Zika virus belongs to the genus *Flavivirus* and is transmitted by *Aedes* mosquitoes, which are also capable of transmitting yellow fever, chikungunya, West Nile, and dengue viruses. Zika virus was first isolated from primates (rhesus monkeys) in Africa in 1947, and subsequently, from *Aedes africanus* mosquitoes trapped in the same forest in 1948. The discovery of Zika virus was the result of yellow fever research sponsored by the Rockefeller Foundation from 1914 to 1970. Zika virus was named after the Zika forest where it was first isolated. In February 2016, Zika virus disease was made a nationally notifiable disease to the CDC, and the World Health Organization (WHO) declared Zika virus disease a “public health emergency of international concern” following the emergence of pandemic spread within the Americas from Brazil in 2015, and its association with neurologic complications, such as microcephaly and Guillain-Barré syndrome (GBS). Most infections are asymptomatic (80%). When symptoms occur, they include fever, arthralgia, maculopapular rash, and conjunctivitis within 2 weeks of acquisition of the disease, but can persist for up to a week (mild dengue-like illness). Specific antiviral treatment or vaccine is unavailable at this time. This is a concise review about the virus during that recent outbreak.
Epidemiology
The first evidence of human infection by serology was reported from Nigeria in 1952. Subsequently, the first report of human infection was published in 1972 by isolation of Zika virus from 3 febrile patients. Zika infection in humans had been rare—most confirmed by serological methods—for the rest of the century, with fewer than 20 documented cases with sporadic appearances in Asia and Africa. The first documented outbreak of Zika virus infection outside of Africa and Asia occurred in April 2007 on Yap Island, Federated States of Micronesia, characterized by a febrile illness with arthralgia that was distinct from dengue because of conjunctivitis. Laboratory testing with rapid assays initially suggested dengue virus, but in June 2007, samples were sent to the CDC Arbovirus Diagnostic and Reference Laboratory, in Fort Collins, Colorado. Reverse transcription–polymerase chain reaction (RT-PCR) confirmed 90% nucleotide identity with Zika virus, concluding that the epidemic was due to Zika. Subsequently, estimates for a 3-month period reported that 5,005 (72%) of the 6,892 residents were infected with Zika virus or had clinical symptoms attributed to Zika.

The largest outbreak occurred in French Polynesia in 2013, affecting 11.5% of the native population. Most cases were asymptomatic, but noted GBS as a complication of Zika for the first time. Infected travelers from French Polynesia were believed to have spread the disease to New Caledonia, the Cook Islands, and Easter Island by late 2013 and early 2014. It is presumed that Zika virus was spread to South America in 2014 during the World Cup soccer competition held in Rio de Janeiro. Additionally, the World Sprint Championship canoe race was held in Rio de Janeiro in August 2014 where teams from French Polynesia, New Caledonia, the Cook Islands, and Easter Island participated, followed by subsequent reports of dengue-like syndrome consisting of arthralgia, fever, and conjunctivitis reported in the city of Natal, in northeastern Brazil. Phylogenetic studies revealed the strain that emerged from patient isolates in Brazil involved matched strains from French Polynesia of the Asian lineage. By late 2015, a rapid risk assessment by the European Centre for Disease Prevention and Control implicated the epidemic of microcephaly seen in Brazil to Zika virus infection during pregnancy. By January 2016, the Zika virus epidemic spread to 13 additional countries (12 in the Americas and 1 in Asia [Thailand]), and currently a total of 84 countries have evidence of vector-borne Zika virus transmission.

In the United States alone, after excluding the cases with congenital disease, a total of 5,285 cases of symptomatic Zika infections had been reported to CDC ArboNET for the period between January 1, 2015, and May 31, 2017. Of these, most (5,013; 94.8%) were acquired by travelers returning from affected areas, and a few by other modes of transmission (224 cases through local transmission from inland mosquitoes, 46 cases by sexual transmission, one case by laboratory transmission, and another case by an unknown route). In the US territories (American Samoa, Puerto Rico, and the US Virgin Islands), the total number of reported cases are 7 times higher (36,583 cases), of which most (36,440; 99.6%) were through local mosquito-borne transmission and the remainder from travelers.

Pathogenesis and Virology
Zika virus is a single-stranded RNA virus, which can be classified phylogenetically into African and Asian lineages. Virus particles are 40 nm in diameter with an outer envelope and inner dense core. After inoculation into a human host, the virus infects dermal cells (keratinocytes, fibroblasts, and dendritic cells) followed by migration to the lymph nodes and subsequently the bloodstream causing viremia. Endothelial cell tropism has...
been demonstrated to be the key factor enabling viremia, hence establishing infection.\textsuperscript{20} Much remains to be elucidated in the pathogenesis of Zika virus infection. Tropism of neural and placental tissue and amniotic membranes is mentioned subsequently.

**Clinical Manifestations**

Infection is asymptomatic in most cases. The incubation period ranges from 3 to 12 days, and all ages are susceptible with a female preponderance.\textsuperscript{21,22} The first well-documented report of Zika virus infection in humans was in 1964 by Simpson of his self-afflicted disease and experience.\textsuperscript{8} Symptoms initially began with headaches, followed by eruption of maculopapular rash on the face, trunk, and upper arms, including the palms and soles; fever and malaise were also present. By the end of the second day, his fever resolved with fading of his rash and improvement of his symptoms. By day 3, the fading rash was his only symptom, which resolved in two more days.\textsuperscript{8,23} In a retrospective study of 57 PCR confirmed cases of Zika virus at a 24-hour acute clinic in Rio de Janeiro, common clinical manifestations included exanthematous rash (98%), headache (67%), fever (67%), arthralgia (58%), myalgia (49%), joint swelling (23%), and conjunctivitis (39%).\textsuperscript{21}

During the Zika epidemic in French Polynesia, neurologic and autoimmune complications were first identified. At that time, 42 cases with GBS were identified (1.3 cases/1,000 population), of which 88% reported a viral syndrome suggestive of Zika virus infection within 30 days prior to the onset of neurologic symptoms. Brazil also witnessed an increase of neurologic complications of Zika.\textsuperscript{9} From January to July 2015, 121 cases were reported in northeastern Brazil, with 62% of patients reporting Zika fever preceding GBS.\textsuperscript{1,25}

In a prospective study to ascertain a causal link between Zika virus and GBS from November 2016 to March 2016 in 6 hospitals in Colombia, a total of 68 patients (97%) had symptoms compatible with Zika infection prior to the onset of neurologic manifestation consistent with GBS.\textsuperscript{26} The mean onset of GBS symptoms after initial Zika virus infection was 7 days. Among the 68 patients, 66 (97%) had limb weakness, 56 (82%) had ascending weakness, 52 (76%) had paresthesia, and 22 (32%) had facial palsy. Thirty-six of 46 patients (78%) who had nerve conduction studies had evidence of acute inflammatory demyelinating polyneuropathy subtype of GBS. Cerebrospinal fluid (CSF) analysis was performed in 55 patients, with 45 (82%) patients having albuminocytologic dissociation indicative of GBS. Among 42 patients who underwent sample testing of Zika via reverse transcription polymerase chain reaction (RT-PCR), results were positive in 17 (42%). The study also observed that GBS may occur simultaneously or immediately after initial Zika virus infection, suggestive of a parainfectious disorder rather than the classic postinfectious profile with other infections, such as *Campylobacter jejuni* infections.\textsuperscript{26}

**Zika Virus Infection in Pregnancy**

Current epidemiology demonstrates an association between Zika virus infection and various congenital central nervous system (CNS) abnormalities in the fetus, including ventriculomegaly, microcephaly, facial abnormalities, ocular abnormalities, hearing loss, and hyperreflexia.\textsuperscript{27-30} Additional defects include neural tube defects, joint contractures, clubfoot, congenital hip dysplasia, and congenital deafness.\textsuperscript{31} Neurotropism has been demonstrated in mouse brain cells and human neural stem cells and supports this association.\textsuperscript{32,33} Moreover, Zika virus also has been isolated from the brain tissue of demised fetuses infected with Zika virus.\textsuperscript{34,35}

Widespread transmission of Zika virus was recognized in Brazil in late 2014. Subsequently this was followed by a surge of reported cases of microcephaly by the Brazil Ministry of Health in October 2015.\textsuperscript{36} More than 85% of cases in Brazil from November 2015 have been reported in the northeastern state of Paraiba. Reported incidences of microcephaly have been between 5.7 per 100,000 live births in 2010 and 99.7 per 100,000 from November 2015 to January 2016.\textsuperscript{37} From November 2015 to February 2016, Brazil reported 5,280 suspected Zika virus–related cases of microcephaly and other CNS malformations, including 108 deaths.\textsuperscript{38} After the Brazilian microcephaly epidemic was reported, French Polynesians reviewed their CNS birth defects among fetuses and newborns of pregnant women during the prior Zika outbreak. Of the 17 cases with CNS malformations, 4 had serological evidence of Zika virus.\textsuperscript{9}

In response to the outbreak of Zika virus in the WHO Region of the Americas, the CDC issued a travel warning on January 15, 2016, advising pregnant women from traveling to Zika-endemic regions due to increasing concerns of risks for Zika-related birth defects. Further epidemiological research by the CDC laid the foundation for the US Zika Pregnancy Registry in 2016, with efforts to monitor pregnant women in the 50 states exposed to Zika virus from January 15 to December 27, 2016. In their analysis period, 1,297 pregnant women in 44 states who reported pregnancy complications were evaluated. The conclusion was that women in the first trimester of pregnancy had a significantly higher risk for Zika-related birth defects. The proportion of Zika birth defects was 50 times higher with Zika exposure compared with the pre-Zika years.\textsuperscript{39}
Transmission

Zika virus is transmitted from one vertebrate to another by the bite of Aedes mosquitoes, which are distributed globally in the tropics and sub-tropics. Zika virus was first isolated from A. africanaus mosquitoes in 1948. Later, the first isolate of Zika virus in Asia was discovered in Malaysia in 1966 in Aedes aegypti mosquitoes (a major vector in Asia). Numerous other species, including Aedes apicoargenteus, Aedes luteocephalus, Aedes albopictus, Aedes bensilli, Aedes vittatus, and Aedes furcifer; also can transmit Zika virus. Following a blood meal from an infected individual or nonhuman primate (reservoirs), Zika virus multiplies and is transmitted to another individual during the next meal. The incubation period in mosquitoes is reported to be 10 days, and viral content remains high from 20 to 60 days. Nonvector modes of transmission that have been described include sexual, vertical, transfusion related, and laboratory exposure. Sexually transmitted Zika virus is a risk to travelers returning from the Americas and nonhuman primates (reservoirs), Zika virus multiplies and is transmitted to another individual during the next meal. The incubation period in mosquitoes is reported to be 10 days, and viral content remains high from 20 to 60 days. Nonvector modes of transmission that have been described include sexual, vertical, transfusion related, and laboratory exposure. Zika virus RNA can be detected through reflex RT-PCR within a week of symptom onset in serum and urine samples, and this should be the first-line test within the first 2 weeks. This test is available through state public health laboratories from the CDC (Trioplex reflex RT-PCR, which detects Zika, dengue, and chikungunya viruses), and results are usually available within 2 weeks.

Positive Zika virus confirms diagnosis, but a negative Zika RT-PCR result does not necessarily exclude diagnosis, because viremia can be brief—as short as 5 days or fewer. Serological testing for Zika virus (immunoglobulin M [IgM] antibodies) is also available, and IgM antibodies usually develop after 7 days from the onset of illness and can last for 12 weeks; this is helpful when RT-PCR is negative. Zika IgM antibody capture enzyme-linked immunosorbent assay is used for qualitative detection of Zika virus IgM antibodies in serum or CSF fluid. Usually serological testing is recommended first line, in patients whose samples are collected more than 2 weeks from symptom onset. Specificity is limited, as false-positive results can arise from antibodies directed against other flaviviruses, such as dengue virus. When serology is performed, a reflex RT-PCR must be done if IgM turns positive, as viral RNA rarely may still be detectable for longer periods for certain specimen types. Serology testing for other endemic flaviviruses in that travel zone of exposure also must be considered.

For pregnant women who have traveled to endemic areas, becomes unreliable. Hence, laboratory diagnosis is essential, and one should also consider testing for dengue and chikungunya viruses in addition to Zika. Common nonspecific abnormalities in all arboviral diseases include leukopenia, thrombocytopenia, and transaminitis. Apart from clinical features, history of travel and activity are important to aid clinical suspicion.

Diagnosis

In an epidemic, preliminary diagnosis of Zika may be made on clinical grounds. Case definition has been issued by the Pan American Health Organization for countries with local transmission: rash that is usually pruritic and maculopapular, low-grade fever (around 38.5°C), arthralgia, myalgia, conjunctival hyperemia or nonpurulent conjunctivitis, and periarticular edema. In areas without local transmission or vectors, additional criteria include a history of travel or residence in a geographic area with known documented local transmission or unprotected sex with someone who traveled to areas with known transmission/vector presence within the prior 2 weeks. However, because clinical presentation of other arboviral diseases, such as dengue and chikungunya, are similar, diagnosis that is based on clinical grounds alone
RT-PCR testing is recommended within 2 weeks on both serum and urine samples, and if more than 2 weeks from last possible exposure and IgM is positive, then RT-PCR testing also must be performed. In endemic areas, surveillance by serology is a recommended part of routine obstetric care, and if positive, RT-PCR is recommended.47

Treatment and Vaccinations

There is no specific treatment for Zika virus other than rest and supportive care. Antipyretics are used for fever. Good hydration is recommended. No vaccines are available at this time. However, bench research and human trials are underway to create a Zika vaccine in the United States. The proposed Zika vaccine would be a third-generation DNA vaccine.48,49 The Zika vaccine, GLS-5700, has achieved animal experimental success with mice, monkeys, and rabbits. It is now in the first phases of clinical trial in humans. First-generation Zika vaccines rely on killed, live, or attenuated whole organisms. Second-generation vaccines use subunits of Zika virus. The third-generation vaccine consists of a DNA vaccine injected subcutaneously and with a technique known as electroporation, of which electrical impulse stimuli force DNA into host cells following recognition by the host immune system, mounting an immune response.50

Research in multiple fronts is ongoing for Zika treatment. Brazilian researchers tested the uridine nucleotide analog antihepatitis C virus drug, sofosbuvir (Sovaldi, Gilead), as a potential cure for Zika, given that HCV also falls under the genus Flavivir.51 Sofosbuvir inhibited Zika virus replication in baby hamster kidney fibroblast (BHK-21) cells and in an SH-SY5Y human-derived cell line. Sofosbuvir targets Zika virus RNA polymerase activity. As opposed to ribavirin and interferon, sofosbuvir is nonteratogenic.50,51

There is ongoing research with chloroquine, an antimalarial drug, and its ability to reduce the number of Zika-infected cells, virus production, and cell death; it has been tested on human brain endothelial cells and neural stem cells. Chloroquine appears to work in the early stages of Zika virus infection. Conversely, chloroquine has no effect on the virus 24 hours post-infection. Chloroquine can also be safely given during pregnancy.51 Azithromycin, the commonly used macrolide antibiotic through unknown mechanisms, also has been shown to inhibit Zika virus replication. Azithromycin inhibited the virus in a glial cell line and prevented viral induced cytopathic effects at clinical achievable concentration.53

Conclusion

Since the advent of the Zika epidemic in Brazil in 2015, there have been significant advancements in understanding the pathogenesis and transmission of Zika virus, particularly the neurologic manifestations and the devastating fetal malformations. More research is on the horizon for treatment and development of vaccines. In the meantime, the CDC recommendations are available for exposed travelers and to promote awareness of Zika worldwide. Recently, with the decline in the prevalence of Zika virus infections in the Americas, the CDC has released updated interim guidance for health care providers caring for pregnant women with possible Zika virus exposure, and for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection.54,55

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