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Zika Virus Induced Neurological Disorders and Impacts on Public Health

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

1. Describe typical symptoms and duration of Zika virus infection.
2. Explain how Guillain-Barre syndrome and microcephaly affect the nervous system.
3. Recognize the most common neonatal neurological disorders associated with a maternal Zika virus infection during pregnancy.
4. Identify available screening tests and therapies to manage conditions associated with long-term Zika virus effects.
5. List preventive measures taken to decrease the spread of Zika virus.

Abstract
Zika virus is a public health emergency of international concern. Zika virus (ZIKV) is a mosquito-borne pathogen that is carried by the Aedes genus. Zika is spread through direct bite and nonvector transmission. Most individuals infected with Zika will be asymptomatic, but some may present nonspecific viral symptoms. A rising number of neurological disorders in newborns whose mothers were infected with ZIKV during pregnancy have been reported due to recent outbreaks. Neurological disorders affect both the central and peripheral nervous systems and can result from bacterial, viral, fungal or parasitic infections of the nervous system or from the immune response to the infection. Guillain-Barre and microcephaly are two complications that can occur due to ZIKV infection. Recent studies have shown there is a stronger correlation between a maternal ZIKV infection during her first trimester of pregnancy and neurological disorders in the neonate. Currently, there is not an available treatment option to change the physical appearance of microcephaly or reverse the complications from Zika virus. However, there are developmental screenings and therapies that can be performed to detect and improve strength and movement needed to perform daily tasks. Precautions, such as mosquito repellents and protective clothing, should be taken to avoid exposure.

Key Terms
Aedes; Fetus; Microcephaly; Pregnancy Trimester First; Zika Virus

Introduction
Zika virus is a mosquito-borne pathogen that is carried by the Aedes genus. In tropical regions the Aedes aegypti is the carrier. In temperate regions the carrier is Aedes albopictus. The Aedes genus also carries dengue fever, chikungunya and yellow fever viruses.1 Transmission of Zika virus (ZIKV) occurs through direct bite. Nonvector transmission primarily involves sexual routes, specifically from symptomatic men to partners, perinatal and blood transfusion. At this time, there is no evidence to support transmission through urine, saliva, breastfeeding or respiratory droplets. Zika virus has an incubation period that has been estimated to be four to seven days. Most individuals infected with the virus are asymptomatic. Infected individuals who are symptomatic typically experience nonspecific viral symptoms such as arthralgia, myalgia, headache, malaise, rash and nonpurulent conjunctivitis that have a two to seven day duration. More serious complications that have been reported include birth defects and long-term neurological complications.2

Zika is a flavivirus consisting of single stranded, positive ribonucleic acid (RNA). The Flaviviridae family includes other human pathogens including dengue, West Nile, yellow fever, tick-borne encephalitis and Japanese encephalitis virus.3 The virus is a 50 nm spherical virion that comprises three structural proteins. It is believed to form one serotype with two main lineages: African and Asian. Outbreaks in the United States have been traced back to the Asian lineage. The Asian lineage has been associated with NS1 codon usage making it better adaptable to humans. The African lineage transmission is sylvatic and has not been associated with symptoms.4 The virus isolate enters human dermal fibroblasts, epidermal keratinocytes and immature dendritic cells.5 The initial immune receptor is the Toll Like Receptor 3 (TLR-3) which detects the infection in human fibroblasts. The activation of TLR-3 pathways in central nervous system (CNS) cells may trigger apoptosis and attenuate neurogenesis, directly con-
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Neurological Introduction
With the recent outbreak of ZIKV there has been a rise in neurological disorders reported in newborns whose mothers were infected with ZIKV during their pregnancy. Neurological disorders affect the central and peripheral nervous systems; this includes the brain, spinal cord, muscles, nerve roots, autonomic nervous system, peripheral nerves, cranial nerves and neuromuscular junctions. The presentation of these disorders varies based on the causative agents and what part of the nervous system is affected. Neurological disorders can result from bacterial, viral, fungal or parasitic infections of the nervous system from the host immune response to the infection. The most common bacterial causes of neurological disorders are Mycobacterial tuberculosis and Neisseria meningitides. The most common fungal infections are Cryptococcus and Aspergillus. Malaria and Chagas are the result of parasitic infections. Lastly, the viruses that can cause neurological disorders are human immunodeficiency virus (HIV), Enteroviruses, West Nile virus, and Zika virus.

When a pregnant mother contracts a ZIKV infection there is a risk her unborn child will develop neurological complications. These neurological complications include Guillain-Barre syndrome, encephalitis, meningoencephalitis, facial paralysis, myelitis and microcephaly. Currently there is little information on the effects of a mild or asymptomatic ZIKV infection during early pregnancy. The risk of a fetus developing a neurological complication is higher when a pregnant woman experiences a symptomatic ZIKV infection. While a ZIKV infection can cause all of the neurological complications mentioned above, it has been observed to most commonly cause Guillain-Barre and microcephaly.

Guillain-Barre
In some cases of Zika there are more serious clinical outcomes reported, including Guillain-Barre syndrome. Guillain-Barre syndrome is an autoimmune and neurological disease, in which the body’s immune system attacks the peripheral nervous system. The syndrome can affect the nerves that control muscle movement as well as those that transmit feelings of pain, temperature and touch. This can result in muscle weakness and loss of sensation in the legs and arms. Guillain-Barre syndrome is triggered by previous infections, typically respiratory or gastrointestinal. Other viruses that have been associated with Guillain-Barre include dengue fever and chikungunya. Guillain-Barre syndrome is not thought to be mediated by antiglycolipid antibodies but is thought to be introduced by neurotoxic factors associated with Zika. The acute phase of Guillain-Barre syndrome is treated with either plasmapheresis or intravenous immunoglobulin and supportive care. The recovery phase typically lasts from six to twelve months but may take up to three years for some patients. Approximately 80 percent of patients can walk independently six months after diagnosis, and 60 percent fully recover motor strength one year after diagnosis.

Microcephaly
Microcephaly is a birth defect where the newborn’s head has a significant degree of reduction in the circumference when compared to other newborns of the same sex and age. The smaller head circumference is a direct result of microcephaly, that is, smaller brains, which did not develop properly, and can lead to impairment in motor, sensory and cognitive functions. Figure 1 compares an infant with a normally developed head to varying severities of microcephaly in infant.
developed head to infants with varying severities of microcephaly. Microcephaly is a result of a decrease in the number of cell divisions in the brain during fetal development, resulting in a decrease in production of functional neurons. A large number of various case reports and studies illustrate a strong correlation between a ZIKV infection in the pregnant mother and the development of microcephaly in the developing baby.

A study by Frietas et al. looked at the overall incidence of ZIKV infections in pregnant mothers and the risk of microcephaly. The results of their investigation showed that more than one million people have been infected with ZIKV since its endemic onset in April 2015. They also uncovered an unusual increase in the number of newborns with microcephaly six months after the onset of the endemic. In 2015 there were 1,248 new cases of microcephaly registered, which corresponded to 99.7 cases per 100,000 live births. This incidence represents a twentyfold increase in microcephaly cases when compared to recent years. This finding helps confirm that the increase in microcephaly cases is due to the current ongoing ZIKV endemic.

**Studies about Zika and the Risk of Various Birth Defects**

A preliminary report conducted by Pacheco et al. investigated the ZIKV outbreak in Colombia by using the national public health surveillance system of the Colombian Instituto Nacional de Salud (INS). This surveillance system serves to collect information for notifiable conditions like dengue, chikungunya, ZIKV, acute flaccid paralysis and congenital infections. The results of reported diseases are published by INS weekly. Patients met inclusion criteria for the study if they had clinical symptoms with or without laboratory confirmation of ZIKV from Aug. 9, 2015, to April 2, 2016. At the time of this study, data collection was still ongoing for the majority of the patients in this group. The researchers performed a subgroup analysis which included the 1,850 patients who had already delivered their babies. All of the patients in the subgroup analysis also reported during which week in their pregnancy they noticed the onset of ZIKV symptoms. In this subgroup, 532 patients became infected during the first trimester, 702 in the second trimester and 616 in the third trimester. For the group of women who were diagnosed with ZIKV in the third trimester, 82 percent of the children were born with a normal birth weight without any neurological disorders. The remaining 18 percent of children born to women diagnosed with ZIKV during the third trimester fell into the following categories: 2 percent were born with a low birth weight, 8 percent were born preterm, 1 percent died during the perinatal period. The remaining 7 percent were still being followed at the time the study was published. There were no reported cases of microcephaly or brain abnormalities in any of the children whose mothers contracted ZIKV during the third trimester of pregnancy.

This study also utilized the INS to look for cases of reported microcephaly. From Jan. 1, 2016, until April 28, 2016, a total of 50 infants were reported to the INS for possible microcephaly. Currently the causes of 26 of the cases are still being investigated. Twenty cases had identifiable causes that were not related to ZIKV and were determined to have been caused by syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes (STORCH) infections, genetic causes or neural tube defects. These 20 children also had negative results of the diagnostic ZIKV RNA reverse transcriptase polymerase chain reaction (RT-PCR) test. The final four infants had microcephaly caused by an asymptomatic ZIKV infection in the mother evidenced by a positive RT-PCR assay, negative STORCH evaluation and normal karyotypes.

Another study conducted by Tang discussed the current evidence linking ZIKV infections as a causative agent for microcephaly. This study reviewed previous ZIKV outbreaks with cases from Bahia and a retrospective study from French Polynesia. It was shown with population level data analyses that there is a strong association between the pregnant mother contracting the ZIKV infection during the first trimester, or the first 12 weeks of pregnancy, and an increased risk of microcephaly in neonates as opposed to being infected during the second or third trimester. The second trimester consists of weeks 13 to 28, and the third trimester is from the 29th to the 40th week. A second study by Johansson et al. confirmed this association when they evaluated the ZIKV and the risk of microcephaly in neonates. They found that the risk of inducing neurological disorders in the fetus was the highest with infection during the first trimester. This study also discovered there is a negligible risk between a ZIKV infection in the second and third trimesters and microcephaly development in the neonate.

The study by Tang further discovered that some infants whose mothers had been infected with ZIKV during their first trimester of pregnancy presented with macular atrophy and a decreased cephalic diameter. This finding was supported by a study done by Frietas et al. which followed 29 mothers who had a confirmed diagnosis of ZIKV while pregnant and gave birth to a newborn with microcephaly. Of the 29 newborns, 10 were found to have ocular abnormalities. These abnormalities included focal pigment mottling, chorioretinal atrophy especially in the macular area and optic disc abnormalities. It is important to note that the mothers did not have any kind of ocular disturbance or conjunctivitis during their pregnancy.

**Treatment Options for Long-Term Effects of Zika Virus**

Microcephaly is one of the most concerning effects of Zika virus; however, there is no treatment that will change the physical appearance, enlarge the infant’s head or reverse the possible complications it can cause. Soon after the infant is born, developmental screenings should be performed at each health care visit. Developmental milestones, growth, sleep, irritability and abnormal movements should all be monitored and reported to the health care provider. A comprehensive eye exam should be performed within one month of birth, and additional vision screenings should be addressed at each follow-up visit. Auditory brainstem responses should be performed within one month of birth and then again at four to six months.
Available treatments focus on ways to manage conditions that stem from the microcephaly. Early childhood intervention programs that include speech, physical and occupational therapy may help patients strengthen abilities. These therapies may improve strength, movement, confidence to perform daily tasks, language skills and even self-esteem issues associated with the condition. Some cases of microcephaly can lead to serious learning and speech disabilities, difficulties with neurological functions and physical complications like seizures and facial deformities. If seizures occur, they may be treated with pharmacologic interventions.

Zika and Public Health

According to the Centers for Disease Control and Prevention (CDC), Zika virus is a public health emergency of international concern. As of Sept. 7, 2016, there have been 671 cases of pregnant women with evidence of Zika virus in the United States alone. Since a vaccine to prevent infection of Zika virus is not currently available, all populations should take precautions to avoid mosquito bites during the day and night. This can include wearing long sleeves and pants, using mosquito repellents (those with DEET or permethrin) and preventing mosquitos from entering the home by using screens on windows and doors. Zika can be spread through intercourse with an infected partner; therefore, male condoms should be used to reduce the risk of acquiring the virus. There are greater central nervous system (CNS) concerns for certain populations, such as women who are either attempting to become pregnant or are presently pregnant; therefore, these women should be tested for Zika virus if a possible exposure has occurred. Women with diagnosed Zika virus and asymptomatic women with a possible exposure should wait at least eight weeks from symptom onset (symptomatic) or Zika virus exposure (asymptomatic) before attempting pregnancy. Regardless of symptom status, men with a possible Zika virus exposure should wait at least six months after exposure or symptom onset before attempting pregnancy with their partner.

The U.S. Food and Drug Administration (FDA) has approved real-time reverse transcription-polymerase chain reaction (rRT-PCR) and considers it the standard test to detect Zika virus. Other tests include assessing immunoglobulin (IgM) levels and a plaque reduction neutralization test (PRNT). It is recommended that a combination of these tests be done for the most accurate results. In pregnant women with a possible Zika exposure, it is recommended that a prenatal ultrasound be performed, regardless of laboratory test results.

Many of these tests require a blood or urine sample and must be performed at a CDC center, state or federal health institution or commercial laboratory. Because the presentation of Zika virus is nonspecific and may be mistaken for other viral infections, a quick and reliable diagnostic test is needed that could be used in less-developed areas where Zika virus is more prevalent and access to diagnostic laboratory equipment is limited. Studies are being conducted to evaluate the effectiveness of a highly sensitive reverse-transcription loop-mediated, isothermal amplification (RT-LAMP) assay for the detection of Zika as a point-of-care test cassette for patients.

To date, there have been no confirmed blood transfusion-transmission cases in the United States. However, there is a strong possibility that Zika may be transmitted through blood, the FDA recommends that whole blood and blood components be screened for the virus once a licensed test becomes available.

To gather and centralize data to understand more about the risks of Zika virus during pregnancy, the CDC established the US Zika Pregnancy Registry and is collaborating with health care professionals at the state, tribal, local and territorial levels. The registry is an active surveillance system that keeps track of pregnant women with laboratory evidence of confirmed Zika virus and pregnant women with a possible infection from confirmed exposure in the United States and its territories. It also includes weekly reporting of the number of women followed in the registry. The CDC encourages patients to submit information after birth as well. All of the information collected in the registry will be used to update recommendations for diagnostic testing, monitoring, counseling and therapy. The CDC has also established Zika Active Pregnancy Surveillance System (ZAPSS) which includes Puerto Rico.

Conclusion

Zika virus epidemic has raised concerns for health care providers worldwide. The quick transmission from mosquito to human and lack of consistent symptoms make the infection difficult to diagnose. Neurological disorders that result from the virus can range from mild to life-threatening. The largest concern arises from pregnant mothers due to interruption of fetal development, especially in the first trimester. Although there are currently no available treatment options for the neurological defects of ZIKV on infants, screening tests and therapies to manage the conditions are available. Caution should be taken by all populations and multiple tests should be performed to receive the most accurate diagnosis after exposure. In order to understand more details about ZIKV, the CDC has established registries and surveillance systems for high risk populations such as pregnant women. These programs will help shape future guidelines and initiatives to prevent Zika infections and long-term complications.

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Assessment Questions

1. Which of the following patients should be screened for Zika?
   A. A young woman presenting with fever and tiredness who recently attended the Olympics in Rio.
   B. An elderly man from Indonesia who is complaining of a rash and nonpurulent conjunctivitis.
   C. A pregnant woman living in Florida who is asymptomatic.
   D. All of the above.
   E. A & B.

2. Zika virus has an incubation period of ___ days and a symptom duration of ___ days.
   A. 2-7, 4-7
   B. 4-7, 2-7
   C. 3-5, 9-13
   D. 1-4, 6-10

3. Guillain-Barre syndrome is thought to be
   A. Mediated by antilysozyme antibodies
   B. Introduced by Zika associated neurotoxic factors
   C. Associated with memory loss
   D. Treated with statin therapy

4. True or False: Microcephaly is a result of a decrease in the number of cell divisions in the brain during fetal development resulting in a decrease in production of functional neurons which leads to motor, sensory and cognitive impairments later in life.
   A. True
   B. False

5. Current studies show a maternal ZIKV infection during the ___ trimester(s) is more likely to result in children born with microcephaly.
   A. Third
   B. Second
   C. First
   D. A & B
   E. B & C
   F. All of the above.

6. All of the following are neurological disorders associated with a ZIKV infection except:
   A. Macular atrophy
   B. Microcephaly
   C. Neuroinfections
   D. Guillain-Barre syndrome
   E. Meningoencephalitis

7. For children born with possible microcephaly, how soon should a comprehensive eye exam and auditory brainstem response test be performed?
   A. At month 2
   B. Within the first month
   C. Within the first year
   D. At month 6

8. Studies are being conducted to evaluate the effectiveness of a highly sensitive reverse-transcription loop-mediated, isothermal amplification (RT-LAMP) assay. How would this test, if available, be administered?
   A. Point-of-care cassette
   B. Laboratory blood draw
   C. Physician administered POC
   D. Self-administered saliva swab

9. Asymptomatic women with diagnosis or possible exposure of Zika virus should wait ______ from symptom onset before attempting pregnancy, and men regardless of symptom status with a possible exposure to Zika virus, should wait ______ before attempting pregnancy with their partner.
   A. 2 weeks, 1 week
   B. 1 year, 6 months
   C. 8 weeks, 6 months
   D. 6 months, 8 weeks

10. Which of the following test(s) is/are currently available to detect Zika virus?
    A. Real-time reverse transcription-polymerase chain reaction (rRT-PCR)
    B. Immunoglobulin (IgM)
    C. Plaque reduction neutralization test (PRNT)
    D. Two of the above
    E. All of the above