Zika virus infection

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INTRODUCTION — Zika virus is an arthropod-borne flavivirus transmitted by mosquitoes. The virus is related to other flaviviruses including dengue virus, yellow fever virus, and West Nile virus. Clinical manifestations of Zika virus infection occur in approximately 20 percent of patients and include acute onset of low-grade fever with maculopapular rash, arthralgia (notably small joints of hands and feet), or conjunctivitis (nonpurulent). Zika virus infection has also been associated with congenital microcephaly and fetal losses among women infected during pregnancy [1,2]. (See 'Perinatal complications' below.)

Currently, there is an ongoing Zika virus outbreak in the Americas and Caribbean; the World Health Organization (WHO) has stated that the virus is "spreading explosively" [3] and has declared Zika virus and its associated complications a Public Health Emergency of International Concern [4].

Online updates regarding Zika virus infection may be viewed at the following websites:

- Pan American Health Organization (PAHO)/WHO website
- United States Centers for Disease Control and Prevention (CDC) website
- European Centre for Disease Prevention and Control (ECDC) website

Issues related to Zika virus infection will be reviewed here. Issues related to other mosquito-borne infections are discussed separately. (See related topics.)

EPIDEMIOLOGY

Geographic distribution — Outbreaks of Zika virus infection have occurred in Africa, Southeast Asia, and the Pacific Islands; currently, there is an ongoing Zika virus outbreak in the Americas [5-7]. In January 2016, the United States Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) advised that pregnant women consider postponing travel to any area where Zika virus transmission is ongoing, given an association between congenital microcephaly in parallel with the Zika virus outbreak in Brazil [1,8,9]. Updates regarding the geographic distribution of Zika virus may be viewed at the CDC website and the Pan American Health Organization/World Health Organization website. (See 'Perinatal complications' below.)

Zika virus is named after the Ugandan forest where it was first isolated in a rhesus monkey in 1947. It subsequently spread to Southeast Asia, where it was associated with sporadic infections. The first major recognized outbreak occurred in the Yap Islands of Micronesia in 2007; more than 70 percent of the population ≥3 years of age was infected [10-12]. Another larger outbreak occurred in French Polynesia in 2013 to 2014, affecting about 32,000 people [13].

Zika virus infection appeared in the Western hemisphere in February 2014 on Chile's Easter Island; the virus

continued to be detected there until June 2014. Zika virus infection in Brazil was confirmed in May 2015 [14].

As of February 2016, countries with autochthonous circulation of Zika virus include Barbados, Bolivia, Brazil, Cape Verde, Colombia, Costa Rica, Curaçao, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Nicaragua, Panama, Paraguay, Saint Martin, Samoa, Suriname, Tonga, and Venezuela [8,15,16].

Zika virus infection has been detected in the United States territories of Puerto Rico, the US Virgin Islands, and American Samoa [17,18]. Local mosquito-borne transmission of Zika virus infection has not yet been reported in the continental United States, but cases of imported Zika infection have been reported in travelers. The first case of Zika-related congenital microcephaly in the United States was reported in January 2016 in Hawaii, in a baby born to a woman who had resided in Brazil during her pregnancy [19]. A case of sexually transmitted Zika virus infection was reported in Texas in February 2016 [20]; this is the first case of locally acquired Zika infection in the continental United States during the 2015 to 2016 outbreak.

Transmission — Zika virus is transmitted to humans primarily via the bite of an infected *Aedes* mosquito; other modes of transmission can also occur. Zika virus RNA has been detected in blood, urine, semen, saliva, cerebrospinal fluid, amniotic fluid, and breast milk [21-25]. Preventive measures based on the modes of transmission described here are discussed further below. (See 'Prevention' below.)

Zika virus is carried by the *Aedes aegyptus* mosquito, which lives only in tropical regions; however, the *Aedes albopictus* mosquito, which lives in temperate regions, is also capable of carrying it (figure 1) [21,26,27]. *Aedes* mosquitoes can also transmit dengue and chikungunya viruses. *Aedes* mosquitoes bite during the daytime as well as at twilight; they breed in standing water [28].

Maternal-fetal transmission can occur including intrauterine transmission resulting in congenital infection as well as intrapartum transmission from a viremic mother to her newborn [1,2,6,29]. (See 'Perinatal complications' below.)

Transmission of Zika virus through breastfeeding has not yet been observed [6,21]. However, transmission of some other flaviviruses via breast milk has been described [30,31].

Anecdotal reports of apparent sexual transmission have been described; this appears to be an infrequent mechanism for Zika virus transmission [20-22,32,33].

Zika virus is transmissible via blood products [23,34]; transmission of other flaviviruses via blood products has also been described [35,36].

CLINICAL MANIFESTATIONS

Symptoms and signs — Symptoms and signs of Zika virus infection typically include acute onset of low-grade fever (37.8 to 38.5°C) with maculopapular rash, arthralgia (notably the small joints of hands and feet), and conjunctivitis (nonpurulent); clinical illness is consistent with Zika virus disease if two or more of these symptoms are present [2]. Other commonly reported clinical manifestations include myalgia, headache, retro-orbital pain, and asthenia [37]. More rarely observed symptoms and signs include abdominal pain, nausea, diarrhea, mucus membrane ulcerations, and pruritus [38].

Symptoms and signs typically occur approximately 2 to 12 days after the mosquito vector bite. The illness is usually mild; symptoms resolve within two to seven days. Asymptomatic infection is common; symptoms develop in 20 to 25 percent of individuals who become infected with Zika virus. Once a person has been infected, he or she is likely to be protected from future infections [39]. Severe disease requiring hospitalization is uncommon, and case-fatality rates are low [37].

Zika virus infection has been associated with complications including congenital microcephaly and fetal losses among women infected during pregnancy and Guillain-Barré syndrome. (See 'Complications' below.)

Complications

Perinatal complications — The spectrum of outcomes that may be associated with infection during pregnancy and the factors that may increase fetal risk are not yet fully understood; further investigation is ongoing. Zika virus infections have been confirmed in several infants with microcephaly, although it is not known how many of the microcephaly cases are associated with Zika virus infection [1,2,40,41]. In addition, Zika virus RNA has been detected in the pathologic specimens of fetal losses, although it is not known whether Zika virus caused the fetal losses [1,2,41].

In January 2016, the United States Centers for Disease Control and Prevention (CDC) and the European Centre for Prevention and Control (ECDC) advised that pregnant women consider postponing travel to any area where Zika virus transmission is ongoing [1,8,9]. (See 'Prevention' below.)

A large number of Brazilian newborns with microcephaly (head circumference ≥2 standard deviations below the mean for sex and gestational age at birth) has been observed in parallel with the current Zika outbreak [40,42-44]. Between March 2015 and February 2016, more than 4000 cases of microcephaly have been reported among newborns born to Brazilian mothers with Zika virus infection; this represents a 20-fold increase in microcephaly compared with previous years [15,45-47].

No birth defects were reported at the time of the outbreak in the Yap Islands of Micronesia in 2007, perhaps due to the relatively small size of the population. Similarly, no fetal abnormalities were identified initially during the French Polynesia outbreak in 2013 to 2014; subsequently, however, a retrospective evaluation did identify 17 cases of fetal or neonatal central nervous system malformations or brainstem dysfunction [48].

In one report including 35 Brazilian infants with microcephaly, computed tomography scans and transfontanellar cranial ultrasonography demonstrated widespread brain calcifications, mainly in the periventricular, parenchymal, and thalamic areas and in the basal ganglia; in approximately one-third of cases, these findings were associated with evidence of cell migration abnormalities (eg, lissencephaly, pachygyria) [40]. Ventricular enlargement secondary to cortical/subcortical atrophy was also frequently observed. A small number of infants had arthrogryposis (congenital contractures), indicative of central or peripheral nervous system involvement [10]. Intracranial calcification has also been associated with other causes of congenital infection. (See "Overview of TORCH infections".)

A subsequent report described evidence of an association between Zika virus infection and both microcephaly as well as fetal demise, by detection of Zika viral RNA and antigens in brain tissues from two infants with microcephaly (born at 36 and 38 weeks gestation who died within 20 hours of birth) and placental tissues from two miscarriages (fetal losses at 11 and 13 weeks) [49].

Ocular involvement has been observed among infants with congenital infection due to presumed Zika virus exposure, including macular atrophy and optic nerve abnormalities [50,51].

There is no evidence to suggest that pregnant women are more susceptible to Zika virus infection or experience more severe disease during pregnancy [29,41]. According to a preliminary analysis of research carried out by Brazilian authorities, the greatest risk of microcephaly and malformations appears to be associated with Zika infection during the first trimester [52]. The rate of vertical transmission and the rate with which infected fetuses manifest complications are unknown [53].

Issues related to diagnosis and evaluation of microcephaly in infants and children are discussed further separately. (See "Microcephaly in infants and children: Etiology and evaluation", section on 'Prenatal evaluation'.)

Thus far, no developmental complications have been observed in otherwise healthy neonates, infants, or children with postnatal Zika virus infection or exposure; however, further study is needed [54].

Guillain-Barré syndrome — Several countries in the Americas have reported unusual increases in cases of Guillain-Barré syndrome (GBS) in parallel with the ongoing Zika virus outbreak [55,56]. An increase in the rate of GBS in association with Zika virus infection has also been observed in other reports [22,42,45]. However, a direct causal relationship has not yet been definitively established.

During the Zika virus outbreak in French Polynesia (2013 to 2014), 74 patients had presented neurologic or autoimmune syndromes after the manifestation of symptoms consistent with Zika virus infection; of these, 42 were classified as GBS [56,57].

Issues related to diagnosis and evaluation of Guillain-Barré syndrome are discussed further separately. (See "Clinical features and diagnosis of Guillain-Barré syndrome in adults".)

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of Zika virus infection includes:

- Other viral causes of arthritis:
  - Dengue fever – Dengue virus and Zika virus infections have similar clinical manifestations and are transmitted by the same mosquito vector. However, dengue infection usually presents with high fever, severe muscle pain, and headache and may also be associated with hemorrhage; unlike Zika infection, dengue is typically not associated with conjunctivitis (table 1). Coinfection with Zika, chikungunya, and dengue viruses has been described [58]. The diagnosis of dengue virus infection is established via serology. (See "Clinical manifestations and diagnosis of dengue virus infection".)
  - Chikungunya – Chikungunya virus and Zika virus cause similar symptoms and signs and are transmitted by the same mosquito vector. However, chikungunya usually presents with high fever and relatively intense joint pain affecting the hands, feet, knees, and back; unlike Zika infection, chikungunya is typically not associated with conjunctivitis (table 1). Chikungunya infection can be disabling, causing patients to bend over such that they cannot walk, and infected individuals may be unable to perform simple manual tasks. Coinfection with Zika, chikungunya, and dengue viruses has been described [58]. The diagnosis of chikungunya virus infection is established via serology. (See "Chikungunya fever".)
  - Parvovirus – Parvovirus infection can present with acute and symmetric arthritis or arthralgia, most frequently involving the small joints of the hands, wrists, knees, and feet. Rash may or may not be present. The diagnosis is established via serology. (See "Clinical manifestations and diagnosis of parvovirus B19 infection".)
  - Rubella – Clinical manifestations of rubella include low-grade fever and coryza. Macular rash begins on the face and spreads to the trunk, and arthritis and lymphadenopathy may be present. The diagnosis is established via serology. (See "Rubella".)
  - A number of other viruses including enterovirus, adenovirus, and alphaviruses may also cause arthritis; these are discussed further separately. (See "Specific viruses that cause arthritis".)
- Measles – Clinical manifestations of measles include fever, cough, sore throat, coryza, conjunctivitis, and lymphadenitis. Koplik spots may precede the generalized rash. The diagnosis is established via serology. (See "Clinical manifestations and diagnosis of measles".)
- Leptospirosis – Leptospirosis is characterized by fever, rigors, myalgia, conjunctival suffusion, and headache. Less common symptoms and signs include cough, nausea, vomiting, diarrhea, abdominal pain, and arthralgia. It may be distinguished from Zika virus infection by the presence of jaundice. The diagnosis is established via serology. (See "Epidemiology, microbiology, clinical manifestations, and diagnosis of leptospirosis".)
- Malaria – Malaria is characterized by fever, malaise, nausea, vomiting, abdominal pain, diarrhea, myalgia, and anemia. The diagnosis of malaria is established by visualization of parasites on peripheral smear. (See "Clinical manifestations of malaria".)
- Rickettsial infection – Rickettsial infections with similar manifestations as Zika virus infection include African tick bite fever and relapsing fever. African tick bite fever is observed among travelers to Africa and the Caribbean and is characterized by headache, fever, myalgia, solitary or multiple eschars with regional

lymphadenopathy, and generalized rash; the diagnosis is established via serology. Relapsing fever is characterized by fever, headache, neck stiffness, arthralgia, myalgia, and nausea; diagnostic tools include direct smear and polymerase chain reaction. (See "Other spotted fever group rickettsial infections" and "Clinical features, diagnosis, and management of relapsing fever".)

- Group A *Streptococcus* – Clinical manifestations of group A *Streptococcus* infection include fever, myalgia, cutaneous manifestations (cellulitis, fascitis), pharyngitis, and shock. The diagnosis established by positive cultures from the blood or other tissues. (See "Group A streptococcal (Streptococcus pyogenes) bacteremia in adults".)

DIAGNOSIS — The approach to Zika virus diagnosis may vary depending on available resources; the approach outlined in the following sections may need to be tailored to local circumstances.

General approach — The diagnosis of Zika virus infection should be suspected in individuals with relevant epidemiologic exposure (residence in or travel to an area where the *Aedes* mosquito is present and where imported or local cases have been reported within two weeks prior to onset of illness, or unprotected sexual contact with a person who meets these criteria) and characteristic clinical symptoms (two or more of the following):

- Low-grade fever (37.8 to 38.5°C)
- Maculopapular rash
- Arthralgia (notably the small joints of hands and feet)
- Conjunctivitis (nonpurulent)

For nonpregnant patients residing in areas where mosquito transmission has been established, the diagnosis of Zika virus infection may be suggested based on symptoms and signs, although differentiation from other illnesses with similar clinical manifestations (eg, dengue, chikungunya) may not be possible [59].

For nonpregnant patients residing in areas where mosquito transmission has **not** been established and laboratory testing is available, diagnostic testing is warranted for individuals with characteristic symptoms and signs and relevant epidemiologic exposure.

The approach to diagnostic evaluation of pregnant women and infants is discussed below. (See 'Pregnant women' below and 'Prenatal fetal evaluation' below and 'Postnatal evaluation for possible congenital infection' below.)

The diagnosis of Zika virus infection is definitively established via reverse-transcription polymerase chain reaction (RT-PCR) for Zika viral RNA or Zika virus serology [1,2,60,61]:

- Within the first seven days after onset of symptoms, the diagnosis of Zika virus infection may be established via RT-PCR of serum for detection of Zika virus RNA. RT-PCR is positive only for a brief window (three to seven days) when the infected person has viremia; therefore, negative results cannot exclude infection. RT-PCR testing for dengue virus and chikungunya virus should also be pursued.

- Four or more days after the onset of symptoms or in asymptomatic pregnant women, the diagnosis of Zika virus infection may be established by Zika virus serologic testing (Zika virus IgM and neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum). Measuring virus-specific neutralizing antibodies is useful for discriminating between cross-reacting antibodies from other flavivirus infections; testing is considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers. Acute and convalescent sera should be obtained to detect an increased antibody titer in paired samples with an interval of two to three weeks. Serologic testing for dengue virus infection and chikungunya virus infection should also be pursued. All serologic results should be interpreted with caution since there can be cross-reactivity with other flaviviruses (including dengue virus and West Nile virus). Cross-reactivity may also be observed in individuals who have been vaccinated against yellow fever or Japanese encephalitis [62].

For patients presenting four to seven days after onset of symptoms, both RT-PCR and serology should be

performed [63]. Laboratory testing for asymptomatic pregnant women with Zika virus exposure should consist of serologic testing [63].

Laboratory testing for Zika virus infection is not commercially available; testing is performed by the Pan American Health Organization/World Health Organization, the United States Centers for Disease Control and Prevention (CDC) Arboviral Diagnostic Laboratory, and some state health departments.

In the United States, state health departments should be contacted to facilitate diagnostic testing for Zika virus infection. Laboratory specimens may also be sent to the CDC Arboviral Diagnostic Laboratory; instructions are available online. Communication should be initiated with the laboratory via telephone (1-970-221-6400) prior to shipment of specimens.

Local health departments can help with laboratory testing as well as facilitate mitigation of transmission risk. (See 'Prevention' below.)

Issues related to diagnosis of dengue virus and chikungunya virus are discussed separately. (See "Clinical manifestations and diagnosis of dengue virus infection" and "Chikungunya fever", section on 'Diagnosis'.)

Pregnant women

Areas with no mosquito transmission — In areas with no mosquito-borne Zika virus transmission, healthcare providers should ask pregnant women about relevant epidemiologic exposure (residence in or travel to an area where mosquito-borne transmission of Zika virus infection has been reported, or unprotected sexual contact with a person who meets these criteria).

Pregnant women with relevant epidemiologic exposure should undergo laboratory testing for Zika virus infection, within 2 to 12 weeks following exposure [2,63]. The approach to laboratory testing depends on whether the patient reports clinical illness consistent with Zika virus infection (presence of two or more symptoms consistent with Zika virus infection [acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis] during or within two weeks of exposure). Laboratory testing for Zika virus infection is not indicated for pregnant women with no Zika virus exposure [2]. (See 'General approach' above.)

Interpretation of serologic test results for asymptomatic pregnant women with Zika virus exposure is complex, given cross-reactivity among related flaviviruses. However, a negative IgM result obtained 2 to 12 weeks following exposure suggests that a recent infection did not occur [63].

Pregnant women with positive/inconclusive Zika virus laboratory testing should undergo further evaluation for presence of intrauterine infection as discussed below. (See 'Prenatal fetal evaluation' below.)

Pregnant women with negative Zika virus laboratory testing should undergo ultrasonography to evaluate for presence of fetal microcephaly or intracranial calcifications. In general, microcephaly as an isolated finding is difficult to diagnose before the third trimester. Intracranial calcifications are sometimes evident in the second trimester but more often in the third trimester. Findings of fetal microcephaly or intracranial calcifications on prenatal ultrasound should prompt repeat maternal serologic testing and consideration of amniocentesis. (See 'Prenatal fetal evaluation' below.)

Pregnant women with negative Zika virus laboratory testing and no ultrasound findings of microcephaly or intracranial calcifications should have routine prenatal care.

Areas with mosquito transmission — In areas with mosquito-borne Zika virus transmission, pregnant women have ongoing risk for infection throughout pregnancy. The diagnostic approach may need to be tailored to local circumstances including levels of Zika virus transmission and available resources.

For pregnant women with clinical illness consistent with Zika virus infection (presence of two or more symptoms consistent with Zika virus infection: acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis), laboratory testing with RT-PCR is warranted during the first week of illness [63] (see 'General approach' above).

For asymptomatic pregnant women, serologic testing is warranted at the initiation of prenatal care; women who have negative initial serologic test results may have repeat serologic testing in the mid-second trimester [63]. Interpretation of serologic testing may be difficult; false-positive Zika serologic test results can occur given the possibility of prior exposure to related flaviviruses. (See 'General approach' above.)

Pregnant women with positive/inconclusive Zika virus laboratory testing should undergo further evaluation for presence of intrauterine infection as discussed below. (See 'Prenatal fetal evaluation' below.)

Pregnant women with negative Zika virus laboratory testing should undergo ultrasonography to evaluate for presence of fetal microcephaly or intracranial calcifications. This testing may be done at 18 to 20 weeks for asymptomatic patients or sooner for patients with clinical illness consistent with Zika virus infection [63]. In general, microcephaly as an isolated finding is difficult to diagnose before the third trimester. Intracranial calcifications are sometimes evident in the second trimester but more often in the third trimester. Findings of fetal microcephaly or intracranial calcifications on prenatal ultrasound should prompt repeat maternal serologic testing and consideration of amniocentesis. In the absence of such findings, routine prenatal care should be continued, with consideration of a repeat ultrasound later in pregnancy. (See 'Prenatal fetal evaluation' below.)

Prenatal fetal evaluation — Tools for prenatal fetal evaluation for Zika virus infection include serial ultrasound examinations and amniocentesis.

Serial ultrasonography (every three to four weeks) is appropriate (with focus on evaluation for microcephaly or intracranial calcifications) for pregnant women with positive or inconclusive laboratory test results for Zika virus infection [6,53]. Ultrasound findings associated with Zika virus infection may be detected as early as 18 to 20 weeks gestation; however, detection can be challenging due to fetal position and fetal motion artifact [41,62,64]. Fetal ultrasound findings may include lower-than-expected head circumference for time of gestation (eg, more than two standard deviations below the mean), focal brain abnormalities in areas such as the cerebellum, and intraocular and brain calcifications [41]. (See "Microcephaly in infants and children: Etiology and evaluation", section on 'Prenatal evaluation' and "Ultrasound examination in obstetrics and gynecology".)

It has been suggested that amniocentesis for Zika virus RT-PCR testing be offered to women at ≥15 weeks gestation with history of Zika virus exposure and positive/inconclusive laboratory testing for Zika virus infection and that amniocentesis be considered for those with ultrasound findings of fetal microcephaly or intracranial calcifications (even in the setting of negative laboratory tests for Zika virus infection) [2]. Amniocentesis may also be useful in the setting of ventriculomegaly (which has been associated with Zika virus infection as well as congenital CMV infection). (See "Fetal cerebral ventriculomegaly" and "Microcephaly in infants and children: Etiology and evaluation".)

The sensitivity and specificity of Zika virus RT-PCR testing of amniotic fluid for diagnosis of congenital infection are not known [29]. It is unknown whether a positive amniotic fluid RT-PCR result is predictive of a subsequent fetal abnormality, and, if so, what proportion of infants born after infection will have abnormalities. The duration of amniotic fluid PCR positivity is also unknown [53]. A positive RT-PCR result on amniotic fluid should be considered suggestive of intrauterine infection [2]; such a result may be useful to guide timing of delivery and level of neonatal care at the delivery site [62]. A negative RT-PCR result on amniotic fluid may prompt evaluation for other causes of fetal microcephaly or intracranial calcifications [62]. Issues related to diagnostic amniocentesis are discussed further separately. (See "Diagnostic amniocentesis".)

Postnatal evaluation for possible congenital infection — The approach to diagnostic evaluation for congenital Zika virus infection may vary depending on available resources; where necessary, the approach outlined in the following sections may need to be tailored to local circumstances.

Live infants — All newborns should undergo thorough evaluation within 24 hours of birth. (See "Assessment of the newborn infant".)

For the purpose of evaluating an infant for possible congenital Zika virus infection, microcephaly is defined as

occipitofrontal circumference greater than two standard deviations below the mean or less than the third percentile based on standard growth charts for sex, age, and gestational age at birth [65,66]. To establish a diagnosis of microcephaly, the occipitofrontal circumference should be disproportionately small in comparison with the length of the infant and not explained by other etiologies or congenital disorders. If an infant's occipitofrontal circumference is equal to or greater than the third percentile but is notably disproportionate to the length of the infant, or if the infant has deficits related to the central nervous system, additional evaluation for Zika virus infection may also be appropriate.

Laboratory testing — Infants who warrant Zika virus laboratory testing include [67]:

- Infants with microcephaly or intracranial calcifications born to women with Zika virus exposure
- Infants born to mothers with positive or inconclusive laboratory test results for Zika virus infection (see 'Pregnant women' above)

The approach to laboratory testing of infants (in either of the above categories) for Zika virus infection includes the following [67]:

- Test infant serum for Zika virus RNA (via RT-PCR) as well as Zika virus IgM and neutralizing antibodies. In addition, test for dengue virus IgM and neutralizing antibodies to discriminate between cross-reacting antibodies. The initial sample should be collected from the umbilical cord or directly from the infant within two days of birth, if possible.
- If infant cerebrospinal fluid (CSF) is available, test CSF for Zika virus RNA (via RT-PCR) as well as Zika virus IgM and neutralizing antibodies. In addition, test for dengue virus IgM and neutralizing antibodies to discriminate between cross-reacting antibodies. CSF specimens need not be collected for the sole purpose of Zika virus testing [68] but may be reasonable for evaluation of infants with microcephaly or intracranial calcifications.
- Consider histopathologic examination of the placenta and umbilical cord, with Zika virus immunohistochemical staining on fixed tissue and Zika virus RNA (via RT-PCR) on fixed and frozen tissue.
- If not already performed during pregnancy, test maternal serum for Zika virus IgM and neutralizing antibodies and dengue virus IgM and neutralizing antibodies. (See 'General approach' above.)

Congenital infection is defined as the presence of Zika virus RNA in any of the samples collected, including amniotic fluid, placenta, umbilical cord, serum, or CSF [67]. In addition, congenital infection may be established by the presence of Zika virus IgM antibodies in the infant serum or CSF, with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers. Test results are inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

Presence of microcephaly or intracranial calcifications — An infant with microcephaly or intracranial calcifications born to a mother who was potentially infected with Zika virus during pregnancy should be tested for Zika virus infection as outlined above (see 'Laboratory testing' above). In addition, the infant should undergo further clinical evaluation as summarized in the Table (table 2). This evaluation should include an ophthalmologic evaluation (including retina examination) and a hearing evaluation in the first month of life [50].

An infant with positive or inconclusive test results for Zika virus infection should have additional assessment for possible long-term sequelae [65]. This includes conducting a repeat hearing screen at age six months (even if baseline hearing screen was normal because of potential for delayed hearing loss) plus appropriate follow-up of hearing abnormalities detected though newborn hearing screening. In addition, the infant should undergo careful evaluation of occipitofrontal circumference and developmental milestones throughout the first year of life, with appropriate consultation with medical specialists as needed.

An infant with microcephaly or intracranial calcifications and negative results on all laboratory Zika virus tests should be evaluated for alternative etiologies of these findings. (See "Microcephaly in infants and children: Etiology

and evaluation" and "Overview of TORCH infections".)

Absence of microcephaly or intracranial calcifications — Further evaluation of an infant without microcephaly or intracranial calcifications born to a mother potentially infected with Zika virus during pregnancy depends on the results from maternal Zika virus testing [67].

An infant with no microcephaly or intracranial calcifications whose mother had negative laboratory test results for Zika virus infection should receive routine care.

An infant with no microcephaly or intracranial calcifications whose mother had positive or inconclusive laboratory test results for Zika virus infection should be tested for Zika virus infection as outlined above (see 'Laboratory testing' above):

- If all of the infant's laboratory test results are negative for Zika virus infection, the infant should receive routine care.
- If any of the infant's laboratory test results are positive or inconclusive, the infant should undergo further clinical evaluation as summarized in the Table (table 2). In addition, the infant should be assessed for possible long-term sequelae; this includes conducting a repeat hearing screen at age six months as well as careful evaluation of occipitofrontal circumference and developmental milestones throughout the first year of life.

Fetal losses — Fetal tissue testing is warranted for fetal losses in women with history of Zika exposure, together with either symptoms consistent with Zika virus infection during or within two weeks of exposure **or** findings of fetal microcephaly. In such cases, Zika virus RT-PCR and histopathologic examination with immunohistochemical staining should be performed on fetal tissues, including the umbilical cord and placenta [2].

MANAGEMENT — There is no specific treatment for Zika virus infection. Management consists of rest and symptomatic treatment including drinking fluids to prevent dehydration and administration of acetaminophen to relieve fever and pain [69]. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDS) should be avoided until dengue infection has been ruled out, to reduce the risk of hemorrhage.

Issues related to evaluation and monitoring of pregnant women and infants are discussed above. (See 'Pregnant women' above and 'Prenatal fetal evaluation' above and 'Postnatal evaluation for possible congenital infection' above.)

PREVENTION — There is no vaccine for prevention of Zika virus infection. Modes of transmission are described above. (See 'Transmission' above.)

Individuals in areas with risk for transmission should take measures to avoid mosquito bites including personal protection as well as environmental control measures [22].

Personal protective measures include:

- Preventing mosquito bites by wearing long sleeves and long pants, using insect repellent, and staying indoors as feasible (with air conditioning, window/door screens, and/or mosquito nets to minimize contact between mosquitoes and people). (See "Prevention of arthropod and insect bites: Repellents and other measures".)
- Individuals with Zika virus infection may reduce spread of infection to others by following the same precautions to avoid mosquito bites during the first week of illness.

Environmental control measures include identification and elimination of potential mosquito breeding sites. Mosquito larvae breed in standing water; therefore, residents should be instructed to avoid allowing standing water to collect outdoors (such as in flower pots, buckets, bottles, jars, and other similar containers near houses). Domestic water tanks should be covered so that mosquitoes cannot enter, and drains that allow stagnant or standing water should be eliminated. Local and district health departments can help facilitate mitigation of

transmission risk. (See "Malaria in endemic areas: Epidemiology, prevention, and control", section on 'Mosquito vector control'.)

Pregnant women should seek routine prenatal care. In addition, pregnant women in areas with mosquito transmission of Zika virus infection should be particularly careful regarding adherence to mosquito protective measures, including use of insect repellant. Pregnant women outside areas with mosquito transmission should be cautious about travel to areas where transmission of Zika virus and other mosquito-borne viruses is high; in January 2016, the United States Centers for Disease Control and Prevention (CDC) and the European Centre for Prevention and Control (ECDC) advised that pregnant women consider postponing travel to any area where Zika virus transmission is ongoing [1,8,9].

Transmission of Zika virus through breastfeeding has not yet been described; further study is needed. Some have recommended that women continue to breastfeed [53,70]. Thus far, no developmental complications have been observed in otherwise healthy neonates, infants, or children with postnatal Zika virus infection or exposure; further study is needed.

It is uncertain how long women of childbearing potential should wait between Zika virus exposure/infection and conception. Zika virus usually remains in the blood of an infected person for a few days to a week, and thus far there is no evidence that a fetus conceived after the virus is cleared from the blood would be at risk for Zika infection [63,71]. However, information regarding the persistence of Zika virus following infection is not known. It has been suggested that infection due to other flaviviruses such as West Nile virus may persist years after initial infection [72-74]; these data are controversial. Pending further study, healthcare providers should encourage women to make such decisions based on their individual circumstances, values, and preferences. (See "The preconception office visit" and "Overview of contraception".)

Anecdotal reports of apparent sexual transmission have been described, although this appears to be an infrequent mechanism for virus transmission. Information regarding the persistence of the virus at different sites following infection is not yet available. Pending further study, it may be prudent for individuals with Zika virus infection/exposure to abstain from sexual activity (vaginal, anal, and oral sex) or use barrier protection; men who have a pregnant partner should follow such guidance for the duration of the pregnancy [75,76]. (See "Male condoms", section on 'Instructions for use'.)

Zika virus is transmissible via blood products [34]. Self-deferral of blood donors for one month following Zika virus infection/exposure is advised [77]. Individuals who have donated blood and subsequently develop symptoms consistent with Zika virus infection within 14 days should notify the donation site so the product can be quarantined [78]. Issues related to blood donor screening are discussed further separately. (See "Blood donor screening: Medical history" and "Blood donor screening: Laboratory testing".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient information: Zika virus infection (The Basics)")

SUMMARY

- Outbreaks of Zika virus infection, caused by an emerging mosquito-borne flavivirus, have occurred in Africa,

Southeast Asia, and the Pacific Islands; currently, there is an ongoing Zika virus outbreak in the Americas. Zika virus is transmitted to humans via the bite of an infected *Aedes* mosquito. This type of mosquito usually bites during the daytime and breeds in standing water. (See 'Epidemiology' above.)

- Clinical manifestations of Zika virus infection include acute onset of low-grade fever with maculopapular rash, arthralgia (notably small joints of hands and feet), or conjunctivitis (nonpurulent); clinical illness is consistent with Zika virus disease if two or more of these symptoms are present. Zika virus infection has also been associated with congenital microcephaly, fetal loss, and Guillain-Barré syndrome. (See 'Clinical manifestations' above.)

- Symptoms and signs typically occur 2 to 12 days after the mosquito vector bite. The illness is usually mild; clinical manifestations usually resolve within two to seven days. Asymptomatic infection is common; symptoms develop in 20 to 25 percent of individuals who become infected with Zika virus. Once a person has been infected, he or she is likely to be protected from future infections. (See 'Symptoms and signs' above.)

- The diagnosis of Zika virus infection should be suspected in individuals with typical clinical manifestations and relevant epidemiologic exposure (residence in or travel to an area where the *Aedes* mosquito is present and where imported or local cases have been reported, or unprotected sexual contact with a person who meets these criteria). (See 'Diagnosis' above.)

- The diagnosis of Zika virus infection is established via serum reverse-transcription polymerase chain reaction (RT-PCR) testing or serology. Within the first seven days following onset of symptoms, the diagnosis may be established via serum RT-PCR for detection of Zika viral RNA. Four or more days after the onset of symptoms, the diagnosis may be established via Zika virus serologic testing. (See 'Diagnosis' above.)

- Pregnant women with Zika virus exposure should undergo laboratory testing for Zika virus infection and ultrasonography to evaluate for presence of fetal microcephaly or intracranial calcifications. (See 'Pregnant women' above.)

- Tools for evaluation of intrauterine infection in pregnant women with positive or inconclusive Zika laboratory test results include serial ultrasonography (every three to four weeks to evaluate for microcephaly or intracranial calcifications) and amniocentesis. (See 'Prenatal fetal evaluation' above.)

- Indications for Zika virus laboratory testing of infants include (see 'Postnatal evaluation for possible congenital infection' above):

    - Infants with microcephaly or intracranial calcifications born to women with Zika virus exposure while pregnant

    - Infants born to mothers with positive or inconclusive laboratory test results for Zika virus infection

- An infant with microcephaly or intracranial calcifications born to a mother who was potentially infected with Zika virus during pregnancy should undergo further clinical evaluation as summarized in the Table (table 2). In addition, an infant with positive or inconclusive test results for Zika virus infection should be assessed for possible long-term sequelae as described above. (See 'Presence of microcephaly or intracranial calcifications' above.)

- There is no specific treatment for Zika virus infection and there is no vaccine for prevention. Management consists of symptomatic treatment. Preventive measures include personal protective measures to prevent mosquito bites and institution of measures to eliminate and control mosquito breeding sites. (See 'Management' above and 'Prevention' above.)

- Pregnant women should be particularly careful regarding adherence to mosquito protective measures and about traveling to areas where transmission of Zika virus is high. In January 2016, the United States Centers for Disease Control and Prevention and the European Centre for Prevention and Control advised that

pregnant women consider postponing travel to any area where Zika virus transmission is ongoing. (See 'Prevention' above.)

- Sexual transmission of Zika virus has been described; further study is needed. It may be prudent for individuals with Zika virus infection/exposure to abstain from sexual activity (vaginal, anal, and oral sex) or use barrier protection; men who have a pregnant partner should follow such guidance for the duration of the pregnancy. (See 'Prevention' above.)

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Topic 106169 Version 20.0

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