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Highlight

# Zika virus disease: Global concerns and making way through it

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## ABSTRACT

The recent upsurge of Zika virus infection has alarmed public health officials because of its possible association with thousands of suspected cases of microcephaly, thereby sparking a public health emergency. This mosquito-borne arboviral disease majorly remains asymptomatic. Unavailability of specific prophylaxis or vaccines or treatment necessitates the need to advocate preventive personal measures to get protected from these daytime bitters. Prevention and control measures should be aimed at reducing the vector density and minimizing the vector-patient contact.

**Key words**: *Aedes* species, microcephaly, prevention, Zika virus outbreak

## INTRODUCTION

Recent Zika virus (ZIKV) outbreak in the Americas and the South Pacific is budding speedily, and its spread is threatening to become a pandemic issue as the vector species *Aedes aegypti* and *Aedes albopictus* are broadly distributed here. Since its outbreak in May 2015, Brazil has already notched around 4000 cases of microcephaly, while before 2015, the country had fewer than 200 cases per year which led to a proactive declaration of a public health emergency by Brazil in November 2015.[1] Since then, the virus has spread to 24 countries and territories in the hemisphere, as reported by the Pan-American Health Organization (PAHO).[2] The World Health Organization (WHO) designated the ZIKV and its suspected complications in newborns as a "public health emergency of international concern," where an 18-member expert panel agreed on the need for an urgent international effort to understand the relationship between ZIKV and congenital malformations and neurological complications.[3]

ZIKV disease is now considered as an emerging infectious disease. Zika is a mosquito-borne viral disease caused by ZIKV, which results in generally a mild febrile illness with maculopapular rash. This member of Flaviviridae virus family was initially identified in 1947 in the Zika forest in Uganda in the Rhesus macaque population, then in mosquitoes (*Aedes africanus*) in the same forest in 1948, and subsequently identified in humans in 1952 in Uganda and the United Republic of Tanzania.[4]

The knowledge of geographical distribution of ZIKV is based on results of serological surveys, viral isolations in mosquitoes and humans, reports of travel-associated cases and few published outbreaks. From 1951 to 1981, serological evidence of human infection has been reported from African countries such as Uganda, Tanzania, Egypt, Central African

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Republic, Sierra Leone, and Gabon and Asian countries namely India, Malaysia, the Philippines, Thailand, Vietnam, and Indonesia.[5] From its discovery until 2007, confirmed cases of ZIKV infection from Africa and Southeast Asia were, however, infrequent. An outbreak was reported on Yap Island, Federated States of Micronesia from April to July 2007. This was the first outbreak of ZIKV identified outside of Africa and Asia.[6] The condition was characterized by rash, conjunctivitis, and arthralgia, and was initially thought to be dengue. The chikungunya and Ross River viruses were also supposed. However, serum samples from patients in the acute phase of illness contained RNA of ZIKV. Between 2013 and 2015, several significant outbreaks were notified on islands and archipelagos from the Pacific region including a large outbreak in French Polynesia. In 2015, ZIKV emerged in South America with widespread outbreaks reported in Brazil and Columbia. ZIKV was isolated in November 2015 in a newborn from the Northeastern state of Ceará, Brazil, with microcephaly and other congenital issues; 739 infants were born with microcephaly since July 2015. In December 2015, PAHO/WHO noted that transmission of ZIKV infection had occurred within nine member states: Brazil, Chile (specifically Easter Island), Colombia, El Salvador, Guatemala, Mexico, Paraguay, Suriname, and Venezuela. PAHO/WHO made recommendations for surveillance, case management, and prevention.[7]

## VIROLOGY

ZIKV is enveloped and icosahedral with a nonsegmented, single-stranded, and positive sense RNA genome.[8] It is most closely related to the Spondweni virus and is one of the two viruses in the Spondweni virus clade. The comprehensive genomic comparison showed different subclades reflecting the existence of two main lineages, one African and one Asia lineage which has recently emerged in the Pacific and the Americas.

## TRANSMISSION

It is transmitted by mosquitoes and has been isolated from a number of species in the genus *Aedes*; *A. aegypti*, *A. africanus*, *Aedes apicoargenteus*, *Aedes furcifer*, *Aedes luteocephalus*, and *Aedes vittatus*. It has been isolated from *A. aegypti* mosquitoes, and experimental infections show that this species is capable of transmitting ZIKV. Other *Aedes* mosquito species (notably *A. africanus*, *A. albopictus*, *Aedes polynesiensis*, *Aedes unilineatus*, *A. vittatus*, and *Aedes hensilli*) are considered as prospective vectors of ZIKV. These species is an aggressive daytime biter (especially in midmorning and between late afternoon and twilight). It also transmits dengue, chikungunya, and yellow fever.[7] Research reveals that the extrinsic incubation period in mosquitoes is almost 10 days. The vertebrate hosts of this virus include monkeys and humans. Pathogenesis is hypothesized to first infect the dendritic cells near the site of inoculation, thereafter spreading to the lymph nodes and bloodstream. In terms of replication, flaviviruses generally replicate in the cytoplasm, but ZIKV antigens have been found in infected cell nuclei.[5]

## CLINICAL FEATURES

The incubation period ranges between approximately 3 and 12 days after the bite of an infected mosquito. Almost 60–80% infections remain asymptomatic. Disease symptoms are usually mild, characterized by a short-lasting, self-limiting, febrile illness of 4–7 days duration without severe complications, with no associated fatalities, and a low hospitalization rate. The main symptoms are macular or papular rash, fever, arthralgia, nonpurulent conjunctivitis/conjunctival hyperemia, myalgia, and headache. The maculopapular rash generally starts on the face, eventually spreading throughout the body. Retro-orbital pain and gastrointestinal signs are represented rarely.[7]

There is no prophylaxis, treatment, or vaccine to protect against ZIKV infection. Therefore, preventive personal measures are recommended to avoid mosquito bites during the daytime. Usually, nonsteroidal anti-inflammatory drugs (NSAIDs) and/or non-salicylate analgesics are used.

Autoimmune, neurological, and neurodevelopmental conditions such as Guillain–Barré syndrome and microcephaly in fetuses and newborns from mothers possibly exposed to ZIKV in the two first trimesters of the pregnancy were notified during recent Zika disease outbreaks in French Polynesia and Brazil. Because data suggest that newborns of mothers who had a ZIKV infection during pregnancy are at an increased risk for microcephaly, it is suspected though not proven, that a transplacental infection of the fetus may lead to microcephaly and brain damage. Detection of ZIKV RNA in human amniotic fluid indicates that the virus can cross the placental barrier, suggesting that fetal infection is possible. Further evidence is, however, required to institute a causal association between these neurodevelopmental impairments and infections with ZIKV.[9]

## CASE MANAGEMENT AND DIAGNOSIS

A provisional case definition for ZIKV infection includes:[10]

### Suspected case

Patient with rash or elevated body temperature (>37.2°C) with one or more of the following symptoms (not explained by other medical conditions):

- Arthralgia or myalgia
- Nonpurulent conjunctivitis or conjunctival hyperemia
- A headache or malaise.

### Confirmed case

A suspected case with laboratory-positive result for the specific detection of ZIKV.

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Sample preservation also follows proper protocol. Serum samples collected in dry tube needs to be refrigerated at 2–8°C if it is to be processed within 48 h. Samples should be frozen at −10 to −20°C, if it is to be processed after the first 48 h or within 7 days and at −70°C, if it is to be processed after a week. The sample can be however even be preserved for extended periods. A biosafety level 2 containment levels is required to handle suspected samples.

Recommendations suggest that the serum sample should be taken during the first 5 days after the onset of symptoms. As a single serum in acute phase stands presumptive, it is recommended that a second sample should be taken 1–2 weeks after the first sample to demonstrate seroconversion or a 4-fold increase on the antibody titer.

### Virological diagnosis

Symptoms due to ZIKV infections are mild. Viral RNA has been detected in serum up to day 10 after the onset of symptoms. ZIKV RNA also has been detected in urine over an extended period in the acute phase.

### Serological diagnosis

The serological tests (ELISA or immunofluorescence) to detect specific IgM or IgG against ZIKV can be positive after 5–6 days following the onset of symptoms. During the first 5–6 days following the onset of symptoms, ZIKV-specific IgM antibodies can be detected in the serum specimens by molecular techniques like ELISA or immunofluorescence assays. Detection of an increase of antibodies in paired sera is suggested. Confirmation of positive results with plaque reduction neutralization test showing at least a 4-fold increase in the titer of neutralizing antibodies to ZIKV is recommended. However, in some patients with a probable prehistory of flaviviral infections, a 4-fold rise or more of neutralizing antibody titer to other flaviviruses has been observed. Interpretation of serological results should be considered very carefully as false positive dengue IgM cross-reactivity both by indirect immunofluorescence assay, and rapid test has been reported in both primary ZIKV-infected patients and also those with a probable history of other prior flaviviral infection. A positive result for dengue IgM antibodies without detection of dengue IgG in paired sera among travelers returning from areas affected by ZIKV should prompt a possible investigation for flavivirus etiology.

Differential clinical diagnostic should be considered as well as co-infection with other mosquito-borne diseases such as dengue fever, chikungunya, and malaria. The reverse transcription-polymerase chain reaction for dengue as the main differential diagnosis should be negative.

A specific algorithm is addressed as an interim guidance for laboratory detection of ZIKV by PAHO/WHO [Figure 1].

## TREATMENT

There is no vaccine or precise antiviral treatment for ZIKV infection, therefore symptomatic and supportive treatment after excluding severe conditions such as malaria, dengue, and bacterial infection is strongly recommended. It is essential to differentiate ZIKV infection from dengue due to severe clinical outcomes in some dengue cases. In addition, cases of co-infection, Zika and dengue, could occur. ZIKV infection has a mild to moderate clinical representation in comparison to dengue with the onset of fever being more acute and shorter in duration. However, no shock or severe bleeding has been observed.[10]

The treatment is mainly based on the use of acetaminophen or paracetamol to relieve pain, fever reduction and use of antihistamines for treating pruritus associated with the maculopapular rash.

Treatment with acetylsalicylic acid and NSAIDs was discouraged because of an increased risk of hemorrhagic syndrome reported with other flaviviral infections as well as the risk of Reye's syndrome after viral infection in children and teenagers. The use of other NSAIDs is not advised either, as the clinical manifestations could be dengue or chikungunya, in which the use of NSAIDs is contraindicated.[7]

Patients should be advised to drink plenty of fluids to replenish fluid lost from sweating, vomiting, and other insensible losses.

## INFECTION CONTROL, PERSONAL PROTECTION, AND PREVENTION

Prevention and control measures should be aimed at reducing the vector density and minimizing the vector-patient contact. Patients along with his surrounding community must be well educated about the various risks of transmission and their minimizing strategies involving reduction of vector population and human-vector contact.[10]

Recommendations for minimizing vector-patient contact:

- Infected patients should avoid being bitten by *Aedes* mosquitoes during the viremic phase of illness. *Aedes* mosquitoes have diurnal biting activities, with highest hours of activities being during midmorning, late afternoon to twilight. Thus, personal protection measures should be applied all day long
- Using long-lasting insecticidal treated mosquito bed nets for inadequately screened accommodations is recommended. Use of wire-mesh screens on doors and windows are suggested
- Patients, other members of the household, physicians, or health-care workers attending ZIKV -infected patients

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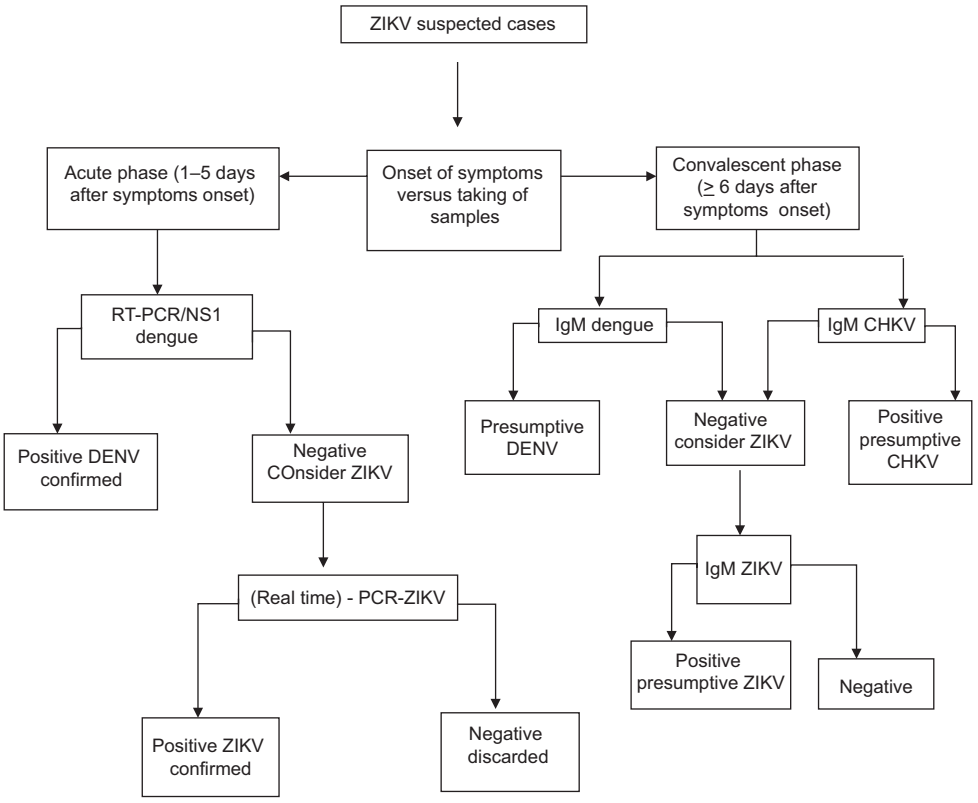


**Figure 1: Algorithm addressed as an interim guidance for laboratory detection of Zika virus by Pan-American Health Organization/ World Health Organization (Ref: Pan-American Health Organization/World Health Organization. Zika virus surveillance in the Americas: Interim guidance for laboratory detection and diagnosis)**

should protect themselves against mosquito bites using insect repellent (DEET, IR3535, or Icaridin) and wearing clothes covering extremities especially during the hours of highest mosquito activity. Repellent use must be strictly done in accordance with the instructions indicated on the product label. For newborn children under 3 months of age, repellents are not recommended
- Before departure health authorities should advise travelers heading to any country with documented circulation of dengue, chikungunya, and/or ZIKV to take the necessary measures to protect themselves from mosquito bites, such as using repellents, wearing appropriate clothing that minimizes skin exposure, and using insecticides or nets. Travelers should be informed of the symptoms of dengue, chikungunya, and ZIKV, to facilitate prior identification during the trip.

Prevention and control measures by national authorities should include the following:
- Strengthening environmental management and eliminating vector breeding sites to prevent/minimize vector propagation and human contact with the vector mosquito
- Prior risk stratification and organizing mass sanitation campaigns for the elimination of breeding sites
- In areas where autochthonous or imported cases of dengue, chikungunya, and/or ZIKV are detected, it is suggested to use adulticide treatment primarily through spraying, for removal of infected adult mosquitoes thereby interrupting their transmission
- Selecting appropriate insecticide (in accordance with PAHO/WHO recommendations), verifying the product label and formula, and considering the susceptibility of mosquito populations to that insecticide
- Maintaining and using spraying equipment in an appropriate manner and maintaining a stockpile of insecticides.

## CONCLUSION

As at present, there is no specific prophylaxis, treatment or vaccine to protect against ZIKV infection, preventive personal measures are advocated, the most important of which is to avoid daytime mosquito bites. Due to the recent upsurge of ZIKV fever along with it is potentially associated complications in different parts of the world and the strength of the arbovirus to extend through other regions where the (*Aedes*) vector is found, there is a need of effective strategies to reduce the *Aedes* transmission, thereby limiting its chance to become a major public health problem in near future.

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## Conflicts of interest

There are no conflicts of interest.

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