REVIEW ARTICLE

Zika Virus - A Review for Family Physicans

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Mosquito-borne viruses have been on the rise in recent years. This becomes especially critical when you consider a virus with a particularly harrowing consequence, like the Zika virus (ZIKV) and infant microcephaly. From its obscure history in Africa, ZIKV diverged into an African and Asian strain, the latter strain traveling from Asia to the islands in the Pacific Ocean and ultimately to the Americas, including the United States. ZIKV spread through this immunologically naïve population through mosquito bites, sexual transmission, intrauterine transmission and blood transfusion. Zika symptoms may include fever, joint pain, and maculopapular rash, all of which are common to other mosquito-borne illnesses such as dengue and chikungunya, also seen in similar locations. Awareness of the symptoms, differential diagnosis and the testing algorithm for Zika may improve detection and facilitate early management. Tests for ZIKV include nucleic amplification assays, IgM serology, and the plaque reduction neutralization test, with decision to test determined by symptom status, pregnancy status, and degree of exposure. While the majority of patients with ZIKV are asymptomatic, the most severe complications are Guillain-Barré Syndrome for adults and Congenital Zika Syndrome for infants born to infected mothers. Since the mainstay of management is supportive care and surveillance, preventive strategies are critical in prevention of these complications. Prevention is multimodal including mosquito population control, mosquito bite prevention, and actions to prevent sexual transmission. Through counseling and early detection, the family medicine practitioner has the unique opportunity to prevent the spread of ZIKV and its potential complications.

INTRODUCTION

In 2016, the World Health Organization (WHO) declared Zika virus (ZIKV) infection a public health emergency of international concern.[1] The virus had spread to 26 countries and territories in the Americas, infecting thousands of individuals and causing complications such as Guillain-Barré Syndrome (GBS) in adults and severe microcephaly in infants born to infected mothers. The increased cases of microcephaly caught the attention of public health authorities and health professionals, compounded by the fact that microcephaly had not been associated with any arbovirus infection to date. Since ZIKV is a reemerging virus with the potential to cause complications, it is important for health professionals to be informed about ZIKV so they can recognize this threat. This paper provides a comprehensive description of the history, transmission, clinical manifestations, diagnosis and prevention of ZIKV infection.

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ZIKV belongs to the Flaviviridae family of viruses, which also consists of other important human pathogens such as West Nile encephalitis virus (WNEV), Dengue virus (DENV), Yellow fever virus and Japanese encephalitis virus (JEV).[2] Before the current outbreak, ZIKV had an unremarkable history. In 1947, Yellow Fever researchers first isolated the virus from a caged Rhesus monkey in the Zika forest of Uganda.[3] From Africa, ZIKV made its way to Asia, where in 1954, it was isolated from mosquitoes in Malaysia and by 1977, it had been isolated from patients in Indonesia.[4,5] Phylogeny reveals two distinct lineages of ZIKV, African and Asian. In 2007, the Asian lineage of ZIKV affected about 70 percent of the population on Yap island in the Federated States of Micronesia, presumably after having arrived from Southeast Asia by air travel.[6] Data implicate this Asian lineage in the ZIKV outbreak in the Americas.[7] After Yap Island, ZIKV infected French Polynesia, other islands across the Pacific Ocean, and subsequently Brazil and the Americas, where it gained notoriety for its complications of microcephaly and GBS.[8] Based on phylogeny, researchers postulate that ZIKV was introduced to Brazil sometime between August 2013 and July 2014.[9] ZIKV infection of this immunologically naïve population may have facilitated its rapid spread in Brazil and neighboring countries. It is thought that the virus circulated undetected for about a year, either because of subclinical

infections or because of misdiagnosis of Zika (ZIKV disease) as one of the other endemic arboviral illnesses, such as Dengue and Chikungunya.

On July 29, 2016, the continental United States (U.S.) recorded its first case of a local, mosquito-borne ZIKV infection in Miami-Dade County, Florida.[10,11] Following this initial report, ZIKV infection was reported in Hidalgo County, Texas.[11,12] ZIKV is not the first arbovirus to cause an outbreak in the United States. The CDC website accounts for provisional Zika cases in the U.S. and its territories, according to which the total number of symptomatic Zika cases in the U.S. from 2015 to 2018 have been 5,700. The number of presumed locally transmitted cases was 231, with Florida showing the highest number at 220 and Texas showing 11 cases. There have been short-lived outbreaks with other arboviruses, such as DENV and Chikungunya virus (CHIKV), in regions of Texas and Florida, when the Aedes aegypti mosquito populations were abundant.[13] In 2016, mosquito surveillance data revealed that approximately one out of 1,600 Aedes aegypti mosquitoes were infected with ZIKV, an infection rate that is consistent with outbreaks of DENV and CHIKV.[14,15] Furthermore, research has shown that human ZIKV infection correlates with abundant Aedes aegypti populations.[16] Using phylogenic analyses of ZIKV from clinical and mosquito samples without passage through cell culture, researchers estimate that ZIKV was likely introduced into Florida at least two months prior to its first detected human case.[15] Because of international travel, outbreaks in the U.S. will likely correspond with ZIKV outbreaks in other parts of the world where Aedes aegypti mosquitoes are in abundance.

MODES OF TRANSMISSION

Current evidence supports the following modes of transmission of ZIKV to humans: mosquito-borne transmission, sexual transmission, intrauterine transmission and transmission through blood transfusion.[17,18] While the Aedes aegypti mosquito is most commonly responsible for transmission of ZIKV to humans, Aedes albopictus can also transmit ZIKV.[19,20] Transmission of ZIKV through sexual intercourse has been reported in male-to-female, male-to-male, and female-to-male sexual contact.[17, 21-27] In addition to the four modes of transmission, rare cases of intrapartum transmission and transmission from laboratory exposure have also been reported.[17,18]

CLINICAL MANIFESTATIONS & MANAGEMENT

The most common symptoms associated with human ZIKV infection include fever, a maculopapular rash, arthralgias, and non-purulent conjunctivitis. Other symptoms that have been reported from the outbreak in Yap Island include headache, myalgias, retro-orbital pain, edema and vomiting,[6,28] as shown in Table 1. Approximately 80 percent of individuals infected with ZIKV are asymptomatic.[6] The incubation period of ZIKV infection varies between three and 14 days.[29] The course of the infection is typically self-limiting, with symptoms lasting for several days to a week.[30] Severe disease requiring hospitalization is uncommon and mortality remains low, with one death reported in 153 hospitalized patients.[11,31] Supportive care of symptomatic patients and fetal surveillance of pregnant women is the mainstay of management for people infected with ZIKV.[31,32]

TABLE 1:

Symptoms of Zika

MOST COMMON SYMPTOMS OF ZIKA	ADDITIONAL SYMPTOMS
Fever	Retro-orbital pain
Maculopapular rash	Edema
Headache	Vomiting
Arthralgia	
Non-purulent conjunctivitis	
Myalgias	

COMPLICATIONS OF ZIKA VIRUS INFECTION IN ADULTS

The complication of greatest concern in adults infected with ZIKV is Guillain-Barré syndrome (GBS), an immune mediated progressive neurologic disorder characterized by tingling, progressive weakness, autonomic dysfunction and pain.[33] GBS has been associated with many infections, most notably Campylobacter jejuni, but also other flaviviruses such as JEV, WNEV and DENV.[33, 34, 35] During the French Polynesia ZIKV outbreak of 2013-2014, 32,000 people sought medical attention for possible ZIKV infection and 42 patients were identified with GBS.[35] This represents a 20-fold increase over baseline incidence of GBS in this population.[34] Associations between the incidence of ZIKV and GBS have been observed during outbreaks in Brazil, Colombia, Dominican Republic, El Salvador, Honduras, Panama, Suriname, and Venezuela.[36, 37] A WHO expert panel reviewed the data and concluded that ZIKV is a trigger for GBS.[35]

COMPLICATIONS IN INFANTS BORN TO MOTHERS INFECTED WITH ZIKV DURING PREGNANCY

A comprehensive review of the literature relative to ZIKV infection in French Polynesia, Brazil, U.S. and Spain identified a constellation of symptoms, now recognized as Congenital Zika Syndrome (CZS).[38] The main features of this syndrome are abnormal cranial morphology, brain anomalies, neurologic sequelae, ocular anomalies, and congenital contractures, with specific examples including fetal brain disruption sequence, cerebral cortex thinning, epilepsy, cataracts, and arthrogyropsis.[38] Continued surveillance and reporting should help better define this syndrome in the future.

The breadth of impact of maternal intrauterine ZIKV infection in the U.S. is still being monitored. The CDC, in collaboration with state, territorial, tribal, and local health departments, has created a registry known as the U.S. Zika Pregnancy Registry (USZPR),

which monitors birth defects in infants born in the U.S. to women potentially infected with ZIKV during pregnancy.[39] A detailed list of possible birth defects and instructions on how to report them is available through the CDC.[40] As of January 2018, the USZPR has reported 17 pregnancy losses with evidence of ZIKV-associated birth defects and 6,106 completed pregnancies with laboratory evidence of possible ZIKV infection among women in the U.S., District of Columbia, U.S. Territories and Freely Associated States.[41] Of the 6,106 completed pregnancies, there were 247 live-born infants with evidence of ZIKV-associated birth defects (4%). A 2017 study evaluated 442 pregnant women and pregnancy outcomes from the USZPR and concluded that 6% of infants had evidence of birth defects, with the rate of birth defects increasing to 11% when the mother was infected in the first trimester.[41, 42] Microcephaly was the most common defect, reported at a rate of 4%, which falls between the rates of birth defects seen in French Polynesia (0.95%) and estimated in Bahia, Brazil (13.2%).[43, 44]

DIFFERENTIAL DIAGNOSIS

Considering current epidemiologic trends, the most relevant differential diagnoses to consider are CHIKV and DENV. High fever (≥104˚F) is an important distinguishing characteristic of Dengue while fever and severe joint pain may be more indicative of Chikungunya.[45, 46] Table 2 provides an inclusive list of differential diagnoses, including other mosquito-borne illnesses and infections that present with fever, rash and arthralgia or myalgia. Currently, the CDC recommends testing for DENV and CHKV for patients at risk of clinically compatible illness.[47] If other diagnoses are suspected at the time of presentation, specific testing should be pursued as well.[47] While awaiting laboratory confirmation of ZIKV, it is important to avoid the use of nonsteroidal anti-inflammatory medications in all patients with suspected DENV due to the increased risk of hemorrhagic complications.[48]

DIAGNOSTIC APPROACH TO PATIENTS WITH POSSIBLE ZIKV EXPOSURE

Currently, there are three main arms of testing for ZIKV infection: Nucleic amplification testing assays (NAT), Anti-Zika IgM serology assays (Zika IgM), and the plaque reduction neutralization test (PRNT). As of January 2018, the FDA has approved 14 NAT and 5 Zika IgM assays for emergency use.[49] A positive NAT result represents the presence of ZIKV RNA in the host specimen sample. NAT is routinely performed on serum and urine samples; however, other fluid and tissue samples, such as cerebrospinal fluid, placental tissue, and amniotic fluid are also under investigation.[50, 51] Since ZIKV RNA is only transiently present in any body fluid, a positive NAT suggests an acute infection.[50, 52, 53] ZIKV IgM assays detect anti-ZIKV IgM antibodies that normally become detectable within 1 week of symptom onset.[32] Though data is limited, one recent study showed that ZIKV IgM may persist for up to 43 days in serum and that the duration of detection varies based on the assay being used.[54] Thus, positive ZIKV IgM is suggestive of ZIKV infection, but does not identify the timing of infection.[47] Given a large cross reactivity between flavivirus antibodies and a false positive rate up to 27% in the U.S., PRNT is used as a confirmatory test to differentiate ZIKV IgM antibodies from other flavivirus antibodies present in the host.[50, 55] However, in areas of high DENV circulation, PRNT does not differentiate between ZIKV and DENV IgM.[56] Thus, PRNT should not be used in areas such as Puerto Rico, which have high rates of DENV infection.[50]

TABLE 2:

Differential Diagnoses

PRESENTATION	DIAGNOSES
Fever, Rash and Arthralgia/Myalgia	Zika Lyme Disease Dengue Rickettsiosis Chikungunya
Fever and Rash	Rubella Measles Parvovirus Adenovirus Scarlet Fever Ehrlichiosis
Fever and Arthralgia/Myalgia	Yellow Fever Leptospirosis West Nile Encephalitis* Malaria

**Most cases are asymptomatic*

Given the changing epidemiology of ZIKV infection and the limitation of available testing, the CDC continuously updates its algorithm for laboratory testing and confirmation of diagnosis.[32] Table 3 summarizes the most recent testing recommendations for pregnant and non-pregnant individuals, released in January 2018 and July 2017 respectively. The most recent updates recommend initial testing with NAT of both serum and urine and/or ZIKV IgM testing.[32, 50, 51] The choice of test is based upon type of exposure, symptom, pregnancy status, and time since symptom onset.[32, 50, 51] Exposure is further categorized as ongoing or limited risk of ZIKV transmission. The term ongoing exposure refers to living in or frequent travel to an area with a risk of Zika or sexual intercourse with a partner who lives in or frequently travels to an area with a risk of Zika. The term limited exposure refers to limited travel to an area with a risk of Zika or sexual intercourse with a partner who has traveled to an area with a risk of Zika. The CDC travel pages provide updated information regarding areas worldwide and in the U.S. at risk of ZIKV infection.[57, 58] The term symptomatic refers to patients presenting with any of the following symptoms of ZIKV infection: maculopapular rash, conjunctivitis, fever or arthralgia.[47]

PREVENTION OF MOSQUITO-BORNE TRANSMISSION OF ZIKV

For people living in or traveling to areas at risk of Zika, preventing contact between mosquitoes and humans is the primary method of reducing infection. Bite prevention should be multimodal, including use of insect repellant, protective clothing, and environmental precautions. Insect repellants containing the following active ingredients have been approved and are endorsed by the CDC and Environmental Protection Agency (EPA): N,N-Diethyl-meta-toluamide (DEET), picaridin, IR35, Oil of Lemon Eucalyptus, para-menthane-diol, and 2-undecanone.[59] The most effective repellents against the Aedes aegypti mosquito contain

TABLE 3:

CDC recommendation for laboratory testing and result interpretation for patients with possible exposure to ZIKV

TIMEFRAME	INITIAL TEST INITIAL TEST	INTERPRETATION OF TEST RESULTS
Symptomatic Nonpregnant		
< 2 weeks from symptom onset	NAT serum and urine for ZIKV	Positive: diagnostic for acute ZIKV Infection Negative: ZIKV unlikely
> 2 and < 12 weeks from symptom onset	IgM serology for ZIKV	Positive or equivocal: PRNT testing to confirm diagnosis, if ZIKV ≥ 10 and DENV <10: confirms ZIKV infection, though timing of infection cannot be determined Negative: ZIKV unlikely
Symptomatic Pregnant		
Up to 12 weeks from symptom onset	NAT serum and urine for ZIKV and IgM for ZIKV*	Either urine or serum NAT Positive and IgM positive: diagnostic for acute ZIKV infection NAT not concordant** and IgM negative: retest original positive sample (urine or serum) for NAT, if negative then test serology 2 weeks from date of original test NAT and IgM negative: no evidence of ZIKV infection
Asymptomatic Pregnant: Ongoing Exposure		
Upon initiation of prenatal care	NAT urine and serum for ZIKV***	Positive: diagnostic for ZIKV infection, no further Zika testing needed Negative: ZIKV infection in pregnancy cannot be ruled out. Retest with NAT two more times in pregnancy.ŧ
Asymptomatic Pregnant: Limited Exposure		
Upon initiation of prenatal care if case-by-case decision makingł suggests testing	NAT urine and serum for ZIKV	Positive: diagnostic for ZIKV infection, no further Zika testing needed Negative: ZIKV infection in pregnancy cannot be ruled out. Retest with NAT two more times in pregnancy.ŧ

Abbreviations: *NAT = Nucleic amplification testing; ZIKV = Zika virus; PRNT = Plaque-reduction neutralization test Information from references (32, 47, 50)*

** Given the extended presence of viral particles in body fluids during pregnancy, all symptomatic pregnant women undergo both NAT-serum/urine and ZIKV IgM testing at initial presentation of symptoms*

*** Positive urine NAT and negative serum NAT or negative urine NAT and positive serum NAT*

**** CDC does not currently recommend IgM serology because IgM can persist for months after ZIKV infection, thus a positive serology result cannot reliably determine if the infection took place before or during pregnancy.*

ŧ At non-coinciding prenatal visits, additional testing may be warranted depending on local trends in ZIKV transmission

ł Given high rate of false positives of NAT and IgM in areas of low-risk, case-by-case decision making between provider and patient should inform the decision to test.

DEET (>5%) and picaridin (16%). However, products containing 25% DEET provide protection for the longest duration of time.[60, 61] The American Academy of Pediatrics cautions against the use of DEET containing products in infants less than 2 months of age.[62]

Aedes aegypti bite during the day and night and dwell both indoors and outdoors. Long sleeved shirts, long pants, socks, and hats are recommended to cover bare skin.[63] In areas where there is no permethrin resistance, permethrin treated clothes are also effective at repelling mosquitoes.[64, 65] Environmental precautions can also decrease exposure. Keeping windows and doors closed or screened and using air conditioning, can reduce the number of mosquitoes present in daytime and nighttime environments. Covering any holes or gaps between doors, walls, and screens can further secure the indoor environment.[65] If sleeping outside, insecticide treated bed nets are recommended.[64, 65]

To prevent continued dissemination of ZIKV, it is also important to prevent transmission from infected humans to mosquitoes. Because humans infected with ZIKV are viremic during the first week of illness and can transmit the virus to a biting mosquito, it is recommended that patients with known ZIKV infection take precautions to prevent mosquito bites during this time.[66, 67] Travelers returning from areas of possible ZIKV infection should prevent mosquito bites for three weeks, which safely covers the range of the ZIKV incubation period and the length of viremia.[66]

According to the CDC and the U.S. EPA, one of the most effective means of decreasing a mosquito population is to remove the habitat and thus interrupt the life cycle at the larval and adult stages. Monitoring areas with standing water is an important aspect of mosquito population control since mosquitoes rely on water for two stages of their life cycle. Areas with standing water, such as old tires, gutters, or toys containing water should be drained, scrubbed and covered. Birdbaths, fountains, or potted plant trays should be emptied and scrubbed once a week. The addition of larvicides to breeding habitats is very effective in reducing populations in nearby locations. Aerial spraying of adulticides, either by aircraft, truck-mounted or backpack sprayers, is effective in reducing the total number of adult mosquitoes over larger areas.[65]

PREVENTION OF SEXUAL TRANSMISSION OF ZIKV & PRECONCEPTION COUNSELING TO PREVENT INTRAUTERINE TRANSMISSION

Though not as common as transmission from mosquitoes, sexual transmission poses an important modifiable risk that, if addressed, can help prevent birth defects associated with ZIKV. To reduce the risk of sexual transmission of ZIKV, all men and women who live in or travel to areas at risk of ZIKV infection should use barrier methods or abstain from vaginal, anal or oral sex.[22] Furthermore, to help prevent possible adverse outcomes in pregnancy, ZIKV prevention counseling should be a routine part of care for women of reproductive age. To promote early detection of ZIKV before and during pregnancy, the American College of Obstetricians and Gynecologists (ACOG) recommends that all women should be informed of the common symptoms of ZIKV infection (Table 1).[68] If pregnancy is not desired, strategies to prevent pregnancy, including family planning and contraceptive options, should be discussed.[22]

For women with ongoing ZIKV exposure who desire pregnancy, the health professional should discuss the possible adverse outcomes of ZIKV infection during pregnancy. Women and their partners should be informed of mosquito bite prevention strategies and reassured that if used according to product labels, EPA registered mosquito repellents can be used safely before and during pregnancy.[69] If a woman with ongoing ZIKV exposure does become pregnant, she should initiate prenatal care immediately and undergo ZIKV testing.[32]

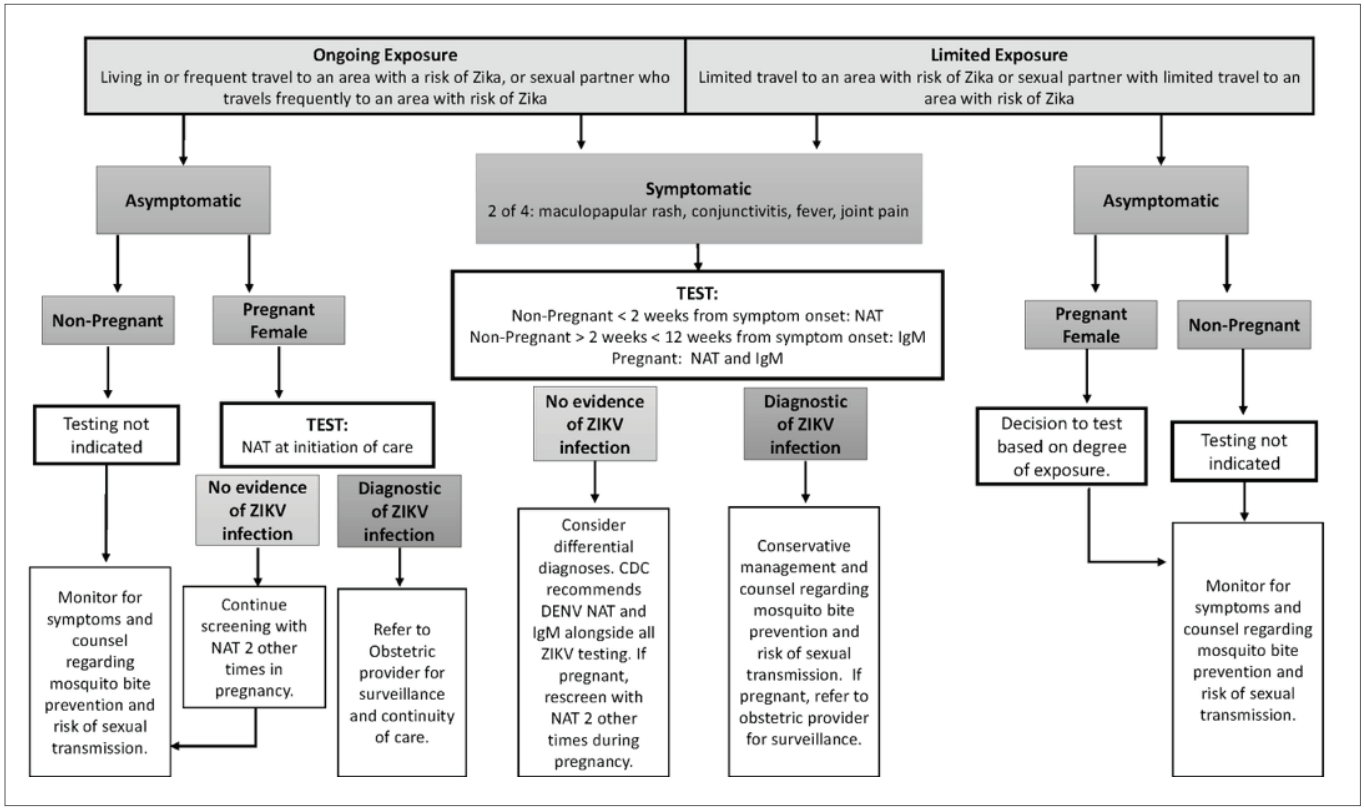
For women with limited ZIKV exposure who desire pregnancy, the health professional should recommend avoiding travel to areas at risk of ZIKV infection.[32] If she or her sexual partner must travel to these areas, they should follow the recommendations listed above to help prevent mosquito bites while traveling. If the woman is possibly exposed to ZIKV through travel or sexual contact with a partner who has traveled, she should prevent conception for the next eight weeks either by abstaining from or using condoms during sexual intercourse.[22, 32] ZIKV may be passed through sexual transmission from an asymptomatic male.[22, 70, 71] and ZIKV RNA has been found in semen up to 188 days after symptom onset.[22, 72] Because of this evidence, the CDC recommends that males should abstain from sex or use condoms for six months following possible exposure.[22] If females become symptomatic, they should avoid unprotected sex for eight weeks from the date of symptom onset or Zika diagnosis. If males become symptomatic, they and their female partners should avoid unprotected sex for six months from the date of symptom onset or Zika diagnosis in the male.[22] Should the woman become pregnant, she should initiate prenatal care immediately. The need for ZIKV testing would be determined based on the degree of possible exposure and shared decision making.[32]

CONCLUSION

An approach to patients with possible ZIKV exposure is illustrated in Figure 1. Armed with this knowledge, through counseling and early detection, the medical community can help prevent the spread of ZIKV and its potential complications. In the absence of FDA approved antivirals and vaccines, the onus for preventing ZIKV infection falls on mosquito eradication efforts, as well as early detection and management. The rapid emergence of ZIKV in the Americas highlights the importance of a gene-based, global surveillance network that can identify the increasing presence of new or reemerging viruses and implement prevention initiatives such as mosquito eradication and immunization programs when available.

FIGURE 1:

Primary Care Approach to Patient with Possible ZIKV Exposure.



AUTHOR DISCLOSURES:
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