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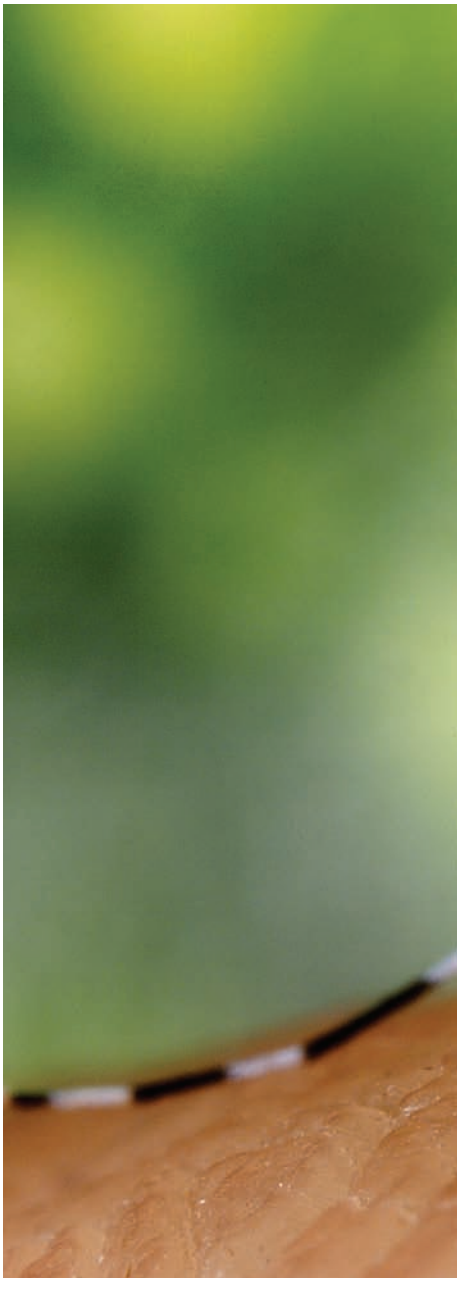
Zika virus

Facing a new threat

By R. Bryan Simon, BSN, RN, CNOR, FAWM, DiMM, and Tiffany L. Carpenetti, PhD



JAMES GATHANY, CDC

LIKE DENGUE and chikungunya, the Zika virus has spread beyond its region of origin in Africa to Central and South America and then to the United States.[1,2] Worried patients are asking their healthcare providers about the virus and its potential for transmission. Concern about this public health emergency is greatest among expectant parents: On February 1, 2016, the World Health Organization (WHO) declared the association of microcephaly with Zika virus infections to be a Public Health Emergency of Global Concern. On April 13, 2016, the CDC declared that the Zika virus can cause development of microcephaly in a developing fetus.[3,4] (See *Picturing microcephaly.*) In addition, Zika virus infection has been linked to Guillain-Barré syndrome (GBS) in adults.[5] However, most people who are infected don't have signs and symptoms, or experience only mild flulike symptoms that are self-limiting.

This article discusses what nurses need to know about Zika virus infection, including how it's transmitted and what healthcare professionals need to teach patients to minimize risks.

Epidemiology

Zika virus was first identified in 1947 in the Zika Forest in Uganda.[6] At the time, scientists were using caged monkeys as sentinels for surveillance of yellow fever virus when a previously unidentified virus was isolated from a febrile sentinel.[7] Since then, the virus has been isolated during outbreaks throughout Africa and Asia, where it's well established. However, the link to microcephaly in infants wasn't recognized until recently.[3,4]

Zika's epidemic potential was first demonstrated in an outbreak on the Yap Island of Micronesia in 2007, where about 70% of the population were infected.[8] The virus has now traveled worldwide, with infections identified in patients throughout Africa, Asia, Polynesia (including a significant outbreak on Easter Island), and the Americas.[9] A recent outbreak in Puerto Rico was confirmed with 1,072 cases of Zika infection identified

between November 2015 and early June 2016.[10]

Zika virus is considered endemic to Africa and Asia, where it's regularly found within portions of the population.[11] The virus circulates between primates and various *Aedes* mosquito species in an enzootic cycle.[12]

This virus has followed a pattern established by other mosquito-borne viruses such as chikungunya in its spread from endemic regions to areas that hadn't experienced outbreaks in the past.[9] This is likely due to the combination of increased global travel and the expanded range of suspected vector species.

The foundation for the new intensity of research into the Zika virus almost 70 years after its discovery was the sharp increase in reported microcephaly cases in Brazil potentially linked to Zika virus infection. From November 2015 until March 2016, 6,776 potential cases of microcephaly (average: 1,355 per month) had been reported. As of May 2016, 1,326 confirmed cases had been documented, with at least 208 resulting in an infant's death.[5,13] The previous average monthly totals from 2001 until 2014 were 13.5 cases per month (163 per year).[5]

The Zika outbreak in Brazil may have originated with infected spectators from endemic regions who attended the 2014 World Cup in Brazil.[14,15] The viruses isolated from the outbreak in the Americas most closely resemble the strains isolated from French Polynesia, suggesting that it was imported to the region by tourists.

The significant size of the current outbreak in Central and South America makes it highly likely that the virus is being transported by visitors to the region.[14] Imported infections occur in people who've traveled to areas with circulating virus who return home and then experience signs and symptoms. Such cases have been documented in Canada, the United States, Australia, Slovenia, and the Netherlands.[11,14,16,17]

Pathophysiology and transmission

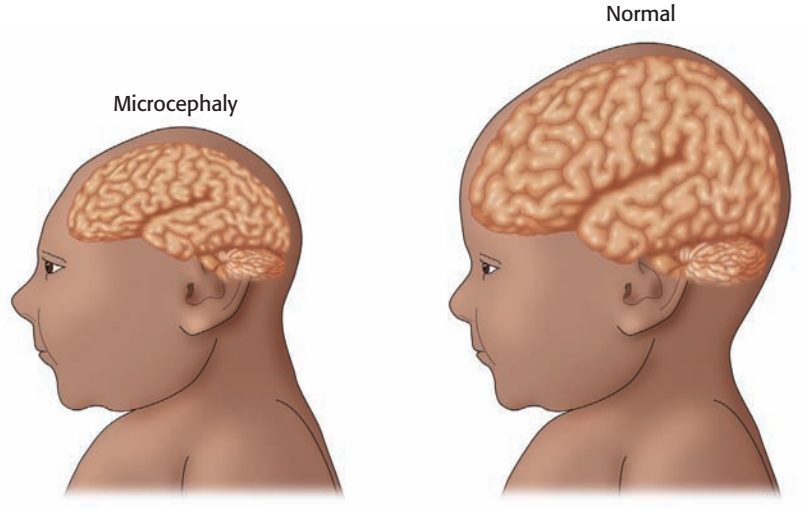
Zika virus is a single-stranded, positive-sense, RNA arbovirus of the *Flaviviridae* family.[6] (See *Glossary of terms*.) This is significant because the genome of +ssRNA viruses acts like mRNA in the cell and therefore doesn't have to cross the nuclear membrane to be made into protein. It's most closely related to Spondweni virus; its next nearest relatives include Ilhéus virus, Rocio, and St. Louis encephalitis viruses. Two major lineages, Asian and African, have been identified, with strains isolated from the outbreak in Brazil more closely resembling the Asian lineage.[6] Pathogenesis of this virus isn't well understood, but it may initially replicate in dendritic cells near the site of the mosquito bite and spread to lymph nodes and into the bloodstream.[12]

Zika virus is transmitted by mosquitoes of the Culicidae family, usually of the genus *Aedes*.[6] *Aedes aegypti* mosquitoes are considered an important vector because of their tendency to cohabitate with humans and breed in small pools of standing water. However, *Aedes albopictus* and many other *Aedes* species have also tested positive for Zika virus.[7] The virus circulates between viremic humans and mosquitoes in densely populated areas.

Combined, *A. aegypti* and *A. albopictus* currently have a range that covers the United States as far north as New York State and as far west as Texas, with sporadic populations appearing in Nevada and California.[18] Predictive models suggest that these ranges could increase to cover most of the United States, even as far north as Canada. If enough cases are imported to the United States for the virus to become established within vector mosquito populations, the Zika virus could spread across the country.

The warmer, wetter climate caused by El Niño, an ongoing pattern that can last for up to 2 years, is likely to increase the population of both significant vector species and their overlapping ranges.[19] Warmer temperatures and an increased risk of standing water pose significant challenges to mosquito population control and increase the likelihood of Zika becoming established in local mosquito populations. Further complicating this issue is the remarkable "ecological plasticity" of *A. albopictus*, as demonstrated by the species' ability to consistently increase its range

Picturing microcephaly



Monica Schroeder/Science Source

year by year, and also the ability to lay diapausing eggs that survive winter in a dormant state and contribute to the cold-hardiness of this vector.[20]

To date, no reservoir species for Zika virus has been identified. However, anti-Zika antibodies have been found in some large mammals and rodents.[6]

Sexual, transfusion, and prenatal transmissions

Besides transmission by mosquitoes, human-to-human sexual transmission of the Zika virus has been confirmed via both vaginal and anal sex with five and one cases reported in published medical literature, respectively, and a total of 10 cases confirmed by the CDC within the United States.[10,21] In one instance, a scientist was infected while traveling to Senegal. When he returned home, his wife, who hadn't left the United States, exhibited symptoms of a Zika virus infection 9 days after his arrival.[11] A man in Tahiti demonstrated replicative Zika virus in semen samples when he sought treatment for hematospermia.[22] Male-to-male sexual transmission was confirmed in a case reported in Texas, and the CDC continues to monitor additional potential cases of sexually transmitted Zika virus within the United States.[2,21]

As with other blood-borne pathogens, Zika virus has the potential for transmission via blood transfusion. This risk is elevated by the relatively high incidence of asymptomatic cases.[23] Historically, other flaviviruses have been transmitted through blood transfusion. Two possible cases of transfusion-derived transmission have been reported in Brazil, and surveillance in French Polynesia is ongoing.[24]

Within the United States, the FDA produced a document for blood collection and transfusion centers with recommendations for areas with and without active vector-borne transmission. As of June 16, 2016, the continental United States was considered a region without active vector-borne transmission. The recommendations for nonactive areas include providing educational materials and collecting a travel and medical history questionnaire from potential blood donors.[24] Areas of active spread of the virus require testing of the collected blood supply. An investigational test has been authorized by the FDA for Puerto Rico, the only current area of widespread active transmission within the United States and its territories.[25]

Widespread reports of the inexplicably high number of cases of microcephaly in Brazil highlighted the risk of perinatal transmission of this pathogen and emphasized the need for further research. Based on additional investigation, the CDC determined in April that the Zika virus is a cause of microcephaly.[3,4] Two possible hypotheses have been discussed in recent literature, including direct transfer and placental mediation.[26] According to the direct transfer hypothesis, the placenta conveys the Zika virus to the fetus and is the primary cause for the resulting teratogenic effects.[26] The placental mediation theory hypothesizes that microcephaly results from the placenta's immunoprotective response.[26]

A recent study in French Polynesia highlights two mothers and newborns with confirmed Zika infections that likely passed from viremic mother to child via the placenta or during delivery.[27] It's very likely the virus crosses the placenta given the anecdotal evidence of Zika virus in placental tissue and neural tissue samples of stillborn and aborted fetuses from infected mothers, and evidence of the virus in amniotic fluid samples of fetuses exhibiting microcephaly.[28]

Signs and symptoms

An estimated 20% of all individuals infected with the Zika virus become ill, and while most of these cases are very mild and self-limiting, signs and symptoms usually last from a few days to a week. The most common signs and symptoms include fever, maculopapular rash, arthralgia, malaise, and conjunctivitis. Other possible symptoms include myalgia and headache.[29,30] Severe symptoms indicating GBS include tingling and weakness in the extremities.

Because clinical manifestations often resemble those of dengue fever (flavivirus) and chikungunya (alphavirus), Zika virus infection is often misdiagnosed.[12,31,32] These diseases can be difficult to distinguish by reverse transcriptase-polymerase chain reaction (RT-PCR). After the first week of onset of signs and symptoms, virus-specific IgM and neutralizing antibodies begin to develop.[33] Because the current geographical distributions of these diseases overlap, coinfections can occur. Other differential diagnoses that should be considered for patients presenting with a similar cluster of signs and symptoms, with or without travel to endemic regions, include malaria, leptospirosis, rickettsia, group A *streptococcus*, rubella, measles, parvovirus, enterovirus, and adenovirus.[33]

Providers should be concerned about the links between Zika virus and microcephaly in newborns and to GBS in adults.[3,4,27,28] The WHO, the CDC, and medical researchers worldwide are currently investigating both neurologic disorders due to the increase of Zika-related microcephaly in nine nations, with substantial increases in Brazil, and the growing understanding of Zika-related GBS in

Glossary of terms

- *mRNA* is messenger RNA, a subtype of RNA containing portions of DNA code used for transmission to other areas of the cell for protein production.
- *Positive-sense* means that the RNA can be directly translated into protein by cellular machinery.
- *A reservoir species* is an animal that maintains blood serum levels of virus sufficient to infect biting mosquitoes.

13 nations.[5,34] (See *Nations with reported microcephaly cases* and *Nations with incidence of GBS after confirmed Zika infection.*) The causal relationship between Zika and microcephaly and GBS isn't clearly understood and continues to be a primary concern of medical research.[5]

Diagnosis and testing

Until recently, no commercially available, FDA-authorized diagnostic tests were available for the Zika virus. The preferred diagnostic test is the RT-PCR, which can be performed on serum, urine, amniotic fluid, and cerebrospinal fluid (CSF) ideally drawn within 7 days of the presentation of signs and symptoms. Throughout the early stages of the crisis, the CDC Arbovirus Diagnostic Laboratory (Division of Vector Borne Diseases—DVBD) located in Fort Collins, Colo., and several other state-level labs throughout the United States were the only facilities available to conduct this test.[33] Additional information about specimen collection and handling can be found at the CDC website; see the *CDC 50.34, Data and Specimen Handing (DASH)* form, which should be used by healthcare providers to properly collect and handle samples.[33]

Nations with reported microcephaly cases

These cases are potentially associated with the Zika virus, as of May 13, 2016.[5]

Country	Cases
Brazil	1,326
Cape Verde	3
Colombia	7
French Polynesia	8
Martinique	2
Marshall Islands	1
Panama	1
Slovenia	1*
United States	2*

*Likely acquired in Brazil, Mexico, Belize, or Guatemala.

In late February 2016, the FDA issued an Emergency Use Authorization (EUA) that authorized the use of a CDC-developed test called the Zika IgM antibody capture enzyme-linked immunosorbent assay (Zika MAC-ELISA) for use on drawn serum or CSF. Because these tests can often result in false positives, any positive or inconclusive test should be followed up with the submission of additional serum samples to the CDC lab in Ft. Collins for RT-PCR testing.[35]

On March 17, 2016, the CDC received a second EUA that allows urine, amniotic fluid, and CSF testing using the Trioplex Real-time rRT-PCR assay for patients suspected of having Zika. Although serum is preferred for accuracy, any tests conducted on urine, amniotic fluid, or CSF should be accompanied by a serum sample.[36] Both of these tests may be conducted at the CDC lab or select qualified labs across the United States.

On April 28, 2016, the FDA issued an additional EUA to Quest Diagnostics to allow use of their RT-PCR test at approved Focus Diagnostic laboratories. This temporary authorization allows providers to conduct the test for patients who have signs and symptoms suggestive of Zika and asymptomatic pregnant women who have a history of travel to an endemic region or have had a male sexual partner who's recently traveled to an endemic region. As with the other tests described, false negatives may occur and additional samples should be sent to CDC laboratories for follow-up analysis.

Because it's a nationally notifiable condition, providers must report any cases of suspected Zika virus to state and local health departments. They should follow the most recent instructions for submission of serum, urine, amniotic fluid, or CSF samples for RT-PCR or other tests listed on the CDC website.[33]

In March 2016, the FDA approved an investigational new drug (IND) application for a Roche Molecular Diagnostics test called cobas Zika to detect and screen for the virus within the donated blood supply in Puerto Rico.[25,37] This IND may be approved for use in the United States if active transmission is identified in the future.

Nations with incidence of GBS after confirmed Zika infection

Cases in these countries are potentially associated with the Zika virus, as of April 2, 2016.[5]

- Brazil*
- Colombia*
- Dominican Republic*
- El Salvador*
- French Guiana
- French Polynesia*
- Haiti
- Honduras*
- Martinique
- Panama
- Suriname*
- Venezuela*
- United States (Puerto Rico)

*These locations have reported an increase in GBS cases since the Zika virus was identified.

Treatment and prevention

At this time, treatment is supportive and consists of resting, maintaining hydration, and using acetaminophen for joint and muscle pain and headaches. Aspirin and nonsteroidal anti-inflammatory drugs aren't recommended until a definitive diagnosis of Zika virus infection is confirmed because these medications can exacerbate the risk of hemorrhagic fever if the patient has dengue instead of Zika virus infection.[33]

Due to concerns about microcephaly and other severe fetal brain defects caused by maternal Zika virus infection, fetuses and infants of women infected with Zika virus during pregnancy should be evaluated for possible congenital infection and neurologic abnormalities.[30]

If a patient develops signs and symptoms of GBS, treatment protocols

for this syndrome should be followed and a detailed recent history should be obtained. An autoimmune condition that affects components of the peripheral nervous system, GBS is often characterized by the gradual spread of weakness or tingling in the legs that progresses upward to the arms and face. Severe weakness or paralysis of chest muscles can result in respiratory difficulty. Some patients require ventilator support until their respiratory muscle strength returns. Although it can be life-threatening, GBS is usually self-limiting and most patients recover fully with no long-term sequelae.

Preventing mosquito bites begins with choosing the proper clothing and wearing it night and day. Wearing light-colored cotton clothing that's loose fitting and fully covers arms and legs is an outstanding preventive measure.[38]

Using synthetic and plant-derived oil repellents on exposed areas of skin is also recommended. The use of 24% DEET (*N,N*-diethyl-*m*-tolumide/*N,N*-diethyl-3-methylbenzamide) on exposed skin effectively reduces bites from the *A. aegypti* mosquito for an average of 5 hours, especially when used in conjunction with proper clothing.[38] Picaridin (1-piperidinecarboxylic acid, 2-[2-hydroxyethyl]-1-methylpropylester) has been found to be equally effective against the *Aedes* mosquito and one study showed it to be more effective against a strain of *A. aegypti* mosquito.[39-41] It's also approved by the CDC and U.S. Environmental Protection Agency (EPA) and is the active ingredient in some commercial products.[10] IR3535 (3-[N-butyl-N-acetyl]-amino-propionic acid ethyl ester) is approved by the CDC and the EPA for use on the skin.[42]

The effectiveness of DEET and other repellents deteriorates with time, while swimming, or when used in conjunction with sunscreen. Reapplication is recommended to ensure protective coverage while outdoors.

Because its signs and symptoms often resemble those of dengue fever and chikungunya, Zika virus infection is often misdiagnosed.

Plant-derived products that are effective repellents include permethrin, oil of lemon eucalyptus, and citronella. Permethrin, approved by the EPA for use only on clothing and gear, is protective due to its toxic effect on mosquitoes. It's the active ingredient in most commercially available clothing-based repellents.[42] A study in 2005 found that the use of permethrin on tents reduced mosquito bites on occupants by 36%.[43] Citronella (3,7-dimethyloct-6-en-1-al) is the least effective of all products against the *Aedes* mosquito, but it does confer some protection and is found in most insect repellent candles.[39] All these products are effective against mosquitoes, and, when used in conjunction with proper clothing choices, act as a substantive barrier to mosquito bites.[42]

All EPA-approved insect repellents are safe for use by pregnant women without added precautions. This is true also for children, although the EPA advises a restriction on the use of oil of lemon eucalyptus for children under age 3.[44] Measures should be taken to reduce mosquito breeding grounds by eliminating areas of standing water near the home. Using screens in windows and doors to prevent mosquito entry to indoor living spaces is recommended.[45]

Prevention of sexual transmission of the Zika virus begins with the use of condoms or abstinence. The CDC recommends that any male living in an endemic area or returning from travel to an area with widespread incidence of Zika virus should either abstain from sexual activity or use a condom during vaginal, anal, or oral sex due to the potential for disease transmission.[22] At this time, the duration of presence of the virus within semen isn't definitively known, but virus has been observed to be present for up to 10 weeks in isolated cases.[22,46]

All women of childbearing potential should observe the prevention recommendations described in this article. The CDC recommends caution when traveling to regions with active vector-borne transmission of Zika. Those considering traveling to the Caribbean, Central America, and South America should consider and understand the risks for both the mother and the fetus.[47] For pregnant women with a history of travel to a region with ongoing Zika virus transmission, the CDC recommends RT-PCR testing.[47]

Ongoing research and vaccine development

Looking ahead, the major topics of concern about Zika virus will be the development and deployment of a fast and reliable method of detection, further research on microcephaly and GBS related to this pathogen, and development of an effective vaccine. Currently, the only reliable method of detection in clinical samples is RT-PCR. This method is expensive and requires specialized equipment in

addition to sample sizes sufficient for RNA extraction. An assay is currently under development by the CDC that will simultaneously test for Zika, chikungunya, and dengue virus RNA.[10]

Unfortunately, the development of vaccines to combat RNA virus infections, especially arboviruses, is difficult and complicated. Due to the highly unstable nature of RNA, these viruses mutate rapidly and exist as "quasi-species" rather than as true species.[48] This complicates not only the development of effective vaccines, but also the creation of reliable diagnostic tests. Rapid changes in the genome of the Zika virus as it spreads across the globe should be expected, as should changes in signs and symptoms associated with this infection.

As with other arboviruses, control should be approached with a combination of vector reduction and vaccine development.[48] In the past, mosquito-borne diseases were effectively controlled with a combination of breeding-site reduction and insecticide application, especially DDT. Over time, however, the use of DDT has fallen out of favor because of its impact on the environment, and modern alternatives have proven less effective. Habitat reduction is still an integral part of reducing disease transmission.

As an alternative to the use of insecticides, some groups have developed genetically modified mosquitoes to combat the spread of mosquito-borne disease. Current techniques involve releasing large numbers of male mosquitoes with lethal traits, including genes that make females unable to fly and mate, and genes that kill mosquito larvae before they complete the pupal life stage.[50] Male mosquitoes don't feed on humans.

These strategies reduce the overall population of vector mosquitoes with reduced risk of persistence of genetically modified mosquitoes in the environment. This approach, which requires infrastructure to rear large numbers of males to be released, has shown promise in trials in the Caribbean and Central America. Local culture and popular opinion about genetically modified organisms can limit the use of this technology.

Information about the identification, diagnosis, treatment, and prevention of the Zika virus and its links to microcephaly and GBS continue to evolve with weekly and sometimes daily updates by the WHO and CDC. Healthcare professionals must stay abreast of these developments and be prepared to assist patients who are concerned or who present with signs and symptoms of this most recent public health emergency. More investigation is needed to determine the method of transmission and preventive measures to inhibit further Zika-related microcephaly birth defects. ■

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R. Bryan Simon, a contract cardiothoracic surgical nurse based in Fayetteville, W.Va., is owner/partner of Vertical Medicine Resources in Portland, Ore., and a director of Appalachian Mountain Rescue Team. He's also a member of the *Nursing2016* editorial board. Tiffany L. Carpenetti, who has a PhD in entomology, is the macromolecular science and engineering graduate degree program coordinator at Virginia Polytechnic Institute and State University in Blacksburg, Va. She's also a freelance/contract technical science writer in Christiansburg, Va.

Except where otherwise indicated, the information in this article was current on June 2, 2016. For updated information, refer to these websites: www.cdc.gov/zika/ and www.who.int/mediacentre/factsheets/zika/en/.

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