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Zika Virus What We Know and Do Not Know

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We keep hearing seemingly every day about Zika virus. With all the hype, we are dreading the coming spring and summer. How great is the risk? What are the symptoms of infection and what can be done? Where are the best sources of evidence for practice and patients?

Zika virus (ZIKV) is a rapidly expanding infection with confirmed cases in 18 countries of the Americas. This virus is related to the large family of other flaviviruses, which include *yellow fever virus, dengue fever virus* (DENV), and *Japanese encephalitis virus*, and most similar to the *spondweni virus* that is usually found in Africa. Transmission to humans is accomplished by a mosquito bite usually of the genus *Aedes*. However, other mosquito species have been identified as vectors as well. The primary vector for the 2015 to 2016 Zika outbreak has been identified as *Aedes aegypti*, which also transmits DENV.^{1,2}

Zika was first isolated in 1947 from a rhesus monkey in Uganda and in humans in 1952. Although the primary mode of transmission of ZIKV is vectorial, limited evidence suggests that transmission may also occur through sexual intercourse and through perinatal and occupational pathways. Sexual transmission has been described in 2 cases and the presence of ZIKV in semen was identified in 1 case.^{1–3}

The current outbreak in Brazil is not the first appearance of ZIKV. Epidemics occurred in western and south Pacific in 2007 and in 2013 to 2014 concomitantly with dengue fever outbreak. In the past, Zika infection was not correlated with significant symptoms and hospitalization rates were

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low. Nearly 80% of infections are asymptomatic and deaths are rare. $^{1,3}\,$

However, for some patients, symptom expression can be mild to severe. Signs and symptoms of ZIKV are similar to DENV and are described in Table 1. Viremia occurs between 3 to 5 days after onset of symptoms. Live virus as well as the viral RNA has been found in semen and urine weeks after initial symptoms and clearance of the virus from blood. Currently, there are no antivirals or vaccines for ZIKV.^{1,2}

The current Zika outbreak in Brazil began at the end of 2014, with reports of cases that were self-limiting and did not require intervention. However, in 2015, health officials identified a rise in neurological syndromes including Guillain-Barre syndrome in persons with history of Zika infection. Increasing numbers of infants born with microcephaly was also noted and reported to the World Health Organization in October 2015. By November, Zika was identified in blood and tissue samples of an infant that died and in cord blood sample from a newborn. The Ministry of Health of Brazil declared a public health emergency.^{1,2} Officials estimate that there were between 440 000 and 1 300 000 Zika cases in 2015 in Brazil. Since 2014, more than 5000 suspected cases of microcephaly have occurred compared to the 2010 to 2014 mean of 163 cases.¹

ZIKV & PREGNANCY

Emerging evidence as this article is being written links ZIKV infection during pregnancy with risks for early pregnancy loss and microcephaly. Pregnant women are advised not to travel to areas with active ZIKV infections. Women are also advised to consistently and correctly use condoms during sex (ie, vaginal intercourse, anal intercourse, or fellatio) and to abstain from sex during pregnancy with male partners who live in or have traveled to areas with active ZIKV transmission (http://www.cdc.gov/zika/geo/ index.html). Pregnant women who live in or must travel

Table 1. Symptom Burden for ZIKVInfection ^{1,2}
Frequent—lasts 2–7 days
Low-grade fever
Rash 4–7 days and pruritus
Conjunctivitis
Headache
Muscle pain
Joint pain
Less frequent
Nausea and vomiting
Gastrointestinal pain
Diarrhea

to areas with active ZIKV transmission should speak to their healthcare provider and strictly follow steps to prevent ZIKV infection acquisition from mosquito bites. Important information can be found at http://wwwnc.cdc.gov/travel/ page/avoid-bug-bites and at http://www.cdc.gov/zika/ transmission/sexual-transmission.html.⁴

On January 5, 2016, the Centers for Disease Control (CDC) issued a travel alert for pregnant women with a request to consider postponing travel to areas with Zika transmission. Early analysis in March of 9 US pregnant women who traveled to areas with Zika transmission revealed that 2 women experienced early pregnancy loss and 2 electively terminated their pregnancies. For the 3 live births, 2 infants were healthy and 1 infant had severe microcephaly. The 2 remaining pregnancies were progressing without complications. In the future, more information will be available on a new CDC registry for US pregnant women with confirmed Zika infection.⁵

The CDC has also updated guidance for persons considering pregnancy based on limited evidence regarding the persistence of ZIKV RNA in blood and semen. Women who have ZIKV disease should wait at least 8 weeks after symptom onset to attempt conception. Men with ZIKV infection should wait at least 6 months after symptom onset to attempt conception. For men and women with possible exposure to ZIKV without symptoms, both should wait at least 8 weeks after exposure to attempt conception. Possible exposure is defined as travel to or residence in an area of active ZIKV.^{6,7}

Although Zika infection is associated with microcephaly, this outcome of Zika infection may be also an interaction of virus, stage of pregnancy, and fetal development. As a result, the actual risk for microcephaly with exposure or infection remains unknown. Further knowledge of the pathophysiology of Zika infection is needed.³ Recent evidence suggests that the link of Zika and microcephaly may

be a function of the very efficient ZIKV infecting human embryonic cortical neural progenitor cells, which results in dysregulated cell cycles and transcription, which leads to inhibited cell growth and increased cell death.⁸

Prevention and risk reduction are needed in light of the rapid spread of infection in the Americas. As of now, there is no test to determine if a baby will be born with microcephaly. For a limited number, ultrasound in the third trimester may reveal microcephaly. Infants with microcephaly have a small head at birth compared with infants of the same age or gender. Microcephaly may also be revealed when the infant head stops growing after birth. Assessment includes head circumference measurement 24 hours after birth and throughout infancy-comparing findings with World Health Organization growth metrics. Microcephaly can range from mild to severe. Babies born with microcephaly may develop convulsions and physical and learning disabilities as they grow older.⁷ Newborns with microcephaly may also demonstrate no symptoms at birth and may develop normally, whereas other infants may develop epilepsy, cerebral palsy, sensory deficits, and learning disabilities.

Microcephaly is associated not only with Zika infection. Microcephaly is also linked with in utero infections such as human immunodeficiency virus, cytomegalovirus, toxoplasmosis, rubella, herpes, or syphilis. In addition, maternal exposure to radiation, mercury, alcohol, and smoking as well as genetic abnormalities such Down syndrome or severe malnutrition during pregnancy can result in microcephaly.⁷

THE FUTURE

There is no one irrefutable piece of evidence that demonstrates that ZIKV infection is a cause of microcephaly and other fetal neurological defects. However, after evaluation of the magnitude of emerging evidence, the CDC

Table 2. Preventative Actions for Zika		
Remove breeding sites		
Screen or shut windows/doors		
Empty, clean, and cover water storage containers		
Clean and/or consider removing flower pots, used tires and roof gutters		
Use insect repellent with N,N-diethyl-meta-toluamide or Icaridin regularly; follow label instructions		
Wear light colored clothing		
Cover as much of the body as possible		
Sleep under mosquito nets during the day		
Exercise special surveillance and care for the young, sick, elderly		
Persons who are planning travel should visit the Centers for Disease Control and Prevention's Travelers' Health site (http://wwwnc.cdc.gov/travel/page/zika-travel-information) for guidelines and Zika updates		

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Table 3. Selected Web Sites for Evidence, Tools, Experts, and Policy ^a		
1. Elsevier Zika Virus Resource Center	https://www.elsevier.com/connect/zika-virus-resource-center	
2. The Lancet Zika Virus Resource Center	http://thelancet.com/campaigns/zika	
3. CDC—Zika Virus	http://www.cdc.gov/zika/index.html	
4. MMWR—Mortality Morbidity Weekly Report	http://www.cdc.gov/mmwr/zika_reports.html	
5. APIC Association for Professionals in Infection Control & Epidemiology	http://www.apic.org/For-Consumers/Patient-safety-resources	
6. American Nurses Association	http://nursingworld.org/zika-virus-information	
7. Association of Women's Health, Obstetric & Neonatal Nurses	https://www.awhonn.org/?ZikaVirus	
8. National Association of Clinical Nurse Specialists	http://www.nacns.org/docs/PR-ZikaResponse1602.pdf	
9. National Center for Biotechnology Information, US National Library of Medicine	http://www.ncbi.nlm.nih.gov/genome/viruses/variation/Zika/	
10. British Medical Journal	http://www.bmj.com/freezikaresources	
Abbreviation: CDC, Centers for Disease Control and Prevention. ^a Accessed April 17, 2016.		

concluded April 13, 2016 that Zika infection can cause microcephaly and other severe fetal brain injury and women infected with Zika during pregnancy have increased risk of having a baby with these health issues. Women are also cautioned that not all women who have ZIKV infection during pregnancy will have babies with microcephaly or other health issues because some infected women during this outbreak have delivered babies that appear to be healthy.⁹

As of today, there have been no local cases of ZIKV infection in United States. However, there have been travel-related cases. It is only a matter of time before Zika comes to the United States.¹⁰ The good news is that Zika viral infection usually does not require intervention. Rest, fluids, and over-the-counter medications for pain are usually effective.^{1,2} The CDC establishment of a causal relationship between Zika and fetal brain defects has provided a first step to focus prevention, research, and communication about Zika infection.⁹

PREVENTION

Diagnosis of Zika infection is a function of symptoms and history, especially if the patient reports travel to areas where Zika is present. Laboratory tests are available to test for ZIKV RNA in blood, urine, or saliva. Prevention and control depends on *reducing the number* of mosquitoes and *reducing human contact* with them and avoiding interaction when mosquitoes are active, which is early morning, late afternoon, and evening hours. Table 2 describes practical methods for prevention.^{1,2}

Also needed is to determine the relationship (if any) of ZIKV infection with the disturbing rise of Guillain-Barre syndrome cases.¹¹ Collaborative actions of science, health-care, and government can further confirm the association of Zika and microcephaly, reduce the spread and transmis-

sion of the virus, and develop better confirmatory testing and treatment through antiviral, vaccine, or immunological pathways.^{1,2} Resources for clinical practice, education, and research are provided in Table 3.

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