



The Commonwealth of Massachusetts  
Executive Office of Health and Human Services  
Department of Public Health  
Bureau of Infectious Disease and Laboratory Sciences  
305 South Street, Jamaica Plain, MA 02130

CHARLES D. BAKER  
Governor

KARYN E. POLITO  
Lieutenant Governor

Clinical Advisory  
Zika Virus  
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MARYLOU SUDDERS  
Secretary

MONICA BHAREL, MD, MPH  
Commissioner

## 1. Zika Virus

Zika virus is a mosquito-borne flavivirus (in the same family as yellow fever, dengue and West Nile viruses) previously found largely in Africa and Southeast Asia. In May 2015, the World Health Organization reported the first local transmission of Zika virus in the Western Hemisphere, in Brazil. Since then it has spread to multiple countries. The first evidence of limited local transmission in the United States occurred in late July 2016 in one neighborhood in Miami, Florida. Surveillance for transmission is ongoing and the most current information about areas with Zika transmission can be found at <http://www.cdc.gov/zika/geo/index.html>. Zika virus infections continue to be reported in travelers returning to the United States from other countries.

An estimated 80% of persons infected with Zika virus are asymptomatic. In symptomatic infection, the incubation period is 3-12 days. Symptomatic disease is generally mild and characterized by at least two of the following:

- acute onset of fever;
- maculopapular rash which may be pruritic;
- arthralgia; or
- nonpurulent conjunctivitis.

Symptoms usually last from several days to 1 week. Severe disease requiring hospitalization is uncommon, and fatalities are rare.

**The most significant concern associated with Zika virus infection is for pregnant women.** In pregnant women who become infected with Zika virus, it is possible for the virus to spread to and through the placenta to the developing fetus. When this happens, it can result in complications of pregnancy and birth defects. The complete range of possible adverse birth outcomes associated with Zika virus infection is unknown at this time but has included: microcephaly; intracranial calcifications; ventriculomegaly; arthrogryposis; abnormalities of the corpus callosum, cerebrum or cerebellum; fetal loss; and abnormalities in both vision and hearing in the neonate. Pregnant women can be infected with Zika virus in any trimester. No evidence exists to suggest that pregnant women are more susceptible to Zika virus infection or experience more severe disease during pregnancy, though some evidence indicates that prolonged maternal viremia can occur during pregnancy. Maternal-fetal transmission of Zika virus has been documented throughout pregnancy; some evidence exists that infection during the first trimester results in the most significant risk to the fetus.

In addition, small numbers of patients have been diagnosed with Guillain-Barré syndrome, meningoencephalitis and thrombocytopenia following Zika virus infection.

## 2. Planning Travel to an Area with a Zika Virus Outbreak

Because there is neither a vaccine nor prophylactic medications available to prevent Zika virus infection, the **Centers for Disease Control and Prevention (CDC) and the Massachusetts Department of Public Health (MDPH) continue to recommend that all pregnant women, and those planning on becoming pregnant within two months, postpone travel to areas with Zika virus outbreaks. Because sexual transmission is possible, the sex partners of women who are pregnant or planning on attempting conception within six months, should also strongly consider postponing their travel.**

If a pregnant woman, a woman who wishes to become pregnant, or the sex partner of these women, **must** travel to an area with Zika virus transmission, they should be counseled that this poses a risk to the unborn child; for couples trying to become pregnant, this travel will result in a recommendation to delay conception. All of these individuals must be advised to strictly follow steps to avoid mosquito bites. Mosquitoes that spread Zika virus bite both indoors and outdoors, mostly during the daytime; therefore, it is important to ensure protection from mosquitoes throughout the entire day. Mosquito prevention strategies, recommended for all travelers to an area with transmission, include:

- wearing long-sleeved shirts and long pants;
- using U.S. Environmental Protection Agency (EPA)–registered insect repellents;
- using permethrin-treated clothing and gear; and
- staying and sleeping in screened-in or air-conditioned rooms.

When used as directed on the product label, insect repellents containing DEET, picaridin, and IR3535 are safe for pregnant women.

## 3. Recommendations about Preventing Sexual Transmission, especially to Pregnant Women, and Delaying Conception for Individuals or Couples with Recent Travel to an Area with a Zika Virus Outbreak

Sexual transmission of Zika virus from both infected men and women to their sex partner is possible. Evidence of Zika virus has been found in semen for up to 93 days after symptom onset and in vaginal fluids up to 11 days. It is not known how frequently Zika virus is found in semen or vaginal fluids or how long it might persist.

**Preventing Sexual Transmission to Pregnant Women:** individuals who reside in or have traveled to an area with a Zika virus outbreak who have a pregnant partner should:

- abstain from sex; or
- consistently and correctly use latex condoms every time they have sex\* for the duration of the pregnancy.

\*Sex includes vaginal, anal and oral sex, as well as the sharing of sex toys.

**Preventing Sexual Transmission and Delaying Conception for Non-Pregnant Couples:** Individuals with a sex partner who lives in, or has traveled to, an area with Zika virus transmission should abstain from sex or use condoms in order to prevent transmission and delay conception for a duration based on the following:

- at least 8 weeks after a Zika diagnosis or start of symptoms if the traveling partner is female;
- at least 6 months after a Zika diagnosis or start of symptoms if the traveling partner is male; or
- at least 8 weeks after returning if the traveling partner (male or female) has no symptoms.

Fact sheets on condoms and information on using condoms correctly are available from the U.S. Department of Health and Human Services and CDC at <https://www.aids.gov/hiv-aids-basics/prevention/reduce-your-risk/using-condoms/> and <http://www.cdc.gov/condomeffectiveness/brief.html#Condom>.

#### 4. Understanding Laboratory Testing for Zika Virus

Two types of laboratory tests are available to assess infection with, or evidence of exposure to, Zika virus.

1. RT-PCR detection of Zika virus RNA indicates the presence of the virus itself. PCR for Zika RNA can be done on serum, urine, cerebral spinal fluid, and amniotic fluid. Although Zika virus RNA is generally only found in serum for 3-4 days, there have been instances of prolonged viremia (up to 10 weeks) in pregnant women. Evidence of Zika virus RNA in urine may also be prolonged following symptom onset or exposure. Approval requirements, sample types and timing of collections for at-risk patients are detailed in the **Diagnostic Testing Guidance** table. This test is available at the MA SPHL for all listed sample types.
2. Anti-Zika virus IgM antibodies provide evidence of recent exposure in patients meeting the designated testing criteria. Testing to detect anti-Zika virus IgM antibodies can be performed on serum samples from potentially exposed, symptomatic or asymptomatic patients as detailed in the **Diagnostic Testing Guidance** table. Anti-Zika virus IgM antibodies reliably appear within 2 weeks following exposure and can last up to 12 weeks. This test is available at the MA SPHL. Serum samples with a positive or equivocal anti-Zika virus IgM result must be confirmed by testing serum for the presence of neutralizing antibodies using the plaque reduction neutralization test (PRNT). Currently, PRNT assays are only performed at the CDC. However, the MA SPHL is working with the CDC to implement PRNT assays here.

In most instances, detection of Zika virus RNA using RT-PCR on samples of serum and urine, early in infection, is optimal to confirm infection with Zika virus. However, the most appropriate application of this test requires that the patient has been currently, or very recently, symptomatic with clinically consistent Zika-like disease. Unfortunately, 80% of individuals exposed to Zika virus remain asymptomatic making this type of laboratory test less suitable because the likely viremic period of the patient cannot be determined.

In many cases, serological testing is the most appropriate diagnostic tool. Interpretation of serology tests may be complicated due to recent and/or prior exposure to another cross-reacting flavivirus (especially dengue virus), or a vaccination history with other flaviviruses such as yellow fever or Japanese encephalitis. Due to the extensive cross-reactivity of Zika and dengue viruses, and the persistence of both dengue and chikungunya viruses in areas with Zika virus transmission, additional testing for these other diseases may be required. Despite testing for additional viruses, in many cases, a positive Zika virus IgM from a single serum with laboratory evidence of neutralizing antibody in both the Zika and dengue PRNT assays will be indicative of “recent exposure to a flavivirus” and a definitive diagnosis may not be possible.

**Selection and interpretation of the appropriate test by the MA SPHL requires specific clinical information including dates and location of travel, evidence of mosquito exposure, symptoms clinically consistent with Zika virus, date of symptom onset, and any previous exposure to dengue virus, yellow fever vaccine or Japanese encephalitis vaccine. This information must be provided when calling for testing approval AND on the specimen submission form that must accompany the sample.**

#### 5. Availability of Laboratory Testing for Zika Virus

**In order to ensure comprehensive testing for high risk patients, all samples from pregnant women with potential exposure to Zika virus should be sent to the MA SPHL. Commercial laboratory testing might be an alternative, but ONLY for individuals who do not meet the criteria for testing at MA SPHL as detailed in the Diagnostic Testing Guidance table, and only if the appropriate test is ordered based on presence/absence of symptoms and on the timing of specimen collection relative to disease onset or last date of possible exposure.**

The table below provides additional information about the types of laboratory testing for Zika virus and where they are currently available. Sample submission should not be based on this information. Specific guidance for individual circumstances is available below in the **Diagnostic Testing Guidance** table.

Test Type	Symptoms?	Sample types	Availability	Turn-around Time
RT-PCR for Zika virus RNA	Symptomatic	serum	<ul style="list-style-type: none"> <li>MA SPHL</li> <li>Commercially available</li> </ul>	MA SPHL < 7 days after sample receipt
	Symptomatic	urine	<ul style="list-style-type: none"> <li>MA SPHL</li> <li>Commercially available</li> </ul>	MA SPHL < 7 days after sample receipt
	N/A	amniotic fluid	MA SPHL	MA SPHL < 7 days after sample receipt
	Symptomatic	CSF	MA SPHL	MA SPHL < 7 days after sample receipt
IgM MAC-ELISA for Zika virus antibodies	Symptomatic and Asymptomatic	serum	<ul style="list-style-type: none"> <li>MA SPHL</li> <li>Commercially available</li> </ul>	MA SPHL < 7 days after sample receipt
Plaque reduction neutralization test (PRNT) for Zika virus neutralizing antibodies	Symptomatic and Asymptomatic	serum	CDC NOTE: MA SPHL: not yet available	CDC – longer than 3 weeks

## 6. Diagnostic Testing Guidance Tables

To discuss/request testing, please contact the MDPH Epidemiology Line at 617-983-6800, available 24/7. If the testing requested meets the current guidelines, testing will be approved. The information requested below **MUST** accompany the sample(s) either on the specimen submission form or on an attached form. **Samples that do not meet the criteria or do not include all the requested information will be rejected for testing.**

When contacting the MDPH, please have the following information available:

- Date of onset of disease symptoms;
- Date of specimen collection;
- Unusual immunological status of patient (e.g., immunosuppression);
- Travel history with dates (e.g., travel to area with current transmission <http://www.cdc.gov/zika/geo/index.htm>);
- Vaccination history (e.g., vaccination against yellow fever, Japanese encephalitis);
- Disease history (e.g., previous history of chikungunya or dengue fever); and
- Brief clinical summary including suspected diagnosis and approximate gestational age

Approved specimens should be submitted using the MA SPHL clinical specimen submission form (<http://www.mass.gov/eohhs/docs/dph/laboratory-sciences/general-submission-form.pdf>) and should include the information provided above for consistency.

**Specific information on specimen collection, storage and shipping is available on the companion document, “Specimen Collection, Storage and Shipment for Molecular and Serological Testing for Zika Virus”. This can be found at [www.mass.gov/dph/zika](http://www.mass.gov/dph/zika) under Information for Healthcare and Public Health Partners.**

Recommendations about Zika virus testing should be adapted to specific patient circumstances. This table provides the current, best available guidance for the most common scenarios. More complex situations should be handled on a case-by-case basis and consultation with MDPH is available 24/7 by calling 617-983-6800.

**DIAGNOSTIC TESTING GUIDANCE TABLE: UPDATED 8-3-2016**

Category	Symptomatic or Asymptomatic	Sample Type and Timing	Additional Notes About Testing	Patient Counseling Recommendations
<b>PREGNANT WOMEN -- TESTING REQUIRES PRE-APPROVAL BY MDPH, CONTACT 617-983-6800</b>				
<p>Women who were pregnant</p> <p>OR</p> <p>conceived during, or within 8 weeks, of <b>travel</b> to an area with a Zika virus outbreak</p>	Symptomatic <sup>1</sup>	≤12 weeks post-symptom onset: serum and urine <sup>3</sup>	Testing is not recommended if more than 12 weeks have passed since symptom onset. Negative results after 12 weeks do not assure absence of exposure.	<ul style="list-style-type: none"> <li>• If the woman's sex partner also has possible exposure to Zika virus because of travel, the couple should be counseled on using latex condoms, consistently and correctly, for all sexual contact for the duration of the pregnancy.</li> <li>• Testing of sex partners for the assessment of risk for sexual transmission is not recommended.</li> </ul>
	Asymptomatic <sup>2</sup>	≤12 weeks after last possible exposure : serum and urine <sup>4</sup>	<ul style="list-style-type: none"> <li>• Convalescent specimen might be requested depending upon timing of specimen collection and test results.</li> <li>• Testing is not recommended if more than 12 weeks have passed since last possible exposure. Negative results after 12 weeks do not assure absence of exposure.</li> </ul>	
<p>Women that became pregnant while <b>residing</b> in an area with a Zika virus outbreak</p> <p>AND</p> <p>Pregnant women that have been in and will be returning to an area with a Zika virus outbreak</p>	Symptomatic <sup>1</sup>	≤12 weeks post-symptom onset: serum and urine <sup>3</sup>	Testing is not recommended if more than 12 weeks have passed since last possible exposure. Negative results after 12 weeks do not assure absence of exposure.	<ul style="list-style-type: none"> <li>• If the woman's sex partner also has possible exposure to Zika virus because of travel, the couple should be counseled on using latex condoms, consistently and correctly, for all sexual contact for the duration of the pregnancy.</li> <li>• Providers may choose to do serial ultrasounds to monitor the development of the fetus during pregnancy in place of, or in addition to, testing.</li> <li>• Testing of sex partners for the assessment of risk for sexual transmission is not recommended.</li> </ul>
	Asymptomatic <sup>2</sup>	Testing recommended during first and second trimester: serum and urine <sup>4</sup>	Because residing in an area a Zika virus outbreak presents a high risk for exposure AND the timing of that exposure is likely not identifiable, testing is recommended but may not be sufficient. Negative results do not assure absence of exposure.	

<sup>1</sup>Symptomatic: One (except where otherwise noted) or more of the following - fever, rash, arthralgia, conjunctivitis - occurring no more than 14 days after last potential exposure

<sup>2</sup>Asymptomatic: absence of symptoms OR with clinical illness **not** characterized by one of the following signs: fever, rash, arthralgia, conjunctivitis

<sup>3</sup>RT-PCR on serum and urine with follow-up IgM ELISA if negative

<sup>4</sup>IgM ELISA with follow-up PRNT if equivocal or positive; follow-up with RT-PCR if positive

<sup>5</sup>RT-PCR on serum and urine WITHOUT follow-up with IgM ELISA if negative

PREGNANT WOMEN continued - - TESTING REQUIRES PRE-APPROVAL BY MDPH, CONTACT 617-983-6800				
Pregnant women, not otherwise exposed, with unprotected sexual contact with a partner that had travel to or resided in an area with ongoing Zika virus transmission	Regardless of presence of symptoms in either partner <sup>1</sup>	For symptomatic or asymptomatic pregnant woman: ≤12 weeks post-symptom onset or after last unprotected sexual contact: serum and urine <sup>3</sup>	Partner may be tested to document sexual transmission but this is dependent upon laboratory capacity and the specific situation: ≤12 weeks post-symptom onset: serum and urine <sup>3</sup>	<ul style="list-style-type: none"> <li>The couple should be counseled on using latex condoms, consistently and correctly, for all sexual contact for the duration of the pregnancy.</li> <li>Providers should discuss with their patients the possibility of serial ultrasounds to monitor the development of the fetus during pregnancy, in addition to, testing.</li> </ul>
COUPLES PLANNING CONCEPTION - - TESTING REQUIRES PRE-APPROVAL BY MDPH, CONTACT 617-983-6800				
Couples planning on attempting conception (naturally or IVF), after travel to an area with ongoing Zika virus transmission	Regardless of presence of symptoms in either partner <sup>1</sup>	Testing not recommended	Testing does not change clinical recommendation.	<ul style="list-style-type: none"> <li>Symptomatic female: delay conception for 8 weeks after symptom onset.</li> <li>Symptomatic male: delay, conception for 6 months.</li> <li>Both partners asymptomatic: delay conception for 8 weeks following the last possible exposure of both individuals.</li> <li>The couple should be counseled on abstinence or using latex condoms, consistently and correctly, for all sexual contact for the appropriate duration.</li> </ul>
FETUSES/INFANTS continued - - TESTING REQUIRES PRE-APPROVAL BY MDPH, CONTACT 617-983-6800				
<b>Possible perinatal infection of infant (infection acquired during delivery):</b> Normal infant whose mother traveled to or resided in an affected area within 2 weeks <b>prior</b> to delivery	Symptomatic infant <sup>1</sup> : <u>Two</u> or more clinical signs/symptoms within 2 weeks <b>after</b> delivery	≤12 weeks post-symptom onset: serum and urine <sup>3</sup>		
	Asymptomatic infant <sup>2</sup>	Testing not recommended		
<sup>1</sup> Symptomatic: One (except where otherwise noted) or more of the following - fever, rash, arthralgia, conjunctivitis - occurring no more than 14 days after last potential exposure <sup>2</sup> Asymptomatic: absence of symptoms OR with clinical illness <b>not</b> characterized by one of the following signs: fever, rash, arthralgia, conjunctivitis <sup>3</sup> RT-PCR on serum and urine with follow-up IgM ELISA if negative <sup>4</sup> IgM ELISA with follow-up PRNT if equivocal or positive; follow-up with RT-PCR if positive <sup>5</sup> RT-PCR on serum and urine WITHOUT follow-up with IgM ELISA if negative				

FETUSES/INFANTS -- TESTING REQUIRES PRE-APPROVAL BY MDPH, CONTACT 617-983-6800				
Pregnant woman with positive or equivocal Zika virus test OR Pregnant woman with possible exposure to Zika virus who was not tested	Prior to delivery <ul style="list-style-type: none"> <li>Fetus with identified abnormalities on ultrasound</li> </ul>	Amniotic fluid can be submitted for RT-PCR testing <sup>5</sup>	Amniocentesis as a procedure has inherent risks and a decision to perform it should be made in the context of the whole situation. The ability of a negative amniotic fluid RT-PCR to exclude infection is not known.	
Pregnant woman with positive or equivocal Zika virus test OR Pregnant woman with possible exposure to Zika virus who was not tested OR Pregnant women with negative test AND infant/fetus with abnormalities consistent with congenital Zika virus	At delivery, miscarriage or termination: <ul style="list-style-type: none"> <li>Normal infant, OR</li> <li>Fetus with identified abnormalities on ultrasound, OR</li> <li>Neonate with identified abnormalities at birth, OR</li> <li>2nd or 3rd trimester fetal loss</li> </ul>	<ul style="list-style-type: none"> <li>Serum from mother if she was not tested or had a negative test for Zika virus</li> <li>Serum from cord blood AND serum from infant ≤ 2 days after delivery</li> <li>Multiple sections from placenta or POC: some sections should be saved as formalin-fixed and some as fresh-frozen tissue. If unable to collect both sets, formalin-fixed tissue should be prioritized.</li> </ul>	<p>Call MDPH either prior to or immediately after delivery/procedure to coordinate appropriate sample collection, handling and submission to MA SPHL. MDPH will obtain permission for specimen submission from CDC</p> <ul style="list-style-type: none"> <li>Specific guidance on specimen collection from infants: <a href="http://www.cdc.gov/zika/hc-providers/test-specimens-at-time-of-birth.html">http://www.cdc.gov/zika/hc-providers/test-specimens-at-time-of-birth.html</a></li> <li>Specific guidance on specimen collection from fetal losses: <a href="http://www.cdc.gov/zika/laboratories/test-specimens-tissues.html">http://www.cdc.gov/zika/laboratories/test-specimens-tissues.html</a></li> </ul>	<ul style="list-style-type: none"> <li>Evaluation of infants with possible congenital Zika virus infection should be guided by the healthcare provider's assessment of the neonate at delivery</li> <li>Additional guidance is available at: <a href="http://www.cdc.gov/zika/hc-providers/infants-children.html">http://www.cdc.gov/zika/hc-providers/infants-children.html</a></li> </ul>
INDIVIDUALS NOT CAPTURED IN OTHER CATEGORIES -- TESTING REQUIRES PRE-APPROVAL BY MDPH, CONTACT 617-983-6800				
Women, men and children with travel to an area with Zika virus transmission not addressed in other categories	Patients with rare manifestations that may be associated with Zika virus	Sample type dependent upon manifestation and timing of sample collection relative to symptom onset	Identified rare manifestations include: Guillain-Barré syndrome, thrombocytopenia, or evidence of neuroinvasive disease	
	Symptomatic <sup>1</sup>	Provider wishing to test will likely be referred to commercially available options	≤14 days post-symptom onset: consider RT-PCR on serum and urine ≤12 weeks post-symptom onset: consider IgM ELISA	Due to the variable duration of viremia and complexities of serologic interpretation, results should NOT be used for decision making about timing of conception or risk of sexual transmission. Provider can call MDPH for assistance with determining test type or result interpretation.
	Asymptomatic <sup>2</sup>	Testing not recommended Provider wishing to test will likely be referred to commercially available options		
<sup>1</sup> Symptomatic: One (except where otherwise noted) or more of the following - fever, rash, arthralgia, conjunctivitis - occurring no more than 14 days after last potential exposure <sup>2</sup> Asymptomatic: absence of symptoms OR with clinical illness <b>not</b> characterized by one of the following signs: fever, rash, arthralgia, conjunctivitis <sup>3</sup> RT-PCR on serum and urine with follow-up IgM ELISA if negative <sup>4</sup> IgM ELISA with follow-up PRNT if equivocal or positive; follow-up with RT-PCR if positive <sup>5</sup> RT-PCR on serum and urine WITHOUT follow-up with IgM ELISA if negative				

## 7. ADDITIONAL RESOURCES

CDC Zika virus web site: <http://www.cdc.gov/zika/index.html>

### [All Areas with Active Zika Virus Transmission](#)

Caring for Pregnant Women and those of Reproductive Age

- UPDATE: [Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States, July 2016 | MMWR](#) (July 29, 2016)
- Webpage: [Clinical Guidance for Healthcare Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure](#)

Caring for Infants and Children

- [Interim Guidelines for Healthcare Providers Caring for Infants and Children with Possible Zika Virus Infection – United States, February 2016](#) (Feb. 26, 2016)
- [Interim Guidelines for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection — United States 2016](#) (January 29, 2016)
- Webpage: [Clinical Guidance for Healthcare Providers Caring for Infants and Children with Possible Zika Virus Infection](#)

Preventing Sexual Transmission

- UPDATE: [Update: Interim Guidance for Prevention of Sexual Transmission of Zika Virus — United States, July 2016 | MMWR](#) (July 29, 2016)
- [Webpage: Zika and Sexual Transmission](#)
- [Guidance for U.S. Laboratories Testing for Zika Virus Infection](#) (July 26, 2016)

Occupational Health and Safety for Healthcare Providers During Delivery

- [Preventing Transmission of Zika Virus in Labor and Delivery Settings Through Implementation of Standard Precautions — United States, 2016](#) (March 25, 2016)