Zika Virus: What We Know So Far

1 Contact Hour

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Kim Maryniak, RNC-NIC, MSN, PhD(c)

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Purpose

The purpose of this course is to educate nurses about the Zika virus, including prevention, potential consequences, and treatment.

Learning Objectives

After successful completion of this course, you will be able to:

1. Define the Zika virus and how it is transmitted
2. Discuss the prevalence of Zika virus worldwide
3. Describe clinical symptoms of Zika virus infection
4. Discuss the current treatments of the Zika virus
5. Identify the potential complications of the Zika virus and high risk populations
6. Explain strategies used to prevent transmission of the Zika virus
7. Identify current recommendations and patient education information

Introduction

There has been much attention focused on the Zika virus lately. The knowledge of this virus, including transmission and potential consequences associated with the Zika virus has increased, even within the past year. However, along with more facts also comes w more myths, which can cause widespread panic. Fear of exposure to this virus has prevented individuals from travelling, and have already shown the impact on the upcoming Olympic Games in Rio.

What is the Zika Virus?

The Zika virus is a mosquito-borne virus which can cause the Zika virus disease (CDC, 2016d). It was first noted in Uganda in 1947 in rhesus monkeys, and then in humans in 1952. Increasing research occurred with outbreaks in 2013 and 2015 in Brazil and French Polynesia (WHO, 2016c).

The Zika virus is related to the West Nile virus, yellow fever, dengue fever, and Japanese encephalitis virus. The Zika virus is a genus of the Flaviviridae family, and is a positive, single-stranded RNA virus.

An arbovirus is one which is transmitted to humans primarily through bites of arthopods, including infected mosquitoes, ticks, midges, and sand flies. The Zika virus is considered an arbovirus, as the primary mode of transmission to humans is through the bites of infected mosquitoes (CDC, 2016a; Petersen, Jamieson, Powers, & Honein, 2016). Other modes of transmission of arboviruses may include blood transfusion, organ transplants, exposure in a laboratory, perinatal transmission, and breastfeeding (CDC, 2016a).

The Zika virus primarily infects humans through bites from infected Aedes species mosquitoes, which includes the Aedes aegypti and Aedes albopictus mosquitoes (CDC, 2016d; Petersen, Jamieson, Powers, & Honein, 2016). These are the same mosquitoes that also transmit the dengue and chikungunya viruses. Humans who become infected may also end up being a reservoir for the Zika virus, and inadvertently be the source for uninfected mosquitoes to acquire the Zika virus (CDC, 2016a).

History of the Zika Virus

As previously stated, the Zika virus was first discovered in 1947, named after the Zika forest in Uganda where the rhesus monkey was found. In 1948, the virus was confirmed in the Aedes species of mosquito, also in the Zika forest. In 1952, the Zika virus was found in humans in Uganda and Tanzania. In Nigeria in 1964, the Zika virus was discovered in some individuals during a jaundice outbreak. The symptoms associated with the virus were described as "mild" (WHO, 2016b).

From the 1960s-1980s, the Zika virus began spreading throughout Western Africa and also in equatorial Asia, including Pakistan, India, Indonesia, and Malaysia. The symptoms were noted as malaise, fever, and rash. Although cases were reported, there were no hospitalizations or outbreaks (WHO, 2016b).

In 2007, the first reported large Zika outbreak in humans was seen in Micronesia, on the Pacific Island of Yap. An estimated 73% of residents of Yap were infected with the Zika virus. Before this time, only 14 cases of human Zika virus disease had been documented anywhere in the world, and no outbreaks were reported. It was theorized that this may have been from under-reporting, or symptoms of illness attributed to another virus rather than the Zika virus. The symptoms of dengue fever and chikungunya virus are very similar to those seen with the Zika virus (WHO, 2016b).

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In 2008, the first documented case of sexually transmission of the Zika virus was found when a researcher, infected by the virus, transmitted it to his wife. Two different strains of the Zika virus were discovered in 2012- the Asian and African strains (WHO, 2016b).

Between 2012 and 2014, more outbreaks of the Zika virus, along with dengue and chikungunya viruses, occurred in the Pacific. New Caledonia, Easter Island, French Polynesia, and the Cook islands were all affected. It was during this time that an association between the Zika virus and congenital malformations, neurological and autoimmune complications was discovered. In 2014, in utero transmissions of the Zika virus from mothers to infants, as well as transmissions through blood transfusions were also identified (WHO, 2016b).

In 2015, locally-acquired occurrences of the Zika virus were found in Brazil. During this year, the potential correlation between Guillain–Barré syndrome (GBS) and the Zika virus was beginning to be studied in Brazil. The country also noted an increase in cases of microcephaly. Throughout 2015, more cases of Zika virus were found throughout the Americas, including Columbia, Venezuela, Suriname, El Salvador, Guatamala, Mexico, and Paraguay. Late 2015 and into 2016, continued reports of increased cases of microcephaly and neurological disorders occurred in the Americas, particularly Brazil (Fauci & Morens, 2016; WHO, 2016b).

Recent Prevalence

In March of 2016, there were 153 travel-associated Zika virus cases reported in the United States, and no cases which were locally acquired. In the U.S. territories (American Samoa, Puerto Rico, and U.S. Virgin Islands), there were 107 locally acquired Zika virus cases, and one which was travel-associated (CDC, 2016d).

As of July, 2016, the number of travel-associated Zika virus cases from 2015-2016 reported in the United States have totaled 1403, and no cases which were locally acquired. In the U.S. territories, there have been 3815 locally acquired Zika virus cases, and 12 which was travel-associated (Centers for Disease Control and Prevention [CDC], 2016d). Within the U.S. territories, Puerto Rico has seen the majority of the cases.

Worldwide, also as of July, 2016, there have been 65 countries which have reported Zika virus cases between 2007 and 2016, including Africa, South America, Asia, and some European countries. This number has increased from the 52 countries reported in March of 2016 (World Health Organization [WHO], 2016c). A current map showing the distribution of the Zika virus worldwide can be found at http://www.who.int/emergencies/zika-virus/situation-report/zika_timeline_2013_2016_v2.JPG?ua=1

Test Yourself

The first large outbreak of the Zika virus in humans was reported in:

1947

1969

2007

Zika Virus Transmission

Transmission of the Zika virus has been confirmed via the following methods:

- Through mosquito bites: Zika virus is transmitted to people primarily through the bite of an infected Aedes species mosquito. Both the Aedes aegypti and the Aedes albopictus live in tropical, subtropical, and some temperate climates. The Aedes aegypti is more likely to spread the Zika virus, as they live around and prefer to feed off humans, whereas the Aedes albopictus prefer to feed off animals. The Aedes mosquitoes live indoors and outdoors, and typically lay eggs in and near standing water (such as buckets, bowls, animal dishes, flower pots and vases). These mosquitoes are aggressive daytime biters, but they can also bite at night. The Aedes mosquito also transmits three other vector-borne diseases, dengue, chikungunya and yellow fever, across tropical and subtropical regions around the world.
- Maternal-child: A fetus can be infected by the Zika virus from a pregnant woman. A pregnant woman who is already infected with Zika virus can pass the virus to her fetus during the pregnancy or around the time of birth. Although there is a potential to pass the Zika virus to an infant through breastfeeding, to date there are no confirmed reports of this transmission.
- Sexual transmission: Males can spread the Zika virus to their sexual partners. In known cases of sexual transmission, the males developed symptoms of the Zika virus infection. From these cases, it was determined that the virus can be spread prior to the start of symptoms, after symptoms were demonstrated, and even after the symptoms resolve. The Zika virus is also known to be present in

semen longer than in blood; it can be present in semen for two weeks to three months. As of July, 2016, only 15 known cases of sexual transmission have occurred in the United States
- Blood transfusions: Confirmed cases of transmission of the Zika virus have occurred from blood transfusions. These have occurred in Brazil, although no cases have been found in the United States
- Laboratory exposure: Few cases have been found to be transmitted via exposure in a laboratory setting. Again, no laboratory exposures have been found in the United States

(CDC, 2016d; March of Dimes, 2016)

Symptoms of Zika Virus Infection

The incubation period of the Zika virus is thought to range between three days to two weeks. The majority of infected individuals are asymptomatic, and those who do have symptoms may not be sick enough to seek medical treatment (CDC, 2016d; WHO, 2016c). Symptoms usually last a few days to a week, and may include:

- Fever
- Rash
- Joint pain
- Conjunctivitis (non-purulent)
- Myalgia and/or arthralgia
- Headache
- Malaise

(CDC, 2016d; Navalkele, 2016)

Very few deaths have been reported with Zika virus disease, and those have been associated with individuals who have other co-morbidities, including immune system compromise (WHO, 2016d).

Diagnosis of Zika Virus Infection

The World Health Organization (2016d) has developed definitions for determining if an individual has been infected with the Zika virus. These include:

- Suspected case: This is when a person presents with a rash and/or fever, as well as at least one of a) arthralgia, b) arthritis, or c) conjunctivitis
- Probable case: This is a suspected case, in which the individual also has the presence of the IgM antibody against Zika virus (with no evidence of other flaviviruses such as dengue or yellow fever). In addition, the individual has a link to the Zika virus through a history of residing in or travelling to an area with local transmission of Zika virus within two weeks prior to onset of symptoms, or contact with a confirmed case
- Confirmed case: This is when a person has laboratory confirmation of a recent Zika virus infection. This may include the presence of Zika virus RNA or antigen in serum or other samples (e.g. saliva, tissues, urine, whole blood), or the IgM

antibody against Zika virus positive and plaque reduction neutralization test (PRNT90) for Zika virus with a positive titer and titer ratio, as well as exclusion of other flaviviruses

More on Testing

There are now commercially available tests for Zika virus infection using real-time reverse-transcription polymerase chain reaction (rRT-PCR) molecular assays. Providers should be aware that when requesting Zika rRT-PCR testing from a commercial laboratory, most of these laboratories currently do not also offer Zika IgM enzyme-linked immunosorbent assay (ELISA) or confirmatory serologic testing (plaque reduction neutralization test, or PRNT). Therefore, if possible, providers should obtain and store a serum aliquot for subsequent Zika IgM ELISA testing if the rRT-PCR assay is negative. rRT-PCR (molecular) testing should be performed for patients potentially exposed to Zika virus who have symptoms consistent with Zika virus infection.

Appropriate samples for molecular testing are serum samples collected within seven days and urine samples collected within 14 days of onset of symptoms. Urine should always be collected with a patient-matched serum specimen. Because Zika Virus may be found in both urine and blood, the Centers for Disease Control and Prevention recommends sending both urine and blood samples for PCR testing. If the PCR is negative, IgM testing should be performed; depending on the lab performing the test, providers may need to send a new blood sample for IgM testing (CDC, 2016c; American College of Obstetricians and Gynecologists, 2016).

Test Yourself

Most individuals who are infected with the Zika virus experience

A. Nausea and vomiting
B. No symptoms
C. Diarrhea

Zika Virus Treatment

There are currently no vaccinations or specific treatment for the Zika virus infection. The symptoms associated with the virus are treated with, rest and plenty of fluids to reduce chances of dehydration. Fever can be treated with acetaminophen or paracetamol. These medications are also used for treating the associated myalgia or arthralgia pain. The use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDS) are not recommended until dengue is ruled out, due to potential for bleeding (CDC, 2016d; WHO, 2016c).

Potential Complications of the Zika Virus

There has been increasing evidence that infection with the Zika virus is associated with other conditions. The increased research in 2016 has confirmed that the Zika virus has

now been identified as a potential cause for these conditions, rather than just a correlation. These include:

- Neurological and auto-immune conditions:
  - Guillain–Barré syndrome
  - Myelitis
  - Meningitis
  - Meningoencephalitis
- Congenital anomalies:
  - Microcephaly
  - Ophthalmological abnormalities

(CDC, 2016d; European Centre for Disease Prevention and Control, 2016; WHO, 2016c)

Guillain–Barré Syndrome

Guillain-Barré syndrome (GBS) can be described as a collection of clinical syndromes that attacks the peripheral nervous system, affecting muscle movement, pain, temperature, and touch. It results in progressive weakness, diminished reflexes, and loss of sensation. It is a rare condition, affecting individuals of all ages, although it is more common in adults and males. Approximately 3-5% of patients with GBS die from complications, including infection, pulmonary embolism, cardiac arrest, or muscle paralysis which impacts the ability to breathe (Andary, 2016; NINDS, 2016a).

GBS occurs when the body's immune system strikes part of the peripheral nervous system. The first symptoms of this disorder usually involve varying degrees of weakness or neuropathy bilaterally in the legs, and then spreading to the arms and upper torso. These symptoms can progress over hours, days, or weeks, and increase in intensity, causing diaphragm and chest muscle paralysis, up to and including total body paralysis. Disruptions in the body's ability to breathe or regulate heart rate and blood pressure becomes a medical emergency. The use of mechanical ventilation and intensive care monitoring of circulation and potential sepsis is necessary at that stage. Most people reach the stage of greatest weakness within the first two weeks after becoming symptomatic, and most (90%) are at their weakest by the third week of the illness. Many persons afflicted with Guillain-Barré syndrome have good recovery, although some may have a certain degree of weakness for the remainder of their lives (Andary, 2016; NINDS, 2016a).

More about Guillain-Barré

It is still unknown what triggers autoimmune diseases in certain individuals, but it is an abnormal response from the immune system which is supposed to destroy invading organisms and foreign material. In an autoimmune disease, the immune system also attacks the body itself. With Guillain-Barré syndrome, the immune system begins to destroy the myelin sheaths around the peripheral nerve axons, and maybe even the axons themselves. The myelin sheath is necessary for transmissions of nerve signals, and with damage to these sheaths the nerves cannot effectively transmit signals. Therefore, the muscles cannot respond to the commands sent from the brain through

the nerves. In addition, the brain cannot receive adequate sensory signals from the body, which disrupts the ability to feel pain, temperature, textures, and other sensations. The inappropriate signals can result in the individual experiencing neuropathy, such as tingling and painful sensations (Andary, 2016; NINDS, 2016a).

Causes of Guillain-Barré

An infection from a virus or bacteria may change the nature of the nervous system cells, so the immune system attacks them as if they are foreign bodies, which may lead to Guillain-Barré syndrome. It is may also be possible that the viral or bacterial infection causes the immune system itself to be unable to discriminate between the body's own cells and the invading organism. This may allow lymphocytes and macrophages to attack the myelin. Sensitized T lymphocytes cooperate with B lymphocytes to produce antibodies against components of the myelin sheath and may contribute to destruction of the myelin. Current research is underway by scientists, who are investing what occurs with Guillain-Barré syndrome and other autoimmune diseases (Andary, 2016; NINDS, 2016a). Although there have been reports of Guillain-Barré syndrome and the Zika virus in Brazil, the Centers for Disease Control and Prevention continue to investigate the link between the two (CDC, 2016d; European Centre for Disease Prevention and Control, 2016).

Diagnosis of Guillain-Barré

Diagnosis of Guillain-Barré syndrome is complicated. A syndrome is a medical condition characterized by a collection of signs and symptoms. The signs and symptoms of GBS can vary from individual to individual, as so it may be difficult to diagnose in the earlier stages. The collection of signs and symptoms may form a pattern which can determine if a person suffers from GBS, or if other conditions can be ruled out. The location and progression of symptoms is a strong indicator of GBS.

Laboratory tests such as complete blood counts and electrolyte panels may also rule out other conditions. Nerve conduction studies and electromyography (EMG) can also be helpful in the diagnosis, detecting abnormalities with nerve transmission. However, normal electro-diagnostic studies does not rule out Guillain-Barré syndrome. A lumbar puncture is also recommended, as an increase in cerebrospinal fluid (CSF) protein may be seen in the acute phase of GBS, which may be as a result of inflamed nerve roots. Imaging studies, including magnetic resonance imaging (MRI) and computed tomography (CT) scanning of the spine, may be used to rule out other neurological disorders (Andary, 2016; NINDS, 2016a).

Treatment of Guillain-Barré

There is currently no known cure for Guillain-Barré syndrome, but there are therapies that lessen the severity of the illness and accelerate the recovery in most patients. Treatments include:

- Plasmapheresis: Plasma exchange is a method by which whole blood is removed from the body and processed to separate the red and white blood cells from the plasma. The blood cells are then returned to the patient without the plasma, which the body quickly replaces. It is still unknown why exactly the

plasma exchange works, but it does seem to reduce the severity and duration of the Guillain-Barré episode.

- High-dose immunoglobulin therapy: Intravenous injections of high doses of immunoglobulins can also lessen the immune attack of GBS on the nervous system. It is also unknown why this treatment works with GBS patients
- Intensive care monitoring and ventilatory assistance: The most critical part of the treatment for Guillain-Barré is to keep the patient's functioning while the nervous system is recovering. Cardiorespiratory monitoring is essential, and mechanical ventilation may be necessary. Vital sign support may require fluids, electrolyte replacement, and even the use of vasopressors in some cases.
- Prevention of complications such as pneumonia, sepsis, venous thromboembolism, and pressure ulcers are also important. Maintaining range of motion, including passive exercises, can assist with maintaining muscle flexibility and preventing deep vein thrombosis. Physical therapy is essential as the patient begins to recover

(Andary, 2016; NINDS, 2016a).

Test Yourself

Which of the following is true of Guillain-Barré syndrome?

A. It is only caused by a bacterial infection
B. It can be ruled out by negative results of electro-diagnostic testing
C. There is currently no cure

Myelitis

During the 2013-2014 outbreaks of the Zika virus, it was also noted a slight increase in the reports of myelitis. The World Health Organization suggested that there may be a link between the two (WHO, 2016c). The first case of a patient with myelitis who tested positive for the Zika virus was found in 2016 (Mécharles et al., 2016).

Myelitis is defined as an inflammation of the spinal cord. Transverse myelitis is a neurological disorder caused by inflammation across both sides of one level, or segment, of the spinal cord. "Transverse" describes the position of the inflammation, that is, across the width of the spinal cord. Similar to GBS, inflammation with myelitis can damage or destroy myelin, causing interruptions in the communication between the spinal cord nerves and the rest of the body.

Symptoms of transverse myelitis occur over hours to several weeks, and include a loss of spinal cord function. Symptoms usually start with a sudden onset of muscle weakness, lower back pain, or neuropathy of the toes and feet, and can quickly progress to urinary retention, incontinence of bladder and bowel, and even paralysis. . Most patients only have one episode, and recover from myelitis without prolonged or minor effects, although some may suffer permanent impairments that affect their ability to perform ordinary tasks of daily living (NINDS, 2015).

Diagnosis of Myelitis

Diagnosis of myelitis, like Guillain-Barré syndrome, is through testing to rule out other conditions. Imaging studies, including magnetic resonance imaging (MRI) and computed tomography (CT) scanning of the spine, should be used to rule out other neurological disorders, such as structural abnormalities of the spine.

Laboratory tests such as complete blood counts and electrolyte panels may also rule out other conditions. Blood tests should be performed to rule out various disorders such as systemic lupus erythematosus, vitamin B12 deficiency, HIV infection, and others. A lumbar puncture is also recommended, as an increase in cerebrospinal fluid (CSF) protein and leukocytes may be seen in myelitis. Imaging studies, including magnetic resonance imaging (MRI) and computed tomography (CT) scanning of the spine, may be used to rule out other neurological disorders (NINDS, 2015).

Treatment of Myelitis

Unfortunately, there is no current cure for myelitis. Treatments are geared towards management of symptoms. These include:

- Corticosteroids: These are used to decrease inflammation and assist with recovery, and may reduce immune system activity. This may include the use of intravenous corticosteroids
- Plasma exchange: This may be used when a patient does not respond to corticosteroids
- Pain management: This is an important consideration for patients with myelitis
- Hospitalization and ventilatory assistance: In severe cases where breathing may be impaired, patients may need to be hospitalized or placed in a rehabilitation facility. In these cases, cardiorespiratory monitoring and mechanical ventilation may be necessary.
- Prevention of complications such as pneumonia, sepsis, venous thromboembolism, and pressure ulcers are also important. Maintaining range of motion, including passive exercises, can assist with maintaining muscle flexibility and preventing deep vein thrombosis. Physical therapy is essential as the patient begins to recover

(NINDS, 2015)

Meningitis

Just like the potential association with myelitis, the Zika virus outbreaks in 2013-2014 also identified increased incidences of meningitis and meningoencephalitis (WHO, 2016c). In 2016, a patient with meningitis and meningoencephalitis also had confirmed Zika virus infection, suggesting a possible link between the two (Carteaux et al., 2016). Meningitis involves the brain meninges, and encephalitis involves the brain itself. When both are present, it is known as meningoencephalitis.

Meningitis is defined as a clinical syndrome where the meninges of the brain are inflamed. The meninges are the three layers of membranes that enclose the brain and

spinal cord, including the dura (outer membrane), arachnoid (middle membrane), and subarachnoid space (inner layer). Meningitis can be caused from a bacterial, fungal, or viral source.

Symptoms of meningitis usually consist of the classic “triad” of symptoms, including headache, fever, and neck stiffness. However, not all patients present with these symptoms. Other symptoms include myalgia, anorexia, nausea and vomiting, photophobia, altered level of consciousness, fatigue, confusion, irritability, delirium, and coma. The symptoms may occur within a few hours to one or two days (Hasbun, 2016).

Diagnosis of Meningitis

Meningitis is considered a medical emergency, and it is recommended to perform a lumbar puncture to examine the CSF when suspected. CSF is sent for cultures, as well as protein, blood count, and glucose. Depending on the source of meningitis, blood counts, protein and glucose levels could be abnormally high or low. Patients at risk for brain herniation should have a CT scan done prior to a lumbar puncture, as the LP may increase the risk for herniation. Complete blood counts and electrolyte panels should also be performed, and a blood culture should be taken in conjunction with the CSF culture (Hasbun, 2016).

Treatment of Meningitis

Treatment of meningitis depends on the source of the infection. Considerations include:

- Intensive care: Acute meningitis, is considered a medical emergency. Fluid and electrolyte replacement is essential. The patient may require the use of vasopressors. Seizure precautions and potential mechanical ventilation should be considered. Antimicrobial therapy should be initiated, and use of corticosteroids may be indicated. Cardiorespiratory monitoring is necessary. Complications including shock, hypoxemia, and increased intracranial pressure (ICP) should be treated appropriately
- Monitoring for other complications such as cardiac arrhythmias, stroke, seizures, and chronic disease exacerbations with immediate interventions should also be undertaken
- Pain management is another important consideration

(Hasbun, 2016)

Encephalitis

Encephalitis is classified as an inflammation of the brain; more specifically the brain parenchyma. It is usually caused by a virus, but may be from bacteria, fungi, or a parasite. Encephalitis causes diffuse or local neurological symptoms.

Symptoms typically include fever, headache, nausea and vomiting, lethargy, myalgia, behavioral and personality changes, altered level of consciousness, neck pain and stiffness, photophobia, seizures (either general, focal, or both), confusion, and paralysis. The degree and progression of symptoms is individualized (Howes, 2016).

Diagnosis of Encephalitis

Encephalitis is diagnosed by a variety of tests, mainly geared towards finding the source of the infection. It is essential to perform a lumbar puncture to examine the CSF when suspected. CSF is sent for gram staining and cultures, as well as protein, blood count, and glucose. Depending on the source of encephalitis, blood counts, protein and glucose levels could be abnormally high or low. A CT of the head with and without contrast is recommended, and an MRI can also provide more information about the brain. Complete blood counts and electrolyte panels should also be performed, and a blood culture should be taken in conjunction with the CSF culture. A brain biopsy is the standard for confirmation of the diagnosis (Howes, 2016).

Treatment of Encephalitis

Treatment of encephalitis also depends on the source of the infection. Considerations include:

- Intensive care: Fluid and electrolyte management is essential, and may include the use of diuretics. Seizure precautions and potential mechanical ventilation should be considered. Antiviral therapy should be initiated, as well as potential antibiotics, and use of corticosteroids may be used. Cardiorespiratory monitoring is necessary. Complications including shock, hypoxemia, and increased intracranial pressure (ICP) should be treated appropriately
- Monitoring for other complications such as cardiac arrhythmias, stroke, seizures, and chronic disease exacerbations with immediate interventions should also be undertaken
- Pain management is also essential

(Howes, 2016)

Test Yourself

Inflammation of the spinal cord is known as

A. Myelitis
B. Meningitis
C. Encephalitis

Microcephaly and the Zika Virus

During outbreaks of the Zika virus infection in Brazil in 2015, it was also noted that there were increased incidents of babies born with microcephaly (CDC, 2016d; Schuler-Faccini et al., 2016). Since those initial reports of a potential link between Zika and microcephaly, researchers across the world began more research to study if a causal relationship existed between Zika during pregnancy and microcephaly. In April, 2016, CDC scientists announced that they determined that there is now enough evidence to conclude that Zika virus infection during pregnancy is a cause of microcephaly and other severe fetal brain defects. This was not based on a single definitive event, but

rather an accumulation of evidence that demonstrated, through strict criteria, a causal relationship was established (CDC, 2016b; Rasmussen, 2016).

Since the causal relationship between the Zika virus and fetal brain defects has been established, there is an increased drive for additional prevention efforts, communication, and focused research. There are many unanswered questions, which is the focus on continued research, as well as prevention and the reduction of the effects of the Zika virus infection during pregnancy (CDC, 2016b; Rasmussen, 2016).

Microcephaly

Microcephaly occurs when the brain of a fetus does not develop properly or stops growing, and causes the circumference of the head to be smaller than normal, noting the occipitofrontal circumference less than the third percentile, based on standard growth charts. Microcephaly can be present at birth or it may develop in the first few years of life. There are many causes of microcephaly, including genetic abnormalities, substance abuse, infections (including cytomegalovirus, varicella, rubella, Zika virus, and toxoplasmosis), severe malnutrition, exposure to toxins, untreated phenylketonuria (PKU), or impaired blood flow to the fetus' brain during pregnancy. Microcephaly can occur alone, or may also occur with Down's syndrome, chromosomal syndromes, and neuro-metabolic syndromes. If the microcephaly is caused by brain injury from a virus, such as Zika, many times there is widespread tissue and cell death and damage. This leads to brain shrinkage rather than just impaired brain growth (CDC, 2016b; NINDS, 2016b; Staples et al., 2016).

The outcomes for children with microcephaly are dependent on the severity of the condition. Children may have impaired cognitive development, seizures, mental retardation, delayed motor functions and speech, feeding problems, cerebral palsy, facial distortions, dwarfism or short stature, hyperactivity, difficulties with coordination and balance, hearing loss, vision impairment, and other neurological abnormalities (CDC, 2016b; NINDS, 2016b).

Diagnosis of Microcephaly

Diagnosis of microcephaly can be done during pregnancy, via ultrasound, or after the infant is born. Measurements of head circumference are done and is plotted on comparison charts. For a diagnosis of microcephaly to be made, the occipitofrontal circumference should be disproportionately small in comparison with the length of the infant and not explained by other causes, such as congenital disorders. If an infant's occipitofrontal circumference is equal to or greater than the third percentile but is notably disproportionate to the length of the infant, or if the infant has deficits that are related to the central nervous system, additional evaluations might be considered. Testing such as CT scans and MRIs provide information about the infant's brain structures, which can help determine severity and potential treatment (CDC, 2016b; NINDS, 2016b; Staples et al., 2016).

Treatment of Microcephaly

Treatment of microcephaly is supportive, and is individualized depending on the severity of the condition. Microcephaly is a lifelong condition. Considerations for treatment include:

- Monitoring: Initially, infants may need intensive care monitoring. Testing and treatment of any infections should be initiated.
- Medications: If and when seizures occur, medications are used to control them. Medications may also be used for hyperactivity and neuromuscular symptoms
- Developmental interventions: The use of physical, speech, and occupational therapies can increase the maximum potential for motor and intellectual abilities of the child.
- Follow up: Children with microcephaly require scheduled follow up to monitor head growth and any disabilities. A pediatric neurologist is also needed.

(CDC, 2016b; NINDS, 2016b)

Questions about the Zika Virus and Microcephaly

As of the writing of this course, it is known that pregnant women can be infected with Zika virus. The most common mode of transmission of the Zika virus is through the bite of an infected mosquito, and can also be spread by a male to his sexual partners. It is also known that a pregnant woman can pass Zika virus to her fetus, either during the pregnancy or at delivery (CDC, 2016b).

It is still unknown what the likelihood is that if a pregnant woman is exposed to the Zika virus she will actually contract the infection. It is also unknown how, or if the Zika virus will affect the pregnant woman or her pregnancy. There are also no known statistics of how likely an infected pregnant women will pass the Zika virus to her fetus. If the fetus is infected with the Zika virus, it is also unclear if the fetus will develop birth defects, or at what point during the pregnancy the infection might harm the fetus. It is also not definitive that an infected fetus will have birth defects. There is also no information if transmission of the Zika virus via infected mosquitoes versus sexual transmission has a different risk for developing birth defects (CDC, 2016b; March of Dimes, 2016).

Test Yourself

Which of the following statements is true about microcephaly?

A. It is always associated with another condition
B. Outcomes are dependent on the severity of the condition
C. Exposure to the Zika virus during pregnancy will always cause microcephaly

Intracranial Calcifications

Along with microcephaly, it was also found there were an increase in the numbers of babies born with intracranial calcifications during the 2015 Brazil outbreaks of the Zika

virus (CDC, 2016d; Schuler-Faccini et al., 2016). Intracranial calcifications can occur in conjunction with microcephaly or other neurological disorders, or may be found alone. It is also a common finding with cytomegalovirus (Wilson et al., 2014).

The effect of intracranial calcifications depends on where they are located in the brain, and the amount of calcifications found. These calcifications are associated with neuromuscular abnormalities, including impaired muscle tone, seizures and epilepsy, hemiplegia, cerebral palsy, and developmental delay. There is no treatment for intracranial calcifications other than just monitoring and supportive therapy for any potential effects (Wilson et al., 2014).

Ophthalmological Abnormalities

The Zika virus is also associated with retinal lesions, often leading to blindness. Infants born with microcephaly have been studied for ophthalmological abnormalities, and were found to have bilateral macular and perimacular lesions, as well as optic nerve abnormalities (de Paula Freitas, 2016).

Retinal lesions can progress, remain unchanged, or occasionally improve. However, the outcomes are dependent both on the initial damage as well as progression. Outcomes are based upon the location and size of the lesion, and may include little to no vision impairment up to and including blindness. Optic nerve abnormalities are almost always associated with vision impairment and blindness (Wright, Spiegel, & Thompson, 2007).

Guidelines for Pregnant Women

The CDC, with support of the American College of Obstetricians and Gynecologists (ACOG) have implemented guidelines for the Zika virus testing of pregnant women. These are determined based upon the potential exposure to the Zika virus, and include:

- For those pregnant women who have a history of travel to an area with known Zika virus transmission, testing should be done if there is clinical signs and symptoms consistent with the Zika virus infection (acute onset of fever, rash, arthralgia, conjunctivitis) during or within two weeks of travel. Testing should include real-time reverse-transcription polymerase chain reaction (rRT-PCR), and Zika IgM. For those women who do not demonstrate clinical illness consistent with Zika virus infection during or within two weeks of travel, testing should be offered 2–12 weeks after exposure with the Zika IgM test.
- For those pregnant women who live in an area of known Zika virus transmission, testing should be done if clinical illness consistent with Zika is noted. Testing should include polymerase chain reaction (PCR) and Zika IgM. For those women who do not have signs and symptoms of Zika virus infection, testing should include a Zika IgM at the first visit, with a repeat in late second trimester given ongoing exposure.

(ACOG, 2016; CDC, 2016c).

Pregnancy Guidelines, con't

There are many challenges of both the management and counseling for pregnant women who have been exposed to the Zika virus. Referral to a maternal–fetal medicine or infectious disease specialist with expertise in pregnancy management is recommended, especially with those patients who have demonstrated maternal infection or concerning fetal findings.

Additionally, providers need to report pregnant women with any laboratory evidence of the Zika virus infection (positive or inconclusive test results) to the state health department and the CDC pregnancy hotline. Follow up from health officials will be done during the pregnancy and at the time of expected birth to collect surveillance data. Any adverse outcomes should also be reported to the state health department. CDC registry staff will work with state health departments to assist with collection of information, and will notify state, tribal, local, or territorial health departments are (ACOG, 2016; CDC, 2016c).

Guidelines for Evaluation of the Fetus

For pregnant women who live in or have traveled to areas with ongoing Zika virus infection, ultrasound examinations are recommended. It is recommended for the first ultrasound to be conducted three to four weeks after symptoms begin, or if there has been exposure for those pregnant women who have traveled to Zika virus areas but have no symptoms. For pregnant women who do not have symptoms and live in an area with the Zika virus, ultrasounds are recommended 18–20 weeks or sooner. The focus of ultrasound examinations should be on brain development, looking at findings such as intracranial calcifications, microcephaly, and other brain abnormalities, as those abnormalities have been most frequently reported in affected pregnancies.

If the initial ultrasound is reassuring (no abnormalities found), serial ultrasounds are recommended if maternal infection is concluded (positive or inconclusive IgM and/or PCR). The serial ultrasounds should occur as frequently as every three to four weeks. If a pregnant women is exposed but no confirmed infection, an additional ultrasound could still be considered after an initial reassuring ultrasound, because the natural history of Zika virus infection in utero is unknown, and the time from exposure and infection to clinical manifestations is uncertain. Thus, one reassuring ultrasound, especially if it is obtained close to the time of infection or exposure, may not rule out later manifestations, and cases with delayed findings have been reported (ACOG, 2016; CDC, 2016c).

Fetal Evaluation, con't

Pregnant women with travel history but no evidence of the Zika virus infection indicated through serologic testing may be appropriate for less frequent ultrasound screening or

routine prenatal care. However, clinicians are currently unable to identify an appropriate evidence-based interval for serial ultrasounds or identify those pregnancies which may not need serial ultrasounds. The CDC notes that negative Zika IgM testing at 2–12 weeks after travel cannot definitively rule out Zika virus infection, but may eliminate the need for serial ultrasounds.

Amniotic fluid evaluation is not routinely recommended. However, when ultrasonic imaging raises suspicion for fetal infection, amniocentesis for Zika virus testing of amniotic fluid may be considered on a case by case basis. While it is assumed that assay performance on amniotic fluid is similar to that with maternal serum, this is not certain. It is also not known how long after a pregnant woman becomes infected she can transmit the virus to the fetus, how long the amniotic fluid will be PCR positive, or how or if the test can determine the presence of fetal injury (ACOG, 2016; CDC, 2016c).

Test Yourself

Which of the following statements is true?

A. An initially negative ultrasound concludes that the fetus has no Zika virus infection
B. Serial ultrasounds are recommended for pregnant women who test positive for Zika virus infection
C. Amniocentesis is routinely recommended

Guidelines for Infants with Abnormalities

Testing of an infant for the Zika virus infection is warranted for the purpose of evaluating an infant for possible congenital Zika virus infection, microcephaly diagnosis, intracranial calcifications, or other central nervous deficits, along with potential exposure during utero. The mother, if not already tested during pregnancy, should also be tested for the Zika virus infection. In addition, further clinical evaluation and laboratory testing is recommended for the infant, including:

- Comprehensive physical examination, including careful measurement of the occipitofrontal circumference, weight, length, and gestational age assessment
- Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly and/or hepatomegaly, and rash or other skin lesions. Documentation of abnormal findings, including dysmorphic features, rash, and/or skin lesions, should include full body photographs. If an abnormality is noted, consultation with an appropriate specialist is recommended.
- Cranial ultrasound should be performed, unless prenatal ultrasound results from third trimester demonstrated no abnormalities of the brain.
- Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within one month after birth. Infants with abnormal initial hearing screens should be referred to an audiologist for further evaluation.
- Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within one month after birth. Infants with abnormal

initial eye evaluation should be referred to a pediatric ophthalmologist for further evaluation.
- Other evaluations specific to the infant's clinical presentation.

(ACOG, 2016; CDC, 2016c; Staples et al., 2016)

Infants with Abnormalities Guidelines, con't

For infants with microcephaly or intracranial calcifications, additional evaluation includes the following:

- Consultations should include a clinical geneticist or dysmorphologist, and a pediatric neurologist to determine appropriate brain imaging and additional evaluation (e.g., ultrasound, computerized tomography scan, magnetic resonance imaging, and electroencephalogram). Other consultations may include developmental and behavioral pediatrics, physical and speech therapy, and a pediatric infectious disease specialist
- Testing should also be performed for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infections.
- Complete blood count, platelet count, and liver function and enzyme tests, including alanine aminotransferase, aspartate aminotransferase, and bilirubin.
- Consideration of and further testing for genetic and other teratogenic causes based on additional congenital anomalies that are identified through clinical examination and imaging studies is another important factor. For infants with microcephaly or intracranial calcifications who have negative results on all Zika virus tests performed, health care providers should evaluate for other possible etiologies and treat as indicated.
- For infants who have any positive or inconclusive test findings for Zika virus infection, health care providers need to file a report to the state, territorial, or local health department and assess the infant for possible long-term sequelae. This includes a repeat hearing screen at age six months, even if the initial hearing screening test was normal, because of the potential for delayed hearing loss as has been described with other infections such as cytomegalovirus

(ACOG, 2016; CDC, 2016c; Staples et al., 2016)

Guidelines for Infants without Abnormalities

For an infant exposed to the Zika virus during pregnancy, but born without microcephaly or intracranial calcifications, subsequent evaluation depends on the results from maternal Zika virus testing.

- If the maternal test results were negative for the Zika virus infection, the infant should receive routine care, such as newborn metabolic and hearing screens. If the maternal test results were positive or inconclusive results for the Zika virus infection, the infant should be tested for a possible congenital Zika virus infection.
- If the results of all of the infant's tests are negative for evidence of Zika virus infection, then no further Zika virus testing and evaluation is recommended.

- If any of the infant's samples test positive or inconclusive for the Zika virus, then the infant should undergo further clinical evaluation, such as those recommended in the previous section. The infant should also be followed to assess for possible long-term consequences, and the infant's case should be reported to the state, territorial, or local health department.
- Infant follow-up should include a cranial ultrasound to assess for subclinical findings, unless prenatal ultrasound results from the third trimester demonstrated no abnormalities of the brain. Ophthalmologic examination and a repeat hearing screen are also recommended, as previously described for infants with microcephaly or intracranial calcifications. Developmental monitoring and screening during the first year of life is recommended for all children with congenital Zika virus infection.

(ACOG, 2016; CDC, 2016c; Staples et al., 2016)

Prevention Strategies

Because there is no current vaccine or treatment for the Zika virus infection, prevention is the key. Strategies include:

- Protection from mosquito bites:
    - The Aedes species of mosquito are more aggressive during the day, but may also bite at night. Prevention against mosquitoes should be implemented at all times
    - Insect repellents approved by the Environmental Protection Agency (EPA) have been proven to be effective and safe, including use with pregnant and breastfeeding women. Repellents which have higher percentages of active ingredients have longer lasting effects. Effective ingredients include DEET, Picaridin (also known as icaridin, Bayrepel, and KBR 3023), oil of lemon eucalyptus or para-menthane-diol, and IR3535. Some insect repellents, such as natural repellents, have not been evaluated by the EPA. It is recommended that only EPA-approved insect repellents be used. A list of approved repellents can be found on the EPA website (see Resources section)
    - The product label instructions should always be followed when using insect repellents, and reapply as directed. Repellent should not be sprayed on the skin under clothing. If sunscreen is also used, it should be applied first, and the insect repellent second.
    - Considerations for children and infants include always following instructions when applying insect repellent to children. Insect repellent should not be used on babies younger than two months old. Insect repellent should not be applied onto a child's hands, eyes, mouth, and cut or irritated skin. Products containing oil of lemon eucalyptus or para-menthane-diol should not be used on children under three years of age. Children should be dressed in clothing that covers arms and legs. An infant's or child's stroller, crib, and baby carrier should be covered with mosquito netting

    - Clothing should be worn, including a hat, a long-sleeved shirt, long pants, shoes and socks. Items such as boots, pants, socks, and tents, should be treated with permethrin; another open is to buy permethrin-treated clothing and gear. Permethrin-treated clothing will have continued protection after multiple washings. Product information should be reviewed to find out how long the protection will last. If items are self-treated, following the product instructions is essential. Permethrin products should not be used directly on the skin

(CDC, 2016d; Staples et al., 2016)

Prevention Strategies, con't

- Controlling mosquitoes:
    - Screens should be used on windows and doors. Holes in screens should be repaired as soon as possible to keep mosquitoes outside.
    - Air conditioning should be used when available.
    - It is recommended that at least once a week, items that hold water should be emptied and scrubbed, turned over, covered, or thrown out. Items may include tires, buckets, planters, toys, pools, birdbaths, flowerpots, or trash containers, both inside and outside of the home. Mosquitoes lay eggs near water
- Protect against sexual transmission:
    - Sexual transmission of the Zika virus has been reported but it is uncertain about the frequency and efficiency of this route of infection. More research is needed, but based on limited data, there is a risk of sexual transmission through exposure to semen of males with the Zika virus infection. Abstinence or the use of protection barriers, such as condoms, is recommended with sexual partners who have been exposed to the Zika virus. Because it is known that the Zika virus can live in semen up to six months, this is the currently recommended length of time for sexual precautions.

(CDC, 2016d; Staples et al., 2016)

Test Yourself

Which of the following is true regarding insect repellents?

A. All insect repellents have the same effect against mosquitoes
B. Insect repellents can be used the same for adults, children, and infants
C. The EPA has a list of approved insect repellents for safety and effectiveness

Prevention Strategies for Pregnant Women

There are also additional considerations for pregnant women. These include:

- Avoid travel:

    - Travel to a Zika-affected area should be avoided unless absolutely necessary.
    - If travel is required, a visit with a health care provider is recommended prior to travel, and mosquito bite prevention is essential. Check CDC travel alerts for updates (see Resources section)
- Protection against sexual transmission:
    - Given the potential risks of maternal Zika virus infection, pregnant women whose male partners have traveled to countries in which Zika virus is reported, or those who have the Zika virus infection should use condoms or abstain from sexual intercourse for the remainder of pregnancy
- Counselling:
    - Health care providers should discuss pregnancy intentions and reproductive options with all women of reproductive age. Preconception care should also include the risk for Zika virus exposure, signs and symptoms, and the potential risks for Zika virus infection. Counselling is critical for women and men who reside in an area with ongoing transmission of the Zika virus.
    - The risk of adverse pregnancy, congenital infections, and birth outcomes associated with the Zika virus infection during pregnancy demonstrates the need to make sure that effective contraception is readily available for women and couples who live in or have recently traveled to areas with known Zika virus infections. When women do not plan a pregnancy, health care providers should discuss strategies to prevent unintended pregnancy and counsel on family planning. Safety, effectiveness, availability, and acceptability should be considered when selecting a contraceptive method.

(ACOG, 2016; CDC, 2016d; March of Dimes, 2016; Staples et al., 2016)

Prevention Strategies for Pregnancy, con't

- Counselling, con't:
    - Women who are diagnosed with Zika virus infection should wait at least eight weeks from symptom onset to attempt pregnancy. Men diagnosed with Zika virus infection should wait at least six months from symptom onset to attempt pregnancy.
    - Routine Zika virus testing (IgM or PCR) is not currently recommended for women or men with possible Zika virus exposure without clinical illness who are attempting pregnancy. It is also not currently known if a positive serologic Zika virus test result in an asymptomatic male would indicate presence of the Zika virus in semen, or if a negative serologic Zika virus test result would preclude the presence of Zika virus in semen
- Breastfeeding:
    - Although there have been reports of the presence of the Zika virus in breast milk, it is in very small amounts and unlikely to be harmful for the neonate. Infection through oral intake is not known and any effects of

neonatal Zika virus infection, as with adults, are likely to be mild and of short-term consequence.
    - The benefits of breastfeeding currently outweigh the potential neonatal risks of the Zika virus infection. Therefore, the recommendation is that women should continue to breastfeed.

(ACOG, 2016; CDC, 2016d; March of Dimes, 2016; Staples et al., 2016)

Considerations for Health Care Professionals

The Zika virus RNA has been detected in many body fluids, such as blood, urine, saliva, and amniotic fluid. Currently, there is no documented case of health care-associated transmission associated with exposure to these bodily fluids. However, it is always essential to minimize exposures to body fluids. Agencies such as the CDC and ACOG recommend the use of standard precautions in health care settings to protect health care professionals, and patients, from infection with the Zika virus as well as from other blood-borne pathogens (including human immunodeficiency virus and hepatitis C). This highlights what should already be common and expected practice, by using the basic infection prevention measures that apply to patient care in all heath care settings, including labor and delivery. The appropriate use of personal protective equipment is important for all health care providers to minimize the risk of transmission of infectious pathogens through exposure to blood and body fluids. The use of masks and/or goggles is recommended if there is a potential for splashing of body fluids. There is no evidence that contact precautions or respiratory isolation of Zika virus-infected patients is warranted (ACOG, 2016; CDC, 2016d; March of Dimes, 2016).

Current Research

There has been an increase in the research and studies being performed around the Zika virus infection. The National Institute of Allergy and Infectious Diseases (NIAID), a branch of the U.S. Department of Health and Human Services National Institutes of Health, is one of the organizations which is focused on Zika virus research. Key areas of current research include:

- Developing clinical diagnostic tests for the Zika virus which are sensitive, specific, and rapid
- Producing treatments for the Zika virus infection, as well as broad spectrum antiviral drugs that would be effective against multiple flaviviruses
- Creating and testing vaccines to protect against Zika virus infection, as well as advancing new vaccination strategies
- Conducting research studies to understand the Zika virus infection, including replication, pathogenesis, and transmission of the virus, as well as the biology of the mosquito vectors
- Developing animal models that simulate the human Zika virus infection, so that researchers can further investigate the progression of disease
- Pursuing studies on how the Zika virus evolves and emerges, including the identification of factors that affect host-range and virulence
- Performing surveillance studies of the history and distribution of Zika virus

- Evaluating the relationships between immune responses to Zika and other flaviviruses that may transpire in the same geographical regions (such as dengue virus and yellow fever virus)
- Conducting research studies focused on investigation of how Zika virus infection affects reproduction, pregnancy, and the developing fetus

(NIAID, 2016)

Vaccine Research

NIAID is also actively investigating and developing multiple vaccine options to prevent the Zika virus infection, including:

- A DNA-based vaccine that is similar to an investigational flavivirus vaccine for the West Nile virus infection. The West Nile virus vaccine was found to be safe and induced an immune response when tested in a Phase I clinical trial.
- A live-attenuated (also known as a live but weakened virus, so that it cannot cause disease) investigational Zika vaccine based on a similar vaccine approach for the closely-related dengue virus. The dengue vaccine is currently being evaluated in a large Phase III study in Brazil, and has been shown to be safe and immunogenic thus far
- An investigational Zika vaccine that uses a genetically engineered version of an animal virus that mainly affects cattle, the vesicular stomatitis virus. This vaccine approach is at an early stage with plans underway to evaluate the Zika vaccine candidate in tissue culture and animal models.
- A whole-particle inactivated Zika vaccine based on a similar vaccine approach used to develop vaccines against the related Japanese encephalitis and dengue viruses.

(NIAID, 2016)

Vaccine Research, con't

It is theorized that an investigational Zika virus vaccine will be ready to enter early-stage human trials in the fall of 2016. This early-stage trial would examine whether an experimental vaccine is safe and generates immune responses in vaccinated volunteers. However, a safe, effective, and fully licensed Zika virus vaccine will probably not be available for several years (NIAID, 2016).

There are some concerns that a vaccine may potentially cause more problems, particularly in relation to auto-immune diseases. One concern is that a vaccine for the Zika virus may increase the incidences of Guillain–Barré syndrome, as it is unclear how the relationship between the two exists. Although this is a concern, that is a reason why there are various strategies in place for vaccine development (NIAID, 2016; Maron, 2016).

Including the research from NIAID, 23 vaccine projects are being worked on by 14 vaccine developers in the United States, France, Brazil, India, and Austria. As the

vaccine will be used to protect pregnant women or women of child-bearing age, it must meet an extremely high standard of safety (WHO, 2016c).

Conclusion

The incidences of Zika virus infection have been increasing at an alarming rate. Within the past few years, there has been an improved understanding of the disease, including causal relationships between the Zika virus and consequences such as Guillain–Barré syndrome and microcephaly. There are also improved guidelines which have been developed for prevention and testing for the Zika virus. Although there is no current vaccine or clear treatment for the Zika virus, increased research efforts show much promise. This is a high priority at a worldwide level, due to the rapid spread and potentially devastating consequences.

As health care professionals, it is important to differentiate between myth and fact when it comes to the Zika virus. Understanding the risk, signs and symptoms, and prevention strategies is essential.

Resources

Centers for Disease Control and Prevention, Zika virus information: www.cdc.gov/zika

Centers for Disease Control and Prevention, travel alerts: http://wwwnc.cdc.gov/travel/notices

Environmental Protection Agency (EPA) insect repellents: https://www.epa.gov/insect-repellents/find-insect-repellent-right-you

March of Dimes: www.marchofdimes.org

World Health Organization: www.who.int

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