Zika Virus in the Americas: A Review for Clinicians

Priya Sampathkumar, MD, and Joyce L. Sanchez, MD

Abstract

Zika virus has recently emerged as a new public health threat. An arthropod-borne virus named after the Zika forest in Uganda, it was first discovered in 1947. The virus caused only sporadic cases of Zika infection in Africa and Southeast Asia until 2007, when the first large outbreak occurred in the Yap State in the Federated States of Micronesia. Another outbreak in French Polynesia in 2013 was notable for being associated temporally with an increase in cases of Guillain-Barré syndrome. In 2015, the virus was first reported in Brazil and since then has spread explosively through several additional countries in South and Central America and the Caribbean. Simultaneously, several of these countries have seen a dramatic increase in the incidence of infants born with microcephaly. The rapid spread of Zika virus through the Americas, together with the association of infection with microcephaly and Guillain-Barré syndrome, has resulted in the World Health Organization declaring a public health emergency. Zika virus has the potential to spread to new areas where the Aedes mosquito vector is present and therefore presents a risk to the United States. This concise review describes the clinical features of Zika virus infection and provides advice for clinicians on counseling travelers and others about the disease.

HISTORY AND EPIDEMIOLOGY

The Zika virus was first identified in 1947 in the Zika forest near Kampala, Uganda, in a rhesus monkey that was part of a yellow fever research study.\(^1\) Serologic studies identified human Zika infections in several African countries including Uganda, Nigeria, Tanzania, Egypt, Central African Republic, Ivory Coast, Sierra Leone, and Gabon over the next several decades. In addition, sporadic cases were reported in Southeast Asia including Malaysia, Indonesia, India, Cambodia, Pakistan, Philippines, Singapore, Thailand, and Vietnam. In April 2007, an epidemic of rash, conjunctivitis, and arthralgia was reported from Yap State, Federated States of Micronesia.\(^2\) This epidemic represented the first documented outbreak of Zika virus infection; it was estimated that 70% of the island’s population was infected with Zika virus over a 13-week period. In 2013, another large outbreak was reported in French Polynesia. This outbreak was notable because although most clinical cases presented with mild disease, an association with Guillain-Barré syndrome (GBS) was first noted.\(^3,4\) The incidence of GBS cases during the outbreak was 20-fold higher than expected. There were subsequent small outbreaks in Oceania but relatively few cases until May 2015, when another outbreak was identified in Brazil.\(^5\) Since then, the virus has been detected at an increasing rate in several countries in South and Central America and the Caribbean (Figure 1).\(^6\) In September 2015, reports of an increase in the number of infants born with microcephaly in Zika virus–affected areas began to emerge.\(^7\) On February 1, 2016, the World Health Organization (WHO) declared that the Zika virus outbreak constituted an international public health emergency because of the possible link to microcephaly and other neurologic syndromes. The WHO declaration represents its highest level of alert and has only been invoked 3 other times so far—in 2009 during the H1N1 influenza epidemic, in May 2014 when poliomyelitis reemerged in Pakistan and Syria, and in August 2014 with Ebola virus.

TRANSMISSION

Zika virus is primarily transmitted to humans through bites from *Aedes* mosquitoes. Both *Aedes aegypti* (confined to tropical and subtropical regions) and *Aedes albopictus* (found in temperate regions in addition to tropical and subtropical areas) are capable of transmitting Zika virus and have been implicated in outbreaks of Zika virus. Both *Aedes* species are present in the United States. *Aedes albopictus* is of particular concern because it has a much wider range than *A aegypti*. It was originally imported from Southeast Asia and has been remarkably adaptable to cooler climates. *Aedes albopictus* is now firmly established in several states in the United States.\(^5\) It is an aggressive daytime biter and thrives in densely populated urban environments. As the number of returning travelers with Zika virus disease increases, the presence of the *Aedes* vector in the United States makes local spread a serious possibility (Figure 2).

Other modes of transmission are possible, but it is unclear how much of a role they play in propagating outbreaks. Sexual transmission of Zika virus was first reported in 2011.\(^10\) An American researcher acquired Zika virus in Senegal, became ill after returning home to Colorado, and transmitted the infection to his wife who had not traveled outside the United States. There have been 2 lab-confirmed cases of sexual transmission of Zika virus in the US during the current Zika outbreak; several additional cases are under investigation.\(^11\) The virus was first isolated from sperm during the Polynesian outbreak.\(^12\) It is not known how long the virus persists in sperm or whether asymptomatic persons infected with Zika virus can transmit infection to sexual partners. The disease is associated with viremia, so not surprisingly, transfusion-related transmission has been reported.\(^13\) The virus is detectable in breast milk,\(^14\) but breastfeeding-associated transmission has not been reported so far.

PATHOGENESIS

Zika virus is an RNA virus that is closely related to other flavirviruses including yellow fever, dengue virus, Japanese encephalitis, and West Nile virus. Little is known about its pathogenesis; however, it is thought that viral replication occurs in local dendritic cells after inoculation from a mosquito with subsequent spread to lymph nodes and the bloodstream. Viremia is generally seen within 3 to
4 days of symptom onset. Virus is detectable in blood as early as the day of illness onset and as late as 11 days after onset. The virus has also been detected in urine, sperm, and saliva of infected individuals.

**CLINICAL MANIFESTATIONS**
Evidence from case reports and experience from related flavivirus infections indicate that the incubation period of Zika virus is likely 3 days to 2 weeks. Approximately 80% of individuals infected with Zika virus have no symptoms. When they occur, the symptoms of Zika infection are typically mild. Most commonly seen are fever, itchy maculopapular rash (Figure 3), nonpurulent conjunctivitis, and arthralgia involving the small joints of the hands and feet. Myalgias and headache, including retro-orbital pain, can also be present. Symptoms generally resolve in a few days. Unlike yellow fever and dengue infections, death, hemorrhagic complications, or severe illness requiring hospitalization are very rare. Zika virus infection does not have features that clearly distinguish it from mild cases of other arboviral diseases, although rash is more common with Zika virus. Guillain-Barré syndrome was first reported in association with Zika virus in the French Polynesian outbreak in 2013. In July 2015, Brazil reported neurologic syndromes in patients with a recent history of Zika virus infection. Of 42 patients with confirmed GBS, 26 (62%) had a history of symptoms consistent
with Zika virus infection. In 2015, a total of 1708 cases of GBS were registered nationwide, representing a 19% average increase from the previous year. Colombia, El Salvador, Suriname, and Venezuela have also reported an observed increase of GBS.20

Most notably, Zika virus has been in the press because of an association with microcephaly in newborns (head circumference \( \geq 2 \text{ SD below the mean for sex and gestational age at birth} \)). Between 2010 and 2014, approximately 150 to 200 children per year were born with microcephaly. In October 2015, the Brazil Ministry of Health reported a 20-fold increase in cases of microcephaly—mostly in northeast Brazil, which also had a high prevalence of suspected cases of Zika virus infection. Although causation has not been established, several investigations have suggested a link between maternal infection and microcephaly in infants. Zika virus RNA has been identified by reverse transcription—polymerase chain reaction in the amniotic fluid of women whose fetuses had microcephaly and in tissues of infants with microcephaly.21 It has also been found in tissue from fetal losses from 4 women who were infected during pregnancy.7 In another study, all mothers of a Brazilian cohort of 35 infants born with microcephaly had lived in or visited an area affected with Zika virus during their pregnancy. Abnormalities in the infants consisted of widespread brain calcifications and ventricular enlargement secondary to cerebral atrophy. All tested negative for other infections including syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus infections. A recent report provided information on a European woman who had a clinical syndrome compatible with Zika virus infection at 13 weeks of gestation while living in Brazil.22 Ultrasonography at 14 and 20 weeks of gestation detected no abnormalities but revealed microcephaly at 29 weeks of gestation. The mother underwent termination of the pregnancy. At fetal autopsy, microcephaly with multifocal calcifications in the cortex and subcortical white matter, severe hydrocephalus, and hypoplasia of the brain stem and spinal cord were noted. The entire Zika virus genome was recovered from fetal brain tissue. No other
genetic abnormalities or other pathogens were found. These reports strongly support a link between maternal Zika infection and microcephaly. A case-control study is under way in Brazil to examine this association further and to determine whether other infections or environmental factors may be playing a role in the increased incidence of microcephaly.

A group of researchers have shown that, in vitro, the Zika virus is capable of infecting human neural progenitor cells. Infection resulted in disruption of cell cycle, increased cell death and attenuated neuron growth. Although this work is preliminary, the creation of this experimental model may pave the way for additional studies to determine the pathogenesis of microcephaly and other neurologic and ocular defects associated with Zika. Further studies are also needed to determine the prognosis for infants with congenital Zika virus infection. For infants with microcephaly from other causes, a spectrum of neurologic deficits ranging from mild to severe are seen and are usually lifelong.

DIAGNOSIS
Zika virus infection is generally diagnosed clinically with subsequent confirmatory testing. Testing for Zika virus should be performed in patients who experience symptoms while traveling in an area where Zika virus transmission has been reported or within 2 weeks of return. Because dengue and chikungunya virus infections have similar symptoms and geographic distribution, patients with suspected Zika virus infection should also be evaluated for these infections. Zika virus testing is currently performed only at the Centers for Disease Control and Prevention (CDC) Arbovirus Diagnostic Laboratory and at some state public health departments. It is not commercially available. Clinicians should contact their state or local health department to facilitate testing. Available tests include (1) reverse transcriptase–polymerase chain reaction on serum if within a week of symptom onset and (2) testing for Zika virus–specific IgM antibodies in serum for infection after 1 week of symptom onset. Cross-reaction with other flaviviruses (eg, dengue virus and yellow fever) is common, and test results should be interpreted with the assistance of an infectious disease specialist and the performing laboratory. The CDC has specific instructions for sending diagnostic specimens and completing the specimen submission form.

ZIKA VIRUS AND PREGNANCY
Women who are pregnant should avoid travel to areas where Zika virus transmission is ongoing. Updated information regarding areas with active transmission can be found on the CDC website.

If a pregnant woman cannot postpone travel, she should be advised to follow mosquito avoidance precautions. All pregnant women should be asked about travel history. Women who experience symptoms while traveling in an area where Zika transmission has been reported or within 2 weeks of return should be tested for Zika virus infection as soon as possible. Asymptomatic women who report travel to such areas while pregnant should be offered serologic testing for Zika virus between 2 and 12 weeks after return and should also undergo fetal ultrasonography (Figure 4). Guidance in this area is evolving rapidly as more data become available, and readers should refer to the CDC website for the latest recommendations. The CDC recently recommended that pregnant women should avoid unprotected sex with a partner who has a history of travel to a Zika infection risk area for the duration of the pregnancy.

Infants should be tested for Zika virus if they are born to women who traveled to an area with ongoing Zika virus transmission and have microcephaly or intracranial calcifications or if the mother has positive or inconclusive Zika virus test results.

Women of childbearing age who are planning travel to Zika-endemic areas should be counseled on ways to prevent unintended pregnancy. Although a causal link between Zika virus and microcephaly has not been established, public health agencies in several countries where Zika virus outbreaks are occurring have taken the unprecedented step of recommending that women living in these countries delay pregnancy for the next several months to years.

TREATMENT
There is no specific antiviral treatment available for Zika virus. Treatment is focused on symptomatic relief including rest and hydration. Fever may be treated with acetaminophen. Aspirin and other nonsteroidal anti-inflammatory drugs can be used after dengue virus has been ruled out
to reduce the risk for hemorrhage but should be avoided in pregnant women. Antihistamines may be helpful to control itching in patients with a rash. Patients with suspected Zika virus infection should be protected from further mosquito exposure during the first few days of illness to prevent other mosquitoes from becoming infected and thus reduce the risk of local transmission.

PREVENTION
There is no vaccine available to prevent Zika virus infection. The mainstay of prevention is minimizing exposure by controlling mosquito populations and avoiding bites. Mosquito control efforts have been hampered recently by a report from Argentina32 blaming pyriproxyfen (a pesticide used to kill mosquito larvae in standing water) rather than Zika for the increase in fetal loss and microcephaly in Brazil. Investigators from the WHO, US Environmental Protection Agency, and European Union have found no evidence that the larvicide affects the course of pregnancy or the development of a fetus. The product has been used in Brazil since the late 1990s without being linked to microcephaly.

For personal protection against mosquito bites, residents of or travelers to Zika transmission areas should be counseled to:

- Wear long-sleeved shirts, pants, and hats
- Apply insect repellent to exposed skin, especially during the day when Aedes mosquitoes are most active. The most effective insect repellent in the United States is diethyltoluamide at the recommended concentration of 20% to 50%. Other options include icaridin (concentration of at least 20%) and lemon eucalyptus extract (concentration of at least 30%). Diethyltoluamide- and icaridin-containing insect repellants are safe for use in pregnancy when used as directed on the product label.
- Treat clothing with permethrin
- Sleep under mosquito nets or in air-conditioned rooms with windows closed

The Table provides additional practical advice for persons considering travel to areas where Zika virus transmission has occurred.

ZIKA VIRUS INFECTION AND PUBLIC HEALTH IMPLICATIONS
Genetic studies indicate that the virus spreading through the Americas is closely related to the Asian strains of Zika virus that caused the outbreaks in Polynesia. The virus was possibly imported to Brazil by travelers attending the FIFA World Cup or alternatively by participants at the August 2014 International Va’a World Sprints canoe championship in which many Pacific island nations participated.33 This news

![Testing algorithm for pregnant woman with history of travel to an area with ongoing Zika virus transmission.27](http://dx.doi.org/10.1016/j.mayocp.2016.02.017)

**TABLE. Advice for Individuals Considering Travel to an Area Where Zika Virus Infection Is Circulating**

<table>
<thead>
<tr>
<th>Before travel</th>
<th>After travel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend personal protective measures to prevent mosquito bites</td>
<td>Recommend travelers to report symptoms compatible with Zika virus infection that occur within 3 weeks of return</td>
</tr>
<tr>
<td>Consider referral to a travel medicine professional</td>
<td>Recommend that travelers avoid donating blood for 28 days after return</td>
</tr>
<tr>
<td>Counsel on ways to avoid unintended pregnancy during travel</td>
<td>Recommend that men avoid unprotected sex with a pregnant partner for the duration of pregnancy</td>
</tr>
<tr>
<td>Recommend against travel if pregnant</td>
<td>Recommend that pregnant women report travel that has occurred during pregnancy to their antenatal care professional so that appropriate monitoring can occur</td>
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comes just as Brazil is preparing to host another enormous sporting event—the Olympic Games in August 2016. An estimated 500,000 visitors including 200,000 from the United States are expected to travel to Brazil to attend the games. If the Zika virus outbreak is not contained by then, some of these visitors could become infected and carry Zika virus infection back to their home country and, given the right mosquito vector, set off additional outbreaks.

The *Aedes* mosquito is well established across the Americas except for Canada and Chile and therefore all these areas are potentially at risk. Experts have stated that because of extensive mosquito control activities in the United States, the risk of Zika virus spread is low. Chikungunya and dengue viruses, other *Aedes*-borne infections, have not spread in the continental United States despite major outbreaks in the Caribbean. In contrast, West Nile virus, another mosquito-borne illness spread by the *Culex* mosquito, first appeared in the United States in 1999 and by 2014 was well established in all 48 contiguous states and the District of Columbia.

Climactic conditions may have played a role in the recent explosive spread of Zika virus in South America. Southern Brazil and Uruguay had an unusually wet winter followed by a warm summer. Standing water on the ground in winter serves as mosquito breeding grounds and may have spurred growth of mosquito populations. *Aedes* mosquitoes are most active in warm weather. Individuals tend to spend more time outdoors in warmer weather, which facilitates transmission of Zika virus. Drought conditions are associated with storage of water in containers around households, which can further promote mosquito breeding.

Zika virus disease is relatively mild. The biggest threat to public health from Zika virus comes from the association with neurologic syndromes including microcephaly and GBS. Managing these conditions is resource intensive and can place considerable strain on the medical system. Like Ebola virus, the disease has exposed vulnerabilities in the ability of resource-limited countries to handle infectious disease emergencies. Finally, Zika virus infection has raised ethical/moral/legal questions in Latin American countries, where health officials have suggested that women postpone pregnancies but women have limited access to birth control.

**Abbreviations and Acronyms:** CDC = Centers for Disease Control and Prevention; GBS = Guillain-Barré syndrome; WHO = World Health Organization

**Correspondence:** Address to Priya Sampathkumar, MD, Division of Infectious Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (samppathkumar.priya@mayo.edu).

**REFERENCES**

ZIKA VIRUS


