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Updates on Zika Virus Disease

Introduction

Zika virus disease is a global issue. While not technically an emergency, concerned patients will come to our departments seeking advice and diagnostic testing. The economic cost to communities from mosquito-transmitted illnesses is significant but not well studied. In fact, few studies have attempted to assess the true financial consequences to a country or region, making the extrapolation of expenditure to a larger area difficult. Dengue has been studied in nine countries throughout the Americas and Asia, and has an estimated average cost of $500 million up to $1.8 billion per year. That estimate just includes people with disease and their families affected by dengue and does not include prevention and surveillance costs.[1] The aim of this article is to discuss the latest recommendations for the prevention of Zika viral disease, the populations and regions still at increased risk, and the latest and most promising research being conducted to develop a Zika virus vaccine and treatment.

Background

Zika virus is a mosquito-borne flavivirus related to the yellow fever, dengue, and West Nile viruses.[2] The Zika virus illness is characterized primarily by rash, myalgia, and conjunctivitis and is often self-limiting, with more than 80% of all infected people asymptomatic but still able to transmit the disease. Although news coverage and public interest have waned, it is still an active health concern.

Although new to the western hemisphere, Zika virus first was isolated from the rhesus monkey in the Zika forest in Uganda during surveillance for yellow fever in 1947. The first documented human case of Zika virus was in 1964.[3,4] The majority of these first cases were seen in individuals between 20 and 40 years of age, with documented cases in people as young as 4 months old and as old as 98 years. Through the mosquito vector and increased mobility, the virus traveled from Africa across equatorial Asia. In 1997 on the Pacific island of Yap, Zika infected more than 5,000 humans.[5] In 2015, Brazil reported the first cases of locally transmitted Zika viral illness in the Americas.[6,7] The virus was similar to the strain that caused an epidemic in the South Pacific. The virus likely traveled to Brazil with participants from the Pacific Islands during the Va'a World Sprint Championship canoe race in August 2014.[8]

In November 2015, the Brazilian Ministry of Health reported a 20-fold increase in the number of cases of neonatal microcephaly in mothers who had been pregnant when they were diagnosed with the Zika viral disease.[9,10] In response to the publication by the Brazilian Ministry of Health, the World Health Organization (WHO) declared Zika viral disease a Public Health Emergency of International Concern in February 2016 when it was confirmed

EXECUTIVE SUMMARY

- Zika virus has been known to infect humans in Africa since the 1960s, but only recently spread to the Americas.
- Zika virus is spread by the *Aedes* mosquito, which is found throughout the world, including in the United States.
- Zika causes severe congenital abnormalities in the fetus (including microcephaly, decreased brain tissue, macular scarring, contractures, and hypertonia). In adults, it causes Guillain-Barré syndrome.
- In addition to mosquito transmission, Zika can be spread from human to human through blood, urine, and sexual contact.
- Most infections are asymptomatic. Serologic testing is necessary to confirm infection.

that Zika viral illness was the cause of microcephaly in a cluster of newborns. In response, the Centers for Disease Control and Prevention (CDC) released travel precautions, as well as prenatal planning recommendations, for those in areas with reported cases of Zika viral disease, including the United States. Additionally, the CDC published fluid guidelines aimed at U.S. healthcare providers regarding counseling and testing for pregnant women and for those planning pregnancy who might be at risk for Zika virus exposure.[11,12] The WHO noted that since 2015, 61 geographic areas have reported Zika virus transmission, with 31 countries reporting fetal and newborn malformations from mothers who were diagnosed with Zika viral illness during their pregnancy.[13] (*See Figure 1.*) During the first four months of 2017, Brazil reported a 95% decrease in cases of diagnosed microcephaly compared to the previous year at the same time and declared its Zika emergency over.

From Jan. 1, 2015 to June 28, 2017, the CDC extrapolated from data reported to ArboNET the following information: U.S. states, 5,359 symptomatic cases reported (5,087 in travelers returning from affected areas); U.S. territories, 36,598 symptomatic Zika virus disease cases (excluding congenital disease cases), with the majority from local mosquito-borne transmission.[14] (*See Table 1.*)

Vector and Infection Overview

It is well known that viruses and other diseases spread throughout densely populated communities and during mass migration of populations. The death toll of soldiers and civilians from World War I was dwarfed by the deaths caused by the Spanish flu of 1918. The Spanish flu was caused by a virulent virus transmitted by droplets from infected humans. As with most influenza A viruses, the virus started in animals and, as a result of a major change in the influenza A virus, became a virus with increased morbidity and mortality to a human population with little or no immunity. During World War I, troop deployments on ships, along with large civilian movement, led to spread of the virus. As public health authorities determined how flu was transmitted, they enacted public health laws that stopped the progression of the Spanish flu.

Some viruses, such as the rabies virus, can be avoided because the vector is visible (i.e., dog, raccoon, or bat) or can be prevented through primary vaccination of the host animal. However, insect-transmitted viruses are much harder to control.

The most common vector of insect-transmitted disease is the mosquito, which caused more deaths between the 17th and 20th centuries than all other etiologies of death, including war, combined.[15] Initially, mosquito-borne illness was regional and and did not spread widely. However, that changed in the 1940s. Because of large movements of troops and materials, such as tires, mosquitoes and other vectors moved across oceans, allowing infected mosquitoes to spread to other habitats and flourish. Now with continued globalization, these vectors continue to move with ease out of their normal environment.[16]

The key to controlling mosquitoes and the diseases they transmit is understanding their life cycle and habitat.

Malaria is the most understood of all the mosquito-borne diseases. It is transmitted by a species of the *Anopheles* mosquito and is said to be the cause of more than 1 million deaths every year. These mosquitoes feed predominantly at dusk and dawn and are found in wet areas.

The West Nile virus now is the No. 1 cause of arboviral meningoencephalitis in the United States. This virus is carried by the *Culex* mosquito, which feeds mainly at dusk and dawn, and requires stagnant water to breed.

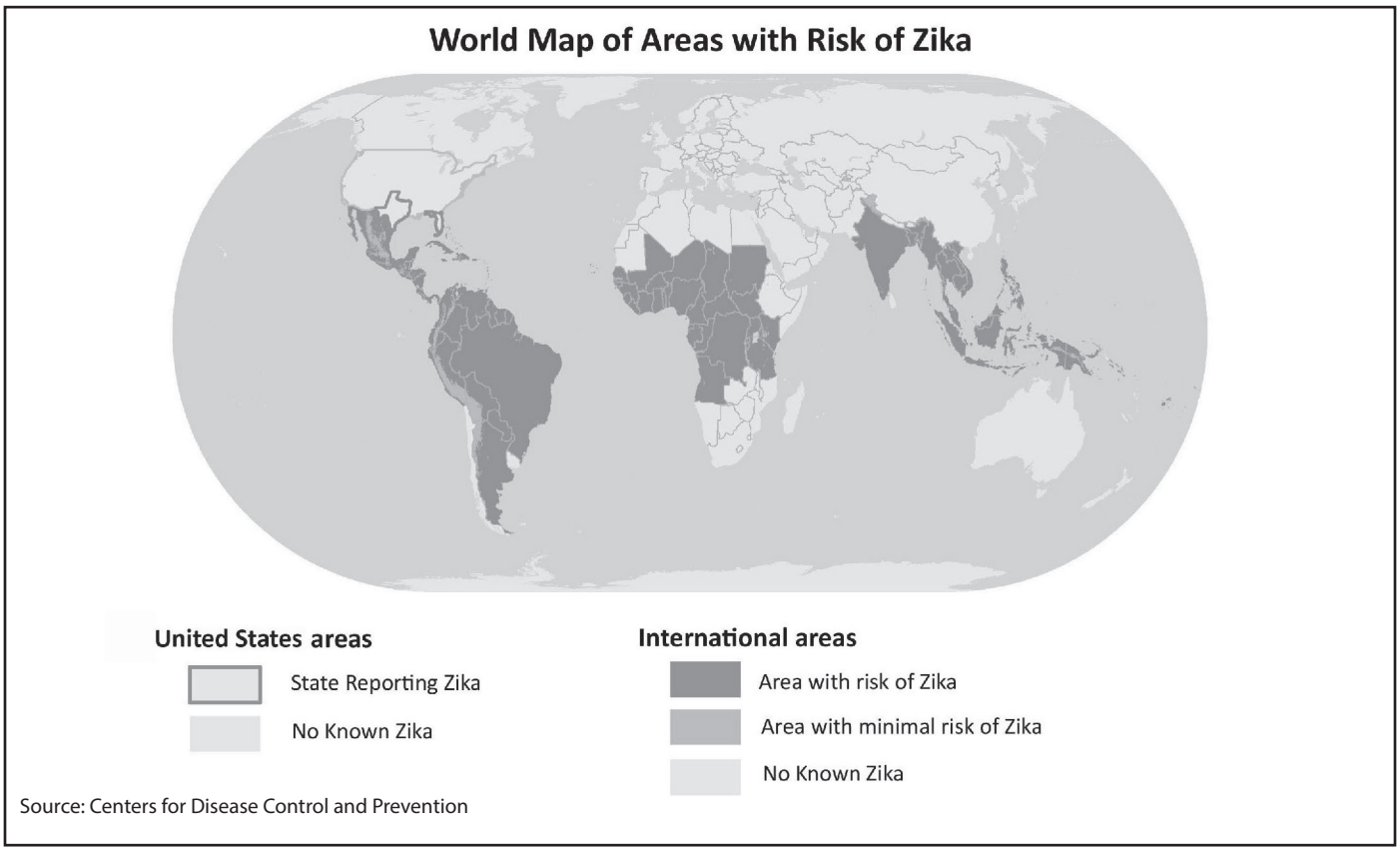
The *Aedes* mosquito is found in a wide geographic region, and transmits Zika, chikungunya, and dengue.[17] While the *Culex* mosquitoes prefer animals for their blood meal, the *Aedes* mosquito is a voracious feeder with no diurnal pattern, and preferentially feeds on humans. Additionally, *Aedes* mosquitoes are adapted to urban living, which includes adjusting to water scarcity, allowing them to breed in small areas of water, such as in window air conditioner units or upturned water bottle caps.[18]

The life cycle of all mosquitoes is complex, and only three of the stages require water and appropriate temperatures. The stages are as follows:

1. Female mosquito lays the eggs in non-flowing water.
2. After two to three days at the right temperature, the eggs hatch in the water, becoming larvae.
3. From larvae, they develop into pupae (approximately four days).
4. The pupae become adults.

The difference between male and female mosquitoes is that males eat nectar and sugars only. On the other

Figure 1. Areas With Risk of Zika



hand, the females require blood meals to lay eggs. If conditions are right, the life span of the female is up to three weeks. During this time, she can lay a raft of 100 and 300 eggs every three days if she is able to have a blood meal before each egg deposit.

Control of the *Aedes* species is more complicated than with other mosquitoes. As mentioned previously, these mosquitoes bite in the daytime and, thus, the normal protection of insecticide-treated bed nets is not effective. Spraying insecticide during the day will indiscriminantly kill other beneficial insects such as pollinating bees. The main method to control the mosquito is to eliminate the breeding habitat. This is done by placing protective covers on containers that have residual water in them, and draining or covering standing water such as in large tanks used to store household water, collections of rain water for drinking or irrigation, used tires, and other items that hold water. Additionally, intensive biological and chemical measures can combat or reduce the *Aedes* species mosquito population.[19] Other methods of control are being investigated. These include releasing sterile male mosquitoes into the population, as well as the use of a synthetic analogue of mosquito juvenile hormones, which prevents the larvae from developing into adults. It is carried by the female mosquito and released onto the eggs when she lays them.[20]

Virology and Genetics

Zika virus is closely related to the Spondweni virus. Zika is a single-stranded positive RNA virus containing a 10,794 nucleotide genome and two major lineages (African and Asian/American strains).[24] Upon transmission, flavivirus virions bind to the surface of target cells by interactions between viral surface glycoproteins and cellular surface receptors (E protein). When they bind, the cell internalizes the virion. Once internalized, the virion uncoats, releasing the viral RNA into the host cell's cytoplasm.[25] Duplication then occurs, the virus particles assemble using the cell's own endoplasmic reticulum, and they are released from the cell.[26] It is theorized that as this cycle repeats, mutations in the Zika RNA will occur, affecting its replication, virulence, and antigenic epitopes, and may cause an overall increase in morbidity and mortality in those who contract the disease.[27]

Signs and Symptoms

Flaviviruses cause many diseases, with significant differences in pathology. For example, yellow fever, which caused numerous outbreaks for more than 500 years, has a mortality rate up to 20%. It is a hemorrhagic fever with symptoms that include fever, chills, nausea, myalgia, and headache. It may progress to liver, renal, and bleeding diorders.[28]

Dengue viral disease is transmitted by the *Aedes* species mosquito and is seen mostly in South and Southeast Asia, but recently migrated to Latin America and the Caribbean. Just as with Zika, most individuals infected with dengue will be asymptomatic. Those who are symptomatic primarily present with high fever, rash, eye pain, myalgia, bleeding, and capillary leaking.

Spondweni virus, the virus most closely related to Zika, is found in sub-Saharan Africa and Papua New Guinea. This virus also is transmitted by infected mosquitoes and is characterized by symptoms of fever, nausea, headaches, malaise, and nosebleeds.[29] In regions where both Zika and Spondweni are found, only serologic assay, virus isolation, or detection of viral nucleic acids by polymerase chain reaction (PCR) can distinguish between the two.

In 80% of cases, Zika virus-infected humans are not symptomatic.[30,31] Those who become symptomatic complain of rash, fever (> 98.96˚F), arthralgia, myalgia, headache, conjunctivitis, retro-orbital eye pain, and fatigue.

It is difficult to diagnose Zika viral illness because the symptoms are similar to the symptoms of dengue and chikungunya viral infections, which are spread by the same mosquitoes that transmit Zika.[32,33] Hemorrhagic components are seen in dengue, while Zika infections are associated with neurological symptoms in adults and microcephaly and other congenital disorders in neonates. (*See Table 2.*)

While dengue and chikungunya are transmitted primarily through the bite of infected mosquitoes and not through human-to-human contact, the Zika virus can be transmitted between humans through saliva, urine, blood, and sexual contact.[34,35,36] The discovery of human-to-human spread complicates prevention.

The primary public health significance of the Zika virus is the neurological effects in neonates and adults. The neurological significance of Zika viral disease was appreciated during the outbreak in French Polynesia in 2013-2014. Seventy-four patients presented with neurological symptoms and tested positive for Zika viral disease.[37] Guillain-Barré syndrome (GBS), a clinical syndrome of multiple autoimmune idiopathic peripheral neuropathies, most often is seen in adults. The most serious of these complications is a progressive paralysis over a one- to three-week period resulting in a 5% death rate, 20-30% incidence of respiratory failure, and up to 20% of patients left with significant lifelong neurological disability.[38,39,40]

In the neonatal population, Zika

Table 1. Laboratory-confirmed Symptomatic Zika Virus Disease Cases and Presumptive Viremic Blood Donors Reports to ArboNET by States and Territories — United States, 2017

	Symptomatic Disease Cases* (N = 125)		Presumptive Viremic Blood Donors† (N = 7)	
States	**No.**	**%**	**No.**	**%**
Alabama	3	(2)	0	(0)
Alaska	1	(1)	0	(0)
Arizona	1	(1)	0	(0)
Arkansas	0	(0)	0	(0)
California	14	(11)	1	(14)
Colorado	3	(2)	0	(0)
Connecticut	0	(0)	0	(0)
Delaware	0	(0)	0	(0)
District of Columbia	0	(0)	0	(0)
Florida	15	(12)	3	(43)
Georgia	1	(1)	0	(0)
Hawaii	1	(1)	0	(0)
Idaho	0	(0)	0	(0)
Illinois	4	(3)	0	(0)
Indiana	1	(1)	0	(0)
Iowa	1	(1)	0	(0)
Kansas	2	(2)	0	(0)
Kentucky	1	(1)	0	(0)
Louisiana	1	(1)	0	(0)
Maine	1	(1)	0	(0)
Maryland	3	(2)	0	(0)
Massachusetts	5	(4)	0	(0)
Michigan	6	(5)	0	(0)
Minnesota	0	(0)	0	(0)
Mississippi	2	(2)	0	(0)
Missouri	1	(1)	0	(0)
Montana	0	(0)	0	(0)
Nebraska	1	(1)	0	(0)
Nevada	0	(0)	0	(0)
New Hampshire	0	(0)	0	(0)
New Jersey	2	(2)	0	(0)
New Mexico	0	(0)	0	(0)
New York	24	(19)	1	(14)
North Carolina	3	(2)	0	(0)
North Dakota	0	(0)	0	(0)
Ohio	3	(2)	0	(0)
Oklahoma	0	(0)	0	(0)
Oregon	1	(1)	0	(0)

(*continued*)

Table 1. Laboratory-confirmed Symptomatic Zika Virus Disease Cases and Presumptive Viremic Blood Donors Reports to ArboNET by States and Territories — United States, 2017 (continued)

	Symptomatic Disease Cases* (N = 125)		Presumptive Viremic Blood Donors† (N = 7)	
States	**No.**	**%**	**No.**	**%**
Pennsylvania	3	(2)	0	(0)
Rhode Island	2	(2)	0	(0)
South Carolina	0	(0)	0	(0)
South Dakota	0	(0)	0	(0)
Tennessee	0	(0)	0	(0)
Texas	10	(8)	1	(14)
Utah	0	(0)	0	(0)
Vermont	2	(2)	0	(0)
Virginia	3	(2)	0	(0)
Washington	2	(2)	0	(0)
West Virginia	0	(0)	1	(14)
Wisconsin	2	(2)	0	(0)
Wyoming	0	(0)	0	(0)
	Symptomatic Disease Cases* (N = 502)		**Presumptive Viremic Blood Donors† (N = 3)**	
Territories	**No.**	**(%)**	**No.**	**(%)**
American Samoa	3	(1)	0	(0)
Puerto Rico	462	(92)	3	(100)
U.S. Virgin Islands	37	(7)	0	(0)

Footnotes
* Includes reported confirmed and probable Zika virus disease cases per the Council of State and Territorial Epidemiologists (CSTE) case definitions.
† Presumptive viremic blood donors are people who reported no symptoms at the time of donating blood, but whose blood tested positive when screened for the presence of Zika virus RNA by the blood collection agency. Some presumptive viremic blood donors develop symptoms after their donation or may have had symptoms in the past. These individuals may be reported as both Zika virus disease cases and presumptive viremic blood donors.
Source: From CDC website: https://www.cdc.gov/zika/reporting/2017-case-counts.html. Accessed June 12, 2017.

syndrome is a unique pattern of birth defects presenting in fetuses and infants whose mothers were infected with Zika virus during the pregnancy. It is characterized by five significant features that can be diagnosed in utero by ultrasound or at presentation shortly after birth:[41]

- Severe microcephaly, in which the skull has partially collapsed;
- Decreased brain tissue, with a specific pattern of brain damage, including subcortical calcifications;
- Damage to the back of the eye, including macular scarring and focal pigmentary retinal mottling;
- Congenital contracture, such as clubfoot or arthrogryposis (congenital joint contractures in two or more areas of the body);
- Hypertonia restricting body movement soon after birth.

Diagnosis of Zika Viral Disease

The diagnosis of Zika viral disease by clinical features is challenging in areas where similar-appearing diseases, such as dengue and chikungunya, are prevalent. In adults, Zika viral disease generally presents with rash, fever (> 98.96˚ F), arthralgia, myalgia, headache, conjunctivitis, retro-orbital pain, and fatigue, which resembles many other viral diseases. Because the symptoms of Zika viral disease are vague and not pathognomonic, serum studies are necessary to confirm diagnosis.

As with many tests, immunoglobulins are used as markers to screen for recent infection (IgM) or history of infection (IgG). Serum tests to screen for the disease have a low sensitivity and specificity, as they cross-react with other flaviviruses, and the IgM will be positive. Serological assays manufactured in Germany and Canada include: Anti-Zika Virus ELISA (IgG/IgM) and IIFT Arborviral Fever Mosadi 2 (IgG/IgM) from Germany, and Zika Virus Rapid Test from Canada.[41] These are followed by a more specific test: real-time PCR molecular testing.[43] At this time, the U.S. Food and Drug Administration (FDA) has not approved any laboratory tests for the the detection of Zika virus. However, the FDA has issued an Emergency Use Authorization (EUA) for several diagnostic tools for the Zika virus, including the Trioplex Real-Time RT-PCR (rRT-PCR) and the Zika IgM Antibiody Capture Enzyme-Linked Immunosorbent Assay (MAC-ELISA).[44]

According to recommendations by the CDC and the WHO, if there is a positive IgM ELISA, a plaque reduction neutralization test (PRNT) should be performed for confirmation. This test measures virus-specific neutralizing antibody titers against similar viruses (dengue and chikungunya, for example) and can be used to confirm the Zika virus in the sample.[45] (*See Table 3.*) The Council of State and Territorial Epidemiologists (CSTE) added Zika to the Nationally Notifiable Diseases List, so that IgM Zika or dengue test results that are positive or equivocal must be reported to the local or state health department or authority.[46]

Transmission and Prevention

The most common method of Zika virus transmission is through the bite of an infected *Aedes* species mosquito.

Table 2. Comparison of Zika, Chikungunya, and Dengue Infectious Signs and Symptoms

Characteristic	Zika	Chikungunya	Dengue
Vector	*Aedes* species	*Aedes* species	*Aedes* species
Endemic Region	Southern United States, Central/ South America, Africa, Asia	United States (including Alaska), Central/South America, Africa, Asia	Central/South America, Africa, Asia
Fever	Low grade	High grade	High grade
Incubation Period	3-7 days	3-7 days	4-7 days
Rash	Maculopapular, erythematous rash	Pruritic, maculopapular rash, petechial rash (rarer)	Pruritic petechiae
Other Signs and Symptoms	Exudative conjunctivitis, myalgia, arthralgia, headache Rare: Guillain-Barré syndrome	Severe arthralgia (esp. small joints), Gastrointestinal symptoms Rare: myelitis, retinitis, meningoencephalitis, conjunctivitis, epistaxis, subconjunctival hemorrhage	DHF: Headache, myalgia, DHS: Headach, myalgia, plus extensive hemorrhage, hepatomegaly, third spacing of fluids, shock
Laboratory Findings	Lymphopenia	Neutropenia	Thrombocytopenia, lymphopenia, hypoglycemia, hypocalcaemia, hypernatremia, lactic acidosis, coagulopathy
Diagnosis	IgM/IgG RT-PCR	IgM/IgG analysis Viral particle analysis of serum/ plasma for virus	IgM ELISA/IgG RT-PCR
Treatment	Supportive	Supportive	Supportive Avoid NSAIDs with dengue
Effect on Infants via Vertical Transmission	Possible increased rates of microcephaly, hearing and vision deficits	Nonspecific viral infection seen in age 3 to 7 days	Increased rate of LBW infants
Vaccination	Investigational	Investigational	Several, CYD-TDV
Complications	Mortality rare, possible association with increased rates of microcephaly and Guillain-Barré	Mortality rare, chronic joint pain	Mortality rare, more common in those with DHF/DSS

Reprinted with permission from: Liu LE, Dehning M, Phipps A, et al. Clinical update on dengue, chikungunya, and Zika: What we know at the time of article submission. *Disaster Med Public Health Prep* 2016;8:1-10.[68-73]

The normal habitat for this mosquito in the United States is the Southeast and Southwest, but it has been found in states as far north as Michigan, New Hampshire, and Washington.[7] Preventing mosquito bites is the most effective way of preventing disease transmission. Travelers to endemic countries should wear insect repellent and protective clothing and use mosquito netting that has been sprayed with insecticide. Pregnant women should be discouraged from travel to Zika viral disease endemic countries. If that is not possible, then the CDC recommends the use of repellents that are safer for pregnancy (if used as directed), such as DEET (30%), picardin (20%), and IR3535 (20%) on any exposed skin and on clothing.[45]

Unlike other mosquito-borne diseases, the Zika virus has other modes of transmission that make preventing the spread of the disease more complicated. For example, during the French Polynesia outbreak, it was noted that 3% of asymptomatic blood donors were positive for acute Zika virus infection. In addition to blood, the Zika virus has been found in semen, saliva, cerebral spinal fluid, and tears. Zika virus also has been found to be transmissable sexually, with women testing positive for Zika viral disease more often than men after having unprotected sexual contact with someone who has traveled recently from a Zika risk area.[48,49] Although most of the infections are contracted through the bite of a mosquito, horizontal transmission of the disease from one individual to another is increasing. Additionally, vertical transmission from mother to offspring is well documented, with mother-to-child viral transmission through the placenta or breast milk.[36,48]

Vaccines

At this time, there are no licensed antiviral drugs to treat Zika disease or vaccines to prevent Zika infection. Research is slow, with one focus on engineering messenger RNAs to attack the E protein on the virus membrane to prevent attachment for the virion to the host cell.[51,52,53] Without contact at this site on the cell membrane, the virus cannot be brought into the cell to allow

Table 3. Interpretation of Results of Antibody Testing for Suspected Zika Virus Infection — U.S., 2016[*, †, §, ¶, **]

Zika Virus and Dengue Virus IgM ELISA	Zika Virus PRNT	Dengue Virus PRNT	Interpretation
Positive or equivocal (either assay)	≥ 10	< 10	Recent Zika virus infection
Positive or equivocal (either assay)	< 10	≥ 10	Recent dengue virus infection
Positive or equivocal (either assay)	≥ 10	≥ 10	Recent flavivirus infection; specific virus cannot be identified
Inconclusive in one assay AND inconclusive or negative in the other	≥ 10	< 10	Evidence of Zika virus infection; timing cannot be determined
Inconclusive in one assay AND inconclusive or negative in the other	< 10	≥ 10	Evidence of dengue virus infection; timing cannot be determined
Inconclusive in one assay AND inconclusive or negative in the other	≥ 10	≥ 10	Evidence of flavivirus infection; specific virus and timing cannot be determined
Any result (either or both assays)	< 10	< 10	No evidence of Zika virus or dengue virus infection
Positive for Zika virus AND negative for dengue virus	Not yet performed		Presumptive recent Zika virus infection
Positive for dengue virus AND negative for Zika virus	Not yet performed		Presumptive recent dengue virus infection
Positive for Zika virus AND positive for dengue virus	Not yet performed		Presumptive recent flavivirus virus infection
Equivocal (either or both assays)	Not yet performed		Equivocal results
Inconclusive in one assay AND inconclusive or negative in the other	Not yet performed		Inconclusive results
Negative for Zika virus AND negative for dengue virus	Not indicated		No evidence of recent Zika virus or dengue virus infection

Abbreviations: ELISA = enzyme-linked immunosorbent assay; IgM = immunoglobulin M antibodies; PRNT = plaque reduction neutralization test.
* For persons with suspected Zika virus disease, Zika virus real-time reverse transcription–polymerase chain reaction (rRT-PCR) should be performed on serum specimens collected < 7 days after onset of symptoms, and on urine specimens collect < 14 days after onset of symptoms.
† In the absence of rRT-PCR testing, negative IgM or neutralizing antibody testing in specimens collected < 7 days after illness onset might reflect collection before development of detectable antibodies and does not rule out infection with the virus for which testing was conducted.
§ Zika IgM positive result is reported as "presumptive positive" to denote the need to perform confirmatory PRNT.
¶ Report any positive or equivocal IgM Zika or dengue results to state or local health department.
** To resolve false-positive results that might be caused by cross-reactivity or nonspecific reactivity, presumptive positive Zika IgM results should be confirmed with PRNT titers against Zika, dengue, and other flaviviruses to which the person might have been exposed. In addition, equivocal and inconclusive results that are not resolved by retesting also should have PRNT titers performed to rule out a false-positive result.
Reprinted from: Rabe IB, Staples JE, Villanueva J, et al. Interim Guidance for Interpretation of Zika Virus. Antibody Test Results. *MMWR Morb Mortal Wkly Rep* 2016;65;543-546.

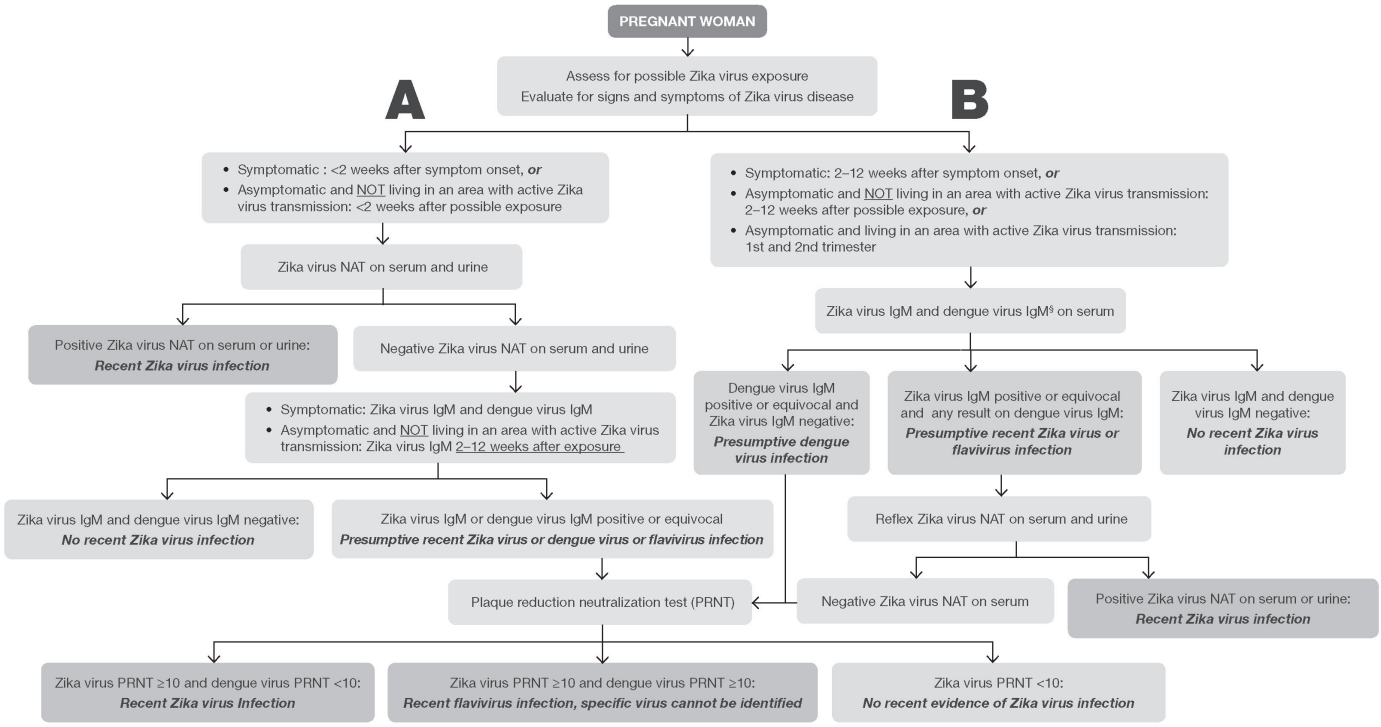
for replication. The creation of neutralizing antibodies directed against the E protein has been effective in protection against other flaviviruses, such as Japanese encephalitis and yellow fever.[54]

Other vaccines under investigation and testing on humans to combat Zika include inactivated whole virions, live-attenuated recombinant, and DNA vaccines.[55] These come with their own potential risks because there is a possibility of triggering the host immune system in unexpected ways. It is unclear which part of the Zika virion causes the autoimmune reaction leading to adverse neurologic outcomes such as Guillain-Barré syndrome or acute myelitis. It is theorized that antibodies that develop after virion exposure to the vaccine also might recognize and target tissues in the human nervous system, thus causing GBS as a side effect of the vaccine.[56]

Treatment

Currently, no clinically approved therapy is available for the treatment of Zika or any other flavivirus infection.[57] Once infection has occurred and the patient is symptomatic, diligent clinical monitoring and supportive care are the mainstays of treatment. Recent studies indicate that Zika, like varicella and other viruses, seems to concentrate in parts of the body that have less immune system vigilance, such as the eyes, placenta, and testes, and can be isolated for months post exposure.[7] Caring for patients with severe Zika disease, especially patients exposed in utero, is challenging and requires substantial healthcare and societal resources that strain both families and society. This includes long-term care for infants with Zika syndrome, as well as for adults who need ventilators or other respiratory support for neurological sequelae.

Figure 2. Testing Guidelines for Pregnant Patients With Possible Zika Exposure



Abbreviations: IgM = immunoglobulin M; PRNT = plaque reduction neutralization test; NAT = nucleic acid testing.
* A pregnant woman is considered symptomatic if one or more signs or symptoms (fever, rash, arthralgia, or conjunctivitis) consistent with Zika virus disease is reported whereas a pregnant woman is considered asymptomatic if symptoms are NOT reported.
† Testing includes Zika virus NAT on serum and urine samples, Zika virus and dengue virus immunoglobulin M (IgM), and plaque reduction neutralization test (PRNT) on serum samples. PRNT results that indicate recent flavivirus infection should be interpreted in the context of the currently circulating flaviviruses. Refer to the laboratory guidance for updated testing recommendations (http://www.cdc.gov/zika/laboratories/lab-guidance.html). Because of the overlap of symptoms in areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection.
§ Dengue IgM antibody testing is recommended only for symptomatic pregnant women.
¶ If Zika virus NAT testing is requested from laboratories without IgM antibody testing capacity or a process to forward specimens to another testing laboratory, storing of additional serum samples is recommended for IgM antibody testing in the event of a NAT negative result.
** Possible exposure to Zika virus includes travel to or residence in an area with active Zika virus transmission (http://wwwnc.cdc.gov/travel/notices/), or sex (vaginal sex (penis-to-vagina sex), anal sex (penis-to-anus sex), oral sex (mouth-to-penis sex or mouth-to-vagina sex), and the sharing of sex toys) without a barrier method to prevent infection (male or female condoms for vaginal or anal sex, male condoms for oral sex (mouth-to-penis), and male condoms cut to create a flat barrier or dental dams for oral sex (mouth-to-vagina) with a partner who traveled to or lives in an area with active Zika virus transmission.

Source: Centers for Disease Control and Prevention.
Available at: https://www.cdc.gov/zika/pdfs/zikapreg_screeningtool.pdf

Guidance for Serum Testing

Although most Zika viral infections probably are transmitted by mosquitoes, Zika virus has other modes of transmission, including sexual contact (anal, vaginal, and oral), intrauterine and intrapartum transmission, laboratory exposure, and blood transfusion.[58,59,60] Although most viral human-to-human transmissions occur from mildly symptomatic men through unprotected sexual contact with their partners, sexual transmission also has occurred from asymptomatic men and from one male who had a vasectomy.[61] Published literature indicates that Zika viral RNA has been isolated in semen at 188 days (approximately six months), with infectious virus reported in semen up to three months.[62,63,64]

If previously exposed to the Zika virus, women planning to become pregnant should consider Zika IgM testing before conception. This is *not* to determine if the woman should become pregnant, but rather for use as a comparison to later tests if the patient became exposed during her pregnancy. This then allows for subsequent discussions, testing, and counseling.[65]

Infants born to mothers with laboratory evidence of the Zika virus detection during pregnancy, and those born with clinical findings suggestive of congenital Zika virus syndrome (microcephaly), should be tested for the virus. The 2017 CDC guidelines for collecting and submitting specimens at the time of birth for Zika virus testing indicate that serum, placenta, fetal membranes, umbilical cord, and infant urine samples should be tested. Since testing standards may change in the future, check local health department guidelines for the most current testing recommendations. (*See Figure 2.*)

Special Population: Pregnant Women

In the United States, the incidence of pregnant women with laboratory evidence of possible recent Zika virus infection and the number of fetuses/

infants with Zika syndrome-associated birth defects is 30 times higher than the baseline of prevalence in the pre-Zika years.[66] To help guide healthcare practitioners, the CDC provides recommendations for the screening and testing of pregnant women:

• It is important to ascertain if the patient is at risk for having contracted the Zika virus.

• Did the patient travel to or live in a Zika risk area? (https://www.cdc.gov/zika/geo/countries-territories.html. Accessed June 12, 2017.)

• During pregnancy, did the patient have unprotected sex (vaginal, anal, or oral) with a partner who has traveled to an endemic area of risk?

If the patient has screened positive for the above questions, then:

• Are there any recent signs or symptoms of viral infection?

• If the patient had an ultrasound, were there any abnormalities of the fetus consistent with Zika syndrome?

If the answer is "yes" to either of these secondary questions, the patient should be considered for immunological testing for viral antigens. (*See Figure 2.*) If the answer is "no" to all of the screening questions, then there is a low risk of Zika virus infection. Patients who are pregnant or planning to get pregnant should be cautioned about travel to Zika virus-prevalent areas. While pregnant, women should use protection during sexual contact with anyone who might have traveled to an at-risk area or who lives in an at-risk area. For patients who have tested positive for Zika virus infection, the CDC recommends serial fetal ultrasounds every three to four weeks to assess fetal anatomy and growth, and discussion of possible amniocentesis.

Conclusions

The Zika virus has emerged as a significant health concern for the Americas and continues to be a health concern for Africa and Asia. The virus is spread primarily by the *Aedes* species mosquito, which is found in many countries, including the United States. Unlike many other mosquito-borne diseases, Zika virus also is transmitted horizontally through sexual contact, blood, and urine, as well as vertically from mother to fetus/newborn, making it more difficult to control locally and allowing spread to non-mosquito areas. Current prevention guidelines recommend that men use condoms or abstain from sex for six months after Zika viral illness, especially with women who are either pregnant, breastfeeding, or of childbearing age to prevent transmission. All pregnant women who have a history of contact with the Zika virus should have an ultrasound to determine any signs of Zika infection sequelae in the fetus. When such abnormalities are present, further testing should be performed to determine if there are Zika antibodies and to discuss the results of the test with the parent to determine the appropriate course of action.

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CME/CE Questions

1. What percentage of those infected with Zika virus are asymptomatic?
   a. 15%
   b. 30%
   c. 80%
   d. 95%
   e. None of the above
2. The Zika virus is most closely genetically related to which of the following?
   a. Dengue virus
   b. Ebola virus
   c. Spondweni virus
   d. West Nile virus
   e. Yellow fever virus
3. A patient presents to the ED after returning from a trip to Brazil. She just found out she is pregnant. She is asymptomatic. The best course of action at this time is:
   a. start an antiviral medication.
   b. reassure the patient because she has no symptoms.
   c. arrange for her to have serologic testing and obstetrician follow up.
   d. suggest that the patient terminate the pregnancy.
4. Adults exposed to Zika may develop which of the following?
   a. Seizures
   b. Guillain-Barré syndrome
   c. Sepsis
   d. Myocarditis
5. During the mosquito life cycle, how many stages of development require standing water?
   a. 1
   b. 2
   c. 3
   d. 4
   e. All of them
6. Male mosquitoes only live about a week, but female mosquitoes live for a few weeks and can lay eggs every three days, depending on:
   a. the number of blood meals.
   b. temperature.
   c. humidity.
   d. geographic location.
   e. All of the above
7. Many viral infections can be spread by the same genus of mosquito and clinically present with similar symptoms. Horizontal and vertical transmission occurs in which of the following?
   a. Chikungunya
   b. Dengue
   c. Malaria
   d. Zika
   e. All of the above
8. The most common mode of Zika virus transmission is through the bite of an infected *Aedes* species of mosquito. Which of the following is appropriate prevention for a pregnant woman?
   a. Abstaining from unprotected sexual contact
   b. Insect repellent (picardin)
   c. Long-sleeve clothing
   d. Mosquito netting
   e. All of the above
9. Zika virus can be found in:
   a. semen.
   b. blood.
   c. cerebrospinal fluid.
   d. All of the above
10. Treatment and prevention of spread of Zika viral disease includes which of the following?
    a. Abstinence
    b. Condoms
    c. Fluids
    d. Nonsteroidal anti-inflammatory drugs
    e. All of the above

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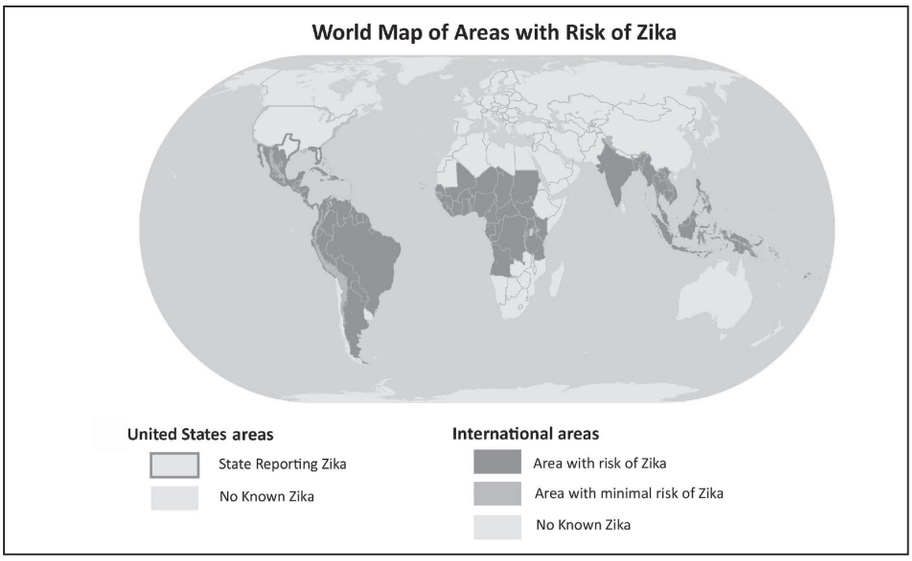
Updates on Zika Virus Disease

Areas With Risk of Zika



Source: Centers for Disease Control and Prevention

Comparison of Zika, Chikungunya, and Dengue Infectious Signs and Symptoms

Characteristic	Zika	Chikungunya	Dengue
Vector	*Aedes* species	*Aedes* species	*Aedes* species
Endemic Region	Southern United States, Central/ South America, Africa, Asia	United States (including Alaska), Central/South America, Africa, Asia	Central/South America, Africa, Asia
Fever	Low grade	High grade	High grade
Incubation Period	3-7 days	3-7 days	4-7 days
Rash	Maculopapular, erythematous rash	Pruritic, maculopapular rash, petechial rash (rarer)	Pruritic petechiae
Other Signs and Symptoms	Exudative conjunctivitis, myalgia, arthralgia, headache Rare: Guillain-Barré syndrome	Severe arthralgia (esp. small joints), Gastrointestinal symptoms Rare: myelitis, retinitis, meningoencephalitis, conjunctivitis, epistaxis, subconjunctival hemorrhage	DHF: Headache, myalgia, DHS: Headach, myalgia, plus extensive hemorrhage, hepatomegaly, third spacing of fluids, shock
Laboratory Findings	Lymphopenia	Neutropenia	Thrombocytopenia, lymphopenia, hypoglycemia, hypocalcaemia, hypernatremia, lactic acidosis, coagulopathy
Diagnosis	IgM/IgG RT-PCR	IgM/IgG analysis Viral particle analysis of serum/ plasma for virus	IgM ELISA/IgG RT-PCR
Treatment	Supportive	Supportive	Supportive Avoid NSAIDs with dengue
Effect on Infants via Vertical Transmission	Possible increased rates of microcephaly, hearing and vision deficits	Nonspecific viral infection seen in age 3 to 7 days	Increased rate of LBW infants
Vaccination	Investigational	Investigational	Several, CYD-TDV
Complications	Mortality rare, possible association with increased rates of microcephaly and Guillain-Barré	Mortality rare, chronic joint pain	Mortality rare, more common in those with DHF/DSS

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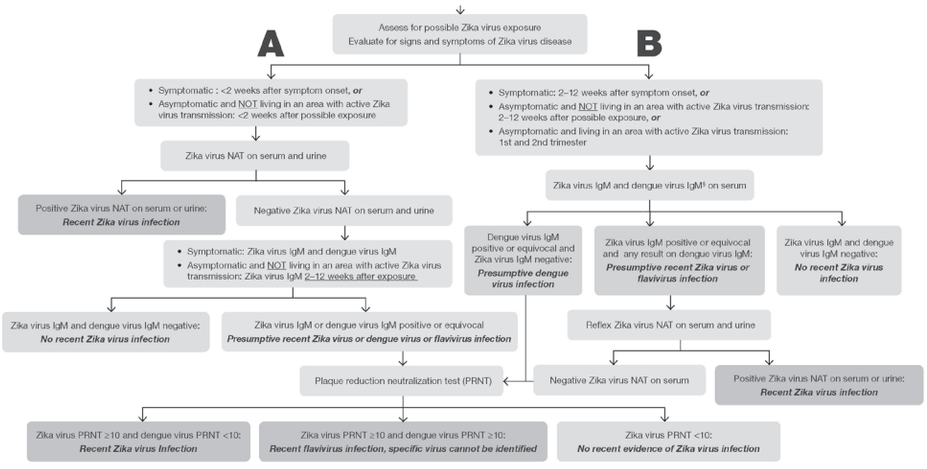
Interpretation of Results for Antibody Testing for Suspected Zika Virus Infection, U.S., 2016*, †, §, ¶, **

Zika Virus and Dengue Virus IgM ELISA	Zika Virus PRNT	Dengue Virus PRNT	Interpretation
Positive or equivocal (either assay)	≥ 10	< 10	Recent Zika virus infection
Positive or equivocal (either assay)	< 10	≥ 10	Recent dengue virus infection
Positive or equivocal (either assay)	≥ 10	≥ 10	Recent flavivirus infection; specific virus cannot be identified
Inconclusive in one assay AND inconclusive or negative in the other	≥ 10	< 10	Evidence of Zika virus infection; timing cannot be determined
Inconclusive in one assay AND inconclusive or negative in the other	< 10	≥ 10	Evidence of dengue virus infection; timing cannot be determined
Inconclusive in one assay AND inconclusive or negative in the other	≥ 10	≥ 10	Evidence of flavivirus infection; specific virus and timing cannot be determined
Any result (either or both assays)	< 10	< 10	No evidence of Zika virus or dengue virus infection
Positive for Zika virus AND negative for dengue virus	Not yet performed		Presumptive recent Zika virus infection
Positive for dengue virus AND negative for Zika virus	Not yet performed		Presumptive recent dengue virus infection
Positive for Zika virus AND positive for dengue virus	Not yet performed		Presumptive recent flavivirus virus infection
Equivocal (either or both assays)	Not yet performed		Equivocal results
Inconclusive in one assay AND inconclusive or negative in the other	Not yet performed		Inconclusive results
Negative for Zika virus AND negative for dengue virus	Not indicated		No evidence of recent Zika virus or dengue virus infection

Abbreviations: ELISA = enzyme-linked immunosorbent assay; IgM = immunoglobulin M antibodies; PRNT = plaque reduction neutralization test.
* For persons with suspected Zika virus disease, Zika virus real-time reverse transcription–polymerase chain reaction (rRT-PCR) should be performed on serum specimens collected < 7 days after onset of symptoms, and on urine specimens collect < 14 days after onset of symptoms.
† In the absence of rRT-PCR testing, negative IgM or neutralizing antibody testing in specimens collected < 7 days after illness onset might reflect collection before development of detectable antibodies and does not rule out infection with the virus for which testing was conducted.
§ Zika IgM positive result is reported as "presumptive positive" to denote the need to perform confirmatory PRNT.
¶ Report any positive or equivocal IgM Zika or dengue results to state or local health department.
** To resolve false-positive results that might be caused by cross-reactivity or nonspecific reactivity, presumptive positive Zika IgM results should be confirmed with PRNT titers against Zika, dengue, and other flaviviruses to which the person might have been exposed. In addition, equivocal and inconclusive results that are not resolved by retesting also should have PRNT titers performed to rule out a false-positive result.
Reprinted from: Rabe IB, Staples JE, Villanueva J, et al. Interim Guidance for Interpretation of Zika Virus. Antibody Test Results. *MMWR Morb Mortal Wkly Rep* 2016;65;543-546.

Testing Guidelines for Pregnant Patients with Possible Zika Exposure



Abbreviations: IgM = immunoglobulin M; PRNT = plaque reduction neutralization test; NAT = nucleic acid testing.
* A pregnant woman is considered symptomatic if one or more signs or symptoms (fever, rash, arthralgia, or conjunctivitis) consistent with Zika virus disease is reported whereas a pregnant woman is considered asymptomatic if symptoms are NOT reported.
† Testing includes Zika virus NAT on serum and urine samples, Zika virus and dengue virus immunoglobulin M (IgM), and plaque reduction neutralization test (PRNT) on serum samples. PRNT results that indicate recent flavivirus infection should be interpreted in the context of the currently circulating flaviviruses. Refer to the laboratory guidance for updated testing recommendations (http://www.cdc.gov/zika/laboratories/lab-guidance.html). Because of the overlap of symptoms in areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection.

Source: Centers for Disease Control and Prevention.
Available at: https://www.cdc.gov/zika/pdfs/zikapreg_screeningtool.pdf

§ Dengue IgM antibody testing is recommended only for symptomatic pregnant women.
¶ If Zika virus NAT testing is requested from laboratories without IgM antibody testing capacity or a process to forward specimens to another testing laboratory, storing of additional serum samples is recommended for IgM antibody testing in the event of a NAT negative result.
** Possible exposure to Zika virus includes travel to or residence in an area with active Zika virus transmission (http://wwwnc.cdc.gov/travel/notices/), or sex (vaginal sex (penis-to-vagina sex), anal sex (penis-to-anus sex), oral sex (mouth-to-penis sex or mouth-to-vagina sex), and the sharing of sex toys) without a barrier method to prevent infection (male or female condoms for vaginal or anal sex, male condoms for oral sex (mouth-to-penis), and male condoms cut to create a flat barrier or dental dams for oral sex (mouth-to-vagina) with a partner who traveled to or lives in an area with active Zika virus transmission.

Supplement to *Emergency Medicine Reports*, July 15, 2017: "Updates on Zika Virus Disease." Authors: Kelly R. Klein, MD, FACEP, Associate Professor, Division of Emergency and Global Health, Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas; and Paul Moore, MSc, NREMT, Paramedic, Clinical Research Manager, Division of Emergency and Global Health, Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas.

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