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Clinical Advisory
Zika Virus
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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 2007, it was found for the first time on the Pacific island of Yap and subsequently in French Polynesia. In May 2015, the World Health Organization reported the first local transmission of Zika virus in the Western Hemisphere, with locally acquired cases identified in Brazil. As of January 15, 2016, local transmission had been identified in at least 14 countries or territories in the Americas, including Puerto Rico (See http://wwwnc.cdc.gov/travel/notices/ for information on current countries and territories in the Americas with Zika virus transmission). Further spread to other countries in the region is likely.

Local transmission of Zika virus has not been documented in the continental United States. However, Zika virus infections have been reported in travelers returning to the United States. With the recent outbreaks in the Americas, the number of Zika virus disease cases among travelers visiting or returning to the United States likely will increase.

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,
- arthralgia, and/or
- nonpurulent conjunctivitis.

Symptoms usually last from several days to 1 week. Severe disease requiring hospitalization is uncommon, and fatalities are rare. Guillain-Barré syndrome has been reported in patients following suspected Zika virus infection, but an association is thus far unproven.

Very recently, Brazil has reported an increase in infants with microcephaly occurring over the same time frame as the Zika virus outbreak in that country. While the association is compelling, it is not known if the increase in microcephaly cases is directly caused by Zika virus infections.

ZIKA VIRUS AND PREGNANT WOMEN

Pregnant women can be infected with Zika virus in any trimester. The incidence of Zika virus infection in pregnant women is not currently known, and data on pregnant women infected with Zika virus are limited. No evidence exists to suggest that pregnant women are more susceptible to Zika virus infection or experience more severe disease during pregnancy. Maternal-fetal transmission of Zika virus has been documented throughout pregnancy. Although Zika virus RNA has been detected in the pathologic specimens of fetal losses, it is not known if Zika virus caused the fetal losses. Studies are under way to investigate the association of Zika virus infection and microcephaly and fetal losses, including the role of other contributory factors (e.g., prior or concurrent infection with other organisms, nutrition, and environment).

Planning Travel to an Area with Zika Virus Transmission

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) recommend that all pregnant women consider postponing travel to areas where Zika virus transmission is ongoing.** If a pregnant woman travels to an area with Zika virus transmission, she should 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.

Recommendations for Men with Recent Travel to an Area with Zika Virus Transmission and Their Pregnant Partners

Sexual transmission of Zika virus from infected men is possible although has been documented rarely. It is not known how frequently Zika virus is found in semen or how long it might persist. **Therefore, until more is known, men who reside in or have traveled to an area of active Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use latex condoms during each act of vaginal, anal, or oral sex for the duration of the pregnancy. Pregnant women should discuss their male partner's potential exposures to mosquitoes and history of clinical illness consistent with Zika virus disease with their healthcare provider.**

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.

Laboratory Testing of Pregnant Women with Recent Travel to an Area with Zika Virus Transmission

Laboratory tests for Zika virus infection diagnosis are of limited availability, but include polymerase chain reaction (RT-PCR) for Zika RNA and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. Given the overlap of symptoms and endemic areas with other viral illnesses, patients should also be evaluated for possible dengue or chikungunya virus infection.

Testing has multiple limitations.

- Currently, only the CDC in Fort Collins, Colorado and a few public health laboratories are able to perform testing.
- There is substantial serological cross-reactivity among the flaviviruses and current IgM antibody assays cannot reliably distinguish between Zika and dengue virus infections. Therefore an IgM positive result in a dengue or Zika ELISA test should be considered indicative of a recent flavivirus infection. Plaque-reduction neutralization tests (PRNT) are more specific, can be performed to measure virus-specific neutralizing antibodies and may be able to discriminate between cross-reacting antibodies in primary flavivirus infections. For primary flavivirus infections, a fourfold or greater increase in virus-specific neutralizing antibodies between acute- and convalescent-phase serum specimens collected 2 to 3 weeks apart may be used to confirm recent infection.
- In patients who have been immunized against yellow fever or Japanese encephalitis virus or who are infected with another flavivirus (e.g., West Nile or St. Louis encephalitis virus) in the past, cross-reactive antibodies in both the IgM and neutralizing antibody assays may make it difficult to identify which flavivirus is causing the patient's current illness.

However, a negative IgM result obtained 2-12 weeks after travel suggests that a recent infection with Zika virus did not occur and can reduce the need for serial ultrasounds.

Consultation about laboratory testing is available through the MDPH in the following circumstances:

1. Pregnant women, with a history of travel to an area with Zika virus transmission, who present during or within 2 weeks of travel with a clinical illness consistent with Zika virus disease (two or more of the following signs/symptoms: acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) can be tested for evidence of Zika virus RNA and anti-Zika antibody up to 12 weeks after travel.
    a. If the test results are either positive or inconclusive, fetal ultrasound(s) should be performed to detect microcephaly or intracranial calcifications.
    b. If the test result is negative, then the patient should be monitored with ultrasound(s) as indicated by clinical judgement and level of concern.
2. Pregnant women, with a history of travel to an area with Zika virus transmission, but without evidence of clinical illness can be tested for evidence of anti-Zika antibody at any time between 2-12 weeks after travel.
3. Non-pregnant women and men are not currently being recommended for testing.

REQUESTING LABORATORY TESTING

At this time, all testing will be performed at the CDC. Testing capacity is very limited and CDC is accepting samples from pregnant women with recent (within 12 weeks) travel to countries with identified transmission.

To discuss testing, please contact the MDPH, Epidemiology and Immunization Program at 617-983-6800, available 24/7. If the testing requested meets current CDC capacity and priority, testing can be approved. Availability of testing may increase in the future, and criteria for approval will change.

If testing is approved, collect serum (≥ 3 mL) in a large, red top tube. Refrigerate serum at 4°C or maintain on ice for no longer than 24 hrs. Samples collected and shipped with expected arrival the same day, can be shipped on cold packs (4°C). If storage/transport will exceed 24 hrs, serum should be frozen at -20°C or lower. These samples should be shipped on dry ice. Follow packing and shipping instructions for Category B, Biological Substances. Specimens should be submitted using the Massachusetts State Public Health Laboratory (MA SPHL)clinical specimen submission form (http://www.mass.gov/eohhs/docs/dph/laboratory-sciences/general-submission-form.pdf) and **must** include:

- 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://wwwnc.cdc.gov/travel/notices/)
- Vaccination history (e.g., vaccination against yellow fever, Japanese encephalitis)
- Disease history (e.g., previous history of chikungunya or dengue fever)
- Brief clinical summary including suspected diagnosis, and including approximate gestational age

Samples with incomplete information will result in delayed reporting of test results.

MA SPHL is working with CDC to bring testing capacity in-house and anticipates being able to offer PCR testing around mid-February.

Acute serum (≥ 3 mL) collected within the first 7 days following symptom onset can be tested by PCR. IgM antibodies may be detectable by day 4 of illness but are more reliably identified later on in the course of infection; convalescent specimens, collected 2-3 weeks later, may be necessary to confirm or rule-out infection.

Resources:

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

CDC, Interim Guidelines for Pregnant Women During a Zika Virus Outbreak: http://www.cdc.gov/mmwr/volumes/65/wr/mm6502e1er.htm?s_cid=mm6502e1er_e

CDC, Updated Interim Guidelines for Pregnant Women During a Zika Virus Outbreak: http://www.cdc.gov/mmwr/volumes/65/wr/mm6505e2er.htm?s_cid=mm6505e2er.htm_w

CDC, Interim Guidelines for Prevention of Sexual Transmission of Zika Virus http://www.cdc.gov/mmwr/volumes/65/wr/mm6505e1er.htm?s_cid=mm6505e1er_w.htm

CDC, travel notices: http://wwwnc.cdc.gov/travel/notices/