



RICHARD O. BRAJER
Secretary

DANIEL STALEY
Director, Division of Public Health

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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 new laboratory testing information and guidance and updated information indicating Zika as a cause of birth defects.

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>. Mosquito borne transmission at elevations greater than 2,000 meters above sea level is unlikely.

To date, no case of local transmission by mosquito has been reported, and 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 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.

Zika virus infection during pregnancy is associated with an increase in certain birth defects, including microcephaly. An increase in Guillain-Barré syndrome has also 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.



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Zika Virus Infection and Pregnancy

Zika virus can be passed from a pregnant woman to her fetus, and infection during pregnancy can cause microcephaly and other severe birth defects.

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 areas 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 with ongoing transmission that are less than 2,000 m in elevation. .

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>.

The North Carolina Division of Public Health is currently working with CDC to enroll all pregnant women (and their infants) with positive or indeterminate Zika virus test results in a national registry to provide more comprehensive information on the effects of infections during pregnancy. Additional information is available at <http://www.cdc.gov/zika/hc-providers/registry.html>.

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

CDC recommends that pregnant women should consider postponing travel to areas with ongoing transmission that are less than 2,000 m in elevation. 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.

Current transmission in South and Central America has been mostly the result of transmission by *A. aegypti*, which is not believed to be widespread in NC. 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/>
- Reducing breeding sites for Aedes species mosquitoes in your yard:
http://epi.publichealth.nc.gov/cd/arbo/mosquito_fs.pdf.



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Additional prevention measures include the following:

- 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.
- Women who are **trying to become pregnant** should wait at least 8 weeks after possible exposure via recent travel or sex without a condom with a man infected with Zika.

Laboratory Testing:

Testing for Zika virus is available at the State Laboratory of Public Health and is now also available commercially.

Approval is required for submission of specimens to the State Laboratory of Public Health. 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 for Zika virus infection 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 with ongoing transmission that are less than 2,000 m in elevation.
- 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.

Testing for Zika virus infection can also be **considered** for 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 with ongoing transmission that are less than 2,000 m in elevation. .
- 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.
- Individuals who did not travel to a Zika affected area but have had ≥ 3 symptoms of Zika virus infection (fever, rash, arthralgia, or conjunctivitis) in the past 14 days not explained by another etiology AND have a history of mosquito bite(s) within 2 weeks of symptom onset.



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.

Real-time reverse transcription–polymerase chain reaction (rRT-PCR) is the preferred test for Zika virus infection because it can be performed rapidly and is highly specific. Zika virus RNA can be detected in serum in the first week of illness in most patients and in urine for at least 2 weeks after the onset of symptoms.

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 make the identification of the infecting virus difficult to discern when individuals have a past history of flavivirus infection or vaccination. 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.

Specimen Type	# days specimen collected after symptom onset*			
	<4 days	4 – 7 days	7 – 14 days	>14 days
Serum	PCR	PCR + ELISA	ELISA	ELISA
Urine**	PCR	PCR	PCR	PCR***

* Testing for asymptomatic pregnant women consists of serologic testing only

** Urine specimens must be submitted with a paired serum specimen.

*** Testing is available within 30 days of symptom onset. If the urine is PCR positive no serological testing will be conducted. If the PCR is negative SLPH will test serum for IgM.

Specific specimen collection, testing, and shipment information for serum, urine and other specimen types is included in the table on the following page.

Where to test

Testing for Zika virus is available at:

- NC SLPH: <http://slph.ncpublichealth.com/zika/default.asp>
- Quest Diagnostics: <http://www.questdiagnostics.com/home/professional-specialty-identified.html>
 - Only PCR testing on serum collected from individuals meeting the criteria outlined in this memo is offered.
 - Testing for Dengue and Chikungunya must be separately ordered in addition to the Zika virus testing if desired

Contact the NCSLPH at 919-807-8600 prior to any shipment to the SLPH 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 conducted at the NCSLPH and/or the CDC:

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.

[‡] A paired serum specimen is required when submitting this specimen type.

**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>.