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John M. Douglas, Jr., M.D. Executive Director

The pages that follow contain information critical to protecting the health of your patients and the citizens of Colorado.

HAN ADVISORY

Number of pages including cover: 12

Subject: **Advisory - Interim Guidelines for Pregnant Women during a Zika Virus Outbreak—United States, 2016**

Message ID: 1/20/2016 1:30:00 PM

Recipients: HAN Community Members.

From: TRI-COUNTY HEALTH DEPARTMENT

Adams, Arapahoe and Douglas County, Colorado

Recipient Instructions: **Tri-County Health Department is forwarding you the attached HAN. You may have already received this broadcast if you are on the CDPHE distribution list, however, we wanted to ensure you did not miss this important information. No response is required.**

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Health Advisory: Provides important information for a specific incident or situation; may not require immediate action.

Health Update: Provides updated information regarding an incident or situation; unlikely to require immediate action.

Info Service/Public Health Brief: Provides general information that is not necessarily considered to be of an emergent nature.

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HEALTH ALERT NETWORK BROADCAST

MESSAGE ID: 01/19/2016 17:30

FROM: CO-CDPHE

SUBJECT: HAN Advisory - Interim Guidelines for Pregnant Women during a Zika Virus Outbreak—United States, 2016

RECIPIENTS: [Local Public Health Agencies / IPs / Clinical Labs / EDs / ID Physicians / Coroners]

RECIPIENT INSTRUCTIONS: Local Health Public Health Agencies - [for your information (OR) please forward to healthcare providers]

HEALTH ADVISORY

Interim Guidelines for Pregnant Women during a Zika Virus Outbreak—United States, 2016
January 19, 2016

******Health care providers: Please distribute widely in your office******

KEY POINTS:

- Health care providers should ask all pregnant women (both sick and healthy) about recent and planned travel.
- Pregnant women or those planning to become pregnant should be counseled on postponing unnecessary travel to areas with active Zika transmission and taking precautions to avoid being bitten by mosquitoes.
- Pregnant women with a history of travel to an area with Zika virus transmission (see background information below for current known countries of transmission) and who report two or more symptoms consistent with Zika virus disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) during or within two weeks of travel, or who have ultrasound findings of fetal microcephaly or intracranial calcifications, should be tested for Zika virus infection.
- Patients with symptoms consistent with Zika virus disease and travel history should also be evaluated for dengue and chikungunya viruses.
- In pregnant women with laboratory evidence of Zika virus infection, serial ultrasound examination should be considered to monitor fetal growth and anatomy.
- Testing for Zika virus is not commercially available at this time. Please consult CDPHE for assistance with testing: 303-692-2700 (regular business hours) or 303-370-9395 (after hours, weekends and holidays).
- Attachments: CDC interim guidance for Zika virus diagnostic testing, and CDC interim guidance for pregnant women during a Zika outbreak. Health care providers should check the CDC website at <http://www.cdc.gov/zika/index.html> for new information.



BACKGROUND INFORMATION:

Zika virus is a mosquito-borne flavivirus transmitted primarily by *Aedes aegypti* mosquitoes. *Aedes albopictus* mosquitoes might also transmit the virus. Outbreaks of Zika virus disease have been reported previously in Africa, Asia and the islands in the Pacific.

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 17, 2016, local transmission has been identified in at least 18 countries or territories in the Americas: Brazil, Barbados, Colombia, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, and Venezuela. 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.

Zika virus infection should be considered in patients with acute onset of fever, maculopapular rash, arthralgia or conjunctivitis, who traveled to areas with ongoing transmission in the two weeks prior to illness onset. Clinical disease usually is mild. However, during the current outbreak, Zika virus infections have been confirmed in several infants with microcephaly and in fetal losses in women infected during pregnancy. We do not yet understand the full spectrum of outcomes that might be associated with infection during pregnancy, nor the factors that might increase risk to the fetus. Additional studies are planned to learn more about the risks of Zika virus infection during pregnancy.

For symptomatic patients within 7 days of illness onset, PCR tests for Zika, dengue and chikungunya viruses are recommended. Serological assays will likely not be useful until >5 days after illness onset. Extensive cross-reactivity of Zika virus with other flaviviruses such as dengue, yellow fever and West Nile virus is expected to occur in serological assays, and can complicate the interpretation of test results. There are commercially available tests for dengue and chikungunya. Refer to the attached CDC memo, **CDC interim guidance for Zika virus diagnostic testing**, for additional guidance with testing for Zika.

RECOMMENDATIONS / GUIDANCE:

- Health care providers should ask all pregnant women (both sick and healthy) about recent and planned travel. Visit the PAHO website at <http://www.paho.org/hq/> for the most up to date information on areas of risk.
- Pregnant women or those planning to become pregnant should be counseled on postponing unnecessary travel to areas with active Zika transmission and taking precautions to avoid being bitten by mosquitoes.
- Pregnant women with a history of travel to an area with Zika virus transmission and who report two or more symptoms consistent with Zika virus disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) during or within two weeks of travel, or who have ultrasound findings of fetal microcephaly or intracranial calcifications, should be tested for Zika virus infection.
- Patients with symptoms consistent with Zika virus disease and travel history should also be evaluated for dengue and chikungunya viruses.
- In pregnant women with laboratory evidence of Zika virus infection, serial ultrasound examination should be considered to monitor fetal growth and anatomy.
- There are no commercially-available diagnostic assays or kits for Zika virus infection. Please consult CDPHE for assistance with testing.



FOR MORE INFORMATION:

- General information about Zika virus and disease: <http://www.cdc.gov/zika/>
- Zika virus information for clinicians: <http://www.cdc.gov/zika/hc-providers/index.html>
- Travel notices related to Zika virus: <http://wwwnc.cdc.gov/travel/notices>
- Information about Zika virus for travelers and travel health providers: <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/zika>
- Pan American Health Organization (PAHO): http://www.paho.org/hq/index.php?option=com_topics&view=article&id=427&Itemid=41484&lang=en
- Information on microcephaly: <http://www.cdc.gov/ncbddd/birthdefects/microcephaly.html>

- For consultation on Zika, chikungunya, and dengue viruses, the Colorado Department of Public Health and Environment (CDPHE) can be contacted at 303-692-2700 (regular business hours) or 303-370-9395 (after hours, weekends and holidays). The Virology Laboratory can be reached at 303-692-3485.



Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016

Emily E. Petersen, MD¹; J. Erin Staples, MD, PhD²; Dana Meaney-Delman, MD³; Marc Fischer, MD²; Sascha R. Ellington, MSPH¹; William M. Callaghan, MD¹; Denise J. Jamieson, MD¹

CDC has developed interim guidelines for health care providers in the United States caring for pregnant women during a Zika virus outbreak. These guidelines include recommendations for pregnant women considering travel to an area with Zika virus transmission and recommendations for screening, testing, and management of pregnant returning travelers. Updates on areas with ongoing Zika virus transmission are available online (<http://wwwnc.cdc.gov/travel/notices/>). Health care providers should ask all pregnant women about recent travel. Pregnant women with a history of travel to an area with Zika virus transmission and who report two or more symptoms consistent with Zika virus disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) during or within 2 weeks of travel, or who have ultrasound findings of fetal microcephaly or intracranial calcifications, should be tested for Zika virus infection in consultation with their state or local health department. Testing is not indicated for women without a travel history to an area with Zika virus transmission. In pregnant women with laboratory evidence of Zika virus infection, serial ultrasound examination should be considered to monitor fetal growth and anatomy and referral to a maternal-fetal medicine or infectious disease specialist with expertise in pregnancy management is recommended. There is no specific antiviral treatment for Zika virus; supportive care is recommended.

Zika virus is a mosquito-borne flavivirus transmitted primarily by *Aedes aegypti* mosquitoes (1,2). These vectors also transmit dengue and chikungunya virus and are found throughout much of the Americas, including parts of the United States. An estimated 80% of persons infected with Zika virus are asymptomatic (2,3). Symptomatic disease is generally mild and characterized by acute onset of fever, maculopapular rash, arthralgia, 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 (4–6).

Pregnant women can be infected with Zika virus in any trimester (4,7,8). 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 (4,7,8). Although Zika virus RNA has been detected in the pathologic specimens of fetal losses (4), it is not known if Zika virus caused the fetal losses. Zika virus infections have been confirmed in infants with microcephaly (4), and in the current outbreak in Brazil, a marked increase in the number of infants born with microcephaly has been reported (9). However, it is not known how many of the microcephaly cases are associated with Zika virus infection. Studies are under way to investigate the association of Zika virus infection and microcephaly, including the role of other contributory factors (e.g., prior or concurrent infection with other organisms, nutrition, and environment). The full spectrum of outcomes that might be associated with Zika virus infections during pregnancy is unknown and requires further investigation.

Recommendations for Pregnant Women Considering Travel to an Area of Zika Virus Transmission

Because there is neither a vaccine nor prophylactic medications available to prevent Zika virus infection, CDC recommends that all pregnant women consider postponing travel



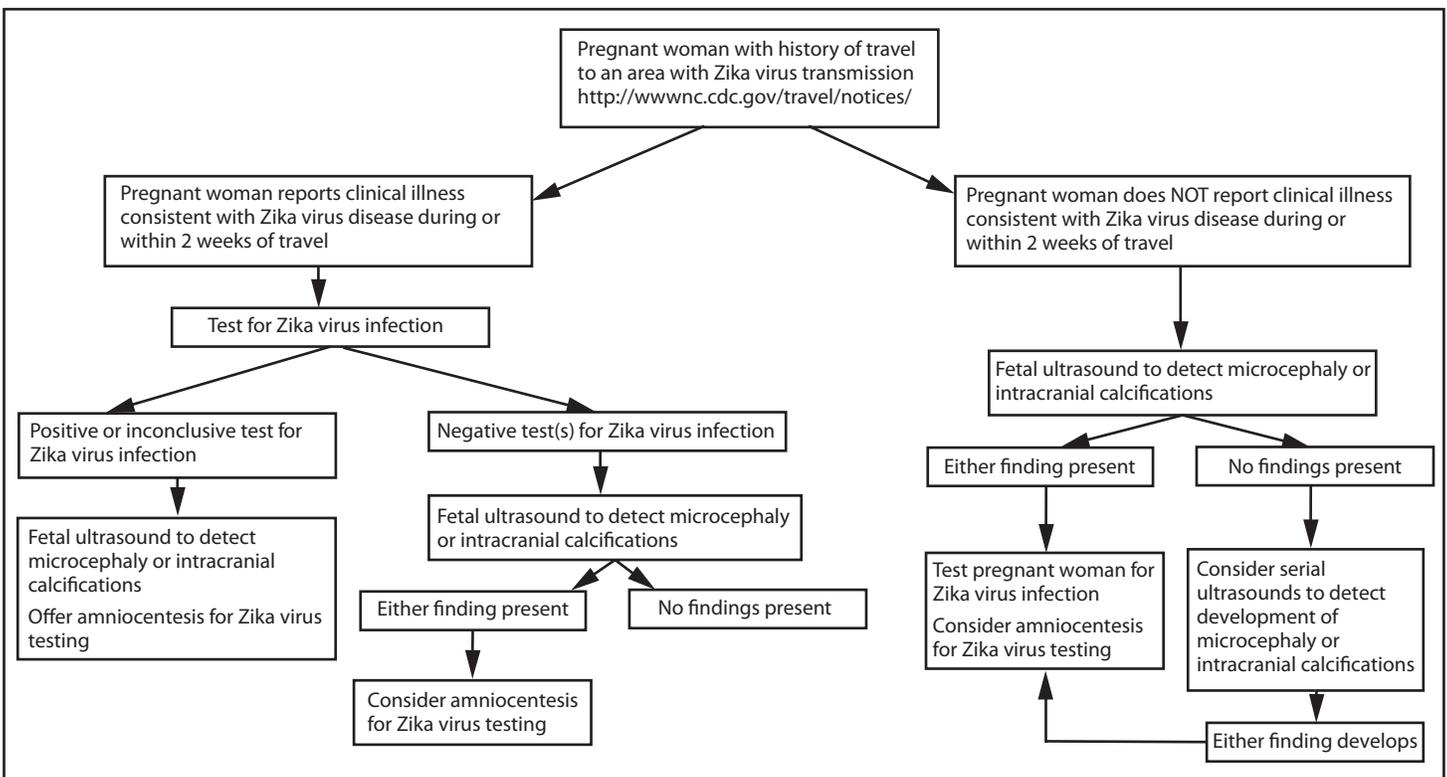
to areas where Zika virus transmission is ongoing (10). If a pregnant woman travels to an area with Zika virus transmission, she should be advised to strictly follow steps to avoid mosquito bites (11,12). Mosquitoes that spread Zika virus bite both indoors and outdoors, mostly during the daytime; therefore, it is important to ensure protection from mosquitoes throughout the entire day (13). Mosquito prevention strategies 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 (14,15). Further guidelines for using insect repellents are available online (<http://wwwnc.cdc.gov/travel/page/avoid-bug-bites>) (11,15).

Recommendations for Pregnant Women with History of Travel to an Area of Zika Virus Transmission

Health care providers should ask all pregnant women about recent travel. Women who traveled to an area with ongoing Zika virus transmission during pregnancy should be evaluated for Zika virus infection and tested in accordance with CDC Interim Guidance (Figure). Because of the similar geographic distribution and clinical presentation of Zika, dengue, and chikungunya virus infection, patients with symptoms consistent with Zika virus disease should also be evaluated for dengue and chikungunya virus infection, in accordance with existing guidelines (16,17).

Zika virus testing of maternal serum includes reverse transcription-polymerase chain reaction (RT-PCR) testing for symptomatic patients with onset of symptoms within the

FIGURE. Interim guidance: testing algorithm^{*,†,§} for a pregnant woman with history of travel to an area[¶] with Zika virus transmission, with or without clinical illness^{} consistent with Zika virus disease**



* Availability of Zika virus testing is limited; consult your state or local health department to facilitate testing. Tests include Zika virus reverse transcription–polymerase chain reaction (RT-PCR) and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. Given the overlap of symptoms and endemic areas with other viral illnesses, evaluate for possible dengue or chikungunya virus infection.

† Laboratory evidence of maternal Zika virus infection: 1) Zika virus RNA detected by RT-PCR in any clinical specimen; or 2) positive Zika virus IgM with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum. Testing would be considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

§ Amniocentesis is not recommended until after 15 weeks of gestation. Amniotic fluid should be tested for Zika virus RNA by RT-PCR.

¶ Updates on areas with ongoing Zika virus transmission are available online (<http://wwwnc.cdc.gov/travel/notices/>).

** Clinical illness is consistent with Zika virus disease if two or more symptoms (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) are present.

previous week. Immunoglobulin M (IgM) and neutralizing antibody testing should be performed on specimens collected ≥ 4 days after onset of symptoms. Cross-reaction with related flaviviruses (e.g., dengue or yellow fever) is common with antibody testing, and thus it might be difficult to distinguish Zika virus infection from other flavivirus infections. Consultation with state or local health departments might be necessary to assist with interpretation of results (18). Testing of asymptomatic pregnant women is not recommended in the absence of fetal microcephaly or intracranial calcifications.

Zika virus RT-PCR testing can be performed on amniotic fluid (7,9). Currently, it is unknown how sensitive or specific this test is for congenital infection. Also, it is unknown if a positive result is predictive of a subsequent fetal abnormality, and if so, what proportion of infants born after infection will have abnormalities. Amniocentesis is associated with an overall 0.1% risk of pregnancy loss when performed at less than 24 weeks of gestation (19). Amniocentesis performed ≥ 15 weeks of gestation is associated with lower rates of complications than those performed at earlier gestational ages, and early amniocentesis (≤ 14 weeks of gestation) is not recommended (20). Health care providers should discuss the risks and benefits of amniocentesis with their patients. A positive RT-PCR result on amniotic fluid would be suggestive of intrauterine infection and potentially useful to pregnant women and their health care providers (20).

For a live birth with evidence of maternal or fetal Zika virus infection, the following tests are recommended: histopathologic examination of the placenta and umbilical cord; testing of frozen placental tissue and cord tissue for Zika virus RNA; and testing of cord serum for Zika and dengue virus IgM and neutralizing antibodies. CDC is developing guidelines for infants infected by Zika virus. If a pregnancy results in a fetal loss in a woman with history of travel to an area of Zika virus transmission with symptoms consistent with Zika virus disease during or within 2 weeks of travel or findings of fetal microcephaly, Zika virus RT-PCR and immunohistochemical staining should be performed on fetal tissues, including umbilical cord and placenta.

There is no commercially available test for Zika virus. Testing for Zika virus infection is performed at CDC and several state health departments. Health care providers should contact their state or local health department to facilitate testing and for assistance with interpreting results (4).

How to Treat Pregnant Women with Diagnoses of Zika Virus Disease

No specific antiviral treatment is available for Zika virus disease. Treatment is generally supportive and can include rest, fluids, and use of analgesics and antipyretics (4). Fever should

be treated with acetaminophen (21). Although aspirin and other nonsteroidal anti-inflammatory drugs are not typically used in pregnancy, these medications should specifically be avoided until dengue can be ruled out to reduce the risk for hemorrhage (4,9,17).

In pregnant a woman with laboratory evidence of Zika virus in serum or amniotic fluid, serial ultrasounds should be considered to monitor fetal anatomy and growth every 3–4 weeks. Referral to a maternal-fetal medicine or infectious disease specialist with expertise in pregnancy management is recommended.

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Memorandum

Date: January 13, 2016

From: CDC, Division of Vector-Borne Diseases, Arboviral Diseases and Dengue Branches

Subject: Updated diagnostic testing for Zika, chikungunya, and dengue viruses in US Public Health Laboratories

Background

Many countries in the Americas now have local transmission of multiple arboviruses that can cause febrile illness with rash, myalgia, or arthralgia. Therefore, laboratory testing has become even more important to confirm the etiology of these diseases. For patients with acute fever, rash, myalgia, or arthralgia and have travelled within the previous 2 weeks to an area with ongoing transmission, Zika, chikungunya, and dengue virus infections should all be considered. Laboratory evidence of recent chikungunya, dengue, or Zika virus infection is generally accomplished by testing serum to detect viral nucleic acid or virus-specific immunoglobulin (Ig) M and neutralizing antibodies. However, serological cross-reactivity is strong between Zika and dengue viruses, so emphasis should be placed on molecular detection in acute specimens. Laboratory testing for all of these agents is currently available at CDC and several state health departments.

Laboratory assays for acute specimens

During the first 7 days of these illnesses, viral RNA can often be identified in serum, and RT-PCR is the preferred test for all three viruses. In addition, for dengue viruses, NS1 antigen can be detected by ELISA in acute phase specimens but this assay is not widely available in the US.

Virus-specific IgM antibodies may be detectable >3 days after onset of illness. However, serum collected within 7 days of illness onset may not have detectable virus-specific IgM antibodies and IgM testing should be repeated on a convalescent-phase sample to rule out infection in patients with a compatible clinical syndrome. IgM antibodies against Zika virus, dengue viruses, and other flaviviruses (e.g., yellow fever and West Nile virus) have strong cross-reactivity possibly generating false positive results in serological tests.

Laboratory assays for convalescent specimens

IgM antibodies typically persist for months. In patients with a compatible clinical syndrome, serum collected more than 8 days after illness onset should be tested by virus-specific IgM ELISA and positive results confirmed by testing for neutralizing antibodies.

There is substantial serological cross-reactivity between 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 IgM ELISA test should be considered indicative of a recent flavivirus infection. Plaque-reduction neutralization tests (PRNT) 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 (e.g., received yellow fever or Japanese encephalitis vaccination) or 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.

Laboratory safety

Zika and dengue viruses are classified as biological safety level (BSL) 2 pathogens while chikungunya virus is classified as a BSL-3 agent. All should be handled in accordance with Biosafety in Microbiological and Biomedical Laboratories (BMBL) guidelines and a risk assessment performed for each laboratory for the specific procedures utilized. In particular, because chikungunya virus produces such high levels of viremia, serum from suspected chikungunya virus cases should be treated as potentially infectious even for serological procedures.

Options for obtaining/conducting Zika, chikungunya, and dengue virus diagnostic testing

CDC

Zika, chikungunya, and dengue virus RT-PCR, IgM ELISA, and plaque reduction neutralization tests (PRNT) are performed at CDC. The specific tests performed will depend on the timing of the specimens relative to illness onset and clinical information as outlined in the algorithm figure. To determine the appropriate testing algorithm and interpret results, please provide the date of illness onset, dates of specimen collection, specimen type, description of clinical illness, travel history, flavivirus vaccination history, and contact information for the submitter. Testing will primarily be performed on serum or CSF but other specimen types, including urine, amniotic fluid, and tissues, can be submitted for evaluation of the utility of these specimen types.

Within Puerto Rico, please call 787-706-2399 for questions about testing. For submission of specimens, please submit a dengue case investigation report (DCIR) for each specimen which can be downloaded from: <http://www.cdc.gov/dengue/clinicalLab/index.html>

For all other states and territories, questions about laboratory testing or sending specimens to CDC should be directed to the Arboviral Diseases Branch on-call epidemiologist at 970-221-6400. A completed DASH form should accompany submitted specimens. More information about submitting specimens to CDC is at:

<http://www.cdc.gov/nceid/dvbd/specimensub/arboviral-shipping.html>.

State Health Department Laboratories

RT-PCR: The CDC chikungunya virus and Zika virus RT-PCR protocols follow essentially the same protocol as the CDC West Nile virus RT-PCR assay. CDC will provide chikungunya and Zika virus primer/probe sequences, an RNA-positive control, and chikungunya and Zika virus RT-PCR proficiency panels to state laboratories that have demonstrated proficiency at the CDC West Nile virus RT-PCR assay. Dengue virus RT-PCR kits can be ordered online using the following link: <http://www.cdc.gov/dengue/clinicalLab/realTime.html>

Zika virus IgM ELISA: The CDC Zika virus IgM ELISA is similar to the CDC West Nile virus IgM ELISA assay. State laboratories that have demonstrated proficiency in performing the CDC West Nile virus IgM ELISA during the 2015 evaluation can request Zika virus antigen, conjugated antibody, and positive control serum for use in the CDC Zika virus IgM ELISA.

To obtain the materials described above, please contact Brandy Russell at bmks8@cdc.gov or 970-221-6400. If your state health department laboratory does not perform the CDC West Nile virus RT-PCR assay or IgM ELISA assay, consider sending specimens to CDC or using one of the commercial laboratory options described below.

Commercially-available testing

There are no commercially-available diagnostic assays or kits for Zika virus infection.

There is an FDA approved kit for anti-DENV IgM antibodies which can be purchased (InBios, USA).

The following commercial reference laboratories perform testing for chikungunya and dengue viruses but none of the assays are FDA-cleared.

- Focus Diagnostics (<http://www.focusdx.com/>) performs a chikungunya virus RT-PCR and IgM and IgG IFA assays as well as an anti-DENV IgM ELISA.
- ARUP Laboratories (<http://www.aruplab.com/>) performs chikungunya virus and dengue virus IgG and IgM ELISA testing.
- Quest Diagnostics (<http://www.questdiagnostics.com>) performs dengue virus IgG and IgM immunoassays.

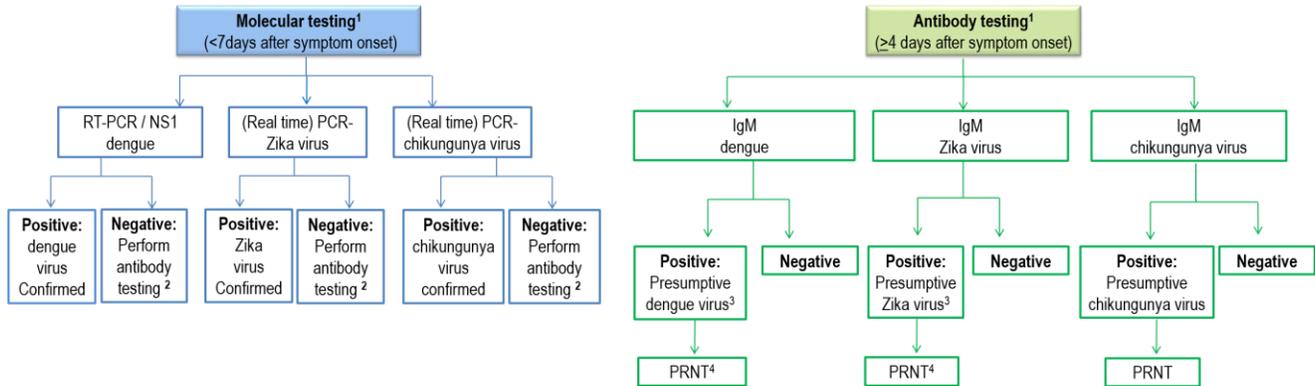
The following chikungunya virus IgM antibody test kits are available for purchase in the United States and provide sensitivity and specificity comparable to that of the CDC assays but not all are FDA-cleared:

- Anti-CHIKV IgM human ELISA kit (Abcam, UK)
- Anti-CHIKV ELISA (IgM) (Euroimmun, Germany)
- Anti-CHIKV IIFT (IgM) (Euroimmun, Germany)
- CHIKjj *Detect* MAC-ELISA (Inbios, USA)

Reporting

Both dengue and chikungunya are nationally notifiable conditions; state health departments should report cases to CDC according to standard CSTE case definitions. Though Zika virus disease is not nationally notifiable, healthcare providers are encouraged to report suspected Zika virus disease cases to their state or local health departments to facilitate diagnosis and mitigate the risk of local transmission. State health departments are requested to report laboratory-confirmed cases of any arbovirus to CDC through ArboNET, the national surveillance system for arboviral disease.

**Tiered algorithm for arbovirus detection for suspected cases of chikungunya, dengue, or Zika
(Testing only performed if travel history indicates travel to affected area.)**



- ¹ Due to extensive cross-reactivity in flavivirus serological assays, for samples collected <7 days post illness onset, molecular detection should be performed first.
- ² Perform if sample ≥4 days after symptom onset
- ³ Extensive cross-reactivity would be expected in samples from DENV/ZIKV circulation areas. A positive IgM assay with either antigen should be confirmed by using PRNT against both ZIKV and DENV as well as any other flavivirus (eg. SLEV, ZIKV, WNV, etc.) that might be found in that geographic area (including travel areas).
- ⁴ PRNT should include any flavivirus (eg. SLEV, ZIKV, WNV, etc.) that might be found in that geographic area (including travel areas).