Zika Virus
What Pediatric Emergency Medicine Physicians Need to Know
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Abstract: Zika virus is a mosquito-borne Flavivirus. It has emerged as an important infectious agent in the recent past, mainly because of its teratogenic effects on the fetus. This review highlights the epidemiology, diagnosis, and treatment of this emerging infection.

Key Words: mosquito-borne infections, Zika

TARGET AUDIENCE
Pediatricians, emergency medicine physicians, advanced practice nurses, physician assistants, and students of all disciplines.

LEARNING OBJECTIVES
After completion of this article, the reader should be able to:
1. Discuss the history of Zika virus and its origins.
2. Identify the signs and symptoms of Zika virus.
3. Discuss the various options for diagnostic testing and the utility of each.
4. Describe treatment and prevention strategies for Zika virus, including current vaccine development.

HISTORY
Zika virus (ZIKV) is a mosquito-borne Flavivirus that was first isolated in Uganda in 1947 from the blood of a febrile rhesus monkey. For the past few years, it has been making an unprecedented emergence in the United States. As part of the Flavivirus genus, it is closely related to other single-stranded RNA viruses, including dengue, West Nile, and yellow fever. Zika virus was mostly contained in Asia and Africa, with few documented human cases until 2007 when the first large outbreak occurred in the Federated States of Micronesia, affecting 72% its residents older than 3 years. Zika virus subsequently became prominent in the Americas after an outbreak in Brazil in 2015.1 From May 2015 until early 2016, there were 1.5 million estimated cases of ZIKV in Brazil.2 The first reported case in the United States, in 2016, was in a patient who returned from Venezuela.3 Locally acquired infections in the United States were first detected in Miami, Florida, in July 2016. On February 1, 2016, the World Health Organization declared ZIKV a public health emergency in an effort to facilitate a coordinated response to further explore the clinical implications of the virus.4,5

HOST AND TRANSMISSION
Humans and nonhuman primates are the primary hosts of ZIKV.3 Antibodies have also been isolated in vertebrates (rodents, birds, sheep, goats, reptiles), suggesting possible roles as hosts in transmission. In the Asian strain, humans are most likely incidental hosts with transmission primarily between nonprimate hosts and mosquitoes, whereas in the African strain, humans have become the prominent host.6

Primary transmission of ZIKV is through the Aedes mosquito.7 The 2 predominant species are Aedes aegypti and Aedes albopictus. In the Northern hemisphere, these are most abundant in June to October and populate mostly the south and southeastern part of the United States, as well as the tropical and subtropical regions. They feed during the day and are able to breed in very small amounts of standing water. The eggs of the Aedes species are enduring and can survive for more than 1 year in dry conditions.4

The most important nonvector transmission is from an infected pregnant woman to her fetus. Acute infection of the pregnant woman is associated with fetal central nervous system malformations including microcephaly. Viral RNA has been detected in the brain, placenta, and serum of fetuses with microcephaly known to be born to mothers with active ZIKV, suggesting the ability of the virus to cross the placenta. Analysis of maternal-fetal transmission is complicated by the fact that there are many other etiologies of microcephaly aside from ZIKV, as well as variable definitions of microcephaly. Although many other viruses are associated with microcephaly, it should be noted that none of those are other flaviviruses.6

There have been reports of transmission through blood transfusions in Brazil.7 Many countries have started testing for flaviviruses, such as West Nile virus, in donated blood, but testing does not yet exist for detecting ZIKV in donated blood.8 The Food and Drug Administration currently recommends screening for travel history and symptoms prior to blood donation with deferred donation for those with positive screens.2

Sexual transmission of ZIKV has now been confirmed. Zika virus RNA has been detected in semen, with transmission mostly from male to female partners. Zika virus RNA has been detected up to 188 days after the onset of symptoms, suggesting the testes as a potential reservoir in apparently healthy individuals.9 Zika virus RNA has also been found in urine, saliva, cerebrospinal fluid, amniotic fluid, and breast milk, but there is no confirmation of transmission through exposure to these fluids.8,9 Currently, documented spread has been confirmed through mosquito bites, blood, and sexual transmission.1 Other flaviviruses have been transmitted through breast milk, but at this time mothers with ZIKV are still encouraged to breastfeed because it is not known if transmission occurs.7

GEографIC DISTRIBUTION AND EVOLUTION
Before the outbreak of ZIKV in the Americas in 2015, human infections were mostly localized to Sub-Saharan Africa and Southeast Asia, with the first reported human case in Nigeria in 1954.10 The first large human outbreak of ZIKV occurred in 2007 in Yap Island, followed by the French Polynesia in 2014.10

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It is hypothesized that the current virus strain belongs to the Asian lineage and was likely introduced to the Americas through Brazil, possibly during the 2014 World Cup or during the 2014 World Spring Canoeing championship. Athletes from the French Polynesia attended these events. The current circulating virus strain most closely resembles the strain isolated from French Polynesian patients with ZIKV.11 Zika virus circulating in the Americas share more than 99% of the identity of the French Polynesian outbreak and approximately 89% of the identity of the African strain.6 As of July 2016, more than 1.5 million cases of ZIKV have been reported across 40 countries in the Americas.6

It is expected that ZIKV will spread further around the world through infected mosquitoes and viremic travelers. Through evolution, ZIKV has allowed humans to serve as the host and multiplier of ZIKV for uninfected Aedes mosquitoes. The virus circulates in human blood for the first several days after acquiring the virus, at which time an uninfected Aedes mosquito can feed on the individual and become infected. For the most part, Aedes mosquitoes become infected from feeding on an already infected human. This cycle between humans and Aedes mosquitoes has the potential to cause and sustain epidemics.6

**CLINICAL MANIFESTATIONS**

Zika virus was first described in the 1950s, but was considered a self-limiting febrile illness in humans warranting little attention. Zika virus causes symptoms in approximately 20% of people, with 80% being asymptomatic.3 Symptoms of fever, maculopapular rash, pruritus, myalgia, arthralgia, nonpurulent conjunctivitis, and headaches tend to arise after the 3- to 12-day incubation period. Symptoms typically last for 2 to 7 days.7 Zika virus in children is mild and follows a similar course as adults.1,5,11 Severe acute infections and deaths from ZIKV are rare.5 Unfortunately, symptoms of ZIKV are nonspecific and similar to those of dengue fever and chikungunya virus.7

One significant concern with acute ZIKV infection is its association with Guillain-Barré syndrome (GBS).6 During the French Polynesian outbreak, it was noted that the incidence of GBS was 20-fold higher than the baseline incidence of approximately 1 to 2 cases per 100,000 population per year. A similar temporal and geographic association was noted in the Americas in 2015–2016, and a case-control study showed ZIKV anti-immunoglobulin M (IgM) or IgG present in 98% of patients with GBS as opposed to 55% of patients with nonfebrile illness in a similar geographic location.8

**FETAL EFFECTS AND RISKS?**

When Are They Greatest?

An association between ZIKV and microcephaly was initially suspected after the outbreak in Brazil in 2015 when there was noted to be a 20-fold increase in congenital microcephaly in areas where ZIKV was present.11 Because there is no standard definition of microcephaly, monitoring its prevalence has proven to be difficult. Definitions range from 2 to 3 SDs below the mean, to below the third or fifth percentile for gestational age.7 It is unclear exactly what causes microcephaly, but 1 hypothesis is that it affects primary progenitor cells preventing their growth.10 Fetuses are at greatest risk of microcephaly and brain malformations when maternal infection is during the first trimester. In a study in Brazil with 345 pregnant women, adverse fetal outcomes occurred in 55% of cases in which the mother was infected during the first trimester, 52% of those infected in the second trimester, and 29% of women infected in the third trimester.5,13

When pregnant women are found to have ZIKV, ultrasound for fetal microcephaly should be offered every 3 to 4 months. Fetal microcephaly is usually diagnosed in the late second and third trimesters. Amniocentesis for isolation of ZIKV RNA is also a possibility for diagnosis.11

Congenital infection has been confirmed by reverse transcription–polymerase chain reaction (RT-PCR), as well as through immunohistochemistry. Zika virus has been found in the amniotic fluid and placenta of mothers who traveled to endemic areas, as well as in the cerebrospinal fluid of babies born to those mothers, suggesting prenatal transmission. Cerebral calcifications, ventriculomegaly, and abnormally formed brain structures have been noted postnatally.7,19 Postnatal findings include ophthalmologic conditions such as cataracts, microphthalmia, and macular chorioretinitis, as well as neurologic conditions that include hypertonia, dysphagia, seizures, and arthrogryposis. Infants with congenital ZIKV are also likely at risk of seizures and cognitive, vision, and hearing impairments in the long term.7,14

**DIAGNOSIS**

Diagnosis of ZIKV starts with a clinical suspicion based on risk factors, most notably travel history to endemic areas and presence of fever. If an exposed patient presents with 2 or more of the following symptoms, one should have a heightened clinical suspicion: low-grade fever, maculopapular rash, arthralgia, and conjunctivitis.3 Emergency physicians should consider sending diagnostic testing in symptomatic patients who have traveled to an endemic country within the past 2 weeks or any patient with signs/symptoms of GBS who traveled to an endemic area within the past month. Also, asymptomatic pregnant women who have returned from an endemic area should be offered testing within 2 to 12 weeks of their return. Infants should be tested if they were born with microcephaly or intracranial calcifications to a mother who traveled to an endemic area or if they are born to a mother who tests positive or has an inconclusive test for ZIKV.7

The diagnosis of acute infection is confirmed using RT-PCR, which is positive only during viremia, the initial 3 to 7 days after onset of symptoms. Zika virus serology testing can be used for diagnosis in those patients who present 4 to 7 days after symptom onset. For those who present within the first 7 days, both RT-PCR and serology testing should be sent.3 Because the viral load is usually small in humans, RT-PCR has reduced sensitivity when run only on the serum. However, sensitivity greatly improves when used in conjunction with saliva/urine samples, which have a higher viral RNA load that lasts for a longer time than in the serum.6,7 Therefore, when there is potentially late detection of ZIKV, both serum and urine/saliva testing should be sent for diagnosis. Polymerase chain reaction testing is not yet available at individual hospitals, and therefore results are not available in a timely fashion.

Enzyme-linked immunosorbent assay for detection of IgM and IgG antibodies in the saliva or serum can also be used for diagnosis. Immunoglobulin M can be detected as soon as 3 days after symptom onset and stay positive for up to 3 months, whereas IgG develops later and can last up to years. However, IgM and IgG do have cross-reactivity with other flaviviruses, most commonly dengue, making false-positive tests fairly common.2,6 Plaque reduction neutralization test quantifies the neutralizing antibody titer and is used to rule out false positives from enzyme-linked immunosorbent assay because it has greater specificity.6

Fetal testing of ZIKV includes ultrasound for fetal microcephaly and/or intracranial calcifications and amniocentesis. Ultrasound findings consistent with ZIKV can be present at 18 to 20 weeks' gestation.3 Prenatal testing usually involves molecular analysis of amniotic fluid. Amniocentesis is offered to infected mothers at 15 weeks' gestation.3 In children, saliva and urine samples are often easier to obtain and therefore are often used in diagnosis.6
TREATMENT AND PREVENTION STRATEGIES

Currently, no antiviral treatment is available for ZIKV; therefore, infections are managed entirely with supportive care. Anti-pyretics can be used for fever and analgesia for pain. However, nonsteroidal anti-inflammatory drugs and acetylsalicylic acid should initially be avoided because they can cause hemorrhagic complications in patients with dengue fever, which can present with similar symptoms. Antihistamines such as diphenhydramine can be used for treatment in patients with a pruritic rash. Hospitalization and mortality from ZIKV are uncommon.

Because there is no specific treatment or vaccines for ZIKV, prevention of transmission is especially important. Mosquitoes are the primary vectors for transmission, so prevention should be aimed at preventing mosquito bites by using repellants, nets, and long-sleeved clothing. Permethrin-treated clothing will also repel mosquitoes. If traveling to an endemic area, it is advised to stay in buildings that are cooler with air conditioning and places with doors and screens. Those in endemic areas should also use protection during sexual activity, especially if the woman is pregnant, to prevent sexual transmission. Women who are pregnant or intend to become pregnant should avoid traveling to endemic areas to avoid exposure. If a woman travels to an endemic area, it is recommended that she wait 28 days after returning before attempting to become pregnant.

Vector surveillance and reduction of propagation can help control the spread of ZIKV. Minimizing standing water can effectively reduce breeding of the Aedes mosquito. The World Health Organization has considered releasing sterile mosquitoes to limit the breeding of infected species to reduce propagation. One cost-effective strategy for reducing the mosquito population is through lethal traps. Puerto Rico was able to reduce their mosquito burden by 50% to 70% using lethal traps.

VACCINE DEVELOPMENT

Although there is currently no approved vaccine against ZIKV, there has been an expedited effort by the World Health Organization and other entities to develop one. There are several different approaches to vaccine development including using inactivated virions, chimeric or genetically engineered live-attenuated viruses, viral-vectorized protein subunits/peptides, and DNA/RNA plasmid vaccines. There are 2 vaccines in phase 1 clinical trials and 1 vaccine (DNA based) in phase 2 clinical trial as of March 2017. Because of the safety profile and speed of manufacturing of DNA vaccines, these are the first to go into phase 1 trials. It is hypothesized that antibodies targeting the envelope proteins on the virus particle will be most successful in protecting against infection. Envelope proteins play a critical role in virus entry and assembly as they protrude farthest from the surface of the virion contributing most significantly to viral attachment. Given that there is little variation between ZIKV strains, it is plausible that creating an effective vaccine against one strain would broadly protect against all circulating strains.

One challenge with ZIKV vaccine development is that clinical trials should include pregnant women because trials in non-pregnant adults would not address adverse fetal outcomes. As one might expect, vaccine trials in pregnant women raise specific ethical and logistical challenges. The most promising potential ZIKV vaccine is either live attenuated or inactivated, given their success in the other flaviviruses. However, live viruses may pose a safety risk in pregnant women. One great difference, however, between ZIKV and the other flaviviruses is that the ZIKV vaccine must not only illicit an immune response protective of the mother, but also prevent vertical transmission to the fetus because the vaccine will initially primarily be given to women who are pregnant and/or of childbearing age. Licensure of a vaccine will take several years, and at the outset, there may not be adequate supply for widespread vaccination. Therefore, targeted groups for vaccine distribution will likely be women of childbearing age and potentially pregnant women in endemic areas. However, ultimately, the goal will be for widespread vaccination of all individuals prior to childbearing age.

SUMMARY

Zika virus is an emerging infectious disease with recent rapid global spread bringing international attention. As emergency physicians, it is important to be aware of the clinical manifestations, transmission, and management of the disease, particularly for women who are pregnant and neonates born to mothers with risk factors for acquiring ZIKV. It is also imperative to keep a broad differential as not to miss other flaviviruses or potentially new emerging infections. Unlike some other disease outbreaks, no quarantining is required for suspected ZIKV cases. The management is largely supportive care, and death or serious complications are extremely rare. Future research includes the development of antiviral therapy and vaccines with a variety of approaches. Although many aspects of ZIKV remain mysterious, significant progress has been made in the past year in understanding the epidemiology, transmission, and clinical manifestations of the disease.

REFERENCES


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1. Transmission of ZIKV has been confirmed through all of the following routes except
   a. mosquito bites.
   b. breast milk.
   c. blood.
   d. sexual intercourse.

2. Fetuses are at greatest risk of microcephaly when maternal ZIKV infection is acquired during the
   a. first trimester.
   b. second trimester.
   c. third trimester.

3. A 42-year-old man presents to the emergency department with fever, maculopapular rash, and conjunctivitis 3 days after returning from a vacation in San Juan, Puerto Rico. You determine he is at risk of ZIKV infection. Which of the following diagnostic tests should initially be sent?
   a. ZIKV IgM and IgG by enzyme-linked immunosorbent assay
   b. RT-PCR on the serum
   c. RT-PCR on the serum and urine
   d. ZIKV serology testing

4. ZIKV was first identified in
   a. Brazil.
   b. French Polynesia.
   c. Venezuela.
   d. Uganda.

5. Which of the following is true regarding ZIKV?
   a. Viral load of ZIKV is greater in the blood than in the semen.
   b. Sexual transmission of ZIKV is more likely to occur from male to female partners than from female to male partners.
   c. The incubation period for ZIKV is approximately 3 to 12 days.
   d. The Aedes mosquito also transmits dengue virus, chikungunya virus, and malaria.
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1 2 3 4 5
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1. Discuss the history of Zika virus and its origins.
2. Identify the signs and symptoms of Zika virus.
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4. Describe treatment and prevention strategies for Zika virus, including current vaccine development.

How many of your patients are likely to be impacted by what you learned from these activities?
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For maintenance of board certification ○ For maintenance of licensure ○
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