Zika virus, a mosquito-borne flavivirus that causes febrile illness associated with rash, has been rapidly emerging in the Western Hemisphere over the past few months. The virus was rarely identified until outbreaks occurred on Yap Island in the Federated States of Micronesia in 2007, French Polynesia in 2013, and Easter Island in 2014. It was initially detected in Brazil in 2015, in the northeast, and was subsequently identified in other states and several South American countries, including Colombia, Ecuador, Suriname, Venezuela, French Guyana, and Paraguay (1). Local transmission has been documented in Central America (Panama, El Salvador, Honduras, and Guatemala), the Caribbean (Martinique, Puerto Rico, Dominican Republic, and Haiti), and Mexico. Transmission has also occurred in travelers returning from the infected regions to nonendemic countries, including the United States, Canada, Japan, and Western Europe. As of 22 January 2016, a total of 20 countries and territories in the Americas have Zika virus circulation (1). The explosive spread mirrors the emergence of chikungunya, which was first detected in the Americas (St. Martin) in 2013 and rapidly disseminated throughout the region (2).

BACKGROUND AND EPIDEMIOLOGY

Zika is an RNA virus in the family Flaviviridae, genus Flavivirus. It is related to dengue, yellow fever, West Nile, and Japanese encephalitis viruses. It was initially isolated in the Zika Forest of Uganda in 1947 from a febrile rhesus monkey that was a sentinel for a surveillance project on jungle yellow fever (3). Subsequently isolated from Aedes africanus mosquitoes in the same forest in 1948 and intermittently from humans and mosquitoes since then, Zika virus is predominantly transmitted through the bite of Aedes mosquitoes; however, risk for infection via blood transfusion and sexual activity exists (4, 5, 6). Phylogenetic analyses suggest 2 major lineages, African and Asian, arising from a common Zika virus ancestor, possibly in Uganda (4). Numerous Aedes species have been reported to be possible vectors, including Ae. hesili in Yap, Ae. aegypti and Ae. polynesiensis in French Polynesia (5, 7, 8). Aedes aegypti and Ae. albopictus are present in much of the Americas, including many parts of the Southeastern and Southcentral United States as well as Hawaii (5).

Although past serologic surveys suggested the presence of Zika virus infections in Africa and Asia, few human cases were reported until 2007, when an outbreak of fever, rash, conjunctivitis, arthralgia, and arthritis occurred on Yap Island, Micronesia (7). Although initial serologic results were positive for dengue IgM, further testing by reverse transcriptase polymerase chain reaction (RT-PCR) confirmed Zika virus as the cause. An estimated 73% of Yap residents aged 3 years or older were infected with Zika virus; about 80% of infections were subclinical (5, 7).

In October 2013, Zika virus was first identified in French Polynesia and suspected to be responsible for an estimated 19,000 cases of a dengue-like syndrome by December of that year; the virus was closest to one isolated in Cambodia in 2010 (8). Circulation of Zika virus was subsequently detected in New Caledonia, Cook Islands, and Easter Island (Chile) in 2014 (1). By March 2015, cases of a dengue-like syndrome reported from Natal in the state of Rio Grande do Norte, Brazil, were confirmed to be Zika by RT-PCR. Thereafter, outbreaks have occurred in several states in Brazil and have spread rapidly in the Americas. As of 22 January 2016, a total of 20 countries and territories in the Americas have reported Zika virus infection (1). The Asian lineage has been responsible for all Zika virus outbreaks in the Pacific and the Americas.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms develop after a bite by a Zika-infected mosquito following an estimated incubation period of 2 to 7 days, similar to other flaviviruses (1). Patients typically present with a maculopapular rash (duration, 2 to 4 days; median, 6 days), arthralgias (duration, 1 to 4 days; median, 3.5 days), and conjunctivitis (7). Other reported symptoms include myalgias, headache, retroorbital pain, joint swelling, vertigo, and vomiting. Zika infection is generally mild and self-limited and resolves in a week (5, 7), whereas chikungunya infection can lead to persistent or relapsing arthralgia lasting months or longer (2). However, neurologic and autoimmune complications have been identified in the French Polynesian outbreak, particularly Guillain-Barré syndrome, as well as perinatal transmission (1, 5). Of great concern, additional cases of Guillain-Barré syndrome and a new association between Zika virus infection and microcephaly have occurred in Brazil, where a dramatic 3530 cases have been recorded as of the first week of 2016 (1, 5).

Diagnosis of infection is confirmed by RT-PCR during the first week of illness; viremia has been demonstrated from days 0 to 11 after symptom onset (4). Serologic testing (IgM on enzyme-linked immunosorbent assay) can detect the virus, although dengue may cause false-positive results; therefore, positive results should be confirmed by plaque reduction neutralization assays. Conversely, Zika virus infection can cause false-positive results for dengue. Zika virus RNA can also be detected in saliva and urine and may remain positive in urine for longer than in serum (9, 10). Further complicating diagnosis is the potential for co-infection with dengue (proven) and chikungunya (potential).
Treatment, Prevention, and Control

Treatment of Zika fever is supportive and primarily involves acetaminophen for fever, headache, or myalgia. As with treatment for dengue, nonsteroidal anti-inflammatory agents should be avoided if thrombocytopenia is present. Given the worldwide spread of dengue and chikungunya and the wide range of *Aedes* mosquitoes that can transmit Zika, prevention of infection relies on mosquito avoidance. These preventive measures include DEET- or picaridin-containing insect repellents to minimize risk from day-biting *Aedes* mosquitoes, drainage of mosquito breeding sites, and application of insecticides. There is no vaccine available.

Clinician Advisory

After the recent dissemination of chikungunya in the Western Hemisphere, the rapid spread of Zika virus since its arrival in the Americas reminds us once again of our global interconnectedness. Since *Aedes* mosquitoes are vectors for Zika as well as chikungunya and dengue, distribution of these infections overlap. Clinicians should advise patients to use antivector measures when traveling to regions with Zika transmission (Appendix Figure, available at www.annals.org). Given the possible association between Zika virus and microcephaly, pregnant women should avoid travel to areas that are reporting outbreaks or practice meticulous mosquito avoidance (including repellents containing DEET, picaridin, or IR3535, considered safe in pregnant and breastfeeding women) (5). Clinicians should consider Zika, dengue, and chikungunya in the differential diagnosis of febrile travelers with rash, arthralgia, and myalgia after travel to Central and South America and the Caribbean. Risk for introduction into the United States is substantial given the presence of *Ae. aegypti* and particularly *Ae. albopictus* mosquitoes in many states.

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Appendix Figure. Countries that have past or current evidence of Zika virus transmission (as of January 2016).