Zika Virus Disease: A CDC Update for Pediatric Health Care Providers

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Zika virus is a mosquito-borne flavivirus discovered in Africa in 1947. Most persons with Zika virus infection are asymptomatic; symptoms when present are generally mild and include fever, maculopapular rash, arthralgia, and conjunctivitis. Since early 2015, Zika virus has spread rapidly through the Americas, with local transmission identified in 31 countries and territories as of February 29, 2016, including several US territories. All age groups are susceptible to Zika virus infection, including children. Maternal–fetal transmission of Zika virus has been documented; evidence suggests that congenital Zika virus infection is associated with microcephaly and other adverse pregnancy and infant outcomes. Perinatal transmission has been reported in 2 cases; 1 was asymptomatic, and the other had thrombocytopenia and a rash. Based on limited information, Zika virus infection in children is mild, similar to that in adults. The long-term sequelae of congenital, perinatal, and pediatric Zika virus infection are largely unknown. No vaccine to prevent Zika virus infection is available, and treatment is supportive. The primary means of preventing Zika virus infection is prevention of mosquito bites in areas with local Zika virus transmission. Given the possibility of limited local transmission of Zika virus in the continental United States and frequent travel from affected countries to the United States, US pediatric health care providers need to be familiar with Zika virus infection. This article reviews the Zika virus, its epidemiologic characteristics, clinical presentation, laboratory testing, treatment, and prevention to assist providers in the evaluation and management of children with possible Zika virus infection.

abstract

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Zika virus is a mosquito-borne virus in the *Flavivirus* genus that is closely related to dengue, West Nile, and yellow fever viruses. After its discovery in 1947,[1] Zika virus was known to cause sporadic cases of mild, self-limited illness in persons living in Africa and Asia. The first widespread outbreak of Zika virus infection was recognized on Yap Island, Federated States of Micronesia, in 2007[2]; outbreaks in Southeast Asia and the western Pacific followed, including a large outbreak in French Polynesia in 2013–2014.[3] The virus in the French Polynesia outbreak has been phylogenetically linked to the virus that emerged in Brazil in May 2015,[4] when the first local transmission of Zika virus in the Americas was reported.[5] Zika virus quickly spread throughout the country, with an estimated 440 000 to 1 300 000 suspected cases by the end of 2015.[6] In October 2015, the Brazilian Ministry of Health reported increasing numbers of infants born with microcephaly.[7] From October 2015 through February 2016, >5000 infants with suspected microcephaly had been reported,

with confirmation of microcephaly in about one-third of the first 1300 infants who underwent evaluation.[8] Guillain-Barré syndrome has also been described in conjunction with Zika virus infection.[9] Although there is increasing supportive evidence, a causal relationship has not yet been established between Zika virus infection and either microcephaly or Guillain-Barré syndrome.

Given the widespread nature of the Zika virus epidemic in the Americas, the temporally associated increase in microcephaly and Guillain-Barré syndrome in Brazil, and the retrospective findings of a cluster of microcephaly and neurologic disorders associated with Zika virus in French Polynesia, the World Health Organization declared Zika virus a Public Health Emergency of International Concern on February 1, 2016.[10] Local transmission was reported in 31 countries and territories in the Americas as of February 29, 2016, including some US territories.[11] Based on the distributions of its primary mosquito vector, *Aedes aegypti*, and another possible vector, *Aedes albopictus*, local Zika virus transmission is possible in the continental United States.[12]

Because Zika virus transmission has been documented in many countries, pediatric health care providers in the United States are likely to become involved in the evaluation and management of infants and children with possible Zika virus infection as well as discussions regarding its prevention. To assist pediatric providers, the present article reviews information on Zika virus, its epidemiologic characteristics, clinical presentation in children, laboratory testing, treatment, and methods of prevention.

ZIKA VIRUS

Vectors

Humans and nonhuman primates are the likely principal vertebrate hosts for Zika virus, which is primarily transmitted to humans through the bite of mosquitoes, most commonly *Aedes aegypti* and possibly *Aedes albopictus*.[12] Within the continental United States, these *Aedes* species are primarily found in the South, Midwest, and the Great Plains, with small pockets in the Southwest and California (http://www.cdc.gov/chikungunya/resources/vector-control.html). *Aedes* species mosquitoes are aggressive daytime feeders. They live in and around human households, are difficult to eradicate, and are able to reproduce in small water containers.[13]

Routes of Transmission

Although mosquito-borne transmission is the main route of exposure, Zika virus infection has also been reported to occur via laboratory exposure[14] and sexual transmission.[15] Maternal–fetal transmission during pregnancy has been well documented,[16–22] and intrapartum transmission has also been reported.[23] Other flaviviruses have been transmitted via breast milk,[24–26] but no cases of Zika virus infection associated with breastfeeding have been reported. Zika virus RNA can be present in breast milk.[23]However, based on current evidence, the potential risk of Zika virus transmission through breast milk is outweighed by the known benefits of breastfeeding.[27] Although Zika virus RNA has been found in saliva[28] and urine,[29] no evidence exists that Zika virus can be transmitted through these routes.

Zika Virus Infection

Most persons with Zika virus infection are asymptomatic.[2] Among those with symptoms, the illness is generally mild and self-limited. Features most often observed include maculopapular rash, fever, arthralgia, and nonpurulent conjunctivitis; symptoms typically last several days to 1 week.[30] The incubation period for Zika virus in humans is unknown but is believed to be similar to that of other flaviviruses, in the range of 3 to 14 days.[31] All age groups are at risk for Zika virus infection; in the Yap Island outbreak, the attack rate for symptomatic Zika virus disease among children (<19 years of age) was lower than that for adults.[2]

CLINICAL FEATURES

Fetal

Although maternal–fetal transmission of Zika virus during pregnancy has been documented,[18–22] the incidence of congenital Zika virus infection and the frequency of adverse outcomes among pregnancies infected with Zika virus are unknown. Although microcephaly is the adverse infant outcome for which there is the most evidence, information on the health effects associated with congenital Zika virus infection is limited. Since Zika virus emerged in Brazil, >5000 newborns with suspected microcephaly have been reported, although the number of cases is likely to be lower when a full investigation is completed.[8] Because no standard definition exists for microcephaly, monitoring its prevalence has been challenging; studies have used different cutoffs (>2 or 3 SDs below the mean for gestational age and gender or below the 3rd or 5th percentile).[32] The number of suspected cases with microcephaly reported to Brazil's Ministry of Health over recent months is markedly higher than the 150 to 200 cases per year previously reported.[33] Some have questioned whether this increase might be due to misdiagnosis related to different cutoffs or overreporting related to increased awareness of the possible association with Zika virus.[34] These questions have led investigators to call for standardized measurement of head circumference and use of appropriate growth standards to improve surveillance of microcephaly that might be associated with Zika virus.[32]

Congenital Zika virus infection has been confirmed by using reverse transcription polymerase chain reaction (RT-PCR) testing (amniotic fluid, placenta, fetal serum, fetal brain tissue, and fetal cerebrospinal fluid) or immunohistochemistry (placenta, fetal brain tissue, and products of conception) in 7 fetuses or infants with microcephaly, 3 early pregnancy losses, and 1 elective pregnancy termination (Table 1).[17–22] Among these fetuses and infants, other congenital anomalies identified on fetal ultrasound and MRI included brain atrophy and asymmetry, hydranencephaly, ventriculomegaly, cerebral calcifications, abnormally formed or absent brain structures (eg, corpus callosum, thalami, pons, cerebellar vermis, brainstem), bilateral cataracts, intraocular calcifications, and hydrops fetalis.[17, 19–22] In addition to microcephaly, postnatal examination findings included ophthalmologic (eg, microphthalmia, cataracts, optic nerve pallor, macular chorioretinitis) and neurologic (eg, arthrogryposis, hypertonia, dysphagia, seizures) abnormalities.[17,20–22] The autopsy of 1 infant revealed agyria, hydrocephalus, and multifocal calcifications in the cortex and subcortex.[19]

Pathologic analyses of some of the aforementioned infants and fetuses have provided insight into the pathogenesis of congenital Zika virus infection.[18,19] In 1 study, Zika virus RNA and antigens were detected on pathologic analysis of brain tissues from 2 newborns with microcephaly and in placental tissues from 2 early miscarriages.[18] In the newborns, detection of Zika virus RNA by RT-PCR and histopathologic changes of infection were limited to the brain. In another autopsy performed after a pregnancy termination, Zika virus, as evidenced by RT-PCR, immunofluorescence, and electron microscopy, was present only in the brain; no other fetal organs were affected.[19] Placental calcifications and a low placental–fetal weight ratio were also seen. These findings have led investigators to suggest that Zika virus is neurotropic and might also cause placental damage.

Reports of infants with suspected congenital Zika virus infection provide additional information (Table 2). Clinical information on the first 35 infants to be enrolled in the Brazilian Ministry of Health microcephaly registry was recently reported.[35] Although none of these infants underwent Zika virus testing, congenital Zika virus infection was suspected on the basis of all mothers residing in areas with local transmission and three-quarters reporting a rash during the first or second trimester of pregnancy. In addition to microcephaly, postnatal neuroimaging results revealed calcifications, ventriculomegaly, and neuronal migration disorders, and the infants had abnormal neurologic findings (eg, hypertonia, hyperreflexia, irritability, seizures). Findings of microcephaly, cortical and subcortical atrophy, and redundant scalp skin in some infants are suggestive of fetal brain disruption sequence, in which disruption of fetal brain growth leads to skull collapse.[36] Other findings included talipes and arthrogryposis, likely to be secondary to neurologic involvement. Ophthalmologic abnormalities (including chorioretinal atrophy, optic nerve hypoplasia and pallor, and lens subluxation) have been described in infants born with microcephaly who are suspected of having congenital Zika virus infection.[37–39]

Because information on infants with congenital Zika virus infection is limited, it is unclear whether other central nervous system manifestations beyond microcephaly might occur (eg, cognitive impairment in the absence of microcephaly or structural abnormalities). Furthermore, while Zika virus seems to exhibit neurotropism,[18,19] involvement of other organ systems cannot be excluded.

Vertical transmission of other flaviviruses seems to occur rarely; this transmission has not been associated with an increased risk for congenital anomalies. Although 1 infant born to a mother with West Nile virus encephalitis at 27 weeks' gestation had cerebral destruction and chorioretinitis,[40] rates of birth defects in a West Nile virus pregnancy registry were not significantly increased compared with baseline,[41] and a follow-up study suggested no adverse effects of West Nile virus on development.[42] Prenatal dengue virus infection does not seem to increase the risk for congenital anomalies.[43] Maternal–fetal transmission of other non-flavivirus infections (eg, rubella virus, cytomegalovirus, lymphocytic choriomeningitis virus, *Toxoplasma gondii*) has been associated with microcephaly.[44] Other manifestations of these congenital infections include various brain abnormalities (eg, intracranial calcifications, hydrocephalus), eye abnormalities (eg, cataracts, glaucoma, chorioretinitis), and hearing impairment.

Although no information on long-term outcomes of infants with microcephaly related to Zika virus infection is available, head circumference at birth generally reflects intrauterine brain growth. Based on microcephaly due to other causes, infants with severe microcephaly associated with Zika virus infection are likely to be at risk for long-term adverse outcomes, including seizures, cognitive impairment, and hearing and vision impairments.[45] Congenital microcephaly can be associated with prenatal exposure to other infectious and noninfectious (eg, alcohol, mercury) agents and with genetic conditions; evaluation for other

TABLE 1 Reports of Laboratory-Confirmed Congenital Zika Virus Infection Cases and Their Clinical Findings, Brazil and the United States, 2015–2016

Report Type, Location of Exposure	Birth Status and Infant Outcome	Maternal Signs/ Symptoms of Zika Virus Infection During Pregnancy	Zika Virus and Other Testing: Type of Specimens and Testing Method	Results of Histopathologic Evaluation, Autopsy, and Imaging Studies	Examination Findings
Case series; Rio Grande do Norte state, Brazil[18]	Live-born at 38 wk gestation, died within 20 h of birth	Fever and rash during first trimester	Zika virus testing: brain tissue sample RT-PCR positive in both infants and IHC positive in 1 infant	Histopathologic findings from infant specimens • Parenchymal calcification • Microglial nodules • Gliosis	• Congenital microcephaly
	Live-born at 36 wk gestation, died within 20 h of birth	Fever and rash during first trimester	Infant specimens negative for dengue virus	• Cell degeneration and necrosis	• Congenital microcephaly
	Pregnancy loss at 13 wk gestation	Fever and rash during first trimester	Zika virus testing: products of conception RT-PCR positive in both fetuses and chorionic villi IHC positive in 1 product of conception	Histopathologic findings from products of conception • Heterogeneous chorionic villi with calcification • Fibrosis • Perivillous fibrin deposition	• Not reported
	Pregnancy loss at 11 wk gestation	Fever and rash during first trimester	Maternal TORCH serology and HIV testing negative; fetal specimens negative for dengue virus	• Patchy intervillositis and focal villitis	• Not reported
Case series; Paraiba state, Brazil[17,20]	Live-born at 40 wk gestation	Fever, myalgia, and rash at 18 wk gestation	Zika virus testing: amniotic fluid RT-PCR positive Maternal TORCH serology, HIV, parvovirus B19, dengue virus, and chikungunya virus testing were negative	Fetal ultrasounds performed at 21, 27, 30, and 40 wk gestation • Microcephaly • Asymmetric cerebral hemispheres • Moderate ventriculomegaly • Brain atrophy with a hypoplastic cerebellum • Brain calcifications: frontal lobes, caudate nucleus, lentostriatal vessels, and cerebellum • Agenesis of the cerebellar vermis • Dysgenesis of the corpus callosum • Enlarged cisterna magna	• Congenital microcephaly, OFC of 30 cm
	Live-born at unknown gestational age	Fever, myalgia, and rash at 10 wk gestation	Zika virus testing: amniotic fluid RT-PCR positive. Maternal TORCH serology, HIV, parvovirus B19, dengue virus, and chikungunya virus test results were negative	Fetal ultrasounds performed at 22, 25, and 29 wk gestation • Microcephaly • Asymmetric cerebral hemispheres • Severe unilateral ventriculomegaly • Brain calcifications: periventricular • Agenesis of the corpus callosum and thalamus • Hypoplasia of the cerebellar vermis • Enlargement of the posterior fossa • Bilateral cataracts and intraocular calcifications	• Microphthalmia • Cataracts • Severe arthrogryposis of all extremities
Case report; Rio Grande de Norte state, Brazil[19]	Termination at 32 wk gestation	High fever, severe myalgia and headache, and rash at 13 wk gestation	Zika virus testing: brain tissue sample RT-PCR positive Autopsy samples negative for dengue, yellow fever, West Nile, tick-borne encephalitis, chikungunya, LCMV, CMV, rubella, varicella zoster, HSV, parvovirus B19, enteroviruses, and *Toxoplasma gondii*	Fetal ultrasound performed at 32 wk gestation • Intrauterine growth retardation • Placental calcifications • Microcephaly (<2nd percentile) • Moderate ventriculomegaly • Transcerebellar diameter <2nd percentile • Intracerebral calcifications Autopsy results • Almost complete agyria • Hydrocephalus • Multifocal dystrophic calcifications in the cortex and subcortical white matter • Cortical displacement • Mild focal inflammation	• Congenital microcephaly, 4 SDs below the mean for gender and gestational age

TABLE 1 Continued

Report Type, Location of Exposure	Birth Status and Infant Outcome	Maternal Signs/ Symptoms of Zika Virus Infection During Pregnancy	Zika Virus and Other Testing: Type of Specimens and Testing Method	Results of Histopathologic Evaluation, Autopsy, and Imaging Studies	Examination Findings
Case report; Salvador, Brazil[21]	Fetal death at 32 wk gestation, induced delivery	Asymptomatic	Zika virus testing: extracts of the cerebral cortex, medulla oblongata, CSF, and amniotic fluid RT-PCR positive Maternal HIV, HTLV, hepatitis C, rubella, *T gondii*, and CMV testing negative	Fetal ultrasounds performed at 14, 18, 26, and 30 wk gestation • Fetal weight 3 SDs less than the mean for gestational age • Microcephaly • Hydranencephaly • Intracranial calcifications • Destructive lesions of the posterior fossa • Hydrops fetalis (hydrothorax, ascites, subcutaneous edema)	• Congenital microcephaly • Arthrogryposis
Case series; Zika virus–affected areas[22]	Spontaneous pregnancy loss at 8 wk gestation	Fever, rash, arthralgia, myalgia, and malaise during travel at 5 wk gestation	Zika virus testing: products of conception RT-PCR positive and IHC positive Maternal Zika virus serology testing confirmed recent infection		
	Elective termination at ∼20 wk gestation	Fever, eye pain, myalgia, and rash after travel at 11–12 wk gestation	Zika virus testing: amniotic fluid RT-PCR positive Maternal Zika virus serology testing confirmed recent infection	Fetal ultrasound performed at 20 wk gestation • Absence of the corpus callosum • Ventriculomegaly • Brain atrophy Fetal MRI • Severe brain atrophy	
	Live-born at 39 wk gestation	Fever, rash, arthralgia, and headache while residing in Brazil at 7–8 wk gestation	Zika virus testing: placenta RT-PCR positive and IHC positive Maternal Zika virus serology testing confirmed recent infection	Postnatal computed tomography scan • Multiple scattered and periventricular brain calcifications	• Congenital microcephaly, OFC of 27 cm • Hypertonia • Dysphagia • Seizures • Pale optic nerve • Mild macular chorioretinitis

CMV, cytomegalovirus; CSF, cerebrospinal fluid; IHC, immunohistochemistry; HSV, herpes simplex virus; HTLV, human T-cell lymphotropic virus; LCMV, lymphocytic choriomeningitis; OFC, occipitofrontal circumference; TORCH, *Toxoplasma gondii*, rubella, cytomegalovirus, herpes simplex, and syphilis.

etiologies needs to be completed when congenital Zika virus infection is excluded.

Neonatal

To date, we are aware of 2 reports of presumed perinatally acquired Zika virus infection.[23] One mother developed pruritic rash 2 days before delivery; her infant remained asymptomatic. The second mother developed fever, myalgia, and pruritic rash 3 days after delivery; her infant developed thrombocytopenia and a transient rash 4 days after birth. Both mother–infant pairs tested positive for Zika virus RNA in serum postnatally and were discharged in good health. Both mothers were likely to have been viremic during labor, raising the possibility of intrapartum transmission. Postnatal transmission via breast milk or saliva was also possible, but transmission via these routes has not been reported in the literature.

Perinatal transmission of other flaviviruses has been associated with severe illness. Neonates who acquire dengue virus infection through presumed perinatal transmission have developed fever, thrombocytopenia, and hemorrhage.[43] A range of illness severity was seen among 3 infants with West Nile virus infection transmitted during the perinatal period (1 each with rash, West Nile virus encephalitis, and West Nile virus meningitis).[41] The spectrum of illness in neonates who acquire Zika virus perinatally is unknown.

Infant and Child

Although data are limited, most children infected with Zika virus through mosquito bites have been mildly affected or asymptomatic, similar to adults. During the Yap Island outbreak, among those with symptoms (age range, 1–76 years), fever, macular or papular rash, arthralgia, and conjunctivitis were most frequently observed. Six publications describe clinical features of Zika virus infection in 10 children ranging in age from 3 to 16 years

TABLE 2 Reports of Suspected Congenital Zika Virus Infection Cases and Their Clinical Findings, Brazil and French Polynesia, 2013–2016

Report Type, Location, and No. of Cases	Laboratory Testing	Maternal Signs/ Symptoms of Zika Virus Infection During pregnancy	Infant Neuroimaging Results	Infant Examination Findings (Percent Affected)		
				Birth Defects	Neurologic	Ophthalmologic
Case series; 8 states, Brazil; [35] 35 infants	No Zika testing Infants' TORCH serology testing negative	Rash during first trimester (57%) or second trimester (14%)	• Widespread brain calcifications (74%), mainly in the periventricular, parenchymal, and thalamic areas, as well as in the basal ganglia • Ventriculomegaly (44%) • Neuronal migration disorders (33%)	• Microcephaly, >2 SDs below the mean for gender and gestational age at birth (100%) • Excessive and redundant scalp skin (31%) • Clubfoot (14%) • Arthrogryposis (11%)	• Hypertonia or spasticity (37%) • Hyperreflexia (20%) • Irritability (20%) • Tremors (11%) • Seizures (9%)	• Abnormal funduscopic examination (18%)
Case series; Brazil; [37] 3 infants	No Zika testing Mothers' and infants' TORCH serology and HIV testing negative	Rash and arthralgia during first trimester (33%)	• Brain calcifications (100%)	• Microcephaly, OFC ≤28.5 cm at birth (100%)		• Loss of foveal reflex (100%) • Gross macular pigment mottling (100%) • Macular neuroretinal atrophy (33%)
Case series; Brazil; [38] 10 infants	No Zika testing Infants' TORCH serology and HIV testing negative	Malaise, rash, and/or arthralgia during first trimester (60%) or later in pregnancy (10%)	• Brain calcifications (100%)	• Microcephaly, >2 SDs below the mean for gender and age (100%)		• Loss of foveal reflex (100%) • Mild to gross macular pigment mottling (90%) • Chorioretinal macular atrophy (20%) • Optic nerve hypoplasia (40%) • Optic nerve pallor (20%) • Increased cup-to-disc ratio (30%)
Surveillance Report ; French-Polynesia; [33] 12 fetuses and 5 infants	No Zika testing	None Pregnancy coincided with a Zika virus outbreak		• Cerebral malformations or polymalformative syndromes (12 fetuses)	• Brainstem dysfunction and absence of swallowing (5 infants)	
Case series; Brazil; [39] 29 infants	No Zika testing Mothers' and infants' TORCH serology and HIV testing negative	Rash, fever, arthralgia, headache, and/ or pruritus during first (62%), second (14%), or third (3%) trimester		• Microcephaly, OFC ≤32 cm (100%)		• Focal pigment mottling (70%) • Chorioretinal atrophy (70%) • Optic nerve abnormalities (40%) • Iris coloboma (10%) • Lens subluxation (10%)

OFC, occipitofrontal circumference; TORCH, *Toxoplasma gondii*, rubella, cytomegalovirus, herpes simplex, and syphilis.

(Table 3).[46–51] Illness duration was <1 week, and common manifestations included fever, malaise, headache, and myalgia. Seven of 10 children described in case reports presented with gastrointestinal symptoms; whether these symptoms occur more frequently in children than in adults is unknown. Although not seen in the 7 children for whom information is available, rash has been prominent in Zika virus outbreaks.[2,6,52] The rash associated with adult Zika virus infection is characterized as pruritic, maculopapular, originating on the trunk, and spreading to involve the face and extremities, and lasting for 2 to 14 days.[2,23,53]

Complications of pediatric Zika virus infection have rarely been reported. Two deaths possibly associated with Zika virus disease among adolescents have been reported. The first, a 16-year-old Brazilian girl, was hospitalized with headache, nausea, and petechiae.[7,54] Zika virus infection was confirmed by RT-PCR; dengue and chikungunya virus test results were unavailable. No further details are available. The second pediatric death occurred in a 15-year-old Colombian girl with sickle cell disease (hemoglobin SC), with no history of vaso-occlusive crises, who was hospitalized with abdominal pain, tachycardia, and tachnypnea.[51] She developed severe acute respiratory distress syndrome, hemothorax, and splenic sequestration. Results of RT-PCR testing were positive for Zika virus RNA; test results for dengue, yellow fever, and chikungunya viruses and malaria were also negative. Deaths related to Zika virus infection in children were not reported after outbreaks on Yap Island or in French Polynesia.[2,9] Among the 38 cases of Guillian-Barré syndrome during the French Polynesia outbreak, none occurred among children.[9] Guillain-Barré syndrome and acute disseminated encephalomyelitis occurred in 6 patients with

TABLE 3 Clinical Features of Confirmed or Suspected Pediatric Zika Virus Infections, 1954–2016

Location	Year	Age, y	Gender	Duration, d	Complete Recovery Documented	Fever	Malaise	Rash	Conjunctivitis	Headache	Dizziness	Arthralgia	Myalgia	GI Symptoms[a]	Other
Nigeria[46]	Early 1950s	10	F	NS	+	+				+					Concurrent malaria infection
Indonesia[47]	1977–1978	12	M	NS	NS	"High"	+	—			+				Constipation
		12	F	NS	NS	"High"	+	—						+	
		13	M	NS	NS	"High"	+	—						+	Hypotension, constipation
		14	M	NS	NS	"High"		—	+		+	+	+	+	Hematuria
		16	F	NS	NS	"High"	+	—			+			+	Chills, leg pain
Cambodia[48]	2010	3	M	4	+	+		—		+					Sore throat, cough
The Philippines[49]	2012	15	M	<21	+	Subjective		—	+	+			+	+	Sore throat
New Caledonia[50]	2014	14	M	3	+	39.5°C				+		+	+		Concurrent dengue virus infection
Colombia[51]	2015	15	F	7	No, patient required intensive care and died	>40°C	+			+		+	+	+	Sickle cell disease (HgbSC); ARDS, hemothorax, splenic sequestration

Empty box, article did not comment on absense or presense of sign or symptom; +, symptom present; —, absense of symptom; ARDS, acute respiratory distress syndrome; F, female; Hgb, hemoglobin; M, male; NS, not stated.

[a] Abdominal pain, anorexia, nausea, vomiting, or diarrhea.

laboratory-confirmed Zika virus infection in Brazil (age range, 2–57 years)[6]; additional details were not provided. Whether these neurologic conditions are caused by Zika virus infection is currently unknown.

Diagnosis

The Centers for Disease Control and Prevention (CDC) has released updated interim guidelines for health care providers caring for infants and children with possible Zika virus infection.[27] Clinical features of Zika virus infection can resemble common childhood illnesses, which might make diagnosing Zika virus infection in infants and children challenging. Because Zika virus antibody tests can cross-react with those for other flaviviruses,[55, 56] laboratory test results must be interpreted with caution. Based on current recommendations, infants and children with epidemiologic risk factors and manifestations of Zika virus infection should undergo Zika virus testing (http://www.cdc.gov/zika/hc-providers/diagnostic.html). Testing will allow further characterization of the clinical manifestations associated with pediatric Zika virus disease and inform public health interventions, such as targeted vector control in areas of newly established local transmission.

Infants born to mothers who traveled to or resided in areas with local Zika virus transmission during pregnancy, or who are born to mothers who had sexual contact with male partners who traveled to or resided in these areas, might be at risk for congenital Zika virus infection. In these cases, the decision to test is informed by the following: (1) presence of microcephaly or intracranial calcifications based on prenatal or postnatal ultrasound; and (2) the mother's prenatal or postnatal Zika virus test results. All infants with the aforementioned epidemiologic risk factors and microcephaly or intracranial calcifications should be tested for Zika virus, regardless of maternal test results. For infants without microcephaly or intracranial calcifications, testing is indicated for infants born to mothers with positive or inconclusive Zika virus test results; those born to mothers with negative test results or who were not tested should receive routine care. Health care providers should exercise clinical judgment when evaluating infants with other abnormalities (eg, hearing loss) born to mothers with travel to or reside in an area with local Zika virus transmission, or who are born to mothers who have had sexual contact with partners who traveled to or resided in these areas. In these scenarios, clinicians can consider testing the mother for Zika virus infection to inform infant evaluation.

Perinatal transmission of Zika virus infection should be suspected in an infant in the first 2 weeks of life if the infant's mother traveled to or resided in an affected area within 2 weeks of delivery and the infant has at least 2 of the following: fever, rash, conjunctivitis, or arthralgia. Although arthralgia is difficult to assess in infants and young children, suggestive findings include refusal to move an affected limb, pain on palpation or with passive range of motion, abnormal gait or limp in ambulatory children, and irritability. Neonates born to mothers with manifestations of Zika virus disease around the time of delivery should be monitored for Zika virus illness; both mother and infant should be tested if such illness develops.

Mosquito-borne transmission of Zika virus infection should be suspected in children who (1) have traveled to or resided in an affected area within the past 2 weeks; and (2) have at least 2 of the following: fever, rash, conjunctivitis, or arthralgia. Testing for other flaviviruses is informed by travel history. Adolescents might also be exposed to Zika virus through sexual contact with a male partner who traveled to or resided in an affected area. Health care providers caring for patients with possible sexual exposure to Zika virus should refer to the CDC's interim guidelines.[15]

At this time, no commercially available US Food and Drug Administration–cleared diagnostic tests for Zika virus are available. Testing is arranged through state, local, and territorial health departments and is performed at the CDC and some state health departments. Arboviruses, including Zika virus, are nationally notifiable diseases.

LABORATORY TESTING

Molecular Diagnostics

Given its high sensitivity and specificity for detecting Zika virus,[56] RT-PCR testing of serum within the first week of illness is preferred for laboratory confirmation of Zika virus infection.[57] RT-PCR may also be used on tissue specimens (eg, placenta, autopsy specimens) in specialized laboratories. A positive RT-PCR test result indicates Zika virus infection. However, RT-PCR can only detect virus in serum during viremic periods, estimated to occur during the first week of illness; a negative result from serum collected on day 5 of illness or later does not exclude infection.

Serology

Zika virus immunoglobulin M (IgM) antibodies have been detected as early as 4 days after illness onset. Based on experience with other flaviviruses, Zika virus IgM antibodies are expected to be present beginning 4 days after illness onset and persist for at least 12 weeks.[57, 58] Because cross-reactivity between Zika and dengue virus IgM assays can occur, IgM-positive results should

be followed by plaque reduction neutralization tests (PRNT).[57] Immunoglobulin G assays are less specific for arboviral antibodies than IgM assays.[59]

PRNT

When serologic test results are equivocal, PRNT can measure virus-specific neutralizing antibodies, which may be useful in discriminating Zika virus from other flaviviruses. However, because cross-reactivity is more likely to occur in patients with previous flavivirus exposure through natural infection or immunization (eg, yellow fever vaccine), PRNT results from these patients must be interpreted cautiously.[57]

TREATMENT

Currently, no specific treatment of Zika virus infection is available. Supportive care consists of rest, fluids, and symptomatic treatment. Acetaminophen and antihistamines have been used to treat fever and pruritus, respectively.[60] Aspirin and other salicylates should be avoided in children due to an association with Reye's syndrome, and nonsteroidal antiinflammatory drugs should be used cautiously in children with dehydration and avoided in infants aged <6 months due to inadequate information on pharmacokinetics and potential for nephrotoxicity.[61] Nonsteroidal antiinflammatory drugs can also increase the risk of hemorrhagic complications in patients with dengue virus infection and thus should be avoided until dengue infection has been excluded.[62] To reduce the risk of transmission to others, infected patients should take precautions to prevent mosquito bites, especially during the first week of illness when they are likely to be viremic.

PREVENTION

No vaccine is available to prevent Zika virus infection. Sexual transmission of Zika virus from male partners has been documented, although it is unknown how long semen remains infectious. Thus, male subjects who reside in or have traveled to an area of active Zika virus transmission and have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sex for the pregnancy duration.[15] If either partner is concerned about sexual transmission to a nonpregnant partner, the male subject might also consider abstaining from sexual activity or using condoms consistently and correctly during sex. Additional information is available in CDC's interim guidelines for prevention of sexual transmission.

Because of the possible risk for Zika virus transmission associated with blood transfusions,[63] the US Food and Drug Administration issued guidance on February 16, 2016, regarding deferral of blood donations from persons who have traveled to areas with active Zika virus transmission, have potential exposure to the virus, or have had a confirmed Zika virus infection (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm486359.htm).

Based on CDC interim travel guidance (http://wwwnc.cdc.gov/travel/notices), pregnant women should postpone travel to areas with ongoing Zika virus transmission. Pregnant women who must travel to 1 of these areas should talk with their health care provider first and strictly follow steps to prevent mosquito bites during their trip. The CDC recommends that all persons who travel to areas with local transmission protect themselves from mosquito bites. Zika virus prevention centers on personal avoidance of mosquito bites and reducing mosquito populations.[64] Personal avoidance measures include staying in buildings with air-conditioning or with window and door screens, wearing full-length garments and socks, and using mosquito repellent.[62] Permethrin-treated clothing can repel mosquitoes. Bed nets are advised for travel to areas in which accommodations are not adequately screened or air-conditioned.

The CDC recommends the use of insect repellents registered by the Environmental Protection Agency according to the instructions on the label.[62] Products containing *N, N*-Diethyl-*meta*-toluamide (DEET), picaridin, oil of lemon eucalyptus, or ethyl butylacetylaminopropionate provide protection from mosquito bites. Higher DEET concentrations are associated with longer duration of action. Efficacy plateaus at a concentration approaching 50%, and the maximum recommended concentration for infants and children is 30%. Products containing DEET should not be used on children aged <2 months; this group can be protected by use of mosquito netting. Mosquito repellents containing oil of lemon eucalyptus (*p*-Menthane-3, 8-diol) should not be used in children aged <3 years. Only adults should handle repellents, which should be applied judiciously to children's exposed skin, avoiding the hands, eyes, mouth, and broken or irritated skin. Skin treated with mosquito repellent should be washed with soap and water after returning indoors, especially before meals. Combination products that include both mosquito repellent and sunscreen should be avoided because sunscreen may need to be applied more frequently and in larger amounts than needed for adequate mosquito bite protection. Sunscreen, when used, should be applied before repellent. Insect repellents should not be applied in enclosed areas or near food or underneath clothing. More information on the prevention of mosquito-borne illnesses can be found at: http://www.cdc.gov/

zika/prevention/ and http://www.epa.gov/insect-repellents/using-repellent-products-protect-against-mosquito-borne-illnesses.

RESOURCES

Information on Zika virus and its consequences is rapidly accruing. Readers may find the following resources helpful to stay abreast of developments:

- Centers for Disease Control and Prevention: http://www.cdc.gov/zika
- National Library of Medicine: https://sis.nlm.nih.gov/dimrc/zikavirus.html
- National Institutes of Health–Fogarty International Center: http://www.fic.nih.gov/ResearchTopics/Pages/infectiousdiseases-zika-virus.aspx,
- World Health Organization: http://www.who.int/csr/disease/zika/en/
- Pan American Health Organization: http://www.paho.org/hq/index.php?option=com_content&view=article&id=11585&Itemid=41688&lang=en

SUMMARY

Less than 1 year after identification of Zika virus in Brazil, transmission is now widespread throughout much of the Americas. Local transmission of Zika virus has been established in US territories, and in addition to travel-associated cases, limited local transmission is likely to occur in some parts of the continental United States. Infants and children living in or traveling to affected areas are at risk for contracting Zika virus, as are neonates born to women who reside in or travel to affected areas where they may be exposed through mosquitoes carrying the virus. Sexual transmission of Zika virus has been reported, and women who have unprotected sexual contact with a male partner who resides in or has traveled to an area of Zika virus transmission are also at risk for infection. Congenital Zika virus infection appears to be associated with microcephaly and possibly other birth defects of the brain and eye. Based on limited data, it seems that most infants and children who contract Zika virus via mosquitoes have no or mild illness, similar to findings in adults. To provide guidance to caregivers and patients, and to evaluate and manage infants and children potentially infected with Zika virus, pediatric health care providers need to know the signs and symptoms, appropriate laboratory tests, and clinical guidelines. Updated information on Zika virus and children can be found at: www.cdc.gov/Zika.

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ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
DEET: *N,N*-Diethyl-*meta*-toluamide
IgM: immunoglobulin M
PRNT: plaque reduction neutralization test
RT-PCR: reverse transcription polymerase chain reaction

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REFERENCES

1. Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. *Trans R Soc Trop Med Hyg*. 1952;46(5):509–520
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(24):2536–2543
3. Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Pacific area. *Clin Microbiol Infect*. 2014;20(10):0595–0596
4. Campos GS, Bandeira AC, Sardi SI. Zika virus outbreak, Bahia, Brazil. *Emerg Infect Dis*. 2015;21(10):1885–1886
5. Zanluca C, de Melo VC, Mosimann AL, Dos Santos GI, Dos Santos CN, Luz K. First report of autochthonous transmission of Zika virus in Brazil. *Mem Inst Oswaldo Cruz*. 2015;110(4):569–572
6. Brazil Ministry of Health. Protocol for surveillance and response to the occurrence of microcephaly related to Zika virus infection. Available at: http://portalsaude.saude.gov.br/images/pdf/2015/dezembro/09/Microcefalia—Protocolo-de-vigil–ncia-e-resposta—vers–o-1—-09dez2015-8h.pdf. Accessed February 2, 2016
7. Pan American Health Organization. Epidemiological alert: neurological

syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas. Available at: www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32405&lang=enAccessed January 30, 2016

8. Brazil Ministry of Health. The Public Health Emergency Operations Center report on microcephaly. Epidemiological week 4 of 2016. Available at: http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/svs. Accessed February 8, 2016
9. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome – December 10, 2015. Available at: http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf. Accessed February 1, 2016
10. World Health Organization. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. Available at: www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/#. Accessed February 3, 2016
11. Centers for Disease Control and Prevention. All countries and territories with active Zika virus transmission. Available at: www.cdc.gov/zika/geo/active-countries.html. Accessed February 24, 2016
12. Centers for Disease Control and Prevention. Surveillance and control of Aedes aegypti and Aedes albopictus in the United States. Available at: www.cdc.gov/chikungunya/resources/vector-control.html. Accessed February 4, 2016
13. Porse CC, Kramer V, Yoshimizu MH, et al. Public Health Response to Aedes aegypti and Ae. albopictus mosquitoes invading California, USA. *Emerg Infect Dis*. 2015;21(10):1827–1829
14. Filipe AR, Martins CM, Rocha H. Laboratory infection with Zika virus after vaccination against yellow fever. *Arch Gesamte Virusforsch*. 1973;43(4):315–319
15. 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(5):120–121
16. Brazil Ministry of Health. The Public Health Emergency Operations Center report on microcephaly. Epidemiological week 1 of 2016. Available at: http://portalsaude.saude.gov.br/images/pdf/2016/janeiro/13/COES-Microcefalias—Inf orme-Epidemiol–gico-08—SE-01-2016—Valida—o-12jan2016—VALIDADO-PELO-CLAUDIO–e-com-os-estados-por-webconfer–n.pdf. Accessed February 2, 2016
17. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol*. 2016;47(1):6–7
18. Martines RB, Bhatnagar J, Keating MK, et al 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(6):159–160
19. Mlakar J, Korva M, Tul N, et al. Zika virus associated with microcephaly. *N Engl J Med*. Available at: www.nejm.org/doi/full/10.1056/nejmoa1600651. Accessed February 12, 2016
20. Calvet G, Aguiar RS, Melo ASO, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. *Lancet Infect Dis*. Available at: www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)00095-5/abstract. Accessed February 19, 2016
21. Sarno M, Sacramento GA, Khouri R, et al. Zika virus infection and stillbirths: a case of hydrops fetalis, hydranencephaly and fetal demise. *PLoS Negl Trop Dis*. 2016;10(2):e0004517
22. 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*. Available at: www.cdc.gov/mmwr/volumes/65/wr/mm6508e1er.htm?s_cid=mm6508e1er.htm_w. Accessed March 1, 2016
23. 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(13):20751
24. Barthel A, Gourinat AC, Cazorla C, Joubert C, Dupont-Rouzeyrol M, Descloux E. Breast milk as a possible route of vertical transmission of dengue virus? *Clin Infect Dis*. 2013;57(3):415–417
25. Centers for Disease Control and Prevention (CDC). Possible West Nile virus transmission to an infant through breast-feeding—Michigan, 2002. *MMWR Morb Mortal Wkly Rep*. 2002;51(39):877–878
26. Kuhn S, Twele-Montecinos L, MacDonald J, Webster P, Law B. Case report: probable transmission of vaccine strain of yellow fever virus to an infant via breast milk. *CMAJ*. 2011;183(4):E243–E245
27. Fleming-Dutra KE, Nelson JM, Fischer M, et al. Update: interim guidelines for health care providers caring for infants and children with possible Zika virus infection—United States, February 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65(7):182–187
28. Musso D, Roche C, Nhan TX, Robin E, Teissier A, Cao-Lormeau VM. Detection of Zika virus in saliva. *J Clin Virol*. 2015;68:53–55
29. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. *Emerg Infect Dis*. 2015;21(1):84–86
30. 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(3):55–58
31. 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(5):882–891
32. Victora CG, Schuler-Faccini L, Matijasevich A, Ribeiro E, Pessoa A,

Barros FC. *Microcephaly in Brazil: how to interpret reported numbers? Lancet*. 2016;387(10019):621–624

33. European Centre for Disease Prevention and Control. Rapid risk assessment: microcephaly in Brazil potentially linked to the Zika virus epidemic. Available at: http://ecdc.europa.eu/en/publications/Publications/zika-microcephaly-Brazil-rapid-risk-assessment-Nov-2015.pdf. Accessed February 1, 2016
34. Butler D. Zika virus: Brazil's surge in small-headed babies questioned by report. *Nature*. 2016;530(7588):13–14
35. 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(3):59–62
36. Corona-Rivera JR, Corona-Rivera E, Romero-Velarde E, Hernández-Rocha J, Bobadilla-Morales L, Corona-Rivera A. Report and review of the fetal brain disruption sequence. *Eur J Pediatr*. 2001;160(11):664–667
37. Ventura CV, Maia M, Bravo-Filho V, Gois AL, Belfort R Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. *Lancet*. Available at: www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00006-4/abstract. Accessed January 30, 2016
38. Ventura CV, Maia M, Ventura BV, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. *Arq Bras Oftalmol*. Available at: http://archopht.jamanetwork.com/article.aspx?articleid=2491896. Accessed February 15, 2016
39. de Paula Freitas B, de Oliveira Dias JR, Prazeres P, et al Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil [published online ahead of print February 9, 2016]. *JAMA Ophthalmol*. doi: 10.1001/jamaophthalmol.2016.0267
40. Alpert SG, Fergerson J, Noël LP. Intrauterine West Nile virus: ocular and systemic findings. *Am J Ophthalmol*. 2003;136(4):733–735
41. 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(3). Available at: www.pediatrics.org/cgi/content/full/117/3/e537
42. Sirois PA, Pridjian G, McRae S, et al. Developmental outcomes in young children born to mothers with West Nile illness during pregnancy. *Birth Defects Res A Clin Mol Teratol*. 2014;100(10):792–796
43. Pouliot SH, Xiong X, Harville E, et al. Maternal dengue and pregnancy outcomes: a systematic review. *Obstet Gynecol Surv*. 2010;65(2):107–118
44. American Academy of Pediatrics. *Red Book Atlas of Pediatric Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015
45. von der Hagen M, Pivarcsi M, Liebe J, et al. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. *Dev Med Child Neurol*. 2014;56(8):732–741
46. 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(2):139–145
47. Olson JG, Ksiazek TG, Suhandiman, Triwibowo. Zika virus, a cause of fever in Central Java, Indonesia. *Trans R Soc Trop Med Hyg*. 1981;75(3):389–393
48. Heang V, Yasuda CY, Sovann L, et al. Zika virus infection, Cambodia, 2010. *Emerg Infect Dis*. 2012;18(2):349–351
49. Alera MT, Hermann L, Tac-An IA, et al. Zika virus infection, Philippines, 2012. *Emerg Infect Dis*. 2015;21(4):722–724
50. 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(2):381–382
51. Arzuza-Ortega L, Polo A, Pérez-Tatis G, López-García H, Parra E, Pardo-Herrera LC. Fatal Zika virus infection in girl with sickle cell disease, Colombia. *Emerg Infect Dis*. Available at: http://wwwnc.cdc.gov/eid/article/22/5/15-1934_article. Accessed February 16, 2016
52. Cao-Lormeau VM, Roche C, Teissier A, et al. Zika virus, French polynesia, South Pacific, 2013. *Emerg Infect Dis*. 2014;20(6):1085–1086
53. 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(5):1035–1038
54. Brazil Ministry of Health. The Public Health Emergency Operations Center report on microcephaly. Epidemiological week 47 of 2015. Available at: http://portalsaude.saude.gov.br/images/pdf/2015/novembro/30/COES-Microcefalias—Informe-Epidemiol–gico—SE-47—30nov2015.pdf. Accessed February 2, 2016
55. 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(8):1232–1239
56. Faye O, Faye O, Dupressoir A, Weidmann M, Ndiaye M, Alpha Sall A. One-step RT-PCR for detection of Zika virus. *J Clin Virol*. 2008;43(1):96–101
57. Centers for Disease Control and Prevention. Memorandum: revised diagnostic testing for Zika, chikungunya, and dengue viruses in US public health laboratories. Available at: www.cdc.gov/zika/pdfs/denvchikvzikv-testing-algorithm.pdf. Accessed February 12, 2016
58. 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(5):122–127
59. Westaway EG, Della-Porta AJ, Reedman BM. Specificity of IgM and IgG antibodies after challenge with antigenically related togaviruses. *J Immunol*. 1974;112(2):656–663
60. 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(7):302–307
61. Sullivan JE, Farrar HC; Section on Clinical Pharmacology and Therapeutics; Committee on Drugs.

Fever and antipyretic use in children. *Pediatrics*. 2011;127(3):580–587

62. Centers for Disease Control and Prevention. In: Brunette GW, ed. *Health Information for International Travel 2016*. New York, NY: Oxford University Press; 2016

63. Musso D, Nhan T, Robin E, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. *Euro Surveill*. 2014;19(14):20761

64. Araújo HR, Carvalho DO, Ioshino RS, Costa-da-Silva AL, Capurro ML. Aedes aegypti control strategies in Brazil: incorporation of new technologies to overcome the persistence of dengue epidemics. *Insects*. 2015;6(2):576–594

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