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## 2018 Report of the Committee on Infectious Diseases

## Zika

**CLINICAL MANIFESTATIONS:** Most Zika virus infections are asymptomatic. In situations in which infection is symptomatic, the clinical disease usually is mild and symptoms last for a few days to a week. Commonly reported signs and symptoms include fever, pruritic maculopapular rash, arthralgia, and conjunctival hyperemia. Other findings include myalgia, headache, edema of the extremities, vomiting, retroorbital pain, and lymphadenopathy. Clinical laboratory abnormalities are observed uncommonly in symptomatic patients but can include thrombocytopenia, leukopenia, and increased liver transaminase concentrations. Severe disease requiring hospitalization and deaths are rare. However, Guillain-Barré syndrome and rare reports of other neurologic complications (eg, meningoencephalitis, myelitis, and uveitis) have been associated with Zika virus infection.

Congenital Zika virus infection can cause fetal loss as well as microcephaly and other serious neurologic anomalies. Clinical findings reported in infants with confirmed congenital Zika virus infection include brain anomalies (eg, subcortical calcifications, ventriculomegaly, abnormal gyral patterns, corpus callosum agenesis, and cerebellar hypoplasia), ocular anomalies (eg, microphthalmia, cataracts, chorioretinal atrophy, and optic nerve hypoplasia), congenital contractures (eg, clubfoot and arthrogryposis), and neurologic sequelae (eg, hypertonia, hypotonia, irritability, tremors, swallowing dysfunction, hearing loss, and visual impairment).

At least 2 cases of perinatal transmission from mothers who were viremic at delivery have been reported. One infant was asymptomatic; the other infant developed mild thrombocytopenia and a transient diffuse rash 4 days after delivery.

**ETIOLOGY:** Zika virus is a single-stranded, RNA virus in the genus *Flavivirus* that is related antigenically to dengue, yellow fever, West Nile, St. Louis encephalitis, and Japanese encephalitis viruses. Two major lineages, African and Asian, have been identified through phylogenetic analyses.

**EPIDEMIOLOGY:** Zika virus is transmitted to humans primarily by *Aedes aegypti* mosquitoes and less commonly by other *Aedes* (*Stegomyia*) species (eg, *Aedes albopictus, Aedes polynesiensis,* and *Aedes hensilli).* In the United States, *Ae aegypti* mosquitoes are found primarily in southern states. *Ae albopictus* mosquitoes have a wider distribution, including not only the southern United States but also extending north into the Ohio Valley and west to a number of the plains states. *Ae aegypti* and *Ae albopictus* mosquitoes can be found in small areas of the southwest and parts of California. Both *Aedes* species of mosquitoes bite humans during the daytime. These are the same vectors that transmit dengue, chikungunya, and yellow fever viruses. Human and nonhuman primates are the main reservoirs of the virus, with humans acting as the primary host

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in which the virus multiplies, allowing spread to additional mosquitoes and then other humans. Additional modes of transmission have been identified, including perinatal, in utero, sexual, blood transfusion, and laboratory exposure. Although Zika virus has been detected in human milk, transmission through breastfeeding has not yet been demonstrated.

Zika virus first was identified in the Zika forest of Uganda in 1947. Prior to 2007, only sporadic human disease cases were reported from countries in Africa and Asia. In 2007, the first documented Zika virus disease outbreak was reported in the Federated States of Micronesia. In subsequent years, outbreaks of Zika virus disease were identified in countries in Southeast Asia and the Western Pacific. In 2015, Zika virus was identified for the first time in the Western hemisphere, with large outbreaks reported in Brazil. Since then, the virus has spread throughout much of the Americas, with 48 countries and territories in the Americas reporting local transmission. During 2016 in the United States, large outbreaks occurred in Puerto Rico and the US Virgin Islands, and limited local transmission was identified in parts of Florida and Texas. Current information on Zika virus transmission and travel guidance can be found at **www.cdc.gov/zika/geo/index.html** and **wwwnc.cdc.gov/travel/page/zika-travel-information**, respectively.

The **incubation period** is 3 to 14 days after the bite of an infected mosquito, with 50% of cases developing symptoms 1 week after exposure.

**DIAGNOSTIC TESTS:** Zika virus infection should be considered in patients with acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis who live in or have traveled to an area with ongoing transmission in the 2 weeks preceding illness onset. Because dengue and chikungunya virus infections share a similar geographic distribution and symptomology with Zika virus infection, patients with suspected Zika virus infection also should be evaluated and managed for possible dengue or chikungunya virus infection. Other considerations in the differential diagnosis include malaria, rubella, measles, parvovirus, adenovirus, enterovirus, leptospirosis, rickettsiosis, and group A streptococcal infections.

Laboratory testing for Zika virus has a number of limitations. Zika virus RNA is only transiently present in body fluids; thus, a negative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) result does not rule out infection. Likewise, a negative immunoglobulin (Ig) M serologic test result does not rule out infection because the serum specimen might have been collected before the development or after waning of IgM antibodies. Alternatively, IgM antibodies might be detectable for months after the initial infection, making it difficult to distinguish the timing of Zika acquisition. Cross-reactivity of the Zika virus IgM antibody tests with other flaviviruses can result in a false-positive test result. Recent epidemiologic data indicate a declining prevalence of Zika virus infection in the Americas; this lower prevalence will result in a lower pretest probability of infection and a higher probability of false-positive test results.

***Zika Laboratory Testing in Nonpregnant Symptomatic Individuals.*** For people with suspected Zika virus disease, Zika virus RT-PCR assay should be performed on serum and urine specimens collected <14 days after onset of symptoms. Serum immunoglobulin (Ig) M antibody testing should be performed if the RT-PCR result is negative or when ≥14 days have passed since illness onset.

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***Zika Laboratory Testing in Pregnant Women.*** Current recommendations from the Centers for Disease Control and Prevention (CDC) take into account the decreasing prevalence of Zika virus disease cases in the Americas that occurred in 2017.[1] Zika virus testing is not routinely recommended for asymptomatic pregnant women who have possible recent but not ongoing Zika virus exposure. Zika virus RT-PCR testing should be offered as part of routine obstetric care to asymptomatic pregnant women with ongoing possible Zika virus exposure; however, because of the potential for persistence of IgM antibodies over several months, serologic testing is no longer routinely recommended to screen asymptomatic women.

***Zika Laboratory Testing for Congenital Infection.*** Zika virus testing is recommended for infants with clinical findings consistent with congenital Zika syndrome and possible maternal Zika virus exposure during pregnancy, regardless of maternal testing results, and for infants without clinical findings consistent with congenital Zika syndrome who are born to women with laboratory evidence of possible infection during pregnancy. Recommended laboratory testing for possible congenital Zika virus infection includes evaluation for Zika virus RNA in infant serum and urine and Zika virus IgM antibodies in serum. In addition, if cerebrospinal fluid (CSF) is obtained for other purposes, RT-PCR and IgM antibody testing should be performed on CSF, because CSF was the only sample that tested positive in a limited number of infants with congenital Zika virus infection.

Laboratory testing of infants should be performed as soon as possible after birth (within the first few days of life), although testing specimens within the first few weeks to months after birth might still be useful. If CSF was not collected for other reasons, testing CSF for Zika virus RNA and Zika virus IgM should be considered to improve the likelihood of diagnosis, especially if serum and urine testing are negative and another etiology has not been identified. Diagnosis of congenital Zika virus infection is confirmed by a positive Zika virus RT-PCR or by a positive Zika virus IgM and neutralizing antibody result. If neither Zika virus RNA nor Zika IgM antibodies are detected on the appropriate specimens obtained within the first few days after birth, congenital Zika virus infection is unlikely.

The plaque reduction neutralization test (PRNT), which measures virus-specific neutralizing antibodies, can be used to help identify false-positive results. If the infant's initial sample is IgM nonnegative (nonnegative serology terminology varies by assay and might include "positive," "equivocal," "presumptive positive," or "possible positive") and RT-PCR negative, and PRNT was not performed on the mother's sample, PRNT for Zika and dengue viruses should be performed on the infant's initial sample. If the Zika virus PRNT result is negative, this suggests that the infant's Zika virus IgM test result is a false positive. For infants with clinical findings consistent with congenital Zika syndrome or maternal evidence of possible Zika virus infection during pregnancy who were not tested near birth, PRNT at age ≥18 months (after maternal antibodies have dissipated from the infant's system) might help confirm or rule out congenital Zika virus infection. If the PRNT result is negative at age ≥18 months, congenital Zika virus infection is unlikely.

[1] Oduyebo T, Polen KD, Walke HT, et al. Update: Interim guidance for health care providers caring for pregnant women with possible zika virus exposure—United States (including U.S. territories), July 2017. *MMWR Morb Mortal Wkly Rep.* 2017;66(29):781–793

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**TREATMENT:** No specific antiviral treatment currently is available for Zika virus disease. Only supportive care is indicated, including rest, fluids, and symptomatic treatment (acetaminophen to relieve fever and antihistamines to treat pruritus). Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue can be ruled out to reduce the risk of hemorrhagic complications.

Guidance is updated as new information is obtained; for the most recent guidance, visit: **www.cdc.gov/Zika.** Figure 3.13 outlines the current recommended evaluation of infants with possible maternal and congenital Zika virus exposure during pregnancy.[2]

***Clinical Management of Infants With Clinical Findings Consistent With Congenital Zika Infection.*** Zika virus testing is recommended (see Zika Laboratory Testing for Congenital Infection), ultrasonography of the head should be performed, and a comprehensive ophthalmologic examination should be performed by age 1 month by an ophthalmologist experienced in assessment of infants. Referrals to a developmental specialist and early intervention are recommended. Additional consultation should be considered by infectious disease (for evaluation of other congenital infections and assistance with Zika virus diagnosis and testing), clinical genetics (for evaluation for other causes of microcephaly or congenital anomalies), and neurology by age 1 month (for comprehensive neurologic examination and consideration for other evaluations, such as advanced neuroimaging and electroencephalography [EEG]). The initial clinical evaluation, including subspecialty consultations, can be performed before hospital discharge or as an outpatient. Ophthalmologic follow-up after the initial examination should be based on ophthalmology recommendations. Infants should be referred for automated brainstem response (ABR) testing by age 1 month if the newborn hearing screen was passed using only otoacoustic emissions (OAE) methodology.

***Clinical Management of Infants Without Clinical Findings Consistent With Congenital Zika Infection but Maternal Laboratory Evidence of Possible Zika Virus Infection During Pregnancy.*** Zika virus testing is recommended (see Zika Laboratory Testing for Congenital Infection), and ultrasonography of the head should be performed by age 1 month to detect subclinical brain findings. All infants should have a comprehensive ophthalmologic examination by age 1 month to detect subclinical eye findings; further follow-up visits with an ophthalmologist after the initial examination should be based on ophthalmology recommendations. Infants should be referred for automated ABR testing by 1 month of age if newborn screen was passed using only OAE methodology. Infants should be monitored for findings consistent with congenital Zika syndrome that could develop over time (eg, impaired visual acuity/function, hearing problems, developmental delay, delay in head growth).

***Clinical Management of Infants Without Clinical Findings Consistent With Congenital Zika Infection Born to Mothers With Possible Zika Virus Infection During Pregnancy but Without Laboratory Evidence of Zika Virus During Pregnancy.*** Zika virus testing is not routinely recommended, and specialized clinical evaluation or follow-up is not routinely indicated. Health care providers can consider additional evaluation in consultation with families. If findings suggestive of congenital Zika syndrome are identified at any time, referrals to the appropriate specialists should be made.

[2] Adebanjo T, Godfred-Cato S, Viens L, et al. Update: interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection—United States, October 2017. *MMWR Morb Mortal Wkly Rep.* 2017;66(41):1089–1099

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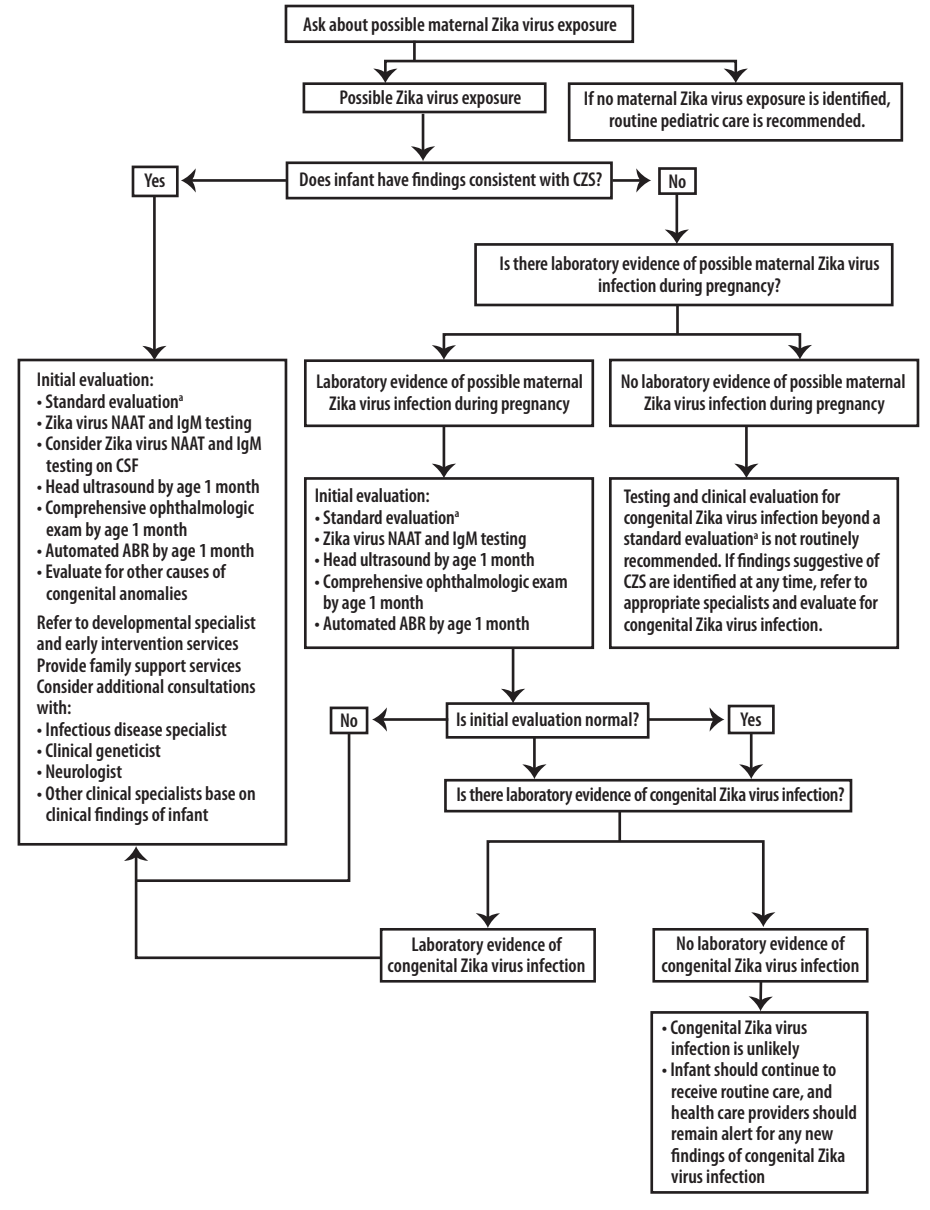
## FIGURE 3.13. Recommendations for the evaluation of infants with possible congenital Zika virus infection based on infant clinical findings,[a,b] maternal testing results,[c,d] and infant testing results[e,f]—United States, October 2017[3]

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## FIGURE 3.13. Recommendations for the evaluation of infants with possible congenital Zika virus infection based on infant clinical findings,[a,b] maternal testing results,[c,d] and infant testing results[e,f]—United States, October 2017,[3] *continued*

[3] Adebanjo T, Godfred-Cato S, Viens L, et al. Update: interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection—United States, October 2017. *MMWR Morb Mortal Wkly Rep.* 2017;66(41):1089–1099

ABR indicates auditory brainstem response; CSF, cerebrospinal fluid; CZS, congenital Zika syndrome; IgM, immunoglobulin M; NAAT, nucleic acid amplification test; PRNT, plaque reduction neutralization test.

[a] All infants should receive a standard evaluation at birth and at each subsequent well-child visit by their health care providers, including (1) comprehensive physical examination, including growth parameters; and 2) age-appropriate vision screening and developmental monitoring and screening using validated tools. Infants should receive a standard newborn hearing screen at birth, preferably using auditory brainstem response.

[b] Automated ABR by age 1 month if newborn hearing screen passed but performed with otoacoustic emission methodology.

[c] Laboratory evidence of possible Zika virus infection during pregnancy is defined as (1) Zika virus infection detected by a Zika virus RNA NAAT on any maternal, placental, or fetal specimen (referred to as NAAT-confirmed), or (2) diagnosis of Zika virus infection, timing of infection cannot be determined or unspecified *Flavivirus* infection, timing of infection cannot be determined by serologic tests on a maternal specimen (ie, positive/equivocal Zika virus IgM and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT value; or negative Zika virus IgM, and positive or equivocal dengue virus IgM, and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT titer). The use of PRNT for confirmation of Zika virus infection, including in pregnant women, is not routinely recommended in Puerto Rico **(www.cdc.gov/zika/laboratories/lab-guidance.html).**

[d] This group includes women who were never tested during pregnancy as well as those whose test result was negative because of issues related to timing or sensitivity and specificity of the test. Because the latter issues are not easily discerned, all mothers with possible exposure to Zika virus during pregnancy who do not have laboratory evidence of possible Zika virus infection, including those who tested negative with currently available technology, should be considered in this group.

[e] Laboratory testing of infants for Zika virus should be performed as early as possible, preferably within the first few days after birth, and includes concurrent Zika virus NAAT in infant serum and urine, and Zika virus IgM testing in serum. If CSF is obtained for other purposes, Zika virus NAAT and Zika virus IgM testing should be performed on CSF.

[f] Laboratory evidence of congenital Zika virus infection includes a positive Zika virus NAAT or a nonnegative Zika virus IgM with confirmatory neutralizing antibody testing, if PRNT confirmation is performed.

**ISOLATION OF THE HOSPITALIZED PATIENT:** Standard precautions are recommended, with attention to the potential for bloodborne transmission. People infected with Zika virus, as well as other arboviruses, should be protected from further mosquito exposure, especially during the first week of illness, to reduce the risk of local transmission to others.

**CONTROL MEASURES:** Vaccines to prevent Zika virus infection currently are not available. Prevention and control measures rely on personal prevention measures to avoid mosquito bites, and community-level programs to reduce vector densities in areas with endemic infection. Personal measures include using insect repellent; wearing long pants, socks, and long-sleeved shirts while outdoors; staying in air-conditioned buildings or buildings with window and door screens; and limiting outdoor activities during peak vector feeding times. Permethrin-treated clothing and gear can repel mosquitoes. Bed nets are advised for travel to areas where accommodations are not adequately screened or air conditioned. Travelers returning to the United States from an area with risk of Zika, even if asymptomatic, should take steps to prevent mosquito bites for 3 weeks to minimize spread to local mosquito populations (**www.cdc.gov/zika/prevention/plan-for-travel.html**).

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Insect repellents registered by the US Environmental Protection Agency (EPA) can be used according to directions on the product labels. Products containing N,N-diethyl-meta-toluamide (DEET), picaridin, oil of lemon eucalyptus, or IR3535 provide protection from mosquito bites. Products containing up to 50% DEET for adults (including pregnant and lactating women) and up to 30% DEET for infants and children are recommended. Insect repellents containing oil of lemon eucalyptus (para-menthane-3,8-diol) should not be used in children younger than 3 years. All travelers should take precautions to avoid mosquito bites to prevent Zika virus infection and other mosquitoborne diseases (see Prevention of Mosquitoborne and Tickborne Infections).

***Sexual Transmission.*** Zika virus can be transmitted sexually. Couples in whom the man or woman has had possible Zika virus exposure who want to maximally reduce their risk for sexually transmitting Zika virus to the uninfected partner should use condoms or abstain from sex for at least 6 months for men or 8 weeks for women after symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). Men should not donate sperm for at least 6 months from infection or last exposure.

***Women Who Are Pregnant or Seeking to Become Pregnant.*** Pregnant women should postpone travel to any area where local Zika virus transmission is ongoing. Pregnant women who do travel to one of these areas should talk to their health care provider before traveling and should strictly follow steps to avoid mosquito bites during travel. There is no restriction on the use of insect repellents by pregnant women if used in accordance with the instructions on the product label. Male partners of pregnant women who have traveled to areas with local transmission of Zika virus should abstain from sex or use condoms for the duration of the pregnancy to avoid sexual transmission to their pregnant partners.

For couples who have possible Zika virus exposure and who are considering pregnancy, the CDC recommends postponing pregnancy for 6 months following potential exposure or diagnosis of Zika infection. These recommendations for couples considering pregnancy are likely to change as more data become available concerning the duration of viremia and persistence of virus in semen for symptomatic and asymptomatic people.

Pregnant women who develop a clinically compatible illness during or within 2 weeks of returning from an area with Zika virus transmission should be tested for Zika virus infection. Fetuses and infants of women with possible Zika virus exposure or known Zika virus infection during pregnancy should be evaluated for possible congenital infection (Fig 3.13).

***Blood and Tissue Donation.*** The US Food and Drug Administration (FDA) recommends temporary deferral of blood donors who recently were infected with Zika virus infection, as well as testing of all blood donations collected in the United States and its territories to reduce the risk for transfusion-associated transmission of Zika virus. Because of universal Zika virus testing of blood donors, people who traveled to areas with local Zika virus transmission and who did not exhibit any evidence of infection may donate blood.

The CDC also has developed guidance to reduce potential Zika virus transmission from human cells, tissues, and cellular and tissue-based products (HCT/Ps). The guidance addresses donation of HCT/Ps from both living and deceased donors, including donors of umbilical cord blood, placenta tissue, or other gestational tissues. The guidance recognizes the potential risk of transmission of Zika virus from HCT/Ps. Living

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donors should be considered ineligible to donate HCT/Ps if they had a diagnosis of Zika virus infection, were in an area with Zika virus transmission, or had sex with a male with either of these risk factors, within the past 6 months. Donors of umbilical cord blood, placenta tissue, or other gestational tissues should be considered ineligible if any of the aforementioned risk factors occurred at any point during pregnancy. This guidance likely will change as more evidence becomes available about persistence of Zika virus in human tissues and fluids.

**REPORTING:** Health care professionals should report suspected Zika virus infection to their state or local health departments to facilitate diagnosis and mitigate the risk of local transmission. Zika virus disease and congenital infections were added to the list of nationally notifiable diseases in 2016 (see Appendix IV: Nationally Notifiable Infectious Diseases in the United States). State health departments should then report cases to the CDC through ArboNET, the national surveillance system for arboviral diseases.

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The recommendations in this publication do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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