

March 31, 2016 (*replaces version dated March 22, 2016*)

To: North Carolina Health Care Providers and Laboratories

From: Megan Davies, MD, State Epidemiologist
Scott Zimmerman, DrPH, MPH, HCLD (ABB), State Laboratory of Public Health
Belinda Pettiford, MPH, Women's Health Branch

Subject: **Zika Virus Diagnosis, Management and Reporting (5 pages)**

This memo is intended to provide information to NC clinicians and laboratories regarding diagnosis, management and reporting of Zika virus infection.

This version has been updated to include more specific information on recommendations for prevention of sexual transmission of Zika virus and testing of asymptomatic pregnant women who traveled in the 8 weeks before conception.

Summary

Zika is a mosquito-borne virus that is currently causing outbreaks in many countries, including reports of infected women giving birth to babies with birth defects. Zika virus is transmitted by *Aedes aegypti* and *A. albopictus* mosquitos. Since 2015, endemic transmission has been occurring in the Western hemisphere. A map of countries and territories with active Zika virus transmission is available at <http://www.cdc.gov/zika/geo/index.html>. A recent CDC analysis found that travel limited to elevations higher than 2,000 m (6,562 ft) above sea level posed minimal (approximately 1%) likelihood for mosquito-borne Zika virus transmission, even within countries reporting active transmission.

To date, most cases identified in the continental United States have been among persons with recent travel to an area of ongoing transmission. However, locally-acquired cases have been reported in the U.S. following sexual transmission from male travelers to female non-travelers.

Clinical and Epidemiologic Features

Approximately 1 in 5 people infected with Zika virus become ill. Symptoms begin about 3–12 days after exposure, last between 2 and 7 days and include mild fever, rash (mostly maculopapular), headaches, arthralgia, myalgia, and non-purulent conjunctivitis. Patients may remain viremic for up to 7 days after symptom onset. Clinical symptoms are often similar to dengue and chikungunya infections.

An increase in Guillain-Barré syndrome has been noted in some areas with active Zika virus transmission and some epidemiologic studies have linked Zika virus with increased risk of developing Guillain-Barré syndrome.

Recent data suggest that sexual transmission is more common than previously reported. Isolated cases of Zika virus transmission through blood transfusion have also been reported. Zika virus, like dengue, can be detected in saliva and urine. However, exposure to these fluids has not been linked to transmission.

Case management

Because of similar geographic distribution and symptoms, patients with suspected Zika virus infections also should be evaluated and managed for possible dengue or chikungunya infection. Similar to dengue and chikungunya infections, no specific antiviral treatment is available for Zika virus infection. Treatment is generally symptomatic and can include rest, fluids, and use of acetaminophen. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen and naproxen, should be avoided until dengue can be ruled out to reduce the risk of hemorrhage.



HEALTH AND HUMAN SERVICES

RICHARD O. BRAJER
Secretary

DANIEL STALEY
Director, Division of Public Health

Zika Virus Infection and Pregnancy

There have been reports of congenital microcephaly and other poor pregnancy outcomes in babies of mothers who were infected with Zika virus while pregnant. Zika virus infections have been confirmed in several infants with microcephaly. Studies are under way to clarify the association between Zika virus infection and microcephaly.

Health care providers should ask all pregnant women about their recent travel and their sexual partners' recent travel. Pregnant women who develop symptoms consistent with Zika virus infection within two weeks of travel to areas <2,000 m above sea level in countries and U.S. territories where Zika virus transmission is ongoing should be evaluated by a health care provider and recommended for testing as described below. Serologic testing for Zika virus can also be offered to asymptomatic pregnant women 2–12 weeks after travel to areas <2,000 m above sea level in countries and U.S. territories with ongoing transmission.

Pregnant women should also be considered potentially exposed and recommended for testing if they have had condomless sex (i.e., vaginal intercourse, anal intercourse, or fellatio) during the current pregnancy with a male partner who has traveled to an area of ongoing transmission and had symptoms of Zika virus disease during travel or within 2 weeks of return.

Recommendations for healthcare providers counseling patients with possible exposure to Zika virus who are interested in conceiving are available at: http://www.cdc.gov/mmwr/volumes/65/wr/mm6512e2er.htm?s_cid=mm6512e2er_w.

CDC and the American Congress of Obstetricians and Gynecologists (ACOG) recommend that an ultrasound evaluation be performed for asymptomatic pregnant women reporting travel at any time during pregnancy to an area with ongoing transmission in order to detect fetal microcephaly or intracranial calcifications. Serial ultrasound screening (every 3–4 weeks) may be considered at the discretion of the provider.

Biparietal diameter and head circumference are used to detect microcephaly on ultrasound. Normally, these measurements are not used before 14 weeks gestation. There is limited information regarding timing or diagnostic accuracy of ultrasound for detection of fetal microcephaly or intracranial calcifications associated with Zika virus infection. Additional recommendations for management of pregnant women with travel history to an area with ongoing Zika virus transmission are available at <http://www.cdc.gov/zika/hc-providers/ga-pregnant-women.html> and <https://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak>.

Recommendations for additional assessment and laboratory testing for infants with possible congenital Zika virus infection are available at <http://www.cdc.gov/zika/hc-providers/ga-pediatrician.html>.

Prevention Measures

- Travel advisory: Due to reports of microcephaly and other poor outcomes in babies of mothers who were infected with Zika virus while pregnant, the CDC recommends the following:
 - Pregnant women should consider postponing travel to areas that are at elevations <2,000 m above sea level in countries and U.S. territories where Zika virus transmission is ongoing.
 - Pregnant women and women trying to become pregnant who do travel to these areas should talk to their healthcare providers first and strictly follow steps to avoid mosquito bites during their trip.
- Mosquito avoidance: The mosquitoes responsible for most Zika virus transmission are not believed to be widespread in North Carolina. However, persons being evaluated for Zika virus infection should still be advised to use personal protective measures to avoid exposure to mosquitoes during the first 7 days after symptom onset. These measures include:
 - Avoiding outdoor exposure when mosquitoes are most active. The mosquitos that transmit Zika virus are aggressive daytime biters, so always use personal preventive measures to prevent bites at all times of day.
 - Using personal preventive measures – i.e., wearing insect repellent and covering up:
<http://www.cdc.gov/features/stopmosquitoes/>



HEALTH AND HUMAN SERVICES

RICHARD O. BRAJER
Secretary

DANIEL STALEY
Director, Division of Public Health

- Reducing breeding sites for *Aedes* species mosquitoes in your yard:
http://epi.publichealth.nc.gov/cd/arbo/mosquito_fs.pdf

Additional measures:

- Refrain from donating or selling any blood products until symptoms have resolved and until 28 days after travel to an area with ongoing transmission.
- 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 condoms during sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for the duration of the pregnancy.
- Men who have traveled to an area with active Zika virus transmission and have **nonpregnant** sex partners:
 - Men with confirmed Zika virus infection or clinical illness consistent with Zika virus disease should consider abstaining from sexual activity or consistently and correctly use condoms during sex for at least 6 months after onset of illness.
 - Men who did not develop symptoms of Zika virus disease should consider abstaining from sexual activity or consistently and correctly use condoms during sex for at least 8 weeks after departure from the area.
- Men who reside in an area with active Zika virus transmission and have **nonpregnant** sex partners and have not developed symptoms of Zika virus disease might consider abstaining from sexual activity or consistently and correctly use condoms during sex while active transmission persists.

Laboratory Testing:

Testing for Zika virus requires consultation with the state or local public health department.

Testing is recommended for the following individuals:

- Pregnant women presenting with signs and symptoms consistent with Zika virus disease within two weeks of travel to areas <2,000 m above sea level in countries and U.S. territories where Zika virus transmission is ongoing.
- Pregnant women presenting with signs and symptoms consistent with Zika virus disease who have had condomless sex (i.e., vaginal intercourse, anal intercourse, or fellatio) during the current pregnancy with a male partner who has traveled to an area of ongoing Zika virus transmission and who has had symptoms of Zika virus disease during travel or within 2 weeks of return.
- Asymptomatic pregnant women who have ultrasound findings of fetal microcephaly or intracranial calcifications and who report travel to an area with ongoing transmission during the current pregnancy.

Serologic testing can also be offered to the following individuals:

- Asymptomatic pregnant women (including those who traveled during the 8 weeks before conception) from 2–12 weeks after return from travel to areas <2,000 m above sea level in countries and U.S. territories where Zika virus transmission is ongoing.
- Asymptomatic pregnant women who have had condomless sex (i.e., vaginal intercourse, anal intercourse, or fellatio) during the current pregnancy with a male partner who has traveled to an area of ongoing Zika virus transmission and who has had symptoms of Zika virus disease during travel or within 2 weeks of return.
- Any person presenting with signs and symptoms consistent with Zika virus disease within two weeks of travel to an area with ongoing transmission.
- Symptomatic persons who have had condomless sex (i.e., vaginal intercourse, anal intercourse, or fellatio) with a male partner who has traveled to an area of ongoing Zika virus transmission and who has had symptoms of Zika virus disease during travel or within 2 weeks of return.

Routine testing of men for the purpose of assessing risk for sexual transmission is NOT recommended.



Public Health
HEALTH AND HUMAN SERVICES

RICHARD O. BRAJER
Secretary

DANIEL STALEY
Director, Division of Public Health

Approval is required for submission of specimens. Please contact the Communicable Disease Branch at 919-733-3419 or your local health department to facilitate testing. If the state or local health department is not immediately available, consider collecting the appropriate specimens from the patient and holding them pending approval.

Testing methods

Because of concurrent circulation of Zika, dengue, and chikungunya viruses and the similarity of illness presentation, CDC recommends concurrent testing for all three viruses in symptomatic patients with a recent history of travel to an affected area and clinically compatible illness.

During the first week after onset of symptoms, Zika virus disease can often be diagnosed by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on serum. Virus-specific IgM and neutralizing antibodies typically develop toward the end of the first week of illness; cross-reaction with related flaviviruses (e.g., dengue and yellow fever viruses) is common and may be difficult to discern. Plaque-reduction neutralization testing can be performed to measure virus-specific neutralizing antibodies and discriminate between cross-reacting antibodies in primary flavivirus infections.

Appropriate testing methods are determined based on how long after symptom onset the specimen is collected.

- Specimens collected <4 days after symptom onset will be subjected to molecular testing (RT-PCR) for all three viruses.
- Serum specimens collected 4–7 days after symptom onset will be subjected to molecular testing and serologic testing for virus-specific IgM antibodies for all three viruses. Because serum collected within 7 days of illness onset may not have detectable virus-specific IgM antibodies, IgM testing should be repeated on a convalescent-phase sample.
- Serum specimens collected >7 days after symptom onset and specimens from asymptomatic pregnant women collected 2–12 weeks after return from travel to areas of ongoing Zika virus transmission will be subjected to serologic testing for virus-specific IgM antibodies.

Where to test

Testing for Zika, dengue, and chikungunya viruses will be coordinated by the NC State Laboratory of Public Health (NCSLPH) and conducted in collaboration with CDC. The provider for each patient should complete the following forms:

- The NCSLPH submission form DHHS 3445, which is available at <http://slph.state.nc.us/virology-serology/special-serology.asp>. (At the bottom of this form, please check “Forward to CDC” and indicate the specific tests requested by checking the box for chikungunya and writing in dengue and Zika. NCSLPH will perform chikungunya molecular and serological testing with a 6 business day turn-around-time.)
- The CDC 50.34 DASH form is available at <http://slph.ncpublichealth.com/forms.asp>. A CDC DASH form needs to be completed electronically and printed for each specimen type submitted.

The following information must be provided with submitted specimens:

- Travel history, onset date, specimen collection date, specimen type, description of clinical illness, vaccination history (specifically yellow fever and Japanese encephalitis vaccines), and submitter contact information.
- If the patient is pregnant, please write that in on page 2 of the CDC DASH form in the Brief Clinical Summary box.
- When submitting perinatal specimens or specimens collected from pregnant women, please include the gestational age of the fetus at the time of travel.

Both forms should be completed for all specimens, acute and convalescent, and should be submitted to the NCSLPH.

For more information on collecting and submitting samples for testing go to <http://slph.ncpublichealth.com/doc/NCSLPH-Zika-FAQs-022616.pdf>



Contact the NCSLPH at 919-807-8600 prior to any shipment or if you have additional questions. Specimen transport using the statewide courier can be coordinated with your local health department or specimens can be directly shipped to the NCSLPH using a professional courier service. All specimens should be packaged and shipped as a Category B infectious substance.

Address all specimen shipments as follows: Attention: Virology/Serology Unit
North Carolina State Laboratory of Public Health
4312 District Drive
Raleigh, NC 27607-5490

Table: Specific specimen collection, testing, and shipment information for Zika, chikungunya and dengue testing:

Specimen	Test Performed (as appropriate)	Specimen Volume	Shipment
Serum*	Chikungunya, dengue, and Zika RT-PCR and virus-specific IgM; Flavivirus PRNT	2–5 mL serum	Refrigerated (4°C), placed on cold packs if shipment is to be received within 72 hrs of collection. For delays exceeding 72 hrs, freeze at -70°C & ship on dry ice.
CSF		1-5 ml	
Urine [‡]	Zika RT-PCR	1–3 ml	Refrigerated (4°C), placed on cold packs if shipment is to be received within 72 hrs of collection. For delays exceeding 72 hrs, freeze at -70°C & ship on dry ice.
Amniotic Fluid ^{**‡}	Zika RT-PCR	0.5–3 ml	
Cord Blood	Zika RT-PCR & IgM; Flavivirus PRNT	0.5–3 ml	Refrigerated (4°C), placed on cold packs
Placental Tissue	Zika RT-PCR; Viral Culture	2–5 grams	Freeze at -70°C & ship on dry ice.
Placental Tissue and Umbilical Cord	Immunohistochemical Staining & Zika virus RT-PCR	2–5 grams of tissue and/or paraffin blocks	Tissue should be formalin-fixed or paraffin-embedded. Ship specimens at room temperature. Note: Request consultation with NCSLPH for specific instructions.

*Biosafety guidance for transportation and testing of specimens is available at www.cdc.gov/zika/state-labs/biosafety-guidance.html.

[‡] This specimen type will only be tested alongside a patient-matched serum specimen and can aid in specifically identifying Zika virus infection.

**Patient and healthcare provider must weigh risks and benefits of testing prior to collection of amniotic fluid.

Surveillance and Reporting:

Physicians and laboratories are required to report suspected or confirmed Zika virus infections. Please contact the Communicable Disease Branch at 919-733-3419 or your local health department if Zika virus infection is suspected.

This is an evolving situation and recommendations are likely to change as new information becomes available. Updated information and guidance are available from CDC at <http://www.cdc.gov/zika>.