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### Zika Virus Today

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**Background:** Zika virus identified in 1940s; human cases reported in 1950s; organism resembles dengue, West Nile virus, yellow fever, and Japanese encephalitis; outbreaks occurred in 2000s in French Polynesia; sporting events in Brazil in 2014 probably not source of virus; autochthonous (vector-transmitted) Zika virus first reported in Brazil in May 2015; increase in rate of microcephaly reported in September 2015; in November 2015, Pan American Health Organization, World Health Organization (WHO), and European Centre for Disease Prevention and Control issued warnings about Zika virus and potential link to microcephaly; in January 2016, United States Centers for Disease Control and Prevention (CDC) issued travel precautions; on February 1, 2016, WHO issued Public Health Emergency of International Concern

**Epidemiology:** Zika virus transmitted primarily by *Aedes* species mosquito; mosquitoes bite during day and at night; mosquitoes attracted by standing water, and more common in nondeveloped areas than in developed areas; 11 cases of sexual transmission of Zika virus reported; virus may be transmitted via blood transfusion or transplantation

**Zika in United States:** requisite mosquito more common in southern and eastern United States and Hawaii; transmission of Zika virus possible in United States, but likelihood decreased due to good public health system and effective vector control

**Presentation:** 80% of infected individuals asymptomatic; symptoms include rash, conjunctivitis, arthralgia, and myalgia; symptoms appear 7 days after exposure and last 4 to 5 days

**Differential diagnosis:** presentation resembles that of other vector-borne illnesses, including chikungunya; Guillain-Barré syndrome associated with Zika virus

**United States:** 195 pregnant women in United States being followed for suspected exposure; if Zika virus reaches United States, uptick expected in summertime

**Congenital Zika syndrome:** manifestations include microcephaly, intracranial calcifications, ventriculomegaly, ophthalmologic abnormalities, intrauterine growth restriction (IUGR), and intrauterine fetal demise (IUFD); microcephaly not unique to Zika virus infection (more commonly associated with cytomegalovirus infection and alcohol abuse); microcephaly defined as head circumference (HC) <2 standard deviations (SDs) below mean; microcephaly may be suspected and diagnosed prenatally, but often diagnosed at birth; associated findings include seizures, intellectual and motor disability, behavioral problems, and neurologic compromise; evidence for congenital Zika syndrome growing

**Epidemiologic evidence:** baseline rate of microcephaly in Brazil 5 to 6 per 100,000 births in early 2000s; rates of microcephaly have increased since autochthonous spread of

Zika virus reported; observed increase in infections probably not due to increased surveillance; reevaluation of Polynesian epidemic showed significant increase in microcephaly  
**Biologic evidence:** 5 key pieces of evidence indicate that Zika virus infection can cause fetal injury; Zika virus neurotropic (preferentially infects nerve progenitor cells); cells infected in vitro show apoptosis; Zika viral receptors identified in every maternal-fetal compartment (clear pathways identified that allow virus to reach fetus); proteins needed by virus to enter various fetal compartments identified; effect of virus on nerve cells and brain demonstrated in mice and primates

**Clinical evidence: case reports**—include asymptomatic and symptomatic mothers, and women living in and traveling to affected areas; manifestations include IUGR, microcephaly, intraocular findings, and IUFD; virus identified in abortuses and amniotic fluid; in newborns, virus identified in serum, urine, and tissue of central nervous system; *Brazilian case series*—included 88 women presenting with rash, of whom 72 tested positive for Zika virus; 2 women miscarried; among 42 women with follow-up data, 2 had IUFD (these women infected at 25 and 32 wk gestation, and delivered fetuses with significant abnormalities consistent with fetal infection with Zika virus); 29% had abnormal ultrasonography; findings included microcephaly, cerebral calcifications, other findings in brain, and IUGR; report included 8 delivered infants (including 2 described above); 2 delivered alive and well; 1 had microcephaly, cerebral calcifications, and other abnormalities of brain; another born early with IUGR and microcephaly; 1 child had severe IUGR and remained in intensive care at time of reporting; *most recent case series published*—included 31 infants with microcephaly in northeastern Brazil; report showed high rates of Zika positivity in these infants

**Criteria for teratogenicity:** Shepard criteria for teratogenicity require proven prenatal exposure, strong epidemiologic evidence, careful delineation of cases, association between rare exposure and rare defect, teratogenicity in experimental models, and biologic plausibility; Zika virus meets each of these criteria

**Addressing concerns:** clinician should determine whether pregnant patient infected and whether fetus infected; if fetus infected, clinician should determine extent of effect and when additional information can be obtained

**Infection in mother:** strategies for assessing maternal infection evolving; for asymptomatic pregnant women who have traveled to areas in which transmission of the Zika virus has been documented, anti-Zika immunoglobulin (IgM) should be measured 2 to 12 wk after return; for symptomatic, pregnant travelers within 7- to 14-day window, clinician should order reverse transcription polymerase chain reaction test of blood or urine and look for anti-Zika virus IgM; recent studies suggest that urine test may be superior to blood test; for unprotected sexual partner of symptomatic traveler, anti-Zika virus IgM should be tested; cross-reactivity possible with similar viruses such as dengue and chikungunya;

obtain history of exposure and vaccination; these tests currently being performed by public health departments (testing not available from commercial sources); IgM and IgG testing likely to become widely available soon; genetic and rapid testing under study

**Infection in fetus:** tools for detection include amniocentesis, ultrasonography, and magnetic resonance imaging (MRI); *amniocentesis*—imperfect but may be discussed with woman with history of exposure and likely infection; however, sensitivity of test and time frame within which amniocentesis likely to be positive unknown; rate of infection in fetuses of pregnant mothers with either positive or negative amniocentesis results unknown; therefore, amniocentesis not best tool; *ultrasonography*—also imperfect, but probably most useful; examiner should look for microcephaly and other findings in brain; microcephaly difficult to diagnose prenatally; microcephaly should be suspected if HC 2 SDs below mean and diagnosed if HC 4 to 5 SDs below mean; unless head profoundly small on ultrasonography, fetus likely to be normal; ultrasonographic findings often subtle; ultrasonography recommended in women who test positive for Zika virus and possibly in women with likely exposure to virus who have not undergone testing; women who have not traveled to endemic areas do not require surveillance ultrasonography; if partner traveled but had no symptoms, follow-up ultrasonography probably not indicated; women who test negative for anti-Zika IgM within 12 wk of travel do not require ultrasonography; *MRI*—may be useful for examining fetal brain, but not always available; fetuses with infection often not identified until late in third trimester

**Screening and counseling:** clinician should ask patients about travel; screening performed according to CDC recommendations; ultrasonography should be performed when indicated; pregnant women should avoid travel if possible; if travel in endemic areas unavoidable, risks and benefits should be discussed; patient should use mosquito repellent and protective clothing; if partner exposed, condoms should

be used; counseling should acknowledge uncertainties; in patients at high risk or with obvious findings, choices include expectant management or termination of pregnancy; expectant management includes serial ultrasonography and antenatal testing; clinician should provide resources, counseling, and support; providers may advocate funding and policy changes to support vaccine development, vector control, education, family planning, surveillance, and support for affected families; abortion inaccessible in some areas of United States and illegal in much of South America

**Summary:** congenital Zika syndrome real and may be associated with serious consequences; previous infection with Zika virus protective; as increasing number of individuals exposed and become immune, Zika virus may become less problematic; likelihood that fetus of infected mother will also become infected undetermined, but estimated to be 1% to 5%; long-term outcomes of neurologic injuries caused by Zika virus infection undetermined; ameliorating and exacerbating factors undetermined; critical windows during pregnancy undetermined (fetus may be at risk throughout pregnancy); exposure should be avoided before and during pregnancy

### *Suggested Reading*

**Bahado-Singh RO et al:** Zika virus and pregnancy. *J Matern Fetal Neonatal Med* 2016 Jun 10;1-2 [Epub ahead of print]; **Cavalheiro S et al:** Microcephaly and Zika virus: neonatal neuroradiological aspects. *Childs Nerv Syst* 2016 Jun;32(6):1057-60; **Citil Dogan A et al:** The Zika virus and pregnancy: evidence, management, and prevention. *J Matern Fetal Neonatal Med* 2016 Jun 17:1-11 [Epub ahead of print]; **De Carvalho NS et al:** Zika virus infection during pregnancy and microcephaly occurrence: a review of literature and Brazilian data. *Braz J Infect Dis* 2016 May-Jun;20(3):282-9; **Gostin LO, Hodge JG Jr:** Is the United States prepared for a major Zika virus outbreak? *JAMA* 2016 Jun 14;315(22):2395-6; **Jin J:** Zika virus disease. *JAMA* 2016 Jun 14;315(22):2482; **Kirtley S:** Zika virus in pregnancy: where to find useful guidance. *BJOG* 2016 Jul;123(8):1256-7; **Wikan N, Smith DR:** Zika virus: history of a newly emerging arbovirus. *Lancet Infect Dis* 2016 Jul;16(7):e119-26.