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Objectives

After completion of this program, the reader should be able to:

1. Discuss the background and origin of the Zika virus, including where the Zika virus has become endemic in the United States.
2. Identify risk factors for contracting the Zika virus and its common routes of transmission.
3. Recognize the signs and symptoms of the Zika virus.
4. Prepare an appropriate plan to manage patients presenting with Zika virus, including diagnostic testing, treatment and counseling points.
5. Explain the logic behind the current investigational vaccines targeted against the Zika virus.

Abstract

The Zika virus has become a growing concern as a global pandemic. Since being identified in Uganda in 1947, the virus has spread around the world, recently emerging in South America with a great impact on Brazil. As of 2016, Zika has made its appearance in the United States and is now actively being transmitted in Florida. The virus is a mosquito-vector flavivirus primarily transmitted by the *Aedes* mosquito which infects a human through biting. Transmission through sexual intercourse is also possible as well as transmission from a pregnant woman to her fetus. This latter form of transmission presents the primary problem with the Zika virus; transmission to the fetus can cause microcephaly as well as other brain and developmental problems. Proper precautions should be taken based on these identified modes of transmission. Symptoms of Zika are similar to flu-like symptoms, such as low-grade fever, muscle pain and headache. About 20 percent of patients that come in contact with the Zika virus will originally present as asymptomatic and will not display symptoms until almost two weeks after initial contact with the virus. Zika virus can remain in the blood for about a week, but can remain in the semen for months. There are a number of methods used to detect the Zika virus—urine, blood or semen samples may be used to assess if a patient is infected.

Key Terms

Aedes; Centers for Disease Control and Prevention (U.S.); Diagnostic Tests; Fetus; Flavivirus; Florida; Microcephaly; Public Health; Sexual Partners; Vaccines; Zika Virus

Introduction

The Zika virus was originally identified in Uganda in 1947. It has since spread around the world as two main strains, Asian and African, distinguishable by detailed analysis of the ribonucleic acid (RNA) sequence.¹ This difference in sequence relates to a variation in availability for potential glycosylation sites in the virus. The Asian strain is responsible for the outbreaks seen in Brazil and the United States, after traveling through Pacific Island countries such as Malaysia (1969), Philippines (2012) and Easter Island (2014). In late 2014 and early 2015, reports to the Brazilian Ministry of Health of an “acute exanthematic disease” began following the 2014 Fédération Internationale de Football Association (FIFA) World Cup, and, in March 2015, the Zika virus was isolated in patients in various regions of Brazil.² By May, the Brazilian Ministry of Health recognized local transmission of the Zika virus. In September, reports of microcephaly began to surface, and on Oct. 23, 2015, the Brazilian Ministry of Health reported the occurrences to the World Health Organization. As the link between Zika virus and microcephaly became more apparent, the Brazilian Ministry of Health published guidelines for the management of microcephaly. There were an estimated 440,000 to 1,300,000 cases of Zika in Brazil in 2015 alone, and 508 cases of microcephaly were confirmed by February 2016.

As of 2016, reports of Zika virus spread to the United States, significantly increasing awareness of the disease. On Jan. 15, 2016, the Centers for Disease Control and Prevention (CDC) released a health alert warning travelers and health care providers to be vigilant for the signs and symptoms of the Zika virus as travel-associated cases had already been reported in travelers returning to the United States.³ Since then, there has been a rise in cases in the United States, most notably in California, Florida, New York and Texas, with 4,389 travel-associated cases reported as of Dec. 7, 2016.⁴ As of the same date, 185 locally acquired cases have been reported in the United States: 184 in Florida and one in Texas. The first reports of local transmission came in late July from Miami, Florida, where Zika virus was isolated in four patients, which was likely caused by local *Aedes aegypti* mosquito bites, as the patients had not recently traveled outside of the United States.⁵ Territories of the United States have also reported locally acquired cases: 32,848 cases in Puerto Rico, 57 cases in American Samoa and 807 cases in the Virgin Islands.

Health care professionals and researchers have worked to gather as much information about the disease as possible, in order to inform the public about proper precautions.⁶ In addition, possible treatments and vaccines are currently in development. New information about the Zika virus is constantly being discovered, and the imperative task of keeping the public informed has become an emerging role of health care professionals.

Etiology and Transmission

The Zika virus is a mosquito-vectored flavivirus which uses several mechanisms to alter host cellular pathways to favor viral replication.⁷ Transmission of the Zika virus can occur through several mechanisms: receiving a bite from an infected mosquito, vertical transmission from mother to child and transmission through sexual activity.⁶ Less commonly, the Zika virus may be transmitted via blood transfusion or through laboratory exposure, though these are typically not a concern in the general population. There have not been any confirmed cases of transmission via blood transfusion in the United States, though there have been cases reported in Brazil. Additionally, the virus has been identified in blood donors in French Polynesia during several outbreaks. In one case study, spread of the virus through sweat and tears was also identified as a possible route of transmission.⁸

Transmission through the bite of a mosquito is the primary mode of transmission associated with the Zika virus.⁶ Mosquitoes of the *Aedes* genus may be infected with the virus, specifically the *Aedes aegypti* and *Aedes albopictus* species. These species of mosquito are primary reservoirs for the virus and can transmit other tropical diseases such as dengue fever and chikungunya. An infected mosquito can transmit the virus to a human through a bite. Likewise, a mosquito may also become infected after biting a human infected with the Zika virus. In turn, the newly infected mosquito may spread the virus to any other human it bites. These mosquitoes are aggressive daytime biters, though biting, and therefore transmission, is also possible at night.

Studies have been conducted that demonstrate vertical transmission as a possible mechanism of survival of the Zika virus in the *Aedes aegypti* mosquito.⁹ This is important when considering environments that act as potential breeding grounds for mosquitoes. For instance, the *Aedes* mosquito often lays eggs in standing water.⁶ This potential form of vertical transmission within the viral reservoir may attribute to disease survival. Vertical transmission in this manner is certainly possible in tropical climates which the mosquitoes currently inhabit and may also be a concern in adverse conditions such as colder climates.⁹ The mosquitoes may lay eggs that will hatch once the environment becomes favorable.^{9,10} The *Aedes* mosquitoes typically exist in tropical climates, but their range has extended to include the southern United States, possibly allowing for local transmission in this area.⁶

If a pregnant female becomes infected, she can pass the Zika virus to her fetus.⁶ Transmission may occur in utero or near the time of birth and may result in a wide range of health

problems for the child. These could include microcephaly, decreased brain tissue, restricted joints, increased muscle tone or damage to the eyes. The Zika virus has been identified in breast milk; however, to date, there have not been any infections associated with breastfeeding. The proven benefits of breast milk currently outweigh the potential risk of Zika virus. Therefore, the CDC is still recommending breastfeeding in areas where the virus is prevalent.

An individual may also transmit the Zika virus to any sexual partners.⁶ Sexual transmission can occur before, during or after the infected individual develops symptoms. It has also been hypothesized that an asymptomatic carrier can still transmit the Zika virus to a sexual partner. The Zika virus has been identified in the semen for up to six months after the dissipation of symptoms, much longer than in the blood, urine and vaginal fluids. For this reason, the CDC is currently recommending the use of condoms for at least six months after a man has returned from an area where Zika virus is endemic or six months after he has received a positive diagnosis of Zika.

Signs, Symptoms and Diagnosis

The Zika virus can manifest itself in many ways once it infects a host. A majority of those infected are asymptomatic or display mild symptoms such as low-grade fever, joint pain, maculopapular rash, arthralgia, nonpurulent conjunctivitis, headaches and myalgia.^{11,12} Approximately one in five patients initially asymptomatic will develop symptoms as late as 12 days after infection. In the asymptomatic population without detectable symptoms, the Zika virus can still be transmitted via blood primarily through blood transfusion and sexual intercourse.¹³ Typically, the Zika virus remains in the blood of an infected individual for about a week, but can remain in other fluids, such as semen, for much longer. If an individual suspects that he or she is infected with the Zika virus by displaying any of the above symptoms, he or she should immediately see their primary health care provider.¹²

A number of factors should be examined in order to give an accurate diagnosis. Factors such as the patient's travel history, symptoms and test results should be examined to determine if the patient is infected with Zika.¹⁴ Available diagnostic tests include a blood (serum) test and a urine test, which are used to confirm the presence of the Zika virus in an individual.¹² Reverse transcription polymerase chain reaction (RT-PCR) tests are utilized to determine if a urine specimen is positive for Zika virus. Viral RNA in urine has been found to be positive as early as the first day of the onset of symptoms and as late as 20 days after onset of symptoms.¹⁵ Serum samples may also be obtained to screen for viral RNA using polymerase chain reaction (PCR). If utilizing serum samples for diagnostic purposes, results are more accurate if obtained within seven days of symptom onset. Serum samples obtained more than one week after symptom onset may not yield as accurate diagnostic results as urine samples. Therefore, urine samples should be used for patients who present more than one week following onset of symptoms.¹² Patients who present as asymptomatic or are unable to give a serum

or urine sample can undergo serology testing to confirm the presence of Zika. This test looks for the body's reaction against the virus in the form of antibodies that are present within a week of being exposed to the virus. Antibodies also remain in the patient's immune system months after infection. This serology testing is time-consuming and may not be specific to the Zika virus. Other viruses with similar structures, such as the yellow fever virus, may cross-react and result in a positive test.

A positive result may, in fact, represent a previous exposure to another virus or past vaccination, and therefore results are difficult to interpret.¹⁶ Although anyone is susceptible to Zika, testing should be reserved for individuals who have traveled to high-risk areas in which the Zika virus is known to be present. Special attention should be given to women who become pregnant within two months of returning from a high-risk area, and they should be tested even if they were originally asymptomatic. Likewise, all symptomatic patients with onset of Zika-like symptoms abroad or within 14 days of return should be offered both viral and serologic testing as part of a workup. There are a number of ways to detect Zika in a potentially infected or asymptomatic individual.¹² It is advised to attempt to gather a serum sample if possible, but urine testing is becoming more favorable, as Zika virus has been found up to 20 days after onset of symptoms. Further investigations are needed to evaluate whether the live virus is excreted in urine. Although larger studies are needed for confirmation, current research strongly suggests that urine is a suitable specimen to be used to detect Zika in patients beyond 14 days after symptom onset.¹⁷ Urine specimens are also likely suitable for use in epidemiologic investigations of a larger scale such as testing returning travelers.

Response from CDC/U.S. Food and Drug Administration (FDA)/National Institute of Allergy and Infectious Diseases (NIAID)

One of the main concerns to patients is the risk of severe fetal brain defects, such as microcephaly, associated with Zika virus infection.¹⁸ In response to this, the CDC has established the US Zika Pregnancy Registry to collect information regarding the timing and risks associated with Zika virus infection and transmission during pregnancy. Patients who are eligible to be enrolled in the registry include pregnant women and their infants who have laboratory evidence of Zika virus infection, with or without symptomatology. This information will be used to update clinical recommendations for the treatment and prevention of Zika virus during pregnancy.

Several health organizations are currently developing vaccines to target the Zika virus.¹⁹ One of these organizations, the National Institute of Allergy and Infectious Diseases (NIAID), is currently investigating several potential vaccine candidates. In a phase I clinical trial, a live-attenuated Zika vaccine based on the Dengue virus vaccine was shown to be safe and induce an immunologic response. This Dengue virus-based vaccine candidate is currently undergoing a large phase III study in Brazil. Dengue virus and Zika virus are both members of the flavivirus genus, and this similarity

was the rationale behind investigating this particular vaccine. West Nile virus is also a member of the flavivirus genus. Consequently, a deoxyribonucleic acid (DNA)-based vaccine for the Zika virus similar to the investigational vaccine for West Nile virus is also under investigation. This vaccine candidate is currently in an early stage trial. Another vaccine candidate includes a genetically engineered vesicular stomatitis virus (VSV). The VSV recombinant vaccine expresses the Zika virus E glycoprotein,²⁰ and is therefore being evaluated for potential use in preventing Zika virus in tissue and animal models.¹⁹ Additionally, a whole-particle inactivated Zika vaccine based on Japanese encephalitis and Dengue virus vaccines is also being investigated. These vaccines are still in early developmental stages and are not expected to be available for several years.

Current Management and Changes

As the vaccines that are currently in development are still several years from FDA approval, current management of Zika consists of symptomatic treatment.²¹ This includes fluid replacement for dehydration, rest and acetaminophen for fever and pain. Due to the presence of similar symptomatology between Zika virus and dengue fever, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue can be ruled out. Administration of NSAIDs to a patient with dengue fever significantly increases hemorrhaging. Differential diagnosis can be performed via a PCR test.

Because there are no current antiviral medications or vaccines available to treat Zika virus, preventing transmission is an important counseling point.²² The most effective way to prevent the transmission of Zika virus is to avoid traveling to areas where Zika is present, when possible. If this is not possible, or the patient lives in an area where Zika is prevalent, he or she should exercise extreme caution to prevent mosquito bites. This includes wearing long-sleeved shirts and long pants that are treated with permethrin, staying in places with window and door screens, sleeping under a mosquito bed net and using United States Environmental Protection Agency (EPA)-registered insect repellents. When using insect repellents and sunscreen, it is important to apply the sunscreen before the insect repellent. Eliminating standing water is vital to prevent further reproduction of the *Aedes* species mosquitos responsible for the transmission of the Zika virus. Sexual transmission of Zika virus can be prevented by using condoms or abstaining from sex. At this time, the CDC is recommending that men who are exposed to Zika virus use condoms or abstain from sex for at least six months after returning from an area where Zika virus is present.²³ Women who are exposed to Zika virus should use these methods for at least eight weeks. Couples should be educated to use a reliable form of contraception to prevent the transmission of Zika virus from mother to fetus.²²

Conclusion

As more information is discovered about the Zika virus, it is important for the public to remain informed about the virus demographics and possible treatments and vaccines. Understanding the virus's transmission, particularly through

mosquito bites, sexual activity and from mother to fetus, is imperative for taking proper preventive measures. As a vaccine for the Zika virus is still several years away from availability, these precautions become even more important. Individuals who have traveled to Zika-infested areas or have a reason to suspect they may have been infected with the Zika virus should know the signs and symptoms of Zika and should understand when or if they should be tested for the virus. It is important for health care professionals to keep up to date as data emerges and recommendations change, so they can use this information to educate patients and address concerns about the Zika virus.

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Assessment Questions

- The first reports of locally transmitted Zika virus in the United States came from _____.
 - Houston, Texas
 - Miami, Florida
 - New Orleans, Louisiana
 - San Diego, California
- After what major event did reports of Zika virus begin to surface in Brazil?
 - 2014 FIFA World Cup
 - Carnival in 2015
 - 2016 Summer Olympics
- Which of the following has not been identified as a pathway of transmission of the Zika virus?
 - Sexual intercourse
 - Respiratory droplets
 - Mother to fetus
 - Bite from a mosquito
- What are the CDC's recommendations on breastfeeding in areas where the Zika virus is prevalent?
 - Zika has not been identified in breast milk, so breastfeeding is recommended.
 - Zika has not been identified in breast milk, but breastfeeding should be avoided as a precaution.
 - Zika has been identified in breast milk, so breastfeeding should be avoided.
 - Zika has been identified in breast milk, but breastfeeding is recommended as the benefits outweigh the risks.
- A patient presents to your clinic suspecting they have symptoms of Zika. Upon questioning, you find they had travelled to Brazil and returned about a month ago, but have only had symptoms on and off for the past 17 days. Which of the following specimens could you test to determine if the patient is infected with Zika?
 - Blood
 - Urine
 - Saliva
 - Semen
- All of the following are potential symptoms for Zika except _____.
 - Fever of 99.8° F
 - Headache
 - Constipation
 - Muscle pain
- Which of the following is unlikely to put a patient at risk for contracting Zika?
 - Traveling to Brazil or other areas known for outbreaks of Zika.
 - Having a blood transfusion from a patient who had recently been in a high risk area for Zika.
 - Not obtaining a proper medical workup after travelling to a high risk area.
 - Travelling to areas known for outbreaks of the yellow fever virus.
- Investigational vaccines for Zika virus often mimic vaccines for which of the following infectious diseases due to their similarities?
 - Human papilloma virus
 - Influenza
 - Herpes zoster
 - Dengue fever
- Appropriate treatment for Zika virus includes which of the following?
 - acyclovir
 - acetaminophen
 - ibuprofen
 - Oseltamivir
- At a minimum, how long should a couple wait before trying to conceive a child if the man has recently traveled to an area infected with Zika virus?
 - Eight weeks
 - One year
 - Six months
 - If symptomatic, until symptoms resolve, otherwise eight weeks.



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