Zika Virus
A Review and Clinical Updates

Jessica L. Anderson, MPAS, PA-C

Abstract: Zika virus is a recent mosquito-borne threat, yet many providers have limited knowledge of the virus and its potential complications. Current research indicates that Zika infection is associated with severe neurological conditions such as Guillain-Barré syndrome and is causative of congenital microcephaly and other birth defects. Given increasing global travel, domestic endemic areas in Florida and Texas, and the virus' diverse transmission routes, medical providers across specialties need basic understanding of the disease and its potential complications, as well as understanding of current Centers for Disease Control and Prevention guidelines.

Key Words: Zika virus, mosquito-borne illness, congenital microcephaly, Guillain-Barré syndrome, arbovirus

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Zika virus recently emerged as a threat in the Western hemisphere, heralded by the outbreak of microcephaly in Brazil in November 2015.[1,2] However, many providers in the United States may have limited knowledge of the virus and its potential complications. Its entrance into the United States through global travel and local transmission are real threats with potential for great morbidity. Zika has been associated with severe neurological complications, including congenital microcephaly if contracted during pregnancy.[3,4] Knowledgeable clinicians are necessary for prevention and public health initiatives to be effective. Because physician assistants are represented across specialties, they should be knowledgeable about Zika virus, its possible effects, and current Centers for Disease Control and Prevention (CDC) guidelines.

ZIKA HISTORY

Zika virus was discovered during surveillance of yellow fever in rhesus monkeys in the Zika Forest of Uganda in 1947.[1] It was originally endemic to Southeast Asia and Africa.[5] Sporadic human illness from Zika was documented starting in 1952, but the first outbreak was in 2007 with approximately 5000 cases reported among inhabitants of the Yap Island of Micronesia.[6,7] Another outbreak occurred in Cambodia in 2010.[7,8] In 2013, a larger outbreak occurred in French Polynesia, affecting at least 28,000 individuals who sought care (approximately 11% of the population).[7,8]

Not until the 2015 outbreak in Brazil was Zika virus a concern in the Americas. Current estimates indicate that 440,000 to 1,300,000 individuals were ultimately infected in Brazil during the 2014 to 2015 season.[2] Although Brazil's Zika epidemic began in late 2014, significant alarm began in November 2015 when Brazilian microcephaly incidence rates were found to have increased from 147 cases in 2014 to nearly 4000 suspected cases in 2015.[8] Since then, more than 26 countries in Central America, South America, and the Caribbean have reported local transmission of Zika.[9] These areas include Barbados, Bolivia, Brazil, Colombia, Costa Rica, Curaçao, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Nicaragua, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, the US Virgin Islands, and Venezuela.[9]

In the United States, 5234 laboratory-confirmed cases of Zika have occurred spanning 2015 to 2017, as of April 12, 2017. All states but Alaska have had at least 1 case, and most are travel related, as seen in Figure 1. All locally acquired cases have occurred in Florida and Texas (217 and 6 total cases each, respectively).[10]

ZIKA AND *AEDES AEGYPTI*

Zika is an RNA virus in the *Flavivirus* genus; it is an arbovirus.[1,5] Although several mosquito species carry Zika, the predominant specie is *Aedes aegypti*.[5,8] This mosquito has adapted to live in smaller bodies of water common in urban areas, such as rainwater collected in small domestic reservoirs.[5] The specie is most active in the morning and late afternoon.[1]

Their habitat has spread over time to tropical and subtropical regions of the Americas.[2,11] Because they have spread, so have the viruses they carry, including Zika, dengue, chikungunya, and yellow fever.[11–13] In fact, the Zika strain isolated during the outbreak in Brazil was closely related to strains isolated from the Cambodian and French Polynesian outbreaks.[8,14] Studies have shown that dengue and chikungunya outbreaks typically precede Zika outbreaks.[13] Moreover, because the *A. aegypti* is the common vector, these arboviruses can hit the same endemic areas in relatively rapid succession. For instance, the height of the Zika epidemic in Brazil was in 2015, and less than 2 years later, in April 2017, the Brazilian Ministry of Health declared an ongoing yellow fever epidemic affecting several Brazilian states.[15]

Although large epidemics of Zika are not expected in the United States, the CDC anticipates limited outbreaks where the *A. aegypti* mosquito is common; such outbreaks have already occurred in Florida and Texas, where warmer temperatures and greater humidity occur.[16] More extensive Zika outbreaks are theoretically possible in the United States because *A. albopictus* (the secondary mosquito vector to carry Zika) is geographically distributed in more northern regions of the continental United States than *A. aegypti*.[17,18] *Aedes albopictus* inhabits at least 32 states, as far north as New England, in both rural and urban settings.[5,17,18] One study found that the *A. albopictus* mosquitoes present in Florida were twice as susceptible to contracting and disseminating recent Zika strains than *A. albopictus* mosquitoes from Brazil.[19]

VIRUS TRANSMISSION

Most Zika transmission occurs from an infected mosquito bite.[20] However, alternate transmission routes exist, including sexual transmission, perinatal transmission, and blood transfusions.

From the Chatham University, Pittsburgh, PA.
Correspondence to: Jessica L. Anderson, MPAS, PA-C, Chatham University, 1 Woodland Rd, Pittsburgh, PA 15232. E-mail: janderson1@chatham.edu.
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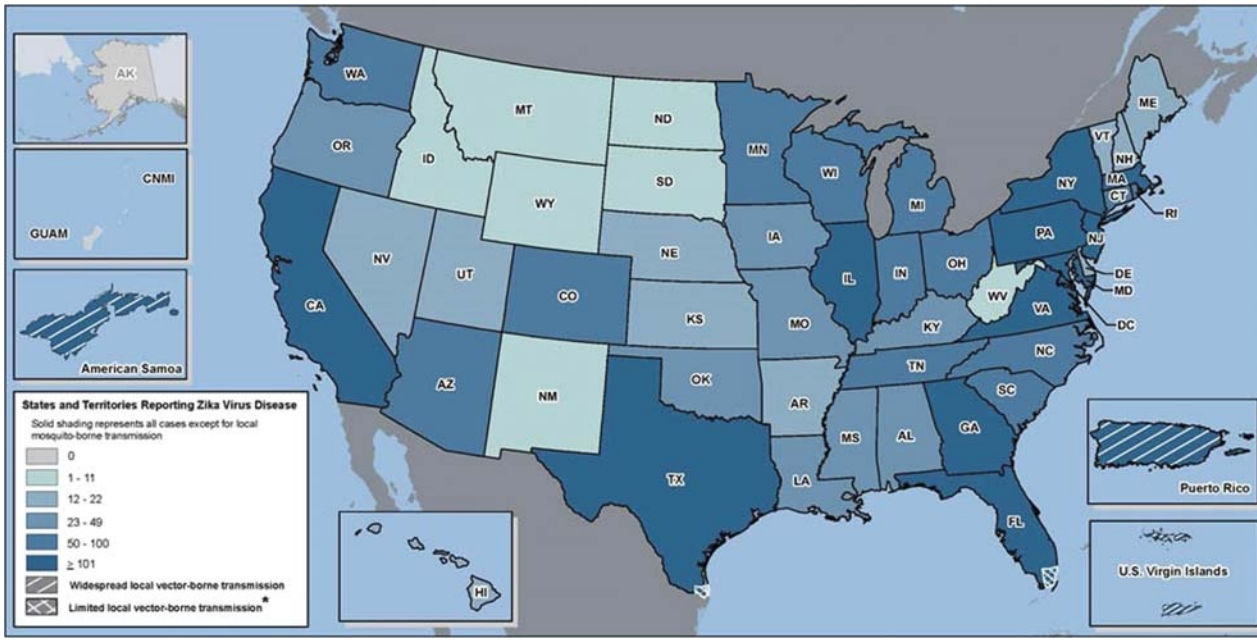

FIGURE 1. Zika cases reported in the United States. Laboratory-confirmed Zika virus disease cases reported to ArboNET by state or territory (as of April 12, 2017). This figure was borrowed in its current form from the CDC, and permission to use the figure has been obtained from the original publisher https://www.cdc.gov/zika/reporting/2016-case-counts.html.

It is impossible to know the extent of sexual transmission where local transmission also occurs; however, cases have been identified in sexual partners of travelers who have returned home to nonendemic areas.[21–24] A suspected case in which a man spread Zika to his wife occurred in Colorado in 2008; the wife tested positive for Zika and had never traveled to an endemic region, but the man, who had returned from travel to Senegal, did not have semen testing, and therefore, Zika status was inconclusive.[24] The first definite case of sexual transmission affecting a nontraveler in the United States occurred in Texas in February 2015.[24] Additional cases have occurred across the country since then.

Semen has been found to harbor active Zika virus up to 6 months after initial infection, during which time it may be transmitted to sexual partners.[25] On the basis of this, the US Food and Drug Administration (FDA) released donor screening recommendations in March 2016, which in part outlined criteria by which men at risk for asymptomatic Zika infection could be ineligible for sperm donation.[26] Ineligibility for sperm donation is based on confirmed diagnosis of Zika virus in the past 6 months, residence in or travel to a Zika-endemic area (including Florida's Miami-Dade, Broward, and Palm Beach counties) in the preceding 6 months, or sexual contact with a man known to have the previously mentioned risk factors within the preceding 6 months.[26,27] These FDA donor screening recommendations were to be implemented within 4 weeks of their initial release.[26]

Sexual transmission was initially thought to occur only in cases of infected men. There have been several cases of male-to-female transmission and 1 case of confirmed male-to-male transmission.[28] More recent reports indicate that female-to-male sexual transmission has occurred as well, and studies have detected Zika virus in vaginal fluid.[18,19] No cases of female-to-female sexual transmission have been reported but are considered possible.

Zika can be transmitted through blood transfusions.[9,10] Standard screening for blood donors would prevent donation by those with symptomatic disease, but not during incubation or asymptomatic infection.

Zika has been detected in amniotic fluid and placental tissue, and perinatal transmission does occur.[29] Evidence of Zika can also be found in breast milk, but studies have not found actively replicating virus in these cases; transmission via breastfeeding is thought to be unlikely.[9,29] Zika has been detected in human saliva, although the effect on transmission is unclear.[30]

CLINICAL PRESENTATION

For most individuals, Zika infection occurs without symptoms; only 1 in 5 individuals has symptoms.[1,20] In symptomatic individuals, it is a denguelike syndrome marked by fever, headache, macular/maculopapular pruritic rash, arthralgias, and conjunctivitis.[1] Symptoms are mild and commonly resolve within a week.[1] The incubation period is thought to be a few days before symptom onset.[1]

Zika virus should be considered in any patient with recent travel to an endemic area or sexual contact with someone who had been to these areas. Any patient with characteristic symptoms should be questioned about travel and sexual history.

No antiviral therapy is approved for Zika. Treatment is supportive. Acetaminophen alleviates pain and fever, whereas antihistamines relieve pruritus.[7]

COMPLICATIONS

Most individuals have no complications from Zika infection, and death is rare.[20] However, there are increased rates of neurological and autoimmune complications among individuals with Zika virus, including Guillain-Barré syndrome and acute disseminated encephalomyelitis.[4,20] There have also been effects to fetuses, including congenital microcephaly and possible miscarriage.[3]

Guillain-Barré syndrome was linked to Zika in the Polynesian and Brazilian epidemics.[4] Acute disseminated encephalomyelitis has been associated with Zika only in the most recent epidemic.[4] Both diagnoses are rare, systemic neurological conditions that can occur after immunological assault. It is suspected

that Zika either infiltrates neurological tissues directly or launches an immunological cascade.[4]

Zika-related microcephaly concerns began in response to the dramatic increase in Brazilian microcephaly rates in 2015. Initial theories for this increase varied. Some believed in causation immediately. Others felt that microcephaly diagnostic criteria were too broadly defined and based this on the fact that some reported cases were later attributed to other causes such as congenital rubella or found to be normal.[31,32] Still, others feared that there was no pathogenic cause but rather attributed cases to toxicity from larvacides used to control mosquitoes in affected regions.[33]

However, further research did determine that Zika causes congenital microcephaly and other abnormalities.[32,33] Congenital Zika infection results in characteristic damage on computed tomography brain imaging, including calcifications, cortical malformations, abnormally enlarged ventricles, abnormal corpus callosum, cerebellar hypoplasia, and hypodense white matter.[3,32–34] Other Zika-related congenital effects include excessive skin growth on the scalp, ocular damage to the macula, loss of foveal reflex, cataracts, and joint deformities.[3,33] A recent US study published in March 2017 reviewed population data in several states and found that the prevalence of these characteristic birth defects is 20 times higher since Zika has become a concerning pathogen in the United States.[35]

Zika's damage to the developing fetus is more severe during first and second trimesters. One study found that, the earlier Zika-related rash occurred during pregnancy, the smaller the head circumference of the infant at birth.[32] In fact, third trimester infection may not result in microcephaly, although other characteristic structural defects may occur.[32]

The CDC officially stated in April 2016 that Zika causes microcephaly and other congenital damage.[33] Current research varies but indicates that Zika-related birth defects are between 1% and 29%.[33] The most recent study looked at 1297 pregnancies affected by Zika in the United States during 2016, and 10% overall had Zika-related defects.[36] This notably included both symptomatic and asymptomatic infections. In addition, when cases involving laboratory-confirmed Zika infection specifically during the first trimester were reviewed, the rate was even higher at 15%.[36]

Zika infection has been implicated in fetal loss in some case studies.[37,38] In one, Zika was detected within various neural tissues of the fetus after fetal demise, subsequent induction, delivery, and autopsy.[37] In another, Zika was detected in placental amniotic epithelium, fetal mesenchymal cells, and perichondrium.[38] The probability of fetal loss with Zika infection remains unknown.

DIAGNOSTIC TESTING

Within 14 days after symptom onset (ideally within 5 days because of peak viremia) or last known exposure, serum is tested for active virus RNA using reverse transcription polymerase chain reaction.[7,39] Concurrently, urine should be tested because active virus can remain detectable longer in urine than blood.[39,40]

Negative serum and urine testing do not rule out Zika infection. If there is high suspicion for Zika, follow-up testing should include Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay testing of serum, which detects Zika-specific IgM antibodies.[7,39]

Serum testing lacks specificity in cases of concurrent or previous infection with dengue, yellow fever, or chikungunya, all of which can cross-react because of similarity of their viral structures; plaque-reduction neutralization testing is recommended to rule out cross-reactivity.[1,39]

Semen testing can detect active Zika virus much longer and at higher viral loads than other testing methods, even months after initial infection, but is not commonly performed because of perceived invasiveness and lack of application to both sexes.[25]

Definitive diagnosis is based on detection of active virus or Zika-specific antibodies. Zika-specific antibodies should be taken a second time after initial infection using plaque-reduction neutralization testing and are confirmatory if results are 4 times higher than initial titer.[7] At this time, testing is available through the CDC, some state/local health departments, and some commercial laboratories using various testing modalities.[39,41] The first commercial test available for Zika virus was through Quest Diagnostics.[42]

PUBLIC HEALTH INITIATIVES

Zika has been given significant attention by public health organizations including the World Health Organization and the CDC. It is a nationally notifiable condition in the United States.[20]

Most public health initiatives focus on surveillance, eradication, and control. At the community level, people are taught to overturn containers that can be filled with water, acting as breeding sites, and to use mosquito netting over beds at night. Topical insect repellants can be distributed for widespread use. Bodies of water and roof gutters can be treated with insecticides.

Research continues to identify and improve insecticides to which the *A. aegypti* mosquito is susceptible; government grants may incentivize such research.[1,16]

Although controversial, with potential environmental consequences, some advocate for release of genetically modified sterile male mosquitoes to thwart successful breeding.[43]

Countries with the greatest increases in microcephaly have recommended delayed childbearing until as late as 2018, when better prevention and eradication measures are hoped to be in place.[44] Travel advisories regarding high-risk areas are provided by the CDC to bring awareness and discourage unnecessary travel to these areas.

CURRENT CLINICAL GUIDELINES

Clinicians must consider Zika virus as a differential in any denguelike syndrome, especially if an individual has recently traveled or currently lives in an endemic area. Testing should proceed according to the most up-to-date guidelines provided by the CDC.

Current CDC guidelines recommend avoiding endemic areas, especially if pregnant.[45,46] If travel to an endemic area is necessary, use of personal protective measures is recommended, including wearing long sleeves and pants, using topical insect repellant, and using mosquito netting at night. These individuals should be educated as to effective and consistent implementation of these measures.

Patients who have traveled or will travel to endemic areas should be alerted of Zika's potential for sexual transmission; their sexual partners should be alerted as well. Current CDC guidelines recommend against all unprotected sexual contact (vaginal, anal, and oral) for a duration of 8 weeks for women and 6 months for men. This delay varies based on how long Zika is detectable within the female genital tract or semen and refers to time since last symptomatic or last possible exposure.[46]

Special care should be taken to discuss Zika's risks with pregnant women and to urge their avoidance of Zika-endemic areas. Prenatal screening with ultrasound for Zika-related abnormalities should be offered to potentially affected pregnancies; the CDC has a Web tool available to guide testing decisions.[45,47] If a pregnant woman has a male partner who will travel to an endemic area, abstinence or a barrier method of contraception should be used at least 6 months or throughout the remainder of the pregnancy.[45–47]

Travel history of the mother should be assessed in any case of infant microcephaly or other characteristic abnormalities to identify possible Zika exposure during pregnancy.

VACCINE PROGRESS

Currently, no vaccination exists for Zika. However, research continues toward production of one, especially considering Zika's potential complications and widespread distribution of *Aedes* mosquitoes.

In a study in *Nature*, researchers described production of both a DNA plasmid vaccine and an inactivated virus vaccine using Zika virus components that were safe and effective on mice.[48] In June 2016, the FDA approved a DNA plasmid vaccine produced by GeneOne Life Science Inc in collaboration with Inovio Pharmaceuticals to enter phase 1 clinical trials in the United States.[49]

Research gives hope that vaccination against Zika is possible, although efficacy and safety studies will likely take years. Also reassuring is success of vaccinations against other flaviviruses such as yellow fever and Japanese encephalitis.

CONCLUSIONS

Zika virus has complex and potentially severe ramifications on human health. Providers across specialties, including but not limited to infectious disease, primary care, infectious disease, women's health, and pediatrics/neonatology, play a vital role in prevention, management, and treatment. This is true even for providers outside endemic areas, because of diverse transmission routes and travel-related cases. All health care providers should have basic understanding of Zika's virology and potential complications on various organ systems. In addition, grasping the most up-to-date CDC guidelines is necessary to provide current and evidence-based management to patients at risk for or affected by Zika infection.

For the most current CDC guidelines regarding Zika virus, visit https://www.cdc.gov/zika/hc-providers/index.html.

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