

MICHELLE S. FLORES, MD

Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, MD

TIMOTHY H. BURGESS, MD, MPH

Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, MD; Infectious Diseases Clinical Research Program, Uniformed Services University of the Health Sciences, Bethesda, MD

MICHAEL RAJNIK, MD

Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, MD

Zika virus: A primer for clinicians

ABSTRACT

The ongoing outbreak of Zika virus infection that began in South America and Central America in 2014 is worrisome because of associations with fetal microcephaly and with Guillain-Barré syndrome. Here we summarize what has happened and what is known so far. As the outbreak continues to evolve, we urge clinicians to watch for updates at cdc.gov.

KEY POINTS

Zika virus infection is spread by the bite of infected mosquitoes and also through sexual contact, blood transfusions, and vertical transmission.

Most Zika virus infections are asymptomatic, and symptomatic cases are often mild and self-limited, with rash, fever, joint pain, and nonpurulent conjunctivitis the most common symptoms.

Polymerase chain reaction testing can detect viral RNA in the blood, but only in the first few days after the onset of symptoms. Immunoglobulin M against the virus becomes detectable at approximately 1 week and persists for about 12 weeks, but cross-reactivity with other viruses is a problem with serologic testing.

As yet, there is no vaccine and no specific treatment.

Pregnant women and women who may become pregnant are advised to defer travel to areas where Zika virus is endemic.

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ON FEBRUARY 1, 2016, the World Health Organization declared Zika virus a public health emergency of international concern due to clusters of microcephaly and neurologic manifestations in areas of Zika virus transmission.¹ On February 8, the US Centers for Disease Control and Prevention (CDC) elevated its response to level 1, its highest.²

Case reports and guidelines have been published to help clinicians better understand the epidemiology, risk, and pathogenesis of Zika virus infection, but much is still unknown. Clinicians must be ready to address the concerns of international travelers and must also consider Zika virus in the differential diagnosis of fever in the returned traveler.

■ FLAVIVIRUSES: DENGUE, WEST NILE ... ZIKA

Zika virus, a single-stranded RNA arthropod-borne virus (arbovirus), is transmitted by mosquitoes. It is a member of the flavivirus family, which consists of over 70 viruses including some well known for causing diseases in humans, such as dengue, yellow fever, Japanese encephalitis, and West Nile virus.³

Phylogenetically, Zika virus is most similar to and included in a clade with Spondweni virus, which, like Zika, originated in Africa.⁴ Genomic analysis has revealed an African and an Asian lineage. The Asian lineage is responsible for the current epidemic in the Pacific and the Western Hemisphere.⁴⁻⁶

■ OUT OF AFRICA AND ASIA

Zika virus is named after a forested area in present-day Uganda, where it was first isolated in a febrile rhesus monkey that was being used to study yellow fever.⁷ Further studies in the 1950s confirmed its transmission to humans, as 6% of the sera tested in Ugandans showed



FIGURE 1. Reported transmission of Zika virus in the Americas.

From US Centers for Disease Control and Prevention.
www.cdc.gov/zika/geo/americas.html

The CDC has elevated its response to level 1, its highest

evidence of specific antibodies to the virus.⁸ In 1978, antibody prevalence studies showed that up to 40% of Nigerians had Zika virus-neutralizing antibodies.⁹ Over the next 38 years, scattered case reports and seroprevalence studies showed infections occurring throughout Africa and Asia.⁹⁻¹¹

In 2007, the first case of Zika virus transmission outside of Asia and Africa occurred on Yap Island in the Federated States of Micronesia.¹⁰⁻¹² No further transmission in the Pacific was noted for 6 years until an outbreak occurred in French Polynesia in 2013.¹³⁻¹⁵ The first time Zika virus was found in the Western Hemisphere was in January 2014, when an outbreak occurred on Chile's Easter Island.¹⁶ Genomic analysis of the Zika virus isolated on Easter Island indicated it was most closely related to isolates from French Polynesia.¹⁶ In 2014, additional cases of Zika virus infection were reported in New Caledonia and the Cook Islands.^{13,14}

In May 2015, the World Health Organization issued an epidemiologic alert in response to dramatic increases in the spread of Zika virus in Brazil.¹⁷ From Brazil, Zika virus has rapidly

spread to most countries in South and Central America and the Caribbean (Figure 1).^{2,5,6}

TRANSMITTED BY MOSQUITO

The *Aedes* (*Stegomyia*) genus of mosquitoes is a well-known source of transmission for several arboviruses, including yellow fever, dengue, chikungunya, and now Zika virus.^{18,19} Zika virus was originally isolated in Uganda from *Aedes africanus* mosquitoes.^{7,20} Subsequently, other species of *Aedes* mosquitoes have been shown to transmit Zika virus, with *Aedes aegypti* being the most important human vector.^{7,8,19-21}

Another species, *Aedes albopictus* has been identified as a human vector in Gabon and is also suspected of being a vector in the Brazilian outbreak.²² Spread of *A. albopictus* from Asia to Europe, the Mediterranean region, and the Americas, including 32 states in the United States, has increased the fear of potential spread of Zika virus infection to a more expansive geographic range.^{13,18,19} Local transmission may become established if local mosquitoes become infected when infected travelers return from endemic areas.²³

OTHER ROUTES OF TRANSMISSION

While mosquito-borne transmission is the most common route of infection with Zika virus, human-to-human transmission has been documented. Potential routes of transmission include sexual intercourse, blood transfusions, and vertical (mother-to-child) transmission.

Sexual transmission. Replicative Zika virus particles were identified in the semen of a patient who presented with hematospermia in French Polynesia.²⁴

Previously, there was a report of Zika virus being sexually transmitted from a US man who had returned from Senegal to his spouse, who had not traveled to a Zika virus-endemic region. Both patients became ill following vaginal intercourse, with the onset of the wife's illness occurring 5 days after the onset of the husband's illness. The husband was noted to have hematospermia.²⁵ Neutralization testing for both patients confirmed infection with Zika virus.²⁵

The first reported case of sexual transmission in the current outbreak in the United States occurred in a traveler returning to

Texas from Venezuela.²⁶ The CDC is currently investigating several other potential cases and an additional two laboratory-confirmed cases. All cases were in symptomatic male travelers who had condomless vaginal intercourse with their female partners after return from Zika virus-endemic areas.²⁷

Blood transfusions. Several arboviruses are known to be transmitted via blood.

In French Polynesia, Zika virus RNA was present in 3% of blood donors.^{28,29} These blood donors had been screened and were asymptomatic at the time of donation. Twenty-six percent of donors who had Zika RNA reported an illness compatible with Zika virus infection in the 3 to 10 days before donation.²⁸

Brazil has reported two cases of Zika virus infection through blood transfusion.³⁰

In May 2015, the European Centers for Disease Control recommended that travelers to affected areas defer blood donation for 28 days.³¹ The Association of American Blood Banks has also recommended that travelers self-defer donating blood for 28 days after travel to an endemic area.³² Most recently the US Food and Drug Administration recommended a 4-week deferral for travelers to Zika virus-endemic areas and after resolution of symptoms for those who have had Zika virus infection.³³ Additional guidance for donors who have had sexual contact with Zika virus-infected persons and areas with active transmission of Zika virus is also available.³³

Vertical transmission. Perinatal and transplacental transmission have also been documented.^{34,35} The extent and frequency of the clinical manifestations of these infections are still being elucidated in light of reports of association with fetal abnormalities.

Although Zika virus has been detected in breast milk, no cases of transmission through breastfeeding have been reported. Currently, women are advised to continue to breastfeed in areas of known Zika virus transmission.^{34,36,37}

■ IS USUALLY ASYMPTOMATIC OR CAUSES MILD SYMPTOMS

Most Zika virus infections are asymptomatic, as illustrated by reports from the Yap Island outbreak, where only 19% of those with immunoglobulin M (IgM) antibodies to Zika vi-

TABLE 1

Differential diagnosis of Zika virus infection

- Dengue
- Chikungunya
- Malaria
- Rickettsia
- Group A streptococci
- Rubella
- Measles
- Parvovirus
- Enterovirus
- Adenovirus
- Leptospirosis
- Alphavirus infections (in addition to chikungunya)

From Centers for Disease Control and Prevention. Zika virus clinical evaluation and disease. www.cdc.gov/zika/hc-providers/clinicalevaluation.html.

rus had symptoms.¹² The illness in symptomatic patients is often mild and self-limited, and most manifestations resolve by 7 days.^{12,25,38,39}

Initial descriptions in the 1950s and 1960s of the clinical features of Zika virus infection in Africa included fever and headache as the most prominent symptoms.^{38,40} Description of the outbreak on Yap in 2007 characterized the predominant symptoms as rash, fever, arthralgia/arthritis, and nonpurulent conjunctivitis in 31 patients,¹² and the current CDC case definition includes at least two of these four symptoms.⁴¹ The arthralgia and arthritis are usually of the small joints of the hands and feet and can persist for as long as a month.^{25,42} The rash can be pruritic.^{15,33,42,43}

Less commonly reported manifestations of Zika virus infection include malaise, stomachaches, dizziness, anorexia, retro-orbital pain, aphthous ulcers, hematospermia, and prostatitis.^{14,15,24,25,44,45}

The initial reports from eight patients in the outbreak in Brazil noted rash and joint pain as the most common manifestations. The maculopapular rash was present in all patients and the joint pain was characterized as severe, with the hands, ankles, elbows, knees, and wrists most consistently described.⁴³

The clinical presentation is similar to those of dengue and chikungunya virus infections, confounding diagnosis, as these viruses

From Brazil, Zika virus has rapidly spread to most countries in South and Central America and the Caribbean

may be cocirculating in the same geographic regions (and indeed are transmitted by the same mosquito vectors).^{11,12,15} The conjunctivitis present in Zika virus infections can also be present in chikungunya but is much less commonly a clinical feature of dengue.^{15,46,47} See **Table 1** for the differential diagnosis of Zika virus infection.

Severe manifestations requiring hospitalization or resulting in death are thought to be uncommon, although neurologic and fetal complications have recently been described.^{12,29,43,48,49}

■ **CLINICAL ASSOCIATIONS**

Primary infection with Zika virus is relatively benign. The greatest and most recent concerns are related to postinfectious complications and those that may occur in pregnant women.

Guillain-Barré syndrome

During the Zika virus outbreak in French Polynesia in 2013–2014, the incidence of Guillain-Barré syndrome was multiplied by a factor of 20.⁵⁰ Prior to the first hospitalization of a patient with Zika virus infection and associated Guillain-Barré syndrome in French Polynesia, there had been no reported hospitalizations for Zika virus infection.⁵⁰

This same association is now being seen in the recent outbreak in the Americas.⁵⁰ In July 2015, Brazilian health officials in the State of Bahia reported 76 patients with neurologic syndromes, of whom 55% had Guillain-Barré syndrome.⁵¹ A history consistent with Zika virus infection was found in 62%.⁴⁸

In January 2016, El Salvador also reported an unusual increase in Guillain-Barré syndrome cases since early December 2015.⁵¹ Between December 1, 2015, and January 6, 2016, there were 46 Guillain-Barré syndrome cases reported, compared with a baseline of 14 cases per month.⁵¹

Other countries where Zika virus infection is endemic are also currently investigating similar trends.⁵¹

Microcephaly

On November 17, 2015, the Pan American Health Organization issued an epidemiologic alert because of increased reports of microcephaly in the Pernambuco State of Brazil. Whereas

there are typically about 10 cases per year, there had been 141 in the previous 11 months.⁵¹ Other states in Brazil such as Paraíba and Rio Grande del Norte also reported increases in the diagnosis of microcephaly. A physician alert published in Brazil described two infants from the Paraíba state who were diagnosed with fetal microcephaly.³⁵ Testing for Zika virus by polymerase chain reaction (PCR) was negative in the maternal blood, but PCR of amniotic fluid was positive in both infants.³⁵

In January 2016, the Brazil Ministry of Health reported that Zika virus had been detected by real-time PCR (RT-PCR) in four infants with congenital malformations in Rio Grande del Norte. Two of these cases were miscarriages and two were infants who died within 24 hours of birth. Immunohistochemistry of tissues from these infants was positive for Zika virus.

A February 2016 case report describes a European woman who developed Zika virus infection at 13 weeks gestation while working in Northeast Brazil and upon return to Europe elected to terminate the pregnancy after ultrasonography showed cerebral calcifications with microcephaly. The infant was found to have a very small brain, hypoplasia of the brainstem and spinal cord with degeneration of spinal tracts, complete absence of cerebral gyri, and severe dilatation of lateral ventricles as well as calcifications throughout the cerebral cortex.⁴⁹ No genetic abnormalities or evidence of other etiologies was found, and large amounts of Zika virus RNA were found in the brain.

The CDC also recently reported confirmation of Zika virus infection from fetal tissues of two miscarriages (fetal loss at 11 and 13 weeks) and two fetal deaths (36 and 38 weeks) received from the state of Rio Grande do Norte in Brazil.⁵² All four mothers reported clinical signs of fever and rash during their first trimester of pregnancy.⁵² Additional testing for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and human immunodeficiency virus were all negative in the mothers who had miscarriages.⁵²

Of critical note, the causality of Zika virus and microcephaly remains under investigation. See **Table 2** for other causes of microcephaly.⁵³

Aedes aegypti is the most important vector, but *A albopictus* can also carry the virus and now lives in 32 US states

Macular atrophy

In January 2016, a case series of three infants with microcephaly and macular atrophy was reported.⁵⁴ These infants were tested for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis, and human immunodeficiency virus (HIV), and all the results were negative. The detection of Zika virus fulfilled the Brazilian Ministry of Health’s definition of vertical transmission of Zika virus, and laboratory diagnostic tests for Zika virus were not performed. In this series, one mother reported an illness with rash and arthralgias during the first trimester.⁵⁴

LABORATORY DIAGNOSTIC METHODS

The diagnosis of Zika virus infection is challenging. The low viremia at initial presentation and cross-reactivity of serologic testing with other flaviviruses, especially dengue, can contribute to misdiagnosis.^{40,50}

In the first 7 days of Zika virus infection, the diagnosis is based on detection of viral RNA in serum by RT-PCR.^{12,55,56} RT-PCR is very specific for Zika virus and is an important tool in differentiating between Zika virus and other flaviviruses often present in areas where Zika virus is circulating.^{12,56} After 3 to 4 days, viremia may decrease to levels that may be below the assay’s level of detection.^{40–42,45}

While Zika virus RNA may be undetectable in the serum, other samples such as saliva, urine, and semen may be positive for longer.^{28,42,57} For example, urine samples were positive by RT-PCR up to 7 days beyond blood RT-PCR in the outbreak in New Caledonia.⁴² A recent report found semen remaining positive on RT-PCR for 62 days after the onset of confirmed Zika virus illness in a traveler returning to the United Kingdom from the Cook Islands in 2014.⁵⁸

Because RT-PCR of blood is only useful early in infection, the current diagnostic guidelines recommend testing an acute-phase serum sample for Zika virus IgM collected as early as possible after the onset of illness and repeated 2 to 3 weeks after the initial set. These IgM antibodies typically develop toward the end of the first week of illness and are expected to be present for up to 12 weeks, based on experience with other flaviviruses.⁴¹ Cross-reactivity with other flaviviruses cir-

TABLE 2

Most common causes of congenital microcephaly

Genetic	Acquired
Isolated	Disruptive injuries
Syndromic	Infections (TORCHES—toxoplasmosis, ^a rubella, cytomegalovirus, ^a herpes simplex virus, syphilis), human immunodeficiency virus
	Teratogens
	Deprivation (malnutrition, placental insufficiency, folate deficiency, maternal hypothyroidism)

^a Congenital toxoplasmosis is associated with diffuse intracranial calcifications; congenital cytomegalovirus is associated with periventricular calcifications.

Based on information in Ashwal S, Michelson D, Plawner L, Dobyns WB; Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Practice parameter: evaluation of the child with microcephaly (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2009; 73:887–897.

culating in the area can occur and has been problematic in areas where dengue is circulating.^{12,41,45,56} IgM-positive specimens should be further tested, by plaque-reduction neutralization, to confirm the presence of Zika virus-specific neutralizing antibodies. Results can be difficult to interpret, especially in those who have been previously infected or vaccinated against other flaviviruses.^{12,41}

If amniocentesis is done, these specimens should be tested by RT-PCR. However, the sensitivity of PCR in amniotic fluid is currently unknown.⁴¹

In infants with findings of cerebral calcifications and microcephaly, IgM serologies with RT-PCR are also recommended and should be drawn within 2 days of birth. Specimens should be drawn concurrently as it is not known which test is most reliable in infants.²³ Additionally, placenta and umbilical cord samples should be collected for immunohistochemical staining at specialized laboratories.³⁶

In the United States, providers should contact their state health departments to determine where tests can be run reliably. Refined diagnostic assays are in development at the time of this publication and are likely to

Several agencies recommend waiting 4 weeks after returning from Zika endemic regions before donating blood

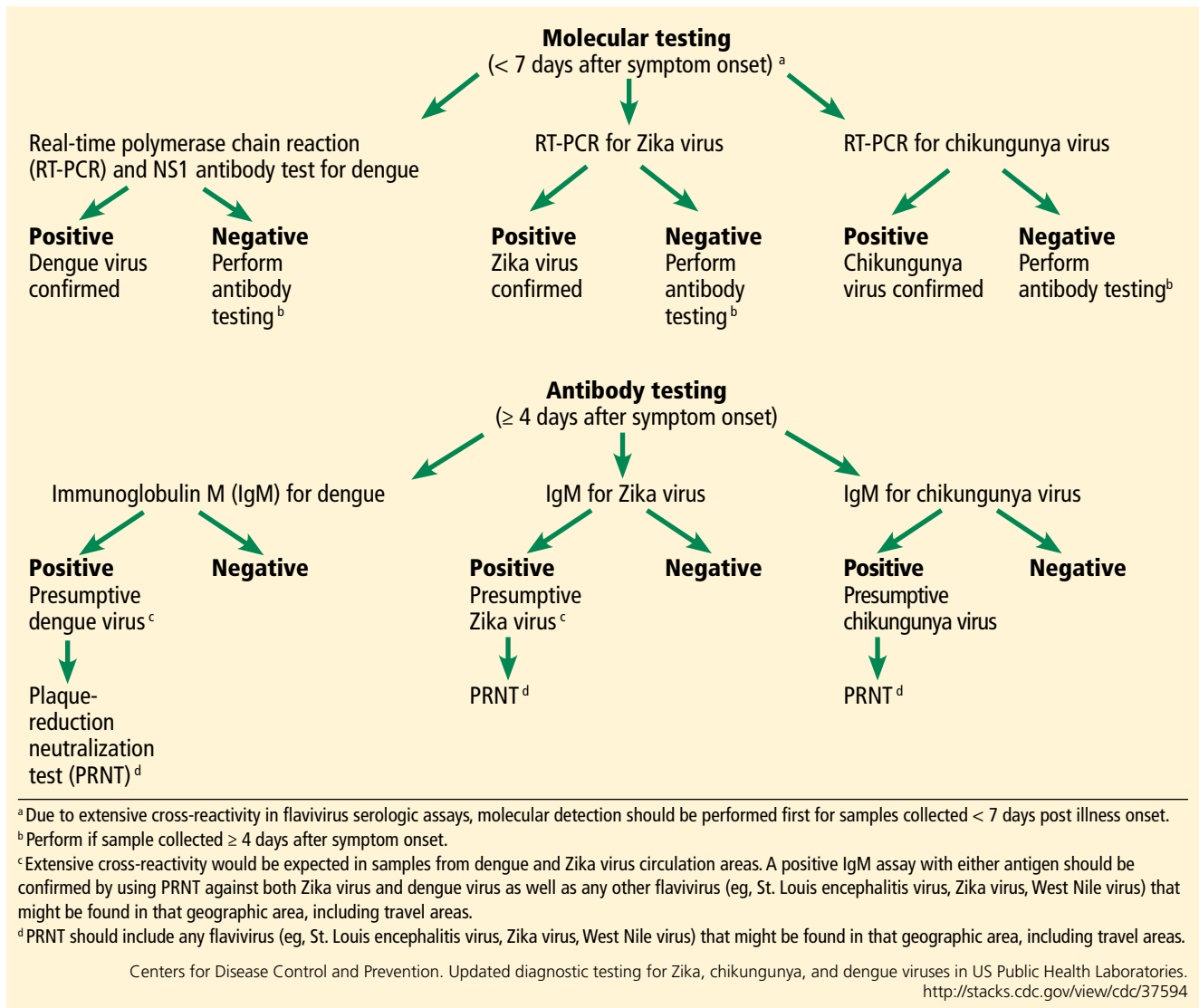


FIGURE 2. Tiered algorithm for arbovirus detection for suspected cases of chikungunya, dengue, or Zika virus infection. Testing is performed only if travel history indicates travel to affected area.

be made available through CDC’s Laboratory Response Network.

See **Figure 2** and **Table 3** for a summary of diagnostic tests.

■ IMPLICATIONS, RECOMMENDATIONS

Pregnant women

The CDC now recommends that asymptomatic pregnant women who returned from travel to a Zika virus-endemic zone in the last 2 to 12 weeks be offered serologic testing.⁴¹ This includes women who may be living in an area with ongoing Zika virus transmission; howev-

er, these women should also have testing at the initiation of prenatal care and then follow-up testing in the middle of the second trimester. Of importance, these results may be difficult to interpret due to potential cross-reactivity between Zika virus and other flaviviruses, and false-positive results in recipients of yellow fever and Japanese encephalitis vaccines.^{41,59}

If a pregnant woman with a positive travel history is symptomatic, testing should be offered during the first week of illness. After day 4 of the illness, testing should include both RT-PCR and IgM serology.^{41,59}

TABLE 3

Diagnostic tests for Zika virus

Population	Test	When used	Limitations
Healthy adults or children	Zika virus immunoglobulin M (IgM) in serum	2–12 weeks of illness	Possible cross-reactivity with other flaviviruses Limited availability
	Real-time polymerase chain reaction (RT-PCR) in serum	First week of illness	May be negative by day 4 of illness Limited availability
	Plaque reduction neutralization assay	Confirmatory testing for patients with positive IgM	Limited availability Labor-intensive
Pregnant women	Fetal ultrasonography	Pregnant women with a positive Zika virus test Pregnant women exposed to Zika virus who present after 12 weeks of exposure	Needs to be repeated every 3–4 weeks during pregnancy Availability may be limited
	RT-PCR of amniotic fluid	Microcephaly or intracranial calcifications present on ultrasonography	Significance of results has not been conclusive
Newborns suspected of being infected	Histopathology of umbilical cord and placenta	Fetal loss, Zika virus suspected Newborn with microcephaly and intracranial calcifications	Presumptive diagnosis Limited availability
	RT-PCR of cord serum, frozen tissue (cord, placenta)	Fetal loss, Zika virus suspected Newborn with microcephaly and intracranial calcifications	Presumptive diagnosis Limited availability

A screening ultrasound scan is recommended for any pregnant woman who has traveled to a Zika virus-affected area to determine if microcephaly or cerebral or intracranial calcifications are present. Those women with confirmed Zika virus infection should continue to have monthly screening ultrasounds, while those who are negative for Zika virus should have another ultrasound at the end of the second trimester or the beginning of the third trimester to ensure that no abnormalities had developed.^{41,59}

At present, pregnant women and women of childbearing age who may become pregnant are advised by the CDC to postpone travel to affected areas until more information becomes available about mother-to-child transmission.⁵⁹

Algorithms for the care of pregnant women and women of childbearing age who may have been exposed to Zika virus are available from the CDC⁴¹ at www.cdc.gov/mmwr/volumes/65/wr/mm6505e2.htm.

Male partners of pregnant women

Since the length of time that Zika virus remains viable in semen is not known, men who have traveled to Zika virus-endemic areas and who have pregnant partners should refrain from having sex or use a condom with every sexual encounter through the duration of the pregnancy.⁶⁰

Guidelines for prevention of sexual transmission of Zika virus are available from the CDC⁵⁹ at www.cdc.gov/mmwr/volumes/65/wr/mm6505e1er.htm.

The clinical presentation is similar to those of dengue and chikungunya, confounding the diagnosis

Infants with possible congenital Zika virus infection

Zika virus testing is recommended for any infant born with microcephaly or intracranial calcifications or whose mother has positive or inconclusive testing if the mother had visited an endemic area during her pregnancy.

Zika virus testing in infants consists of serologic IgM determination and RT-PCR for both dengue and Zika virus drawn concurrently in the first 2 days of life.³⁶ Umbilical cord blood can be used. In addition, if cerebrospinal fluid is being collected for other reasons, it can also be tested for Zika virus. The placenta and umbilical cord should be saved for immunohistochemistry testing for Zika virus.⁶¹

An infant who tests positive or inconclusive for Zika virus, regardless of the presence of microcephaly or intracranial calcifications, should have a complete physical examination specifically evaluating growth parameters, estimated gestational age, and signs of neurologic disease, skin rashes, hepatosplenomegaly, or any dysmorphic features. Additional evaluation includes an ophthalmologic examination in the first month of life to evaluate for macular atrophy.³⁶ An ultrasound scan of the head should be completed if it has not been done. Hearing is screened in all newborns, and hearing testing should be repeated at 6 months of age.³⁶

Infants with microcephaly or intracranial calcifications should also have consultations with specialists in genetics, neurology, and pediatric infectious diseases.⁶¹ These infants should have blood work including complete blood cell counts and liver function testing that includes alanine aminotransferase, aspartate aminotransferase, and bilirubin levels.³⁶

All infants with possible congenital Zika virus infection should be followed long-term with close attention to developmental milestones and growth parameters including occipital frontal head circumference measurements.^{61,62}

Infants without microcephaly or calcifications whose mothers had negative Zika virus test results or were not tested for Zika virus should have routine care.³⁷

Guidelines for the care of infants with Zika virus infection are available from the CDC³⁶ at www.cdc.gov/mmwr/volumes/65/wr/mm6503e3.htm.

TREATMENT

There is no treatment for Zika virus infection, and care is supportive. Most infections are mild and self-limited.^{12,15} Avoidance of aspirin and other nonsteroidal anti-inflammatory drugs that may affect platelets is important until dengue infection has been ruled out.

PREVENTION

There is currently no vaccine to prevent Zika virus infection. Women who are pregnant should avoid travel to any area where Zika virus transmission is occurring.^{41,59} The CDC advises pregnant women and women of child-bearing age who may become pregnant to postpone travel to Zika virus-affected areas.⁵⁹ Patients can find travel alerts for specific areas at wwwnc.cdc.gov/travel/notices/alert/zika-virus-south-america.

Avoiding mosquito bites is the best way to prevent the spread of Zika virus. *Aedes aegypti* and *A albopictus*, the most common vectors of Zika virus, can bite at night but are known more for being aggressive daytime biters.⁶³ Travelers should apply an Environmental Protection Agency-registered insect repellent as directed, wear long-sleeved shirts and long pants, use permethrin-treated clothing and gear, and stay in places with screens or air conditioning. Any containers with standing water should be eliminated as they are breeding areas for mosquitoes. It is also important that symptomatic people in the first week of illness use mosquito precautions to prevent the spread of Zika virus.

Patient handouts and posters for mosquito bite prevention can be found at www.cdc.gov/zika/fs-posters/index.html.

WATCH FOR UPDATES

Many questions remain regarding the epidemiology of this infection and its relationship to neurologic and pregnancy complications. However, due to its rapid spread across the Western hemisphere and its potential for significant complications, much is being done at the local and international levels to better understand the virus and halt its spread. More information will continue to be available as results from ongoing studies are conducted and potential associations are investigated. Until

more is known, providers should familiarize themselves with the latest guidelines in order to better counsel their patients who may live

in or travel to Zika virus endemic areas. We advise clinicians to follow the CDC's web site, www.cdc.gov/zika/.

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ADDRESS: Michael Rajnik, MD, Department of Pediatrics, F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814; michael.rajnik@usuhs.edu