OHIO DEPARTMENT OF HEALTH
246 North High Street
Columbus, Ohio 43215
614/466-3543
www.odh.ohio.gov
John R. Kasich/Governor
Richard Hodges/Director of Health

M E M O R A N D U M

DATE: June 7, 2016

TO: Healthcare Providers

FROM: Mary DiOrio, MD, MPH
Medical Director

SUBJECT: Zika Precautions for Ohio Residents

Zika outbreaks are currently occurring in many countries and territories. The purpose of this memorandum is to provide information and resources to you and your patients about Zika virus.

- Zika virus is spread to people primarily through the bite of an infected mosquito.
- The primary mosquito (*Aedes aegypti*) that transmits the virus is not established in Ohio, but the Asian tiger mosquito (*Aedes albopictus*) is established in parts of Ohio and could potentially pick up and transmit the disease.
- The most common symptoms of Zika virus are fever, rash, joint pain, and conjunctivitis (red eyes).
- The illness is usually mild with symptoms lasting for several days to a week.

Zika virus infection is of greater concern during pregnancy and for women that are trying to get pregnant because prenatal transmission has been identified with Zika virus. Adverse outcomes that have been associated with Zika virus infection during pregnancy include:

- Microcephaly including absent or poorly developed brain structures
- Pregnancy loss
- Eye defects
- Growth restriction, both intra-uterine and post-natal

Unfortunately, very little is known about the timing, absolute risk, or continuum of outcomes associated with Zika virus infection during pregnancy. There is currently no vaccine or medication to prevent Zika virus infection.

The Centers for Disease Control and Prevention (CDC) has recently released a webinar focused on updated guidance related to reproductive health and sexual transmission of Zika virus. Please take some time to review the webinar for *Updated Interim Zika Clinical Guidance for Reproductive Age Women and Men, Sexual Transmission of Zika, and the U.S. Zika Pregnancy Registry* by clicking here. The CDC's most updated guidance to healthcare providers caring for women of reproductive age with possible Zika virus infections is available at http://www.cdc.gov/mmwr/volumes/65/wr/mm6512e2.htm?s_cid=mm6512e2_w.

The CDC's most updated guidance to healthcare providers caring for infants and children with possible Zika virus infections, including information on collecting specimens at the birth of infants born to women with Zika virus infections or suspected of having congenital Zika virus infections, is available at http://www.cdc.gov/mmwr/volumes/65/wr/mm6507e1.htm?s_cid=mm6507e1_w.

The CDC also recommends special precautions for pregnant women. Women who are pregnant should avoid travel to areas where Zika virus transmission is ongoing (http://www.cdc.gov/zika/pregnancy/index.html). If you have a patient who is pregnant and has traveled to an area with active Zika virus transmission, CDC recommends testing for Zika virus infection:

- Asymptomatic pregnant women (women who do not report clinical illness consistent with Zika virus disease) should be offered serologic testing 2–12 weeks after return from travel.
- For pregnant women with clinical illness consistent with Zika virus disease, testing is recommended during the first week of illness.
- Please contact the local health department where your patient lives to coordinate submission of samples to the Ohio Department of Health (ODH) Laboratory for testing at ODH Laboratory and/or CDC. Healthcare providers should discuss reproductive life plans, including pregnancy intention and timing, with women of reproductive age in the context of the potential risks associated with Zika virus infection.

Zika virus can also be spread by a man to his sexual partners. In known cases of sexual transmission, the men developed symptoms of Zika virus infection. From these cases, we know the virus can be spread through sexual contact when the man is experiencing symptoms, before symptoms start and after symptoms resolve. In one case, the virus was spread a few days before symptoms developed. The virus is believed to be present in semen longer than in blood. For a pregnant woman with a partner who has traveled to endemic areas, either abstinence or intercourse with condoms for the duration of the pregnancy is recommended for prevention.

The best way to avoid Zika virus infection and other mosquito-borne diseases is to prevent mosquito bites (http://www.cdc.gov/vitalsigns/zika/infographic.html#graphic-b) by:

- Removing their breeding sites
    - Empty standing water from flower pots, buckets and barrels.
    - Change the water in pet dishes, and replace the water in bird baths weekly
    - Drill holes in tire swings so water drains out
    - Keep children's wading pools empty and on their sides when they aren't being used
    - Keep trash can lids closed to prevent rain from collecting inside.
- When outdoors, wearing Environmental Protection Agency (EPA)-registered insect repellents. All EPA registered insect repellents have been evaluated for effectiveness. When used as directed, EPA-registered insect repellents are proven safe and effective, even for pregnant women. Always follow the product label instructions.
- Making sure to use insect repellent and wearing long sleeves and pants when and where these mosquitoes are active. Unlike many mosquitoes, the Asian tiger mosquitoes are most active during the day and are most common in shade conditions.
- Making sure you have good screens on your windows and doors to keep mosquitoes out.

Note: Asian tiger mosquitoes are container-breeding mosquitoes. They do not breed in ponds, puddles or marshes.

Actions by ODH

The ODH Laboratory conducts Zika virus testing to identify suspected Zika virus infection in symptomatic individuals with an acute illness of less than 7 days' duration. The genetic material of the Zika virus often can be detected in blood specimens collected within seven days of symptom onset. Blood specimens tested by the ODH Laboratory and collected 4 or more days after illness onset will be forwarded to the CDC for antibody testing.

ODH coordinates with local health jurisdictions and healthcare providers if a human case of Zika virus infection is diagnosed during mosquito season in Ohio by local transmission or sexual transmission. Additional public health response activities will occur. ODH will work with local health departments and other local partners to carry out mosquito surveillance. Local agencies use this information to issue alerts and target control efforts to reduce the number of mosquitoes that could potentially transmit Zika virus. ODH also provides press releases to alert the public at the first sign of mosquito activity and again if a locally-acquired case were to be reported.

For more information about ODH's activities please check the ODH website at http://www.odh.ohio.gov/zika

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Update: Interim Guidance for Health Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016

Emily E. Petersen, MD[1]; Kara N. D. Polen, MPH[2]; Dana Meaney-Delman, MD[3]; Sascha R. Ellington, MSPH[1]; Titilope Oduyebo, MD[1,4]; Amanda Cohn, MD[5]; Alexandra M. Oster, MD[6]; Kate Russell, MD[4,7]; Jennifer F. Kawwass, MD[1,8]; Mateusz P. Karwowski, MD[4,9]; Ann M. Powers, PhD[10]; Jeanne Bertolli, PhD[6]; John T. Brooks, MD[6]; Dmitry Kissin, MD[1]; Julie Villanueva, PhD[11]; Jorge Muñoz-Jordan, PhD[10]; Matthew Kuehnert, MD[12]; Christine K. Olson, MD[1]; Margaret A. Honein, PhD[2]; Maria Rivera, MPH[1]; Denise J. Jamieson, MD[1]; Sonja A. Rasmussen, MD[13]

CDC has updated its interim guidance for U.S. health care providers caring for women of reproductive age with possible Zika virus exposure (*1*) to include recommendations on counseling women and men with possible Zika virus exposure who are interested in conceiving. This guidance is based on limited available data on persistence of Zika virus RNA in blood and semen (*2–5*). Women who have Zika virus disease* should wait at least 8 weeks after symptom onset to attempt conception, and men with Zika virus disease should wait at least 6 months after symptom onset to attempt conception. Women and men with possible exposure to Zika virus but without clinical illness consistent with Zika virus disease should wait at least 8 weeks after exposure to attempt conception. Possible exposure to Zika virus is defined as travel to or residence in an area of active Zika virus transmission (http://www.cdc.gov/zika/geo/active-countries.html), or sex (vaginal intercourse, anal intercourse, or fellatio) without a condom with a man who traveled to or resided in an area of active transmission. Women and men who reside in areas of active Zika virus transmission should talk with their health care provider about attempting conception. This guidance also provides updated recommendations on testing of pregnant women with possible Zika virus exposure. These recommendations will be updated when additional data become available.

The current Zika virus outbreak was identified in Brazil in May 2015, and knowledge about Zika virus infection, its potential adverse effects on pregnancy, and transmission is rapidly evolving. As of March 23, 2016, there were 39 countries and U.S. territories reporting active Zika virus transmission (*6*). Updates on areas with active Zika virus transmission are available online at http://wwwnc.cdc.gov/travel/notices.

Zika virus is primarily transmitted through the bite of infected *Aedes* species mosquitoes. However, Zika virus can also be sexually transmitted from a man infected with the virus to his sexual partners (*3*,*5*,*7–10*). Based on data from a previous outbreak, most persons infected with Zika virus are asymptomatic (*11*). Signs and symptoms, when present, are typically mild, with the most common being acute onset of fever, macular or papular rash, arthralgia, and conjunctivitis (*11*).

Increasing epidemiologic, clinical, laboratory, and pathologic evidence supports a link between Zika virus infection during pregnancy and adverse pregnancy and birth outcomes, including pregnancy loss, microcephaly, and brain and eye abnormalities (*12–16*). A critical knowledge gap for health care providers counseling women is the level of risk for adverse pregnancy and birth outcomes associated with Zika virus infection. That risk is currently unknown, but two recent studies might be informative. A retrospective analysis of the 2013–2014 Zika virus outbreak in French Polynesia identified eight fetuses and infants with microcephaly; using mathematical modeling, it was estimated that microcephaly affected approximately 1% of fetuses or infants born to women infected with Zika virus during the first trimester of pregnancy (*17*). In a recent study from Brazil, among 42 women with laboratory-confirmed Zika virus infection at any time during pregnancy who underwent prenatal ultrasonographic studies, 12 (29%) had abnormal findings; these included microcephaly, intracranial

* Zika virus disease is defined as having at least one of the following signs or symptoms: acute onset of fever, rash, arthralgia, conjunctivitis; and laboratory confirmation of Zika virus infection. Persons who had possible Zika virus exposure and display one or more signs or symptoms consistent with Zika virus disease (acute onset of fever, rash, arthralgia, conjunctivitis) but did not have testing performed should follow recommendations for persons with Zika virus disease.

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calcifications, other brain abnormalities, abnormal cerebral artery flow, intrauterine growth restriction, and fetal death (*16*). Further studies are underway to better estimate this risk, but it is important to recognize that microcephaly caused by viral destruction of brain tissue is likely to be part of a spectrum of neurological damage; the percentages in both studies may substantially underestimate the proportion of infants affected.

The risk for adverse pregnancy outcomes associated with maternal Zika virus infection around the time of conception is currently unknown. However, early reports suggest there might be adverse outcomes associated with Zika virus infection in early pregnancy: two women with Zika virus disease at <7 weeks' gestation both had pregnancy losses, with Zika virus RNA detected in products of conception, and another woman with clinical illness consistent with Zika virus disease at 7–8 weeks' gestation delivered a full-term infant with severe microcephaly (*15*). Other viral infections (e.g., cytomegalovirus, rubella, and parvovirus) that have occurred around the time of conception have been associated with congenital infection and associated adverse pregnancy and birth outcomes (*18*–*22*); however, in these cases the exact timing of infection relative to timing of conception was often unknown.

Because currently available data are limited, providing preconception counseling following possible Zika virus exposure is challenging. Decisions about pregnancy timing are personal and complex, and discussions with patients should be individualized. CDC and state health departments have received numerous inquiries from health care providers requesting information on how best to counsel patients regarding timing of pregnancy following possible Zika virus exposure and diagnosis of Zika virus disease. CDC has developed updated interim guidance to address these concerns. This guidance is based on expert opinion, the limited available data on Zika virus, and knowledge about risks for other viral infections in the periconceptional period. CDC continues to evaluate all available evidence and to update recommendations as new information becomes available.

Preconception Counseling Recommendations For Women With Possible Exposure to Zika Virus Who Do Not Reside In an Area With Active Zika Virus Transmission

There is no evidence that Zika virus will cause congenital infection in pregnancies conceived after the resolution of maternal Zika viremia. Data on the incubation period for Zika virus disease and the duration of Zika viremia are limited. Evidence from case reports and experience from related flavivirus infections indicate that the incubation period for Zika virus disease is likely 3–14 days (*7*,*23*,*24*). After symptom onset, the duration of Zika viremia may range from a few days to 1 week (*24*–*26*); the longest duration of viremia in the published literature was 11 days (*4*).

Health care providers should provide preconception counseling to women with possible Zika virus exposure. Discussions should include information about the signs and symptoms of Zika virus disease and the potential adverse outcomes associated with Zika virus infection in pregnancy. Women with Zika virus disease should wait until at least 8 weeks after symptom onset before attempting conception. No data are available regarding the risk for congenital infection among pregnant women with asymptomatic infection. Based on the estimated upper limit of the incubation period for Zika virus disease (14 days) and approximate tripling of the longest published period of viremia after symptom onset (11 days), and given the limited data on duration of Zika viremia and the potential for individual immune system variability, asymptomatic women with possible Zika virus exposure should be advised to wait at least 8 weeks after the last date of exposure before attempting conception. Health care providers should provide information on available strategies to prevent unintended pregnancy, including use of the most effective contraceptive methods that can be used correctly and consistently (*27*). In addition, patients should be counseled that correct and consistent use of condoms reduces the risk for sexually transmitted infections.

Preconception Counseling Recommendations For Men With Possible Exposure to Zika Virus Who Do Not Reside In an Area With Active Zika Virus Transmission

Sexual transmission of Zika virus can occur, although data about the risk are limited. CDC has reported six laboratory-confirmed cases of sexually transmitted Zika virus disease (*9*,*28*). To date, all reported cases have involved sexual transmission from a man with symptoms, and have occurred within 3 weeks of symptom onset (*7*,*9*,*10*). Infectious Zika virus has been isolated from the semen of two men (one with hematospermia) at least 2 weeks after symptom onset (*5*) and possibly up to 10 weeks after symptom onset (*3*). A third report documented Zika virus RNA in semen 62 days after symptom onset (*2*). The duration and pattern of Zika virus persistence in semen is not known; further testing was not performed to document when replicative Zika virus or Zika virus RNA were no longer present in the men's semen.

Based on these data, men and their female partners should wait to attempt conception until the risk for sexual transmission is believed to be minimal. Men who have had a diagnosis of Zika virus disease should wait at least 6 months after symptom onset before attempting conception. This interval

was recommended based on limited information regarding persistence of Zika virus in semen, and it allows for three times the longest period that Zika virus RNA has been detected in semen after symptom onset.

It is not known whether men with asymptomatic Zika virus infection can transmit the virus sexually. There have been no reported cases of sexual transmission from asymptomatic men. Although it has not been documented, it is biologically plausible that men who have been infected with Zika virus but display no symptoms of Zika virus disease might shed Zika virus in the semen. In the absence of data and to be consistent with other recommendations, men who have possible Zika virus exposure without clinical illness consistent with Zika virus disease should wait at least 8 weeks after possible exposure before attempting conception. If symptoms do not develop, the couple could consider attempting conception or waiting longer. Given the limited data, health care providers should discuss with couples the many factors that might influence a decision about attempting conception, such as level of risk for Zika virus exposure and reproductive life plans.

Preconception Counseling Recommendations For Women and Their Partners Residing In Areas With Active Zika Virus Transmission

Health care providers caring for women and men residing in areas with active Zika virus transmission who have Zika virus disease should recommend they wait until the risk for viremia or viral shedding in semen is believed to be minimal to avoid potential adverse outcomes that have been linked with Zika virus infection in pregnancy. Women with Zika virus disease should wait at least 8 weeks from symptom onset before attempting conception; men with Zika virus disease should wait at least 6 months from symptom onset before attempting conception.

Women and men who reside in an area with active Zika virus transmission, but who do not have clinical illness consistent with Zika virus disease and who desire pregnancy should talk with their health care providers. Particularly in the context of Zika virus transmission, it is important for women and their partners to plan their pregnancies. As part of that planning process, women and their partners should discuss the risks for active Zika virus transmission with their health care providers, and providers should discuss their patients' reproductive life plans in the context of potential Zika virus exposure (Box). An assessment of the risk for Zika virus exposure includes evaluating the presence of mosquitoes in and around the home, protective measures practiced, and levels of active Zika virus transmission. Taking protective measures to avoid mosquito bites has been demonstrated to reduce the risk for mosquito-borne diseases (*29*,*30*); however, it might not be possible to eliminate the risk for Zika virus exposure during pregnancy. The expected duration of a Zika virus outbreak in any particular location is unknown. Health care providers should discuss factors that might influence timing of pregnancy, including fertility, age, reproductive history, medical history, and personal values and preferences. The decision about timing of pregnancy should be made by the woman or couple in consultation with a health care provider.

As part of counseling with health care providers, some women and their partners residing in areas of active Zika virus transmission might decide to delay pregnancy. Health care providers should discuss strategies to prevent unintended pregnancy, including use of the most effective contraceptive methods (*27*). In addition, patients should be counseled that correct and consistent use of condoms reduces the risk for sexually transmitted infections.

BOX. Recommendations for counseling persons in areas of active Zika virus transmission interested in attempting conception

Assess risk of Zika virus exposure

Environment
- Air conditioning, window screens in home
- Work environment
- Residence in area with high mosquito density
- Level of Zika viru transmission in the local area

Personal measures to prevent mosquito bites
- Protective clothing
- Use of EPA-registered insect repellent
- Emptying/removing standing water in containers

Personal measures to prevent sexual transmission
- Willingness to use condoms or abstain from sex throughout pregnancy

Discuss Zika virus infection in pregnancy
- Signs/symptoms of Zika virus disease
- Possible adverse consequences of Zika virus infection during pregnancy
- Unknown duration of epidemic

Explore reproductive life plan
- Fertility
- Age
- Reproductive history
- Medical history
- Personal values, preferences

Discuss risks/benefits of pregnancy at this time with woman and her partner
- If pregnancy not desired now, discuss contraceptive options

Recommendations For Testing of Persons Attempting Conception

Testing of serum for evidence of Zika virus infection should be performed in persons with possible exposure to Zika virus who have one or more of the following signs or symptoms within 2 weeks of possible exposure: acute onset of fever, rash, arthralgia, or conjunctivitis (*31*). Routine testing is not currently recommended for women or men who are attempting conception who have possible exposure to Zika virus but no clinical illness. The performance of the test in asymptomatic persons is unknown, and results might be difficult to interpret. It is not known whether a positive serologic test result in an asymptomatic man would indicate possible presence of Zika virus in semen, or if a negative serologic test result would preclude the presence of the virus in semen.

Reverse transcription-polymerase chain reaction (RT-PCR) testing of semen has not yet been validated. Intermittent shedding of other viruses in semen is recognized (*32*,*33*); however, the pattern of Zika virus shedding in semen is unknown. Further, the detection of Zika virus RNA in semen does not necessarily indicate the presence of infectious virus in semen. Because of these concerns, a positive or negative semen test result might not provide sufficient data to guide recommendations regarding attempting conception. Thus, testing of semen is not currently recommended. Studies are underway to better understand the performance of these tests, the persistence of Zika virus in semen, and how best to interpret the results.

Special Considerations For Women Undergoing Fertility Treatment

No instances of Zika virus transmission during fertility treatment have been documented, but transmission through donated gametes or embryos is theoretically possible, given that Zika virus can be present in semen, and sexual transmission has occurred (*2*,*7*–*9*). Zika virus is not likely to be destroyed in the cryopreservation process. Fertility treatment for sexually intimate couples using their own gametes and embryos should follow the timing recommendations for persons attempting conception, although recommendations might need to be adjusted depending on individual circumstances. The Food and Drug Administration (FDA) has developed guidance for donated tissues in the context of a Zika virus outbreak, including donated sperm, oocytes, and embryos (*34*); the guidance states that living donors will be deemed ineligible for anonymous donation if they have any of the following risk factors: medical diagnosis of Zika virus infection in the past 6 months; residence in or travel to an area with active Zika virus transmission within the past 6 months; or within the past 6 months had sex with a male partner who, during the 6 months before this sexual contact, received a diagnosis of or experienced an illness consistent with Zika virus disease, or had traveled to an area of active Zika virus transmission. FDA guidance applies to anonymous donors, but does not apply to sexually intimate couples. In accordance with previous FDA guidance, directed (or known) donors must undergo the same evaluation and eligibility determination as anonymous donors. However, gametes or embryos from directed donors who are ineligible may be used, per FDA guidance, if the tissue is properly labeled to indicate potential increased risk, all participating parties are aware of and willing to incur the risk, and physicians are aware of the status of gametes or embryos. Professional organizations recommend recipients be informed and counseled about potential risks before use of the donated tissue (*35*).

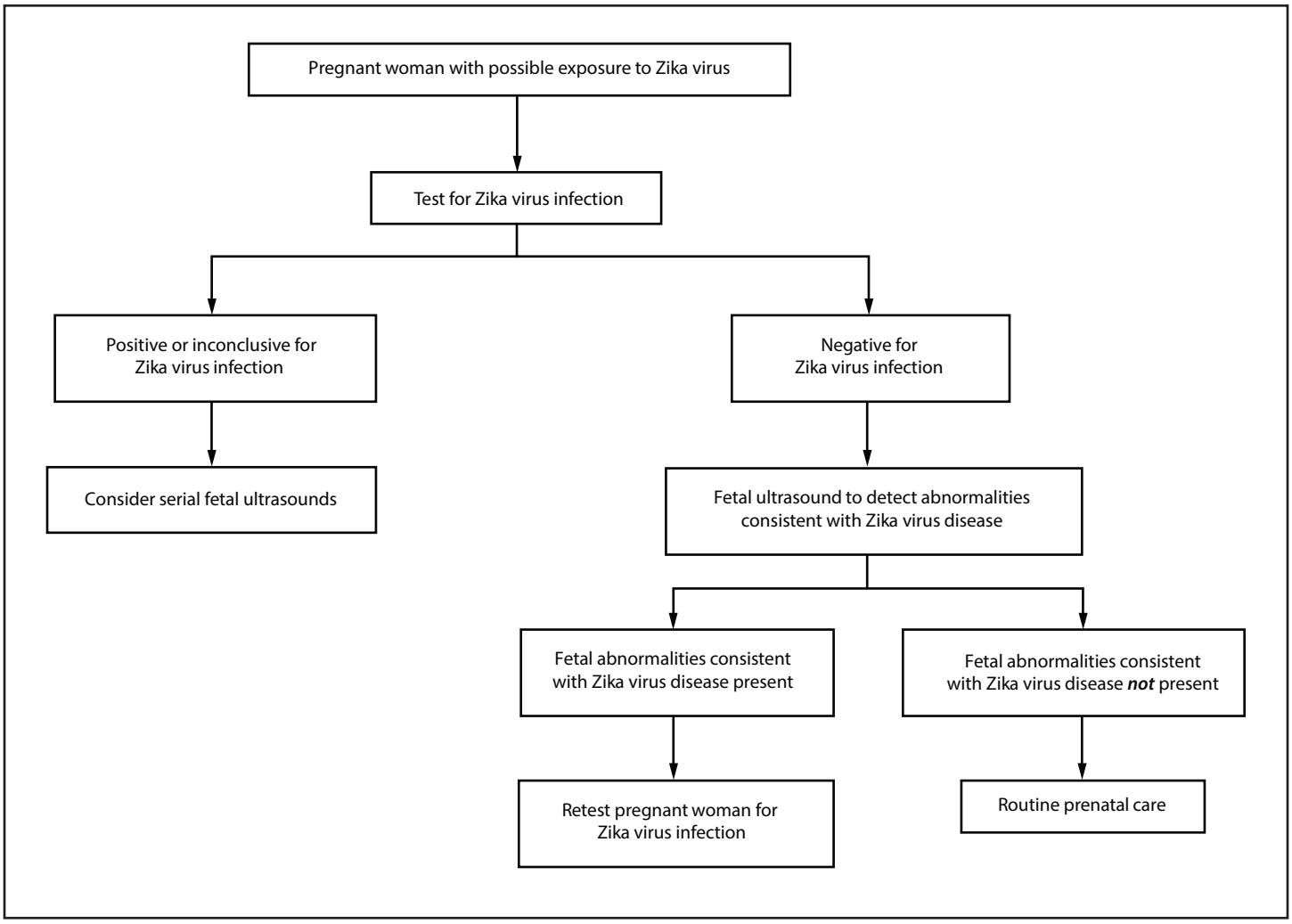
Updated Recommendations For Testing Pregnant Women With Possible Zika Virus Exposure

Pregnant women who had possible exposure to Zika virus who do not reside in an area with active transmission should be evaluated for Zika virus infection and tested in accordance with CDC Updated Interim Guidance (Figure 1). Similarly, pregnant women who reside in an area with active Zika virus transmission should be evaluated and tested in accordance with CDC interim guidance (Figure 2); a decision to implement testing of asymptomatic pregnant women should be made by local health officials based on information about levels of Zika virus transmission and laboratory capacity. A negative immunoglobulin M test result obtained 2–12 weeks after known exposure would suggest that a recent Zika virus infection did not occur and could obviate the need for serial ultrasounds.

Health care providers should assess their patients' travel histories. In certain circumstances, such as patients with frequent travel (e.g., daily or weekly) to areas of active Zika virus transmission, health care providers should follow CDC's interim guidance for pregnant women residing in areas with active Zika virus transmission (Figure 2). Health care providers who care for pregnant women who reside along the U.S.-Mexico border should assess their patients' travel histories, including frequency of cross-border travel, and destinations. Areas of active Zika virus transmission in Mexico not bordering the United States have been reported. There are currently no reports of active Zika virus transmission along the U.S.-Mexico border. However, if active transmission occurs, local health officials should determine when to implement testing of asymptomatic pregnant women based on information about levels of Zika virus transmission and laboratory capacity.

As previously recommended (*8*), men who travel to or reside in an area with active Zika virus transmission and have a pregnant partner should correctly and consistently use

FIGURE 1. Updated interim guidance: testing algorithm*,†,§,¶ for a pregnant woman with possible Zika virus exposure not residing in an area with active Zika virus transmission**



* Testing is recommended for pregnant women with clinical illness consistent with Zika virus disease, including one or more of the following signs or symptoms: acute onset of fever, rash, arthralgia, or conjunctivitis during or within 2 weeks of travel or possible sexual exposure. Testing includes Zika virus reverse transcription-polymerase chain reaction (RT-PCR), and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. More information is available at http://www.aphl.org/Materials/CDCMemo_Zika_Chik_Deng_Testing_011916.pdf. Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection.

† Testing can be offered to pregnant women without clinical illness consistent with Zika virus disease. If performed, testing should include Zika virus IgM, and if IgM test result is positive or indeterminate, neutralizing antibodies on serum specimens. Testing should be performed 2–12 weeks after travel.

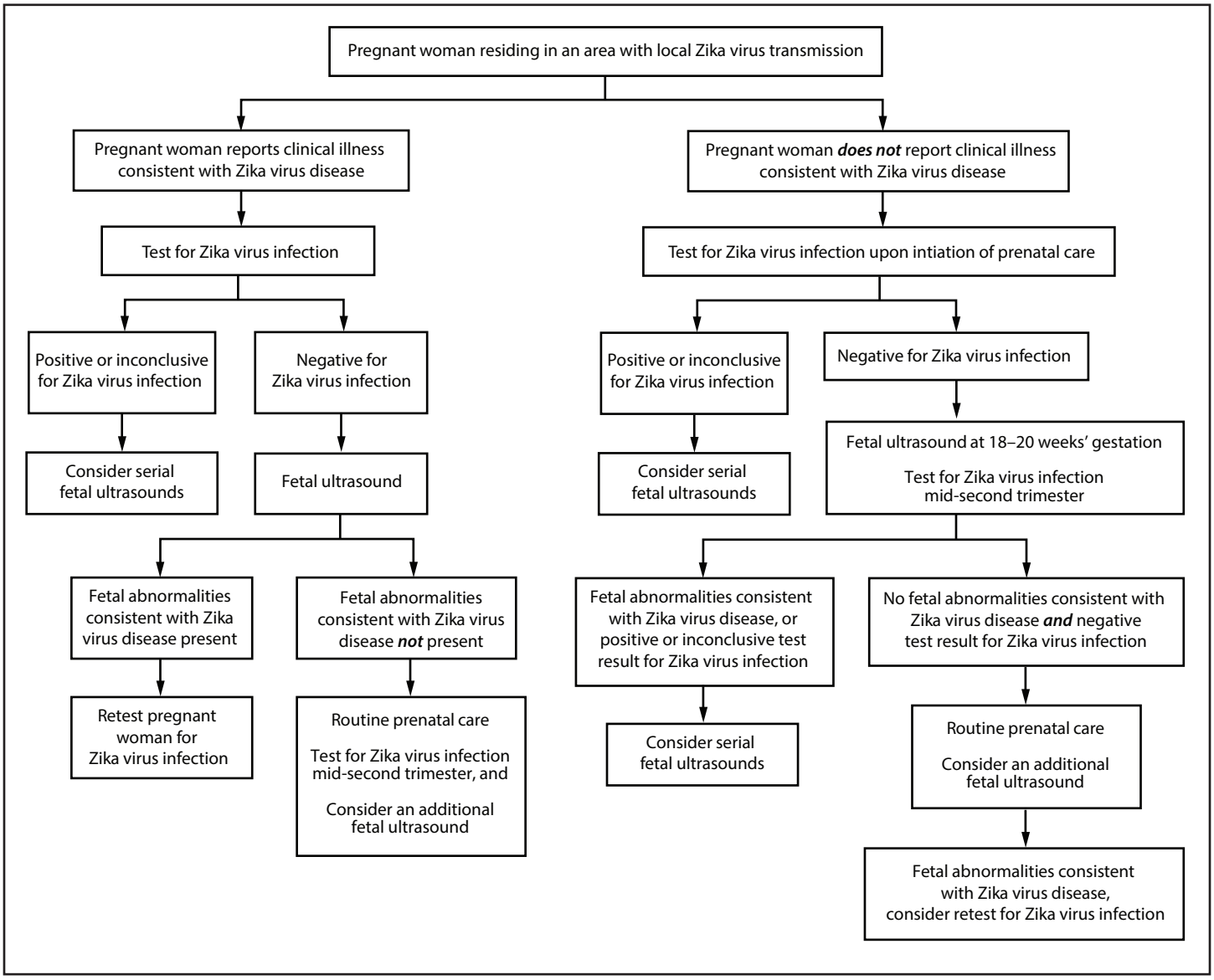
§ Laboratory evidence of maternal Zika virus infection: 1) Zika virus RNA detected by RT-PCR in any clinical specimen; or 2) positive Zika virus IgM with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum. Testing is considered inconclusive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

¶ Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasounds might not detect abnormalities until late second or early third trimester of pregnancy.

** Possible exposure to Zika virus includes travel to an area with active Zika virus transmission (http://wwwnc.cdc.gov/travel/notices), or sex (vaginal intercourse, anal intercourse, or fellatio) without a condom with a man who traveled to, or resided in, an area with active Zika virus transmission. Testing is not currently recommended for pregnant women with possible sexual exposure to Zika virus if both partners are asymptomatic.

condoms or abstain from sex for the duration of pregnancy. This course is the best way to avoid even a minimal risk for sexual transmission of Zika virus, which could result in adverse fetal effects if contracted during pregnancy. Pregnant women who have had sex without a condom with a male partner with possible Zika virus exposure should be tested for evidence of Zika virus infection if the woman develops at least one sign or symptom of Zika virus disease or if her male partner has had diagnosed Zika virus disease or a clinical illness consistent with Zika virus disease.

FIGURE 2. Updated interim guidance: testing algorithm*,†,§,¶ for a pregnant women residing in an area with active Zika virus transmission, with or without clinical illness†† consistent with Zika virus disease**



* Tests for pregnant women with clinical illness consistent with Zika virus disease include Zika virus reverse transcription-polymerase chain reaction (RT-PCR), and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. More information is available at http://www.aphl.org/Materials/CDCMemo_Zika_Chik_Deng_Testing_011916.pdf. Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection. If chikungunya or dengue virus RNA is detected, treat in accordance with existing guidelines. Timely recognition and supportive treatment for dengue virus infections can substantially lower the risk of medical complications and death. Repeat Zika virus testing during pregnancy is warranted if clinical illness consistent with Zika virus disease develops later in pregnancy.

† Testing can be offered to pregnant women without clinical illness consistent with Zika virus disease. If performed, testing should include Zika virus IgM, and if IgM test result is positive or indeterminate, neutralizing antibodies on serum specimens. Results from serologic testing are challenging to interpret in areas where residents have had previous exposure to other flaviviruses (e.g., dengue, yellow fever) because of cross-reactivity with other flaviviruses.

§ 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 titer.

¶ Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasounds might not detect abnormalities until late second or early third trimester of pregnancy.

** http://wwwnc.cdc.gov/travel/notices/. Local health officials should determine when to implement testing of asymptomatic pregnant women based on information about levels of Zika virus transmission and laboratory capacity.

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

Pregnant women who do not reside in areas with active Zika virus transmission who have had possible Zika virus exposure during the 8 weeks before conception (6 weeks before the last menstrual period) can be offered serologic testing within 2–12 weeks of this exposure. As previously recommended, all persons with possible exposure and clinical illness consistent with Zika virus disease should be tested for Zika virus infection.

An additional update to previously published guidance relates to amniocentesis. Consideration of amniocentesis should be individualized for each clinical circumstance; thus, amniocentesis has been removed from the updated testing algorithms (Figure 1) (Figure 2). Similar to evaluation of other congenital infections, amniocentesis may be considered in the evaluation of potential Zika virus infection. It is unknown how sensitive or specific RT-PCR testing of amniotic fluid is for congenital Zika virus infection, whether a positive result is predictive of a subsequent fetal abnormality, and if it is predictive, what proportion of infants born following infection will have abnormalities. The optimal time to perform amniocentesis to diagnose congenital Zika virus infection is not known; Zika virus RNA has been detected in amniotic fluid as early as 4 weeks after maternal symptom onset, and as early as 17 weeks' gestation (unpublished data). Health care providers should discuss the risks and benefits of amniocentesis with their patients.

The algorithms have also been updated to reflect accumulated data on ultrasonographic findings that might be consistent with Zika virus disease, including microcephaly, intracranial calcifications, and brain and eye abnormalities. This guidance will be updated as additional information becomes available (http://www.cdc.gov/zika/).

[1]Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, CDC; [2]Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; [3]Office of the Director, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), CDC; [4]Epidemic Intelligence Service, CDC; [5]Office of the Director, National Center for Immunization and Respiratory Diseases (NCIRD), CDC; [6]Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC; [7]Influenza Division, NCIRD, CDC; [8]Division of Reproductive Endocrinology & Infertility, Department of Gynecology & Obstetrics, Emory University School of Medicine; [9]Division of Environmental Hazards and Health Effects, National Center for Environmental Health, CDC; [10]Division of Vector-Borne Diseases, NCEZID, CDC; [11]Division of Preparedness and Emerging Infections, NCEZID, CDC; [12]Division of Healthcare Quality Promotion, NCEZID, CDC; [13]Division of Public Health Information Dissemination, Center for Surveillance, Epidemiology, and Laboratory Services, CDC.

Corresponding author: Emily E. Petersen, 770-488-7100, ZikaMCH@cdc.gov.

References

1. Oduyebo T, Petersen EE, Rasmussen SA, et al. Update: interim guidelines for health care providers caring for pregnant women and women of reproductive age with possible Zika virus exposure—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:122–7. http://dx.doi.org/10.15585/mmwr.mm6505e2
2. Atkinson B, Hearn P, Afrough B, et al. Detection of Zika virus in semen [letter]. Emerg Infect Dis. Published online May 2016. http://dx.doi.org/10.3201/eid2205.160107
3. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis 2015;21:359–61. http://dx.doi.org/10.3201/eid2102.141363
4. Lanciotti RS, Kosoy OL, Laven JJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis 2008;14:1232–9. http://dx.doi.org/10.3201/eid1408.080287
5. Mansuy JM, Dutertre M, Mengelle C, et al. Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen? Lancet Infect Dis 2016;16:405. http://dx.doi.org/10.1016/S1473-3099(16)00138-9
6. CDC. All countries and territories with active Zika virus transmission. Atlanta, GA: US Department of Health and Human Services, CDC; 2016. http://www.cdc.gov/zika/geo/active-countries.html
7. Foy BD, Kobylinski KC, Chilson Foy JL, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis 2011;17:880–2. http://dx.doi.org/10.3201/eid1705.101939
8. Oster AM, Brooks JT, Stryker JE, et al. Interim guidelines for prevention of sexual transmission of Zika virus—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:120–1. http://dx.doi.org/10.15585/mmwr.mm6505e1
9. Hills SL, Russell K, Hennessey M, et al. Transmission of Zika virus through sexual contact with travelers to areas of ongoing transmission—continental United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:215–6. http://dx.doi.org/10.15585/mmwr.mm6508e2
10. Venturi G, Zammarchi L, Fortuna C, et al. An autochthonous case of Zika due to possible sexual transmission, Florence, Italy, 2014. Euro Surveill 2016;21:30148. http://dx.doi.org/10.2807/1560-7917.ES.2016.21.8.30148
11. Duffy MR, Chen T-H, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med 2009;360:2536–43. http://dx.doi.org/10.1056/NEJMoa0805715
12. Calvet G, Aguiar RS, Melo AS, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect Dis. Published online February 17, 2016. http://dx.doi.org/10.1016/S1473-3099(16)00095-5
13. Mlakar J, Korva M, Tul N, et al. Zika virus associated with micrcephaly. N Engl J Med 2016;374:951–8. http://dx.doi.org/10.1056/NEJMoa1600651.
14. Martines RB, Bhatnagar J, Keating MK, et al. Notes from the field: evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses—Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65:159–60. http://dx.doi.org/10.15585/mmwr.mm6506e1
15. Meaney-Delman D, Hills SL, Williams C, et al. Zika virus infection among US pregnant travelers—August 2015–February 2016. MMWR Morb Mortal Wkly Rep 2016;65:211–4. http://dx.doi.org/10.15585/mmwr.mm6508e1
16. Brasil P, Pereira JP Jr, Raja Gabaglia C, et al. Zika virus infection in pregnant women in Rio de Janeiro—preliminary report. N Engl J Med 2016. Published online March 4, 2016. http://dx.doi.org/10.1056/NEJMoa1602412

17. Cauchemez M, Dub T, Guillemette-Artur P, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–2015: a retrospective study. Lancet. Published online March 15, 2016. http://dx.doi.org/10.1016/S0140-6736(16)00651-6
18. Enders G, Miller E, Nickerl-Pacher U, Cradock-Watson JE. Outcome of confirmed periconceptional maternal rubella. Lancet 1988;331:1445–7. http://dx.doi.org/10.1016/S0140-6736(88)92249-0
19. Daiminger A, Bäder U, Enders G. Pre- and periconceptional primary cytomegalovirus infection: risk of vertical transmission and congenital disease. BJOG 2005;112:166–72. http://dx.doi.org/10.1111/j.1471-0528.2004.00328.x
20. Picone O, Vauloup-Fellous C, Cordier AG, et al. A series of 238 cytomegalovirus primary infections during pregnancy: description and outcome. Prenat Diagn 2013;33:751–8. http://dx.doi.org/10.1002/pd.4118
21. Revello MG, Zavattoni M, Furione M, Lilleri D, Gorini G, Gerna G. Diagnosis and outcome of preconceptional and periconceptional primary human cytomegalovirus infections. J Infect Dis 2002;186:553–7. http://dx.doi.org/10.1086/341831
22. Nunoue T, Kusuhara K, Hara T. Human fetal infection with parvovirus B19: maternal infection time in gestation, viral persistence and fetal prognosis. Pediatr Infect Dis J 2002;21:1133–6. http://dx.doi.org/10.1097/00006454-200212000-00009
23. Rudolph KE, Lessler J, Moloney RM, Kmush B, Cummings DA. Incubation periods of mosquito-borne viral infections: a systematic review. Am J Trop Med Hyg 2014;90:882–91 http://dx.doi.org/10.4269/ajtmh.13-0403
24. Fonseca K, Meatherall B, Zarra D, et al. First case of Zika virus infection in a returning Canadian traveler. Am J Trop Med Hyg 2014;91:1035–8. http://dx.doi.org/10.4269/ajtmh.14-0151
25. Ioos S, Mallet HP, Leparc Goffart I, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. Med Mal Infect 2014;44:302–7. http://dx.doi.org/10.1016/j.medmal.2014.04.008
26. Bearcroft WG. Zika virus infection experimentally induced in a human volunteer. Trans R Soc Trop Med Hyg 1956;50:438–41. http://dx.doi.org/10.1016/0035-9203(56)90090-6
27. CDC. Contraception. Atlanta, GA: US Department of Health and Human Services, CDC; 2015. http://www.cdc.gov/reproductivehealth/unintendedpregnancy/contraception.htm
28. CDC. Zika virus disease in the United States, 2015–2016. Atlanta, GA: US Department of Health and Human Services, CDC; 2015. http://www.cdc.gov/zika/
29. Nasci RS, Wirtz RA, Brogdon WG. Protection against mosquitoes, ticks, and other arthropods. In: CDC health information for international travel, 2016. New York, NY: Oxford University Press; 2015. http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/protection-against-mosquitoes-ticks-other-arthropods
30. Banks SD, Murray N, Wilder-Smith A, Logan JG. Insecticide-treated clothes for the control of vector-borne diseases: a review on effectiveness and safety. Med Vet Entomol 2014;28(Suppl 1):14–25. http://dx.doi.org/10.1111/mve.12068
31. CDC. Updated diagnostic testing for Zika, chikungunya, and dengue viruses in US Public Health Laboratories. Atlanta, GA: US Department of Health and Human Services, CDC; 2016.
32. Bujan L, Daudin M, Alvarez M, Massip P, Puel J, Pasquier C. Intermittent human immunodeficiency type 1 virus (HIV-1) shedding in semen and efficiency of sperm processing despite high seminal HIV-1 RNA levels. Fertil Steril 2002;78:1321–3. http://dx.doi.org/10.1016/S0015-0282(02)04344-3
33. Pasquier C, Bujan L, Daudin M, et al. Intermittent detection of hepatitis C virus (HCV) in semen from men with human immunodeficiency virus type 1 (HIV-1) and HCV. J Med Virol 2003;69:344–9. http://dx.doi.org/10.1002/jmv.10295
34. Food and Drug Administration. Donor screening recommendations to reduce the risk of transmission of Zika virus by human cells, tissues, and cellular and tissue-based products. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2016. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM488582.pdf
35. Practice Committee of American Society for Reproductive Medicine: Practice Committee of Society for Assisted Reproductive Technology. Recommendations for gamete and embryo donation: a committee opinion. Fertil Steril 2013;99:47–62e1. http://dx.doi.org/10.1016/j.fertnstert.2012.09.037

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Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016

Katherine E. Fleming-Dutra, MD[1]; Jennifer M. Nelson, MD[2,3]; Marc Fischer, MD[4]; J. Erin Staples, MD, PhD[4]; Mateusz P. Karwowski, MD[2,5]; Paul Mead, MD[4]; Julie Villanueva, PhD[6]; Christina M. Renquist, MPH[7]; Anna A. Minta, MD[2,8]; Denise J. Jamieson, MD[9]; Margaret A. Honein, PhD[7]; Cynthia A. Moore, MD, PhD[7]; Sonja A. Rasmussen, MD[10]

CDC has updated its interim guidelines for U.S. health care providers caring for infants born to mothers who traveled to or resided in areas with Zika virus transmission during pregnancy and expanded guidelines to include infants and children with possible acute Zika virus disease (*1*). This update contains a new recommendation for routine care for infants born to mothers who traveled to or resided in areas with Zika virus transmission during pregnancy but did not receive Zika virus testing, when the infant has a normal head circumference, normal prenatal and postnatal ultrasounds (if performed), and normal physical examination. Acute Zika virus disease should be suspected in an infant or child aged <18 years who 1) traveled to or resided in an affected area within the past 2 weeks and 2) has ≥2 of the following manifestations: fever, rash, conjunctivitis, or arthralgia. Because maternal-infant transmission of Zika virus during delivery is possible, acute Zika virus disease should also be suspected in an infant during the first 2 weeks of life 1) whose mother traveled to or resided in an affected area within 2 weeks of delivery and 2) who has ≥2 of the following manifestations: fever, rash, conjunctivitis, or arthralgia. Evidence suggests that Zika virus illness in children is usually mild (*2*). As an arboviral disease, Zika virus disease is nationally notifiable. Health care providers should report suspected cases of Zika virus disease to their local, state, or territorial health departments to arrange testing and so that action can be taken to reduce the risk for local Zika virus transmission. As new information becomes available, these guidelines will be updated: http://www.cdc.gov/zika/.

Zika virus is primarily transmitted to humans through the bite of *Aedes* species mosquitoes, most commonly *Aedes aegypti* and possibly *Aedes albopictus* (*3*). Zika virus was first detected in the Region of the Americas (Americas) in Brazil in the spring of 2015 (*4*) and had spread to 26 countries and territories in the Americas as of February 17, 2016 (http://www.cdc.gov/zika/geo/active-countries.html). In October 2015, a marked increase in the number of infants with microcephaly was reported in Brazil (*5*). Because of the temporal and geographic occurrence of Zika virus infection in pregnant women before the reported increase in microcephaly, a possible association with prenatal Zika virus infection was postulated (*5*). Laboratory evidence from a limited number of cases with microcephaly has supported this potential association (*6*,*7*). Other documented modes of Zika virus transmission include intrapartum transmission from a mother with viremia to her infant, sexual transmission, and laboratory exposures (*8*–*11*). Additionally, blood transfusion (*10*) and organ or tissue transplantation pose theoretical risks for transmission. There is no reported evidence of transmission through breastfeeding, although Zika virus RNA has been found in breast milk (*9*).

Although the exact incubation period of Zika virus disease has yet to be determined, evidence from case reports and experience from related flavivirus infections indicate that the incubation period likely is 3 days to 2 weeks (*12*). Symptomatic disease is generally mild and characterized by two or more of the following: acute onset of fever, rash, arthralgia, or nonpurulent conjunctivitis (*2*,*13*). The rash associated with Zika virus disease has been described as pruritic (*13*) and maculopapular (*14*).

The spectrum of Zika virus disease in neonates infected in the perinatal period is unknown. Perinatal transmission of Zika virus infection to infants from mothers infected near the time of delivery has been reported in two cases; one of these infants was asymptomatic, and the other had thrombocytopenia and a diffuse rash (*9*). Mother-to-infant transmission of dengue virus, a related flavivirus, during the perinatal period has resulted in findings in the newborn ranging from no symptoms to severe illness (including fever, thrombocytopenia, and hemorrhage), most often with fever onset during the first week of life (*15*).

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Similarly West Nile virus, another mosquito-borne flavivirus, has been transmitted during the perinatal period from three mothers to their infants, with each infant having one of the following manifestations: rash, viral encephalitis, and viral meningitis (*16*). The clinical features that might be observed in infants who acquire Zika virus during the perinatal period are currently unknown.

Available evidence regarding the spectrum of Zika virus disease in infants and children who are infected through mosquito bites indicates that most children are asymptomatic or have mild illness, similar to the findings seen in adults infected with Zika virus disease. In the outbreak in Yap Island, Micronesia, in 2007, among persons with clinical illness (age range = 1–76 years), fever, macular or papular rash, arthralgia, and conjunctivitis were the most common signs and symptoms (*2*). In that outbreak, children aged 0–19 years had lower attack rates of confirmed and probable Zika virus disease than did adults aged 20–59 years (*2*). Additional published data are available for 10 children, aged 3–16 years (*17*–*22*) with Zika virus disease in Africa, Asia, South America, and the Pacific. All 10 children had fever, but none had rash, two had conjunctivitis, and three had arthralgia. Vomiting was reported in two children (*17*,*22*), and diarrhea was reported in two children (*22*). Among eight recent travel-related cases among children in the United States, all had rash and at least one other sign or symptom (fever, arthralgia, nonpurulent conjunctivitis) (CDC, unpublished data, 2016).

Deaths from Zika virus infection appear to be rare in persons of all ages. One death was reported in a female aged 15 years with sickle cell disease (hemoglobin SC), who experienced 4 days of fever, myalgia, abdominal pain and jaundice (*18*). A blood sample collected 5 days after illness onset was positive by reverse transcription–polymerase chain reaction (RT-PCR) for Zika virus RNA and negative for dengue, chikungunya, and yellow fever viruses (*18*). This patient died from complications of sickle cell disease after developing severe acute respiratory distress syndrome, hemothorax, and splenic sequestration (*18*). An additional death was reported in a female aged 16 years whose symptoms included headache, nausea, and petechiae; blood samples obtained 7 days after illness onset were positive by RT-PCR for Zika virus RNA (*23*). No further information was reported (*23*).

Guillain-Barré syndrome has been reported following Zika virus infection, although a causal link has not been established. Overall Guillain-Barré syndrome incidence appears to increase with increasing age (*24*). However, it is unclear how often Guillian-Barré syndrome after Zika virus infection has occurred in children (*10*). In French Polynesia, among 38 reported cases of Guillian-Barré syndrome after Zika virus infection, none occurred among children (*25*). One report from Brazil refers to six patients, aged 2–57 years, with neurologic syndromes (four with Guillain-Barré and two with acute disseminated encephalomyelitis) after laboratory-confirmed Zika virus infection; however, no further data were reported (*13*).

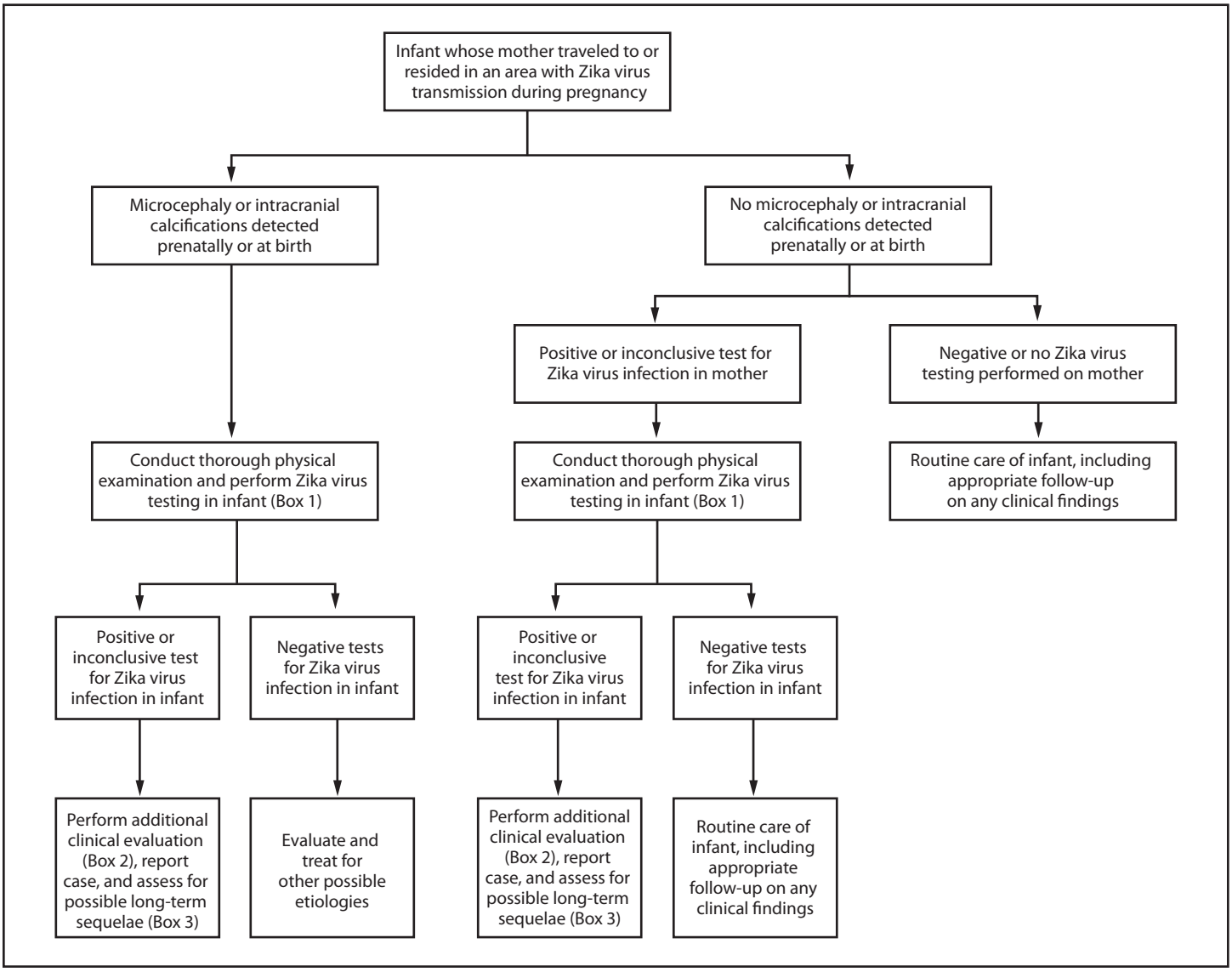
Updated Recommendations for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection

Congenital infections result from intrauterine transmission from mother to fetus during pregnancy. Testing of infants with possible congenital Zika virus infection who were born to mothers who traveled to or resided in areas affected by Zika virus during pregnancy should be guided by 1) whether the infant had microcephaly or intracranial calcifications detected prenatally or at birth and 2) the mother's Zika virus testing results. The results of previous prenatal ultrasounds and maternal Zika virus testing should be reviewed, and a thorough newborn physical examination, with assessment of head (occipitofrontal) circumference, length, and weight, should be performed (*26*,*27*). The evaluation of infants with microcephaly or intracranial calcifications or infants whose mothers have positive or inconclusive test results for Zika virus infection remains the same as described in the recommendations released on January 26 (Figure) (Box 1,2,3) (*1*). Infants without microcephaly or intracranial calcifications whose mothers have negative Zika virus test results or who were not tested for Zika virus should receive routine care (Figure). Because information on the effects of congenital Zika virus infection is limited, health care providers should exercise clinical judgment in the assessment of newborns with abnormalities other than microcephaly or intracranial calcifications who were born to mothers who traveled to or resided in an area with active Zika virus transmission during pregnancy. For these infants, health care providers should consider testing the mother before testing the infant. These guidelines will be updated as additional information becomes available.

Guidelines for Evaluation and Management of Infants and Children Aged <18 Years with Possible Acute Zika Virus Disease

Acute Zika virus disease should be suspected in an infant or child aged <18 years who 1) traveled to or resided in an affected area within the past 2 weeks and 2) has two or more of the following manifestations: fever, rash, conjunctivitis, or arthralgia. Acute Zika virus disease should also be suspected in an infant in the first 2 weeks of life 1) whose mother traveled to or resided in an affected area within 2 weeks of delivery and 2) who has two or more of the following manifestations: fever, rash, conjunctivitis, or arthralgia. Arthralgia can be difficult to detect in infants and young children and can manifest as irritability, walking with a limp (for ambulatory children),

FIGURE. Interim guidelines for the evaluation and testing of infants whose mothers traveled to or resided in an area with ongoing Zika virus transmission* during pregnancy†,§,¶



Adapted from: Staples, JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:63–7.

* Areas with Zika virus transmission are listed on the CDC website at http://wwwnc.cdc.gov/travel/page/zika-travel-information.

† Microcephaly defined as occipitofrontal circumference less than the third percentile for gestational age and sex based on standard growth curves (*26,27*), not explained by other etiologies.

§ Laboratory evidence of Zika virus infection includes 1) detectable Zika virus, Zika virus RNA, or Zika virus antigen 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 or cerebrospinal fluid. Testing is considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

¶ For infants, perform reverse transcription–polymerase chain reaction (RT-PCR) testing for Zika virus RNA and Zika virus and dengue virus IgM and neutralizing antibodies on serum collected from the umbilical cord or directly from infant within 2 days of birth, if possible. If cerebrospinal fluid is obtained for other reasons, test for Zika virus RNA, Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies. Consider histopathologic evaluation of the placenta and umbilical cord with Zika virus immunohistochemical staining on fixed tissue and Zika virus RT-PCR on fixed and frozen tissue. More information on laboratory testing for Zika virus infection is available at http://www.cdc.gov/zika/state-labs/index.html.

difficulty moving or refusing to move an extremity, pain on palpation, or pain with active or passive movement of the affected joint. Infants and older children can acquire Zika virus through mosquito-borne transmission. Infants can also be infected perinatally if the mother became infected with Zika virus during travel to or residence in an area with Zika virus transmission within 2 weeks of delivery. Infants whose mothers reported illness consistent with Zika virus disease near the time of delivery should be monitored for signs and symptoms of Zika virus disease. If an infant shows signs and

symptoms of acute Zika virus disease within the first 2 weeks of life, both the mother and infant should be tested for Zika virus infection. Persons might be exposed to Zika virus infection through sexual contact with a person who has traveled to or resided in an area affected by Zika virus (*11*).

BOX 1. Recommended Zika virus laboratory testing for infants and children when indicated*,†,§

For possible congenital Zika virus infection

- Test infant serum for Zika virus RNA, Zika virus immunoglobulin M (IgM) and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies. The initial sample should be collected either from the umbilical cord or directly from the infant within 2 days of birth, if possible.
- If cerebrospinal fluid is obtained for other studies, test for Zika virus RNA, Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.
- Consider histopathologic evaluation of the placenta and umbilical cord with Zika virus immunohistochemical staining on fixed tissue and Zika virus reverse transcription-polymerase chain reaction (RT-PCR) on fixed and frozen tissue.
- If not already performed during pregnancy, test mother's serum for Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.

For possible acute Zika virus disease

- If symptoms have been present for <7 days, test serum (and, if obtained for other reasons, cerebrospinal fluid) for Zika virus RNA by RT-PCR
- If Zika virus RNA is not detected and symptoms have been present for ≥4 days, test serum (and, if obtained for other reasons, cerebrospinal fluid) for Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies

Adapted from: Staples, JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:63–7.

* Indications for testing for congenital infection include 1) an infant with microcephaly or intracranial calcifications born to a woman who traveled to or resided in an area with Zika virus transmission while she was pregnant, or 2) an infant born to a mother with a positive or inconclusive test result for Zika virus infection.

† Indications for testing during acute disease include: Infants and children aged <18 years who 1) traveled to or resided in an affected area within the past 2 weeks and 2) have ≥2 of the following manifestations: fever, rash, conjunctivitis, or arthralgia. Infants in the first 2 weeks of life 1) whose mothers have traveled to or resided in an affected area within 2 weeks of delivery and 2) have ≥2 of the following manifestations: fever, rash, conjunctivitis, or arthralgia.

§ More information on laboratory testing for Zika virus infection is available at http://www.cdc.gov/zika/state-labs/index.html.

BOX 2. Recommended clinical evaluation and laboratory testing for infants with possible congenital Zika virus infection

For all infants with possible congenital Zika virus infection, perform the following:

- Comprehensive physical examination, including careful measurement of occipitofrontal circumference, length, weight, and assessment of gestational age.
- Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions. Full body photographs and photographic documentation of any rash, skin lesions, or dysmorphic features should be performed. If an abnormality is noted, consultation with an appropriate specialist is recommended.
- Cranial ultrasound, unless prenatal ultrasound results from third trimester demonstrated no abnormalities of the brain.
- Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 month after birth. Infants with abnormal initial hearing screens should be referred to an audiologist for further evaluation.
- Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within 1 month after birth. Infants with abnormal initial eye evaluation should be referred to a pediatric ophthalmologist for further evaluation.
- Other evaluations specific to the infant's clinical presentation.

For infants with microcephaly or intracranial calcifications, additional evaluation includes the following:

- Consultation with a clinical geneticist or dysmorphologist.
- Consultation with a pediatric neurologist to determine appropriate brain imaging and additional evaluation (e.g., ultrasound, computerized tomography scan, magnetic resonance imaging, and electroencephalogram).
- Testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infections. Consider consulting a pediatric infectious disease specialist.
- Complete blood count with platelet count and liver function and enzyme tests, including alanine aminotransferase, aspartate aminotransferase, and bilirubin.
- Consideration of genetic and other teratogenic causes based on additional congenital anomalies that are identified through clinical examination and imaging studies.

Adapted from: Staples, JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:63–7.

BOX 3. Recommended long-term follow-up for infants with possible congenital Zika virus infection

For all infants with possible congenital Zika virus infection, recommended long-term follow-up:

- Report case to state, territorial, or local health department and monitor for additional guidance as it is released.
- Consider conducting additional hearing screen at age 6 months. Refer any child with developmental delay for an audiologic evaluation. Ensure that appropriate follow-up of abnormal newborn hearing screening has occurred.
- Carefully evaluate occipitofrontal circumference and developmental characteristics and milestones throughout the first year of life, in consultation with appropriate medical specialists (e.g., pediatric neurology, developmental and behavioral pediatrics, physical and speech therapy).

Adapted from: Staples, JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:63–7.

Evaluation of infants and children for acute (symptom onset within the past 7 days) Zika virus infection should include testing of serum and, if obtained for other reasons, cerebrospinal fluid (CSF) specimens for evidence of Zika virus RNA using RT-PCR. If Zika virus RNA is not detected and symptoms have been present for ≥4 days, serum may be tested for Zika virus immunoglobulin M (IgM) and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies (Box 1). Laboratory evidence of Zika virus infection in an infant or child would include, in any clinical specimen, detectable Zika virus in culture, Zika virus RNA or antigen, or a clinical specimen positive for Zika virus IgM with confirmatory neutralizing antibody titers ≥4-fold higher than dengue virus neutralizing antibody titers (*1*). If Zika virus antibody titers <4-fold higher than dengue virus neutralizing antibody titers, test results for Zika virus are considered inconclusive (*1*). More information on laboratory testing can be found at http://www.cdc.gov/zika/state-labs/index.html. Health care providers should notify their local, state or territorial health department of suspected Zika cases to arrange testing and so that action can be taken to decrease the risk for local transmission in areas with *Aedes* species mosquitoes.

Illness associated with Zika virus is usually mild in children, and treatment of Zika virus infection involves supportive care. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue virus is ruled out as the cause of illness, because of the potential for hemorrhagic complications of dengue fever, and should be avoided in all children aged <6 months (*28*,*29*). Aspirin should not be used in children with acute viral illnesses because of its association with Reye's syndrome (*30*). The decision to obtain additional laboratory tests, diagnostic studies, and infectious disease consultation should be based on clinical judgment as guided by findings from a complete history and physical examination. Information on long-term outcomes among infants and children with acute Zika virus disease is limited (*10*); until more evidence is available to inform recommendations, routine pediatric care is advised for these infants and children.

Guidelines for Breastfeeding for Mothers with Zika Virus Infection

Zika virus RNA has been identified in breast milk, but attempts to culture the virus have been unsuccessful (*9*). No cases of Zika virus infection associated with breastfeeding have been reported. CDC encourages mothers with Zika virus infection and living in areas with ongoing Zika virus transmission to breastfeed their infants. Current evidence suggests that the benefits of breastfeeding outweigh the theoretical risks of Zika virus transmission through breast milk.

Prevention of Zika Virus Infection in Infants and Children

Prevention of mosquito bites is the primary means of preventing Zika virus infection in persosns of all ages traveling to or residing in areas with local Zika virus transmission. Mosquito bite prevention includes using air conditioning or window and door screens when indoors, wearing long-sleeved shirts and long pants, using permethrin-treated clothing and gear, and using insect repellents. When used as directed on the product label, most Environmental Protection Agency–registered insect repellents can be used to protect children aged ≥2 months against mosquito bites. Oil of lemon eucalyptus should not be used in children aged <3 years (http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/protection-against-mosquitoes-ticks-other-arthropods). Mosquito netting can be used to cover infants in carriers, strollers, or cribs to protect them from mosquito bites. Information on the safe use of insect repellents in children is available at http://www.epa.gov/insect-repellents/using-insect-repellents-safely-and-effectively.

Persons with Zika virus infection should take steps to prevent mosquito bites for at least the first week of illness to decrease the risk for human-to-mosquito-to-human transmission. Health care providers should educate parents and caregivers about mosquito bite prevention in infants and children if they are traveling to or residing in areas affected by Zika virus; mosquitoes also carry other viruses in addition to Zika. More information about prevention of Zika virus infection can be found at http://www.cdc.gov/zika/prevention/index.html.

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[1]Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [2]Epidemic Intelligence Service, CDC; [3]Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease and Health Promotion, CDC; [4]Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC;[5]Division of Environmental Hazards and Health Effects, National Center for Environment Health, CDC; [6]Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [7]Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, CDC; [8]Division of Parasitic Diseases and Malaria, Center for Global Health, CDC; [9]Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, CDC; [10]Division of Public Health Information Dissemination, Center for Surveillance, Epidemiology, and Laboratory Services, CDC

Corresponding Author: Katherine E. Fleming-Dutra, eocbirthdef@cdc.gov.

References

1. Staples JE, Dziuban EJ, Fischer M, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:63–7. http://dx.doi.org/10.15585/mmwr.mm6503e3
2. Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med 2009;360:2536–43. http://dx.doi.org/10.1056/NEJMoa0805715
3. Ioos S, Mallet HP, Leparc Goffart I, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. Med Mal Infect 2014;44:302–7. http://dx.doi.org/10.1016/j.medmal.2014.04.008
4. Hennessey M, Fischer M, Staples JE. Zika Virus Spreads to New Areas - Region of the Americas, May 2015-January 2016. MMWR Morb Mortal Wkly Rep 2016;65:55–8. http://dx.doi.org/10.15585/mmwr.mm6503e1
5. Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al.; Brazilian Medical Genetics Society–Zika Embryopathy Task Force. Possible association between Zika virus infection and microcephaly—Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65:59–62. http://dx.doi.org/10.15585/mmwr.mm6503e2
6. Martines RB, Bhatnagar J, Keating MK, et al. Notes from the field: Evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses—Brazil. MMWR Morb Mortal Wkly Rep 2016;65:159–60. http://dx.doi.org/10.15585/mmwr.mm6506e1
7. Mlakar J, Korva M, Tul N, et al. Zika virus associated with microcephaly. N Engl J Med 2016; Epub ahead of print. http://dx.doi.org/10.1056/NEJMoa1600651
8. The Subcommittee on Arbovirus Laboratory Safety of the American Committee on Arthropod-Borne Viruses. Laboratory safety for arboviruses and certain other viruses of vertebrates. Am J Trop Med Hyg 1980;29:1359–81.
9. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill 2014;19:20751. http://dx.doi.org/10.2807/1560-7917.ES2014.19.13.20751
10. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barre syndrome. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2015.
11. Oster AM, Brooks JT, Stryker JE, et al. Interim guidelines for prevention of sexual transmission of Zika virus—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:120–1. http://dx.doi.org/10.15585/mmwr.mm6505e1
12. Rudolph KE, Lessler J, Moloney RM, Kmush B, Cummings DA. Incubation periods of mosquito-borne viral infections: a systematic review. Am J Trop Med Hyg 2014;90:882–91. http://dx.doi.org/10.4269/ajtmh.13-0403
13. Minstério de Saúde. Protocolo de vigilância e resposta à ocorrência de microcefalia relacionada à infecção pelo vírus Zika 2015. http://portalsaude.saude.gov.br/images/pdf/2015/dezembro/09/Microcefalia---Protocolo-de-vigil--ncia-e-resposta---vers--o-1----09dez2015-8h.pdf
14. Kwong JC, Druce JD, Leder K. Zika virus infection acquired during brief travel to Indonesia. Am J Trop Med Hyg 2013;89:516–7. http://dx.doi.org/10.4269/ajtmh.13-0029
15. Pouliot SH, Xiong X, Harville E, et al. Maternal dengue and pregnancy outcomes: a systematic review. Obstet Gynecol Surv 2010;65:107–18.
16. O'Leary DR, Kuhn S, Kniss KL, et al. Birth outcomes following West Nile Virus infection of pregnant women in the United States: 2003-2004. Pediatrics 2006;117:e537–45. http://dx.doi.org/10.1542/peds.2005-2024
17. Alera MT, Hermann L, Tac-An IA, et al. Zika virus infection, Philippines, 2012. Emerg Infect Dis 2015;21:722–4. http://dx.doi.org/10.3201/eid2104.141707
18. Arzuza-Ortega L, Pérez-Tatis G, López-García H, et al. Fatal Zika virus infection in girl with sickle cell disease, Colombia[Letter]. Emerg Infect Dis 2016. Epub ahead of print. http://dx.doi.org/10.3201/eid2205.151934
19. Dupont-Rouzeyrol M, O'Connor O, Calvez E, et al. Co-infection with Zika and dengue viruses in 2 patients, New Caledonia, 2014. Emerg Infect Dis 2015;21:381–2. http://dx.doi.org/10.3201/eid2102.141553
20. Heang V, Yasuda CY, Sovann L, et al. Zika virus infection, Cambodia, 2010. Emerg Infect Dis 2012;18:349–51. http://dx.doi.org/10.3201/eid1802.111224
21. MacNamara FN. Zika virus: a report on three cases of human infection during an epidemic of jaundice in Nigeria. Trans R Soc Trop Med Hyg 1954;48:139–45. http://dx.doi.org/10.1016/0035-9203(54)90006-1
22. Olson JG, Ksiazek TG, Suhandiman, Triwibowo. Zika virus, a cause of fever in Central Java, Indonesia. Trans R Soc Trop Med Hyg 1981;75:389–93. http://dx.doi.org/10.1016/0035-9203(81)90100-0
23. Centro de operaçõs de emergênecias em saúde pública sobre microcefalias. Informe epidemiológico no 02/2015—Semana epidemiológica 47 (22 a 28/11/2015): Monitoramento dos casos de microcefalias no Brasil. http://portalsaude.saude.gov.br/images/pdf/2015/novembro/30/COES-Microcefalias---Informe-Epidemiol--gico---SE-47---30nov2015.pdf
24. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology 2011;36:123–33. http://dx.doi.org/10.1159/000324710
25. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus infection outbreak, French Polynesia. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2014.
26. World Health Organization. The WHO child growth standards. Geneva, Switzerland: World Health Organization. http://www.who.int/childgrowth/standards/en/
27. University of Calgary. Welcome to the Fenton Preterm Growth Chart: 2013 Growth Chart. http://ucalgary.ca/fenton/2013chart
28. Sullivan JE, Farrar HC; Section on Clinical Pharmacology and Therapeutics; Committee on Drugs. Fever and antipyretic use in children. Pediatrics 2011;127:580–7. http://dx.doi.org/10.1542/peds.2010-3852
29. Tomashek KM, Sharp TM, Margolis HS. Dengue. Chapter 3. In: Brunette GW, ed. CDC Health information for international travel 2016.
30. Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service study of Reye's syndrome and medications. Report of the main study. JAMA 1987;257:1905–11. http://dx.doi.org/10.1001/jama.1987.03390140075030

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