IV. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that evaluation, including rRT-PCR, histopathologic examination, and immunohistochemical staining of placental and fetal tissue specimens, is **medically necessary** for any of the following:

- A. Testing of placental tissue after live birth in symptomatic pregnant women and women with infants with possible Zika virus–associated birth defects, without a definitive diagnosis of laboratory-confirmed Zika virus infection during pregnancy;
- B. Testing of placental tissue after live birth in asymptomatic pregnant women who have recent possible Zika virus exposure and a fetus or infant with possible Zika virus–associated birth defects;
- C. The evaluation of fetal loss and stillbirth if the woman had recent possible Zika virus exposure.<sup>10</sup>

V. It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that diagnostic tests to evaluate for Zika virus infection are considered **experimental/investigational** under any of the following circumstances:

- A. Testing for non-pregnant asymptomatic individuals;
- B. Preconception screening.

### 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.<sup>1</sup> 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.<sup>1</sup> Zika virus was first identified in the Americas in March 2015 in Brazil.<sup>1</sup> A summary of the 2016 Zika virus epidemic reported 5,168 cases of noncongenital Zika virus disease, with diagnoses in 49 states and the District of Columbia, although 48% were reported from three states: Florida, New York, and California.<sup>14</sup> 95% of cases occurred in travelers returning from areas with Zika virus transmission, 4% of cases were locally transmitted, and 1% were acquired through sexual transmission, laboratory transmission, or an unknown route (1 person).<sup>14</sup> Compared to the first 8 months of 2016, the first 8 months of 2017 had significantly fewer reported cases of Zika virus - 4,205 vs. 331. In 2018, no local mosquito-born Zika virus transmission has been reported in the continental United States.<sup>17</sup>

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.<sup>3</sup> Documented sexual transmission of the Zika virus has occurred from infected males to their sexual partners,<sup>4</sup> and from females to male sexual partners.<sup>14</sup> At the present time, testing for risk for sexual transmission of Zika virus is of uncertain value unless either partner is symptomatic, and the couple is wishing to conceive, because of the limited understanding of the shedding of the virus in the male genitourinary tract.<sup>4</sup>

The virus can also be transmitted from mother to fetus during any trimester of pregnancy.<sup>3</sup> Although most persons infected with Zika virus are asymptomatic, the most common symptoms of Zika virus disease are fever, rash, joint pain, and conjunctivitis; these symptoms usually last for up

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to one week.<sup>2</sup> No antiviral medication is available, and supportive care is recommended. A causal relationship exists between prenatal Zika virus infection and congenital microcephaly, as well as other serious brain and eye anomalies.<sup>5</sup> Preliminary research has found that the risk of congenital birth defects is greatest with Zika virus infection in the first and second trimesters.<sup>12</sup>

Furthermore, a temporal and geographical observation has been made between Zika virus infection and Guillain-Barre syndrome.<sup>1</sup> 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 for Zika virus infection include NAT and serologic testing. Most tests that have received FDA emergency use authorization are rRT-PCR tests 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,<sup>7</sup> 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.<sup>8</sup>

Serologic testing includes the Zika IgM MAC-ELISA and PRNT tests for the respective detection of viral specific IgM and neutralizing antibodies to Zika virus. While virus specific IgM antibodies may be detectable  $\geq 4$  days after onset of illness, serum collected within 7 days of illness onset may not have detectable levels of these antibodies.<sup>7</sup> IgM antibodies to Zika virus remain present for approximately 2-12 weeks, although there are reports of prolonged IgM responses with Zika virus infection, as with other flaviviruses.<sup>13</sup> Furthermore, Zika antibodies may be detectable in pregnant women months after infection with the virus, making it difficult to determine whether they were infected before or after conception.<sup>13</sup> 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.<sup>7</sup> Therefore, PRNT assays can be used to discriminate between cross reacting antibodies in cases that are positive for IgM.<sup>7</sup>

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  $\geq 4$  fold higher than dengue virus neutralizing antibody titers in serum by PRNT.<sup>10</sup> Testing is inconclusive if Zika virus neutralizing antibody tiers are  $< 4$  fold higher than dengue virus neutralizing antibody titers.<sup>10</sup>

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed.	05/16	06/16

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Reviews, Revisions, and Approvals	Date	Approval Date
<p>Defined sexual contact for purposes of this policy.</p> <p>Added the following to indications for section I. rRT-PCR testing: Asymptomatic pregnant women within 14 days of contact with exposure from travel, residence, or sexual contact; asymptomatic pregnant women with a positive or equivocal MAC-ELISA test, 2-12 weeks from exposure; amniocentesis specimens if collected for a purpose other than Zika testing; men or women within 14 days of onset of symptoms of Zika virus infection, who want to conceive, and one or both partners live in an area of ongoing Zika virus transmission. Loosened requirement for neonates to have rRT-PCR testing performed within 2 days of birth.</p> <p>Edited the following indications for section II. MAC-ELISA with subsequent PRNT testing: added “even if rRT-PCR result was negative” to asymptomatic pregnant women with exposure through travel or sexual contact, within 2 – 12 weeks; added “Symptomatic men or women who want to conceive, are within 2-12 weeks of onset of symptoms of Zika virus infection, and one or both partners live in an area of ongoing Zika virus transmission”; noted that PRNT testing is not currently recommended in Puerto Rico.</p> <p>Added section III. PRNT testing for infants ≥ 18 months old who either: 1) had Zika positive IgM results and positive PRNT results in either mother or infant’s sample 2) Were negative for Zika IgM but are symptomatic, and born to mothers with positive IgM or rRT-PCR test for Zika.</p> <p>Edited background to reflect literature and CDC guidance updates.</p>	05/17	06/17
<p>Simplified definition of possible Zika exposure.</p> <p>Section I (nucleic acid testing): Specified that medically necessary tests include FDA EUA nucleic acid testing, including rRT-PCR; added indication for symptomatic nonpregnant individuals; changed indication for asymptomatic pregnant women with any exposure in the past 14 days to asymptomatic women with ongoing exposure; added indication for testing of asymptomatic pregnant women without ongoing exposure, if epidemiologic considerations warrant it; added indication for pregnant women with recent possible exposure and ultrasound findings suggestive of congenital Zika syndrome; added indication for testing of pregnant women with fetal ultrasound findings consistent with congenital Zika syndrome; changed “neonates with microcephaly or intracranial calcifications” to “infants with findings suggestive of congenital Zika virus syndrome” in indication for testing of infants born to women with possible Zika exposure; changed “neonates without microcephaly or intracranial calcifications” to “infants without findings suggestive of congenital Zika virus syndrome” in indication for testing of infants born to women with positive or inconclusive Zika virus test results; added indication for repeat testing if first result is inconclusive or equivocal.</p> <p>Section II (IgM/ PRNT): Changed medical necessity statement to say that PRNT is necessary for testing of “nonnegative” samples, instead of</p>	05/18	05/18

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<p>“positive samples; added indication for “symptomatic non-pregnant individuals with possible Zika virus exposure, if &lt; 14 days from symptom onset and rRT-PCR is negative, or if ≥ 14 days after symptom onset;” specified that testing of asymptomatic pregnant women with possible exposure via travel or sexual contact be done if epidemiologic considerations warrant it; removed indications for testing of asymptomatic pregnant women with ongoing exposure, as well as testing of symptomatic individuals wanting to conceive (included in another indication); changed “neonates with microcephaly or intracranial calcifications” to “infants with findings suggestive of congenital Zika virus syndrome” in indication for testing of infants born to women with possible Zika exposure; changed “neonates without microcephaly or intracranial calcifications” to “infants without findings suggestive of congenital Zika virus syndrome” in indication for testing of infants born to women with positive or inconclusive Zika virus test results; added indication for repeat testing if first result is inconclusive or equivocal.</p> <p>Section III (PRNT Testing): Added indication for “infants whose initial sample is IgM nonnegative and rRT-PCR results were negative, if PRNT was not performed on the mother’s sample;” added “or who was not tested at birth” to indications for “Infants ≥ 18 months old, whose initial (neonatal) sample was negative;” changed “Infants ≥ 18 months old, whose initial (neonatal) sample was negative” indication to require that the mother had lab evidence of possible zika infection in pregnancy; edited neurologic and ophthalmologic findings of congenital Zika syndrome findings per CDC guidelines; added indication for ambiguous IgM testing if not resolved by retesting.</p> <p>Section IV (placental and fetal tissue): Added indications for testing placental tissue if the pregnant woman was symptomatic without a definitive Zika diagnosis but with an infant with findings of congenital Zika syndrome, and for asymptomatic pregnant women who tested positive for Zika and had an infant with findings of congenital Zika syndrome.</p> <p>Section V (experimental): simplified indication to state testing of nonpregnant asymptomatic individuals, and pre-conception counseling.</p> <p>Background: Updated with 2016 and 2017 prevalence statistics; clarified that NAT tests include, but are not limited to, rRT-PCR tests.</p>		
References reviewed and updated. Coding reviewed.	04/19	05/19

**References**

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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.

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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, LCDs, and Medicare Coverage Articles 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.

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