Background

Zika belongs to the flavivirus family of viruses and is closely related to a number of other human pathogenic viruses, including the viruses that cause yellow fever, dengue fever, and chikungunya. These infections are spread via the bite of the Aedes species mosquito, which is found in many tropical and subtropical locations, including parts of the United States. Many people infected with the Zika virus will not exhibit any symptoms. Of those who do, most develop an acute febrile illness that lasts several days to a week and then resolves completely. Hospitalization is rare. The most common symptoms of Zika are fever, rash, joint pain, and conjunctivitis (red eyes).

To date, the most critical clinical issue is the strong association between Zika infection in pregnancy and the development by the fetus of congenital abnormalities. The most concerning of these is microcephaly, in which an infant's head is significantly smaller than children of the same age and gender. This condition is often associated with developmental delay and other neurological issues. Much is still unknown about the precise relationship between development of this condition and the preceding Zika infection. Additionally, in areas affected by Zika, the reports of Guillain-Barré syndrome (uncommon sickness of the nervous system) have increased.

Researchers continue to work to understand more about the spread of the virus, as well as the impact to pregnant women and unborn fetuses.

Current Concern

Prior to 2015, there had been no outbreaks of Zika outside of Africa, Southeast Asia, and the Pacific Islands. In May 2015, the first confirmed case of infection was reported in Brazil, and cases have now been reported in numerous countries in Central and South America. On July 29, 2016, the Centers for Disease Control and Prevention (CDC) reported the first cases of local mosquito-borne Zika virus transmission in the continental US (Florida). However, since early 2017, the reported incidence of Zika virus disease in the region has declined. The CDC is actively involved in monitoring the situation and developing improved case definitions and diagnostic test options. In addition, the CDC has issued a travel advisory recommending that pregnant women defer travel to areas of the world where Zika transmission is ongoing.

Zika Infection and Diagnosis

The diagnosis of Zika virus infection is made through molecular and serologic testing. Test methods include (1) nucleic acid amplification (NAA), (2) immunoglobulin M (IgM) detection, and (3) plaque reduction neutralization test (PRNT) for Zika virus antibodies.

Zika and Pregnancy

On July 24, 2017, the CDC updated its interim guidance for US health care providers who are caring for pregnant patients with possible exposure to Zika virus. The CDC noted that “All pregnant women in the United States and U.S. territories should be asked about possible Zika virus exposure before and during the current pregnancy at every prenatal care visit.” Possible exposures to Zika virus include travel to or residence in an area with active Zika virus transmission, or sex with a partner who has traveled to or resides in an area with active Zika virus transmission without using condoms or other barrier methods to prevent infection.

The clinical guidance also focuses on key points related to testing for symptomatic and asymptomatic pregnant women with exposure to Zika. Please see Figure 1 and Figure 2 for “updated interim guidance: testing and interpretation recommendations” from the CDC for pregnant women with possible exposure to Zika virus.

What can health care providers do for pregnant patients?

- Know the symptoms of Zika and ask patients about their travel history. The most common symptoms of Zika are fever, rash, joint pain, and conjunctivitis.
- Contact their state and local health departments for laboratory testing.
- Educate a pregnant woman and her partner about how to prevent Zika transmission.
- Call CDC and the state or local health department for clinical consultation. Notify state and local health departments when they have cases of Zika.
- Offer testing to pregnant women and others with symptoms of Zika who have traveled to areas with Zika. The CDC has made available testing algorithms and additional clinical guidance on their website for health care providers. Please visit www.cdc.gov for more information.
### Testing for Zika Infection: CDC Testing Algorithm

**Figure 1.** Updated interim testing recommendations*1,5,8,9,11,15 and interpretation of results**4 for symptomatic pregnant women with possible Zika virus exposure**3,11 — United States (including U.S. territories), July 2017.

#### ASK pregnant women about

- **WHOM to test?**
  - Asymptomatic pregnant women with ongoing possible Zika virus exposure

- **WHEN to test?**
  - Three times during pregnancy: First test at initiation of prenatal care

- **WHICH tests?**
  - Zika virus NAT (serum and urine)

#### RESULTS and ADDITIONAL tests

<table>
<thead>
<tr>
<th>INTERPRETATION</th>
<th>Positive Zika virus NAT</th>
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</tr>
<tr>
<td>Zika virus exposure before the current pregnancy, positive IgM represents recent Zika virus infection</td>
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#### Abbreviations:

- **IgM** = immunoglobulin M; **NAT** = nucleic acid test; **PRNT** = plaque reduction neutralization test

- *Most current* for Zika virus NAT testing before and during current pregnancy; other tests might limit interpretation of Zika virus IgM results, protect counseling can help inform testing decisions. Some patients may choose not to receive Zika virus IgM testing.

- Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (persistent Zika virus RNA and/or a positive Zika virus PRNT ≥10 and dengue virus PRNT <10 results).

- The algorithm also applies to pregnant women with possible Zika virus exposure who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome.

- The duration of detectable Zika virus RNA in pregnant women following infection is not known. Preliminary data suggest that NAT might remain positive for several weeks after symptom onset in some pregnant women.

- Zika virus IgM antibodies are most likely to be detected within 2-3 weeks after infection; however, light antibody titters might be detected for months after infection, testing the ability to determine whether infection occurred before or during the current pregnancy.

- Dengue virus IgM antibody testing is recommended for symptomatic pregnant women. For laboratory interpretation in the presence of dengue virus IgM results, refer to https://www.cdc.gov/dengue/diagnosis/lab.html.

- Nonpositive results include "positive," "equivocal," "presumptive positive," or "possible positive." These are examples of assay interpretations that might accompany test results; nonnegative screening morphology varies by assay. For explanation of a specific interpretation, refer to the instructions for use for the specific assay performed. Information on each assay can be found at https://www.fda.gov/MedicalDevices/Safety-Emergency/situat10/n174919.html under the "Labtest" tab for the specific assay.

#### Note from LabCorp:**

**Please contact your LabCorp representative about the dengue virus IgM test.** Per the CDC, dengue virus IgM antibody testing is recommended only for symptomatic pregnant women.

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### Reference

- **Abbreviations:** IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test.

- *Ask about type and duration of Zika virus exposure before and during the current pregnancy. Exposure before the current pregnancy might limit interpretation of Zika virus IgM results, protect counseling can help inform testing decisions. Some patients may choose not to receive Zika virus IgM testing.

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- Dengue virus IgM antibody testing is recommended for symptomatic pregnant women. For laboratory interpretation in the presence of dengue virus IgM results, refer to https://www.cdc.gov/dengue/diagnosis/lab.html.

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- *Currently, PRNT confirmation is not routinely recommended for pregnant women living in Puerto Rico. For laboratory interpretation in the absence of PRNT testing, refer to https://www.cdc.gov/dengue/diagnosis/lab-table.html.*

- **Despite the high specificity of NAT, false-positive NAT results have been reported. If both serum and urine specimens are NAT-positive, regardless of light antibody results, results should be interpreted as evidence of acute Zika virus infection. If either serum or urine specimen is NAT-negative in conjunction with a positive Zika virus IgM result, results should be interpreted as evidence of acute Zika virus infection.** If repeat NAT testing is negative, results are indeterminate and health care providers should repeat Zika virus IgM antibody testing on a serum specimen collected ≥2 weeks after symptom onset. For repeat NAT results the positive, negative or indeterminate and light and if negative, interpret as no evidence of Zika virus infection.

- **Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https://wwwnc.cdc.gov/travel/page/zika-travel-information) during pregnancy or the periconceptional period (8 weeks before conception [6 weeks before the last menstrual period], or on without a condom during pregnancy or the periconceptional period, with a partner who travels to, or resides in an area with risk for Zika virus transmission.**

- **For the purpose of this guidance, recent possible Zika virus exposure or Zika virus flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.**

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**Figure 2.** Updated interim testing recommendations*1-5 and interpretation of results*4 for asymptomatic pregnant women with possible Zika virus exposure***3-5,9,11 — United States (including U.S. territories), July 2017.

#### ASK pregnant women about

- **WHOM to test?**
  - Asymptomatic pregnant women with ongoing possible Zika virus exposure

- **WHEN to test?**
  - Three times during pregnancy: First test at initiation of prenatal care

- **WHICH tests?**
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#### Abbreviations:

- **IgM** = immunoglobulin M; **NAT** = nucleic acid test; **PRNT** = plaque reduction neutralization test.

- *Ask about type and duration of Zika virus exposure before and during the current pregnancy. Exposure before the current pregnancy might limit interpretation of Zika virus IgM results, protect counseling can help inform testing decisions. Some patients may choose not to receive Zika virus IgM testing.

- Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (persistent Zika virus RNA and/or a positive Zika virus PRNT ≥10 and dengue virus PRNT <10 results).

- The algorithm also applies to pregnant women with possible Zika virus exposure who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome.

- The duration of detectable Zika virus RNA in pregnant women following infection is not known. Preliminary data suggest that NAT might remain positive for several weeks after symptom onset in some pregnant women.

- Zika virus IgM antibodies are most likely to be detected within 12 weeks after infection; however, light antibody titters might be detected for months after infection, testing the ability to determine whether infection occurred before or during the current pregnancy.

- Dengue virus IgM antibody testing is recommended for symptomatic pregnant women. For laboratory interpretation in the presence of dengue virus IgM results, refer to https://www.cdc.gov/dengue/diagnosis/lab.html.

- Nonpositive results include "positive," "equivocal," "presumptive positive," or "possible positive." These are examples of assay interpretations that might accompany test results; nonnegative screening morphology varies by assay. For explanation of a specific interpretation, refer to the instructions for use for the specific assay performed. Information on each assay can be found at https://www.fda.gov/MedicalDevices/Safety-Emergency/situat10/n174919.html under the "Labtest" tab for the specific assay.

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- **Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https://wwwnc.cdc.gov/travel/page/zika-travel-information) during pregnancy or the periconceptional period (8 weeks before conception [6 weeks before the last menstrual period], or on without a condom during pregnancy or the periconceptional period, with a partner who travels to, or resides in an area with risk for Zika virus transmission.**

- **For the purpose of this guidance, recent possible Zika virus exposure or Zika virus flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.**

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**Note from LabCorp:** Please contact your LabCorp representative about the dengue virus IgM test. Per the CDC, dengue virus IgM antibody testing is recommended only for symptomatic pregnant women.
Testing for Zika infection: CDC Clinical Management

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Testing of placental tissues</th>
<th>Testing of placental and fetal tissues</th>
<th>Testing of placental and infant autopsy tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy loss, possible Zika virus—associated birth defects</td>
<td>Should be considered to aid in maternal diagnosis</td>
<td>May be considered to aid in maternal diagnosis on a case-by-case and jurisdictional basis. Not routinely recommended for asymptomatic women with possible Zika virus exposure but without ongoing possible exposure</td>
<td>Not indicated†††</td>
</tr>
<tr>
<td>Pregnancy loss, no obvious Zika virus—associated birth defects</td>
<td>May be considered to aid in fetal diagnosis</td>
<td>May be considered to aid in maternal diagnosis</td>
<td></td>
</tr>
<tr>
<td>Infant death following live birth</td>
<td>Should be considered to aid in infant diagnosis</td>
<td>Should be considered to aid in infant and maternal diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

**Testing of placental tissues**

- Live birth, possible Zika virus–associated birth defects
  - Not indicated†††
  - Should be considered to aid in fetal diagnosis

- Live birth, no obvious Zika virus–associated birth defects at birth
  - Not indicated†††
  - Should be considered to aid in fetal diagnosis

**Testing of placental and fetal tissues**

- Pregnancy loss, possible Zika virus—associated birth defects
  - May be considered to aid in fetal diagnosis

- Pregnancy loss, no obvious Zika virus—associated birth defects
  - Not indicated†††

**Testing of placental and infant autopsy tissues**

- Infant death following live birth
  - Should be considered to aid in infant diagnosis

### Abbreviations:

- IHC = immunohistochemistry; NAT = nucleic acid test; RT-PCR = reverse-transcription polymerase chain reaction.
- Placental tissues include placental disc, umbilical cord, and fetal membranes. Zika virus RNA can be focal within placental tissues, and testing of three sections of placenta, one section of umbilical cord, and one section of fetal membrane is recommended (https://www.cdc.gov/zika/laboratories/test-specimens-tissues.html). For pregnancy losses and infant deaths, submission of placental tissues in addition to fetal or infant tissues, if available, is preferred, but if not available will not preclude placental testing.
- Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https://www.cdc.gov/zika/geo/index.html) during pregnancy or the periconceptional period (8 weeks before conception to 6 weeks before the last menstrual period), or sex without a condom, during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.
- Zika virus testing is not routinely recommended for asymptomatic pregnant women with recent possible Zika virus exposure but without ongoing exposure and who have a fetus or infant without Zika virus–associated birth defects.
- In the event of a confirmed maternal acute Zika virus infection or confirmed congenital Zika virus infection in the infant (e.g., a positive NAT), placental testing from live births is not indicated. Currently, placental testing does not routinely provide additional diagnostic information in the setting of a maternal or infant diagnosis of acute or congenital Zika virus infection, respectively.
- For women with no possible Zika virus exposure before the current pregnancy, a positive IgM result likely represents acute Zika virus infection, and placental testing is not indicated.
- All or part of possible maternal Zika virus exposure, or symptom onset occurred >12 weeks before maternal serum specimen was collected.
- Includes pregnant women with negative Zika virus NAT and negative Zika virus IgM ≤12 weeks after symptom onset or exposure. Possible Zika virus–associated birth defects that meet the CDC surveillance case definition include the following: brain abnormalities and/or microcephaly, intracranial calcifications, ventriculomegaly, neural tube defects and other early brain malformations, eye abnormalities, or other consequences of central nervous system dysfunction including arthrogryposis (joint contractures), congenital hip dysplasia, and congenital deafness (https://www.cdc.gov/zika/geo/pregnancy-outcomes.html).
- In all cases, infants or fetuses with possible Zika virus–associated birth defects should also be evaluated for other etiologies of congenital anomalies.

LabCorp now offers a Zika virus NAA test (Aptima® Zika Virus Assay) and a Zika virus IgM test (LIAISON® XL Zika Capture IgM) authorized by the FDA for emergency use.

### Table 1. Interim guidance for Zika virus testing of formalin-fixed, paraffin-embedded placental, fetal, or infant autopsy tissues for completed pregnancies with possible Zika virus exposure during pregnancy — United States (including U.S. territories), July 2017

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Maternal Zika virus test results on nontissue clinical specimens (e.g., serum, urine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Zika virus infection**</td>
<td>Zika virus infection; timing of infection cannot be determined†††</td>
</tr>
<tr>
<td>&gt;12 weeks after symptom onset or exposure,†‡ with either negative maternal Zika virus IgM, or no maternal testing conducted</td>
<td>No evidence of Zika virus infection†††</td>
</tr>
</tbody>
</table>

### Test Name | Test Number | Additional Information |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zika Virus Comprehensive Profile, NAA, Serum and Urine</td>
<td>139600</td>
<td>• This test has not been FDA cleared or approved; • This test has been authorized by FDA under an Emergency Use Authorization (EUA) for use by authorized laboratories; • This test has been authorized only for the detection of RNA from Zika virus and diagnosis of Zika virus infection, and not for any other viruses or pathogens; and • This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of in vitro diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.</td>
</tr>
<tr>
<td>Zika Virus IgM, Serum</td>
<td>163049</td>
<td></td>
</tr>
</tbody>
</table>

For more information about specimen collection, please refer to the online Test Menu at [www.LabCorp.com](http://www.LabCorp.com).

### References