EDUCATIONAL COMMENTARY – ZIKA VIRUS

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Learning Objectives

On completion of this exercise, the participant should be able to

- discuss the history of Zika virus and its relationship to other mosquito-borne viruses;
- identify the classification and viral properties of Zika virus;
- describe the epidemiology and recent spread of Zika virus;
- describe the clinical course of Zika virus infection, including the mode of transmission, signs and symptoms, complications, and treatment;
- review the diagnostic methods available for detecting Zika virus infection, describing the limitations and challenges in the interpretation of results; and
- discuss the strategy of Zika virus prevention and the challenges that contribute to the difficulty of controlling the spread of this infection.

History and Viral Classification

The Zika virus was discovered in 1947 during research into the vector that transmits yellow fever. Rhesus monkeys were placed in cages in the canopy of Uganda’s Zika Forest, and one of the monkeys developed a fever. Scientists isolated a transmissible agent from the serum of this monkey, and it became known as the Zika virus. The first human case was recorded in 1954, when the virus was isolated from a 10-year-old Nigerian girl.1

Zika virus is considered an arthropod-borne virus, often abbreviated as arbovirus. Arboviruses are maintained in nature through biological transmission between a susceptible vertebrate host and a blood-sucking arthropod such as a mosquito, tick, or sandfly.1 More than 130 arboviruses are known to cause human disease and most of those with public health importance belong to 1 of 3 genera: Flavivirus, Alphavirus, or Orthobunyavirus.2 Zika virus is a member of the genus Flavivirus. It is related to the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. The Zika virus is a 50- to 60-nm icosahedral viral particle possessing single-stranded RNA.3

Epidemiology and Recent Spread

Following the discovery of the Zika virus, serologic surveys were conducted and the data suggested that Zika virus was endemic to sub-Saharan Africa and several countries in Asia. It is now known that this data must be interpreted with caution, because cross-reactions among several arboviruses can occur with the assays used to detect antibodies to Zika.1 Reported cases of Zika virus were rare until 2007, when an outbreak was reported in Yap Island, Micronesia, outside the previously identified endemic regions of Africa and Asia. The population of Yap State is about 7500 and it is estimated that approximately 5000 of
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its residents were infected. The illness was mild; there were no hospitalizations and no deaths. Before this outbreak, 14 cases had been reported in humans.\(^1\) Another outbreak of an estimated 30,000 cases of Zika fever occurred in French Polynesia in 2013. The high number of cases was possibly a result of the low level of immunity to Zika virus in the population and the high number of mosquito vectors. Further outbreaks were then reported in locations in the South Pacific including New Caledonia, the Cook Islands, and Easter Island.

In 2015, the Zika virus emerged in the Americas, with the first confirmed cases in Brazil. Authorities hypothesized that the outbreak was related to the increased flow of foreign visitors during the 2014 World Cup, combined with the widespread distribution of the mosquito vector. Throughout 2015, the Zika virus continued to spread to areas of South and Central America and the Caribbean. In January of 2016, the Centers for Disease Control and Prevention (CDC) issued a Travel Alert for people traveling to regions where Zika virus transmission is ongoing.\(^4\) Imported cases of Zika infection are now reported in travelers returning to the United States from these areas. These cases increase the potential for the dissemination of the virus in areas where mosquito vectors are present. As of January 25, 2017, reported cases of Zika fever in the United States are as follows:\(^5\)

<table>
<thead>
<tr>
<th></th>
<th>Reports</th>
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</thead>
<tbody>
<tr>
<td>Travel-associated cases</td>
<td>4,710</td>
</tr>
<tr>
<td>Locally acquired mosquito-borne cases</td>
<td>219</td>
</tr>
<tr>
<td>Laboratory acquired cases</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>4,930</td>
</tr>
</tbody>
</table>

Clinical Course of Zika Virus Infection

Mode of Transmission

The primary method of transmission for Zika virus to humans is through the bite of an infected female mosquito of the *Aedes* genus. The main vector is *Aedes aegypti*, but other species can also transmit this virus.\(^6\) A blood meal is required for these mosquitoes to lay eggs, and they are most active during daylight hours, peaking during early morning and late afternoon to early evening. They prefer to bite humans and they will live indoors and outdoors near people. These mosquitoes lay their eggs in standing water in and around the home, such as in buckets, flower pots, vases, and animal bowls.\(^7\)

After the mosquito has ingested a Zika-infected blood meal, the virus replicates in the cells of the mosquito’s midgut and then disseminates to the salivary glands. Zika can be found in the mosquito’s saliva after 5 to 10 days. On a subsequent blood meal, the virus is injected into human skin, where it infects epidermal cells, skin fibroblasts, and Langerhans cells. The virus then spreads to local tissues, cells, and regional lymph nodes, from which it may disseminate to the bloodstream and to other organs and tissues.\(^8\)
Zika virus can also be spread through sexual contact. A person infected with Zika can transmit the virus before symptoms appear, while symptoms are present, and after symptoms end. In addition, the virus may be transmitted by an individual who is carrying the virus and is asymptomatic. A report published in 2015 described the detection of viral particles in the semen of a man 2 weeks after being diagnosed with Zika infection. Studies are underway to determine how long Zika can be shed in semen and vaginal fluids; the RNA of Zika has been found in semen for up to 62 days. In October 2016, the CDC advised men who had travelled to an area of active Zika virus transmission to properly use condoms or not engage in sexual activity for at least 6 months after their return, even if they never develop symptoms.

A third route of transmission for Zika virus is from mother to child during pregnancy or at delivery. Perinatal transmission was first recognized during the French Polynesian outbreak, in which viral RNA was detected in the serum of two Zika-infected mothers and their infants. One infant demonstrated a rash and thrombocytopenia; the other infant was asymptomatic. The mothers and infants recovered with no complications. Maternal-fetal transmission was confirmed in Brazil, where viral RNA was detected in amniotic fluid, blood, and tissues from neonates born to infected mothers. Transplacental transmission noted in Brazil revealed more severe malformations in the neonate.

The last routes for transmission include blood transfusion and laboratory/health care setting exposure. During the French Polynesian outbreak, nucleic acid testing found that 2.8% of blood donors demonstrated evidence of Zika virus RNA. The first reported case of infection with Zika virus via blood transfusion was reported in Brazil in December 2015. No transfusion-associated cases or infections from exposure in the health care setting have been reported in the United States. However, there has been one case of laboratory-acquired Zika virus. A report on June 15, 2016, described transmission via a needlestick injury to a US laboratory worker who was working with the Zika virus. The CDC has provided safety guidelines for laboratory workers and other health care workers who may collect or handle diagnostic specimens.

Signs and Symptoms
Because the onset of symptoms for Zika virus disease is rather insidious, it is difficult to assess the incubation period, but it is estimated to be 3 to 10 days. Common symptoms include fever, maculopapular rash, joint and muscle pain, conjunctivitis, headache, and fatigue. The clinical features of Zika virus are similar to other arbovirus infections including dengue and chikungunya. The symptoms are usually mild and last for approximately 1 week. In addition, up to 80% of infected people are asymptomatic.
Complications
The first human cases of Zika fever were described as a mild self-limiting febrile illness with no significant complications and rare hospitalization. The French Polynesian outbreak changed that characterization with the report of severe neurologic complications. During this outbreak, an unexpectedly high number of new Guillain-Barré Syndrome (GBS) cases were noted among persons who had been infected. Guillain-Barré Syndrome is an uncommon autoimmune response in which the individual’s own immune system damages nerve cells, causing muscle weakness and possible paralysis. The link between Zika virus and GBS has not been formally established, but 42 cases of GBS were reported following the outbreak in French Polynesia. Further reports of increased GBS occurring during the Brazil outbreak in 2015 reinforce the hypothesis of a relationship between Zika virus and GBS.¹,⁶

In addition to the increased reports of GBS during the Brazilian outbreak, the Brazilian Ministry of Health reported a 20-fold increase in the rate of microcephaly in newborns. Health authorities from Brazil, the Pan American Health Organization, the CDC, and other agencies have been investigating the relationship between Zika virus infection and microcephaly or other congenital abnormalities. Most cases reported in the literature describe women who gave birth to a newborn with microcephaly and reported having symptoms of Zika infection in their first or second trimester of pregnancy. Additional reports describe ophthalmic abnormalities and intracerebral calcifications in neonates whose mothers showed clinical features of Zika virus infection. Further findings revealed RNA particles of Zika virus in the amniotic fluid of women whose fetuses showed radiologic evidence of microcephaly. This suggests that the virus crosses the placenta and can be implicated in producing these congenital anomalies.¹ Congenital Zika syndrome describes the pattern of birth defects found in fetuses and infants infected with Zika virus during pregnancy. There are 5 features found in congenital Zika syndrome:¹²

- Severe microcephaly in which the skull is partially collapsed
- Decreased brain tissue demonstrating a specific pattern of brain damage
- Damage to the back of the eye
- Joints with limited range of motion (e.g., clubfoot)
- Increased muscle tone that restricts body movement shortly after birth

Currently, there is no evidence indicating that Zika infection in a nonpregnant woman can affect future pregnancies.

Treatment
There is no antiviral drug or specific medication available for treating Zika infection. It is recommended to treat the symptoms and provide supportive care. Acetaminophen can be used to reduce fever and pain, and an antihistamine can be administered to relieve itching from the rash. Fluids should be administered
to prevent dehydration and the patient should get plenty of rest. The use of aspirin or other nonsteroidal anti-inflammatory drugs is not recommended until dengue fever has been ruled out, owing to the increased risk for hemorrhagic syndrome that can occur in dengue infection. In the early stages of infection, it is recommended that the patient be isolated to avoid mosquito bites and prevent further spread of the infection.1

Diagnostic Testing

The laboratory diagnosis of Zika virus infection is complicated for several reasons. The clinical features of Zika virus infection are similar to those of other arbovirus infections, including dengue virus and chikungunya virus. Dengue virus is also a member of the genus *Flavivirus*; chikungunya is of the genus *Alphavirus*. A positive test result for one of these viral agents does not exclude infection with the others, as coinfections as well as cross-reactivity can occur. Multiple tests and sample types can be needed to detect Zika virus infection because of the sequential appearance and disappearance of biologic indicators.

Viral RNA is the first measurable indicator and can be detected in plasma, whole blood, cerebrospinal fluid, and amniotic fluid in addition to serum and urine. However, once the immune response develops, immunoglobulin M (IgM) antibody levels in the blood begin to rise and the levels of viral RNA diminish. The primary specimens for diagnostic testing are serum and urine. Other specimen types, including plasma, whole blood, cerebrospinal fluid, and amniotic fluid, can be tested, but it is also necessary to collect a serum specimen for reflex IgM testing.13

Testing methods used to detect Zika virus include molecular tests and antibody detection methods. In symptomatic patients, RNA NAT (nucleic acid testing) should be performed on serum and urine collected during the first 2 weeks after the onset of symptoms. A positive RNA NAT result on either sample confirms Zika virus infection, and no additional testing is necessary. A negative RNA NAT result does not eliminate Zika virus infection, however, and serum should be tested for IgM antibody.14

In asymptomatic pregnant women who have travelled to areas with active transmission of Zika virus, RNA NAT testing should be performed on urine and serum within 2 weeks of the last possible exposure date. In areas with active Zika virus transmission, asymptomatic pregnant women should be tested for IgM antibodies as part of routine prenatal care during their first and second trimester. If IgM antibodies to Zika virus are detected in these women, they should then be tested with RNA NAT.14 Infants born to mothers who test positive for Zika virus or who have clinical findings suggestive of congenital Zika virus should also be tested. Testing of the infant should include RNA NAT on serum and urine as well as IgM antibody testing of the infant serum.
Because of the similarity of symptoms between Zika virus and other arboviral infections, an additional molecular test that is recommended in some cases is the Trioplex real-time polymerase chain reaction (RT-PCR) assay. This assay allows detection and differentiation of RNA from Zika, dengue, and chikungunya viral infections. The US Food and Drug Administration (FDA) has not approved this test but has authorized its use under an Emergency Use Authorization.\textsuperscript{13}

One of the challenges in the serodiagnosis of Zika virus is that in areas where Zika virus is endemic, other arboviruses are also endemic, which can result in cross-reacting antibodies. Current or past infection, or even vaccination for another flavivirus, can result in false-positive or uninterpretable antibody results. Antibodies (IgM) directed against Zika virus normally begin to appear as the viral RNA becomes undetectable. The Zika IgM antibody-capture enzyme-linked immunosorbent assay (Zika MAC-ELISA) is used to detect Zika virus IgM antibodies. The greatest limitation of this assay is that cross-reactions with other flaviviruses, as well as other nonspecific reactions, can make the results difficult to interpret. Therefore, test results that are categorized as presumed positive, equivocal, or inconclusive must be forwarded to the CDC for confirmation by a plaque-reduction neutralization test (PRNT). The PRNT measures virus-specific neutralizing antibodies to determine the cause of the infection and differentiate between Zika and other flavivirus infections.\textsuperscript{14}

Testing algorithms have been developed to determine the appropriate test based on the presence of symptoms, pregnancy status, and the time between symptom onset or exposure and specimen collection. In symptomatic patients, the time between the onset of symptoms and specimen collection will determine the appropriate test. In asymptomatic pregnant women who meet epidemiologic criteria for testing, the time from exposure or return from travel to an area of active transmission will determine the appropriate test to order.\textsuperscript{13}

Infection with Zika virus is nationally notifiable and health care providers should report suspected cases to their state or local health department to facilitate testing and minimize the risk for local transmission. Laboratory-confirmed and probable cases should be reported to the CDC.

Prevention and Control

Preventing the spread of Zika virus is challenging because there is currently no effective treatment and no vaccine. Thus, the major strategy for prevention is directed at protection against mosquito bites along with vector control.\textsuperscript{15} Methods for the prevention of mosquito bites include the use of physical barriers such as wearing long-sleeve shirts and pants, closing doors or windows, using window screens, and sleeping under mosquito nets. Chemical barriers are also recommended through the use of insect
repellants containing DEET, IR3535, or icaridin. It is important to follow the product application instructions on the label and reapply as recommended.

Vector control involves the elimination of mosquito breeding sites in and around the home along with the spraying of insecticides. Because mosquitoes lay eggs near a water source it is important to empty and scrub, turn over, cover, or discard items that hold water, such as buckets, planters, toys, tires, birdbaths, or trash containers. Insect sprays can be used to kill mosquitoes in areas where they rest, such as dark humid places under the sink, under furniture, or in the laundry room.

Attempts to prevent the spread of Zika virus through sexual transmission should also be made. In areas with active transmission of Zika, the World Health Organization (WHO) recommends that counseling be provided to sexually active men and women about the potential adverse pregnancy and fetal outcomes due to Zika virus. Pregnant women residing in Zika-active locations should refrain from sexual activity for the duration of their pregnancy or use condoms. In areas with no active transmission of Zika, the WHO recommends that men or women who return from an area of active Zika transmission practice safer sex or abstinence for a period of 6 months. Sexual partners of pregnant women living in or returning from areas where local transmission of Zika virus occurs should practice safer sex or abstain from sexual activity throughout the pregnancy.\textsuperscript{15}

Persons planning to travel to a Zika-active area should take precautions. The CDC posts updates on travel notices and provides recommendations on how to protect oneself if travelling to an active Zika area.\textsuperscript{16} Women who are pregnant are advised not to travel to an active Zika area. Individuals, and their partners, who are attempting to become pregnant should avoid nonessential travel to an active Zika area.

Several groups are working to develop an effective vaccine to control the spread of Zika virus infection and prevent potential birth defects. The National Institute of Allergy and Infectious Diseases began testing an investigational vaccine in August 2016.\textsuperscript{17} However, a safe and licensed vaccine will not be available for several years. Additional research is also being conducted to develop an effective antiviral therapy.

The FDA has published recommendations to reduce the risk of transmission by the transfusion of blood and blood components.\textsuperscript{18} It is recommended that all donations collected in the United States and its territories be tested for Zika using an investigational donor nucleic acid test (ID-NAT), or a licensed test, when available. It is also recommended to implement pathogen-reduction technology for platelets and plasma using an approved pathogen-reduction device.
Global Response
There has been a dramatic emergence of epidemic arboviruses over the last several years, including dengue, West Nile virus, chikungunya, and now Zika virus. Factors that have contributed to this emergence include globalization and global population growth, urbanization, and a lack of effective vector control.¹

The WHO has outlined a Zika Strategic Response Framework to provide support to countries in controlling Zika virus. The plan has 4 objectives: detection, prevention, care and support, and research. These objectives are summarized in the Response Framework as follows¹⁵:

- Define and prioritize research into Zika virus disease by convening experts and partners.
- Enhance surveillance of Zika virus and potential complications.
- Strengthen capacity in risk communication to engage communities to better understand risks associated with Zika virus.
- Strengthen the capacity of laboratories to detect the virus.
- Support health authorities to implement vector control strategies aimed at reducing Aedes mosquito populations.
- Prepare recommendations for the clinical care and follow-up of people with complications related to Zika virus infection, in collaboration with experts and other health agencies.

Summary
Zika virus has raised a great deal of concern globally, as it is the first infectious agent in many years to be associated with an epidemic of birth defects. The WHO has declared this pandemic a public health emergency of international concern, and pregnant women have been instructed to avoid travel to affected regions.¹⁶ There are several challenges ahead in the ability to control the spread of Zika virus and its clinical consequences. The presence of this flavivirus in areas where other flaviviruses exist makes diagnosis difficult and testing unreliable. The development of laboratory assays for rapid and accurate diagnosis must be a priority. The need for improved antibody testing to detect specific Zika epitopes is also imperative. The future of Zika virus is unpredictable, but the recent spread suggests that it will continue to be a serious global public health problem.

References


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