Recommendations for Zika Virus Testing and Follow-Up

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Background

Zika virus is a flavivirus that is transmitted to humans primarily by *Aedes* species mosquitoes; in the Americas, *Aedes aegypti,* is the most common vector. Other documented modes of transmission include intrauterine resulting in congenital infection, intrapartum from a viremic mother to her newborn, sexual, blood transfusion and laboratory exposure. Only about 1 in 5 people who are infected with Zika virus show symptoms. In those that do, the most common symptoms are fever, rash, joint pain, and conjunctivitis. Human disease has been seen in Africa, Asia, and the Pacific islands. Since 2016, reported cases of Zika virus in the Americas have declined and are now outnumbered by dengue cases. However, there are still areas of the world known to have endemic Zika virus transmission, and travelers, especially pregnant women, should take necessary precautions to reduce the risk of infection. (https://www.cdc.gov/zika)

The first case of sexual transmission documented in the United States occurred in Dallas, Texas, in February 2016. Since that time, the U.S. Centers for Disease Control and Prevention (CDC) has reported additional cases from both men and women to their sexual partners. For guidance on prevention of sexual transmission of Zika virus, visit https://www.cdc.gov/mmwr/volumes/67/wr/mm6731e2.htm?s_cid=mm6731e2_e.

In Brazil, a substantial increase in the number of infants born with microcephaly was noted in 2015, and Zika virus infection has been identified in several infants born with microcephaly and other fetal losses. In August 2018, CDC published outcomes of Zika virus infection among infants from Zika positive mothers reported to the U.S. Zika Pregnancy and Infant Registry. One out of seven infants born to laboratory confirmed mothers had a Zika-associated birth defect, a neurodevelopmental abnormality possibly associated with congenital Zika virus infection, or both. (https://www.cdc.gov/mmwr/volumes/67/wr/mm6731e1.htm?s_cid=mm6731e1_e)

In May 2016, the CDC reviewed the evidence that Zika virus causes birth defects and determined that there is a causal association between Zika virus infection and adverse pregnancy outcomes (Rasmussen SA et al. *N Engl J Med* 2016:374:1981-1987). Therefore, CDC is recommending that pregnant women avoid traveling to areas with a risk of Zika. Women who traveled to these areas while pregnant should be evaluated according to the guidance found at the following websites. The websites include recommendations for women who want to get pregnant after recent travel to an area with active Zika virus transmission. (https://www.cdc.gov/zika/prevention/sexual-transmission-prevention.html)

Zika-Affected Areas/Travel Information

Pregnant women should avoid traveling to areas with Zika virus outbreaks, and carefully consider the risks of travel to areas where there is a risk of Zika virus. However, if a pregnant woman must travel, she

should consult with her doctor and strictly follow steps to prevent mosquito bites and avoid sexual exposure during the trip. Testing recommendations differ based on symptom status and where the pregnant woman traveled. There are no restrictions for travelers entering the United States who have contracted Zika virus. CDC has issued travel precautions for people traveling to international destinations and overseas U.S. territories where there is current Zika virus transmission. These notices include maps that show elevation levels in countries with Zika. Prolonged local transmission of Zika virus within the continental United States and Hawaii is unlikely due to environmental conditions (e.g., temperate climate, lower population density, widespread use of air conditioning, and screens, and reduced mosquito habitat). CDC's approach to domestic travel guidance differs from international travel guidance because of the low likelihood of local transmission. There are multiple types of geographic areas. See descriptions below. There is no current transmission of Zika virus in the continental United States, including Florida and Texas, which last reported local transmission in 2016-2017.

- **Zika active transmission area (red area):** Zika virus transmission presents a significant risk to pregnant women. Not recommended to travel.
- **Current or past transmission, but no current outbreak (purple):** Local transmission has been identified in the past, but evidence is lacking that the intensity of transmission is comparable to that in a red area. Although the specific level of risk in purple areas is unknown, there is still a risk to pregnant women. Pregnant women should consult with their healthcare provider about potential risks, and follow steps to prevent mosquito bites and avoid sexual exposure to Zika virus during travel.
- **Mosquito vector present, but no reported cases (yellow):** There have not been reported cases of Zika virus in this area; however, the *Aedes aegypti* vector is present. Travelers should take steps to prevent mosquito bites during travel.
- **No mosquito (green):** No Zika precautions are recommended for these locations.

For more information, visit: https://wwwnc.cdc.gov/travel/page/zika-information.

Recommendations for Diagnostic Testing for Zika

Diagnostic testing for Zika virus is recommended for symptomatic pregnant patients who have traveled to an area with Zika virus transmission or have had unprotected sex with a person who has recently traveled to such an area. Symptoms include fever, rash, joint pain, conjunctivitis (red eyes), muscle pain, and headache (http://www.cdc.gov/zika/symptoms/). Symptoms typically begin within a few days after being bitten by an infected mosquito. Specimens should be collected as soon as possible after symptom onset and should include Dengue and Zika virus NAAT or RT-PCR testing and IgM testing for Dengue virus only. Zika virus IgM is not recommended for symptomatic pregnant women. Diagnostic testing is not routinely recommended for men and women regardless of symptoms, asymptomatic women regardless of pregnancy status, and children regardless of symptoms.

For more information for testing recommendations, visit: https://www.cdc.gov/zika/hc-providers/testing-guidance.html.

Follow-up of Pregnant Women and Infants

For pregnant women where exposure to Zika virus is a real concern, the clinician should follow the pregnancy with serial fetal ultrasounds and other tests to detect abnormalities. If fetal abnormalities are detected during the pregnancy, Zika virus testing should be conducted. Interim guidance for evaluation and testing of infants with microcephaly or intracranial calcifications whose mothers traveled to or resided in an area with Zika virus transmission during pregnancy can be found at https://www.cdc.gov/pregnancy/zika/testing-follow-up/zika-in-infants-children.html. If the clinical provider has questions regarding further testing of pregnant women or infants, contact the **UDOH, Bureau of Epidemiology at 801-538-6191.**

If a pregnant woman has a partner who lives in or traveled to an area with active Zika virus transmission, the couple should correctly and consistently use condoms or abstain from sex ***for the duration of the woman's pregnancy, regardless of Zika test results***. Sex includes vaginal, anal and oral sex and the sharing of sex toys. Zika virus has been detected in semen long after the virus is no longer present in blood.

Pregnant women who test positive for Zika virus will be followed up by public health at labor and delivery to determine pregnancy outcomes. The infant will also be tested at birth for Zika virus to determine possible infection.

Couples Planning Pregnancy

Couples in which the man has traveled to an area with active Zika virus transmission should postpone pregnancy for three months, regardless of Zika test results. If the woman has traveled to an area with active Zika virus transmission, pregnancy should be postponed for two months, regardless of Zika virus test results.

Zika Laboratory Testing Information

Laboratory tests for Zika virus infection diagnosis includes nucleic acid amplification testing (NAAT) using polymerase chain reaction (RT-PCR) technology, Zika virus IgM antibody testing, and plaque reduction neutralization antibody testing (PRNT). Zika NAAT and Zika virus IgM tests are available through commercial laboratories and through the Utah Public Health Laboratory (UPHL). (UPHL) performs the InBios Assay for Zika virus IgM assay and the Trioplex RT-PCR tests. UPHL charges $45 for the InBois IgM test. Trioplex RT-PCR testing will continue to be free of charge and will need approval from Bureau of Epidemiology before testing (http://health.utah.gov/epi/diseases/zika/Zika_IgM_Testing_Fee.pdf). Equivocal or inconclusive IgM test results will be sent to the CDC laboratory in Fort Collins, CO, for confirmation, including PRNT testing. If testing cannot be confirmed at UPHL, the specimen will be sent to CDC in Fort Collins for confirmatory testing.

<u>Symptomatic pregnant patients</u>

- Serum and urine from symptomatic pregnant woman should be collected as soon as possible after symptom onset. The maternal serum will be tested for dengue and Zika virus by NAAT or reverse transcription-polymerase chain reaction (RT-PCR) along with dengue IgM testing only.
    - If Zika NAAT or RT-PCR is positive on a single specimen, the Zika NAAT or RT-PCR should be repeated on a newly extracted RNA from the same specimen to rule out false-

positive Zika NAAT or RT-PCR results. If the dengue NAAT or RT-PCR is positive, this provides evidence of a dengue infection, and no further testing is indicated.
    - If dengue IgM is positive, this is adequate evidence of dengue infection, and no further testing is indicated.
- Zika virus IgM testing is not recommended for symptomatic pregnant women due to the persistence of Zika IgM antibodies for months to years following infection along with the cross reactivity between dengue IgM and Zika IgM antibodies during serologic testing.

Asymptomatic pregnant patients

- Zika virus IgM antibody and RT-PCR or NAAT testing is not recommended for asymptomatic pregnant women with recent travel to an area with Zika virus transmission.

Symptomatic non-pregnant patients

- Zika virus testing is not currently recommended for this group based on the current epidemiology of the viruses. Symptomatic non-pregnant patients should be tested for dengue. (https://www.cdc.gov/dengue/testing

Asymptomatic non-pregnant patients

As per previous guidance, asymptomatic non-pregnant patients should NOT be tested for dengue or Zika viruses.

Congenital Zika virus infection in an infant

- Pregnant women who have a fetus with ultrasound findings consistent with congenital Zika, who currently live, have lived, or traveled to a Zika-affected area, should be tested by Zika virus NAAT or RT-PCR and IgM testing on maternal serum and NAAT or RT-PCR on maternal urine.
    - If Zika NAAT or RT-PCR is negative and the IgM is positive, confirmatory PRNT should be performed against Zika and dengue.

Requesting laboratory testing in Utah

- The InBios Zika IgM assay will costs $45 and will not require prior approval. Approval is still required for the Triplex RT-PCR testing. RT-PCR testing may be limited; therefore, UPHL is requesting that the Bureau of Epidemiology at the Utah Department of Health or the local public health department approve testing requests. **To discuss testing, please contact your local health department or UDOH, Bureau of Epidemiology at 801-538-6191.** Visit https://www.cdc.gov/zika/laboratories/lab-guidance.html for Interim Guidance for Interpretation of Zika Virus Antibody Test Results.

Serum specimen collection and transport

General Instructions	Storage	Shipping
Collect serum (≥ 3 mL) in a large serum separator tube.	Samples collected and shipped with expected arrival the same day can be shipped on cold packs (4°C); not frozen.	If storage/transport will exceed 24 hours, serum should be frozen at -20°C or lower. Ship samples on dry ice to UPHL.

Urine specimen collection and transport

General Instructions	Storage	Shipping
Provide 1.0 mL of urine in a 1.8 mL cryotube or 2.0 mL microtube with sterile screw capped vial secured with thermoplastic, self-sealing lab film.	For RT-PCR testing, specimens should be kept cold (2–6 °C) if shipped within 24 hours or frozen (-70 °C) for storage and shipping greater than 24 hours. For virus isolation testing, specimens should be frozen (-70°C) as soon as possible.	Urine specimens should always be accompanied with a serum specimen.

Collecting & submitting specimens for Zika virus testing at time of birth

Specimen Type	General Instructions	Storage	Shipping
Infant serum (within first 2 days of life)	At least 1.0 ml Transfer serum to a plastic tube measuring approximately 50 mm tall and 15 mm in diameter (e.g., 1.8 mL cryotube or 2.0 mL microtube) with screw cap and secure with thermoplastic, self-sealing lab film.	For cold specimens, the sample should be placed in an insulated container with adequate ice packs to ensure specimen (cold chain) integrity. For frozen specimens, ship the sample on enough dry ice to ensure specimens remain frozen until received.	If storage/transport will exceed 24 hours, serum should be frozen at -20°C or lower. Ship samples on dry ice to UPHL.
Infant urine (within first 2 days of life)	Provide 0.5-1.0 mL of the specimen in a sterile screw capped vial secured with thermoplastic, self-sealing lab film. Please ensure a tight seal as leaking specimens cannot be accepted.	For RT-PCR testing, specimens should be kept cold (2–8 °C) if shipped within 24 hours or frozen (-70 °C) for storage and shipping greater than 24 hours. For virus isolation testing, specimens should be frozen (-70°C) as soon as possible. For frozen specimens, ship the sample on enough dry ice to ensure specimens remain frozen until received.	Urine specimens should always be accompanied with a serum specimen.

Refer to the following websites for more information.

- https://www.cdc.gov/zika/laboratories/test-specimens-tissues.html, and
- https://www.cdc.gov/pregnancy/zika/testing-follow-up/evaluation-testing.html.

Follow packaging and shipping instructions for Category B, Biological Substances.

Laboratory Forms Required for Testing by UPHL and CDC

The Infectious Disease Test Request Form should be securely emailed or faxed to UDOH and accompany the original with the specimen to Utah Public Health Lab (UPHL). The UPHL form is available at http://health.utah.gov/epi/diseases/zika. If a provider needs assistance with completing the form, work with the local health department (LHD) or UDOH epidemiology staff. Additional forms may be required if confirmation testing is necessary. Samples with incomplete information will result in delayed testing and reporting of results. Answers to questions about specimen types or shipping can be found at: http://www.cdc.gov/ncezid/dvbd/specimensub/arboviral-shipping.html

- Arrangements must be made with the UDOH or LHD for specimen shipping and delivery to the UPHL in advance.
- Turnaround time for preliminary results is 7-10 days. If the samples must be sent to CDC for confirmation, turnaround time is 21-28 days.