

Review Article

Zika virus and its clinical implications: a comprehensive review

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ABSTRACT

Recent Zika virus outbreak in Latin America and the Caribbean has drawn the world's attention toward this relatively unknown virus, with WHO declaring it a public health emergency of international concern (PHEIC). India has had its own tryst with Zika virus with that "significant numbers" of Indians had already been exposed to Zika as early as 1950s. An exponential spread of Zika virus is a potential public health concern, with implications requiring immediate action. The devastating complications of Zika virus infection, particularly congenital and neurological, makes imperative a thorough, thoughtful, and level-headed public health approach in dealing with this infection especially during pregnancy. We review the data on this deadly infection in this brief review including its history, epidemiology, clinical features and management aspects particularly in pregnant women.

Keywords: Pregnancy, Zika virus

INTRODUCTION

The recent Zika virus outbreak in Latin America and the Caribbean has drawn the world's attention toward this relatively unknown virus. The steep increase in the number of cases since 2015 has led to WHO declaring it a public health emergency of international concern (PHEIC) on February 1, 2016. As a PHEIC, the current epidemic must: 1. constitute a health risk to other countries through international spread; 2. potentially require a coordinated response being unexpected, serious, or unusual; and 3. have implications beyond the affected country requiring immediate action.¹

Zika virus is an arthropod borne neurotropic flavivirus. It is an autochthonous infection primarily transmitted by *Aedes aegyptus* mosquito.^{2,3} Though related to other arthroporne flavivirus infections like dengue, chikungunya, yellow fever, and Japanese encephalitis,

Zika infection in pregnancy can lead to serious maternal and fetal complications particularly neurological abnormalities in the new-born. Pregnant women at risk of acquiring this grave infection should be managed properly to prevent congenital malformations in the fetus like microcephaly and intracranial calcifications.

The recent association of Zika virus infection with congenital microcephaly is alarming.⁴ Major concern has risen over this outbreak considering that upcoming August will see Brazil host Olympic Games, and religious mass gatherings like Umrah between June and September and Hajj in September. More than 7 million pilgrims may reach Saudi Arabia from all over the world, including Latin America, potentially triggering a Zika spread. India may not be spared if and when this occurs.⁵⁻⁷ The chances of Zika infection after exposure, exact timing, chances of fetal infection during pregnancy, are not clearly known. A thorough, thoughtful, and level-

headed preventive public health approach is imperative.⁸ Proper knowledge among physicians, obstetricians, and public health consultants regarding the prevention, diagnosis and management of this disease is of prime importance. We review the current literature on this ongoing epidemic briefly in this review article.

HISTORY

ZIKA virus was first isolated in 1947 in a rhesus monkey in Ugandan forest. Its name comes from this forest of Africa.⁹ The first human case was reported in 1952 in Uganda and Tanzania. The first large epidemic however, occurred in 2007 on the pacific island of Yap. Nearly 75% of the population was infected.^{10,11} Another outbreak was reported in 2013 in French Polynesia.¹²

The virus has been known to be associated with sporadic infections in Africa and Asia. It was subsequently detected in Chile's Easter Island in 2014 and Brazil in May 2015.¹³ Since then it has been spreading explosively to United States territories of Puerto Rico, the US Virgin Islands and American Samoa.¹⁴⁻¹⁶ As of now we don't have any medication or vaccine which might control the infection. The first case of Zika related neonatal microcephaly was reported in Hawaii in January 2016.¹⁷

India has had its own tryst with Zika virus, albeit in a subtle form. When India's National Institute of Virology, Pune was first set up in 1952, a group of scientists was commissioned to work out what diseases it should focus on. A list of 15-insect borne viruses was drawn, including Zika virus. The researchers had discovered that "significant numbers" of Indians had already been exposed to Zika, with 33 having immunity against it out of 196 tested. Zika virus can therefore definitely attack Indians, considering that the first human case was only registered later.^{18,19}

How Zika entered Brazil has been speculated much. It might have been introduced during the World cup soccer games held in Brazil between June and July 2014.²⁰ A second possibility is that the virus entered Brazil during 2014 world sprint championships, held in Rio de Janeiro in August 2014.^{21,22} Most likely, the virus entered through Natal, Recife, Salvador and/or Fortaleza during the soccer games 2014.²²

EPIDEMIOLOGY

The ongoing Zika virus outbreak has spread across America, Caribbean and the Pacific island. It does not occur in regions above 6500 feet (2000 meters), since the mosquitoes transmitting Zika virus are rare at this level.²³

As of April 2016, countries with autochthonous (borne) circulation of Zika virus include Aruba, Barbados, Bolivia, Bonaire, Brazil, Cape Verde, Colombia, Costa Rica, Cuba, Curaçao, Dominica, Dominican Republic, Ecuador, El Salvador, Fiji, French Guiana, Guadeloupe,

Guatemala, Guyana, Haiti, Honduras, Jamaica, Kosrae (Federated States of Micronesia), Marshall Islands, Martinique, Mexico, New Caledonia, Nicaragua, Panama, Paraguay, Saint Martin, Sint Maarten, Saint Vincent and the Grenadines, Samoa, Suriname, Tonga, Trinidad and Tobago, and Venezuela.²⁴⁻²⁶

In the United States, Zika has been detected in Puerto Rico, the US Virgin Islands, and American Samoa. First Zika-related congenital microcephaly in the United States was reported in January 2016, in Hawaii.¹⁷ A sexually transmitted case has been reported in Texas.²⁷ India has so far been free from any current epidemic related case.²⁸

AETIOLOGY

Causative agent

Zika virus

ZIKA virus is an arbovirus or arthropod-borne flavivirus. It is a single-stranded RNA virus transmitted by the Aedes mosquito to humans and other primates. The virus is related to other flaviviruses including Dengue, Chikungunya, Japanese encephalitis, Yellow fever and West Nile virus.^{2,3} ZIKV has been shown to have a rapid mutation rate varying between 12 and 25 bases a year, in a viral genome of 10272 bases.²⁹

Modes of transmission

Vector-mediated

Zika virus is primarily a vector-borne disease. It is transmitted to humans via the bite of an infected *Aedes aegyptus* mosquito. *Aedes albopictus* is also capable of carrying it.^{30,31}

Vertical transmission

Maternal-fetal transmission can occur in the antepartum or intrapartum period. Transmission of Zika virus through breastfeeding has not yet been observed.³¹⁻³⁴

Sexual transmission

Few cases of sexual transmission have been reported.^{31,35}

Parenteral transmission

ZIKA virus may also be transmitted through blood products, laboratory exposure, and organ transplantation.³¹⁻³³

CLINICAL MANIFESTATIONS

Clinical presentation of ZIKV infection has not been fully established and restricted to reports of isolated cases and case series.³⁶ The incubation period between mosquito

bite and onset of symptoms ranges from 2 to 14 days.^{8,37} The clinical manifestations appear in only 20-25% of infected cases. Infact, most people infected with Zika virus won't even know they have the disease because they won't have symptoms. It is usually associated with mild illness with low case-fatality rate. The symptoms usually resolve within a week.^{8,38}

Symptoms and signs³⁸⁻⁴⁰

Fever

Zika fever is usually acute in onset and low grade (37.8 to 38.5°C) in nature. However, high fever reaching 39°C have been reported.

Maculopapular rash

A pruriginous maculopapular rash involving face, trunk, limbs, hands, palms and soles has been described on the second day. It may spread downward from the face to the limbs.

Arthralgia (notably the small joints of hands and feet)

Muscle and joint pains and low grade back pain has been reported but these are less intense and usually affect hands, knees and ankle joints, unlike chikungunya. These usually decline by one week.

Conjunctivitis (usually nonpurulent)

Other common features include headache, retro-orbital pain, anorexia, dizziness and asthenia. Abdominal pain, nausea, vomiting, diarrhea, and pruritus has been reported in few cases. Patients with genitourinary symptoms like hematuria, dysuria, perineal pain, and haemospermia often have detectable viral RNA or infectious particles in urine and/or semen. There has been an unusual increase in the cases of Guillain-Barre syndrome in association with Zika virus. Other neurological manifestations linked to ZIKV include encephalitis, meningoencephalitis, myelitis, paresthesia, vertigo, facial paralysis, and ophthalmological (photophobia, hypertensive iridocyclitis) and auditory manifestations.^{20,35,36,39-43}

Hematological abnormalities like transient and mild leucopenia, neutropenia, lymphopenia or activated lymphocytes, monocytosis, thrombocytopenia, and elevated serum lactate dehydrogenase, aspartate aminotransferase, gamma glutamyl transferase, fibrinogen, ferritin, C-reactive protein, and ESR may occur during viraemic phase.^{38,44,45} Zika and dengue coinfection has been reported but synergistic effect regarding severity or clinical presentation hasn't been shown. Some suggest that ZIKV infection could be distinguished from dengue and Chikungunya fevers by more prominent oedema of the extremities, less severe

headache and malaise, and milder thrombocytopenia. However, this distinction is not absolute.^{10,39,43,45}

Shock and haemorrhage occur with other flaviviruses like dengue, but have not been documented in ZIKV infection and severe acute illness seems rare.^{39,46} Fewer than 10 ZIKV related deaths in adults, and an additional three from Guillain-Barre syndrome have been reported in individuals with symptoms of Zika infection.^{44,47} The WHO has come up with their case definitions for Zika infection (Table 1).⁴⁸

Table 1: WHO case definitions for Zika virus infection.

WHO case definitions	
Suspected case	A person presenting with rash and/or fever and at least one of the following signs or symptoms: <ul style="list-style-type: none"> • Arthralgia; or • Arthritis; or • Conjunctivitis (non-purulent/hyperaemic).
Probable case	A suspected case with presence of igm antibody against Zika virus ¹ and an epidemiological link ²
Confirmed case	A person with laboratory confirmation of recent zika virus infection: <ul style="list-style-type: none"> • Presence of Zika virus rna or antigen in serum or other samples (e.g. Saliva, tissues, urine, whole blood); or • Igm antibody against Zika virus positive and prnt₉₀ for zika virus with titre ≥20 and Zika virus prnt₉₀ titre ratio ≥4 compared to other flaviviruses; and exclusion of other flaviviruses

Effect of Zika virus on pregnancy

It is currently not known, how likely it is for an exposed pregnant woman to suffer from infection. How likely she might transmit the infection to her fetus, or if the infected fetus will develop birth defects or not, is also not certainly known.^{38,41}

Zika virus is said to be associated with serious maternal and fetal complications. It can be transmitted to the fetus during antepartum, intrapartum or postnatal period. There has been >20-fold rise in microcephaly between March 2015 and 2016 in newborns of Brazilian mothers with Zika virus infection.⁴⁹⁻⁵¹ Zika virus infection has also been linked to fetal growth abnormality, poorly developed brain structures, ocular and hearing defects.^{52,53} Immune reactions following ZIKV infection might be a source of cross reactions with brain-specific proteins and might contribute to the ZIKV-associated neuropathologic sequelae.⁵⁴ The maternal and fetal complications of Zika virus disease in pregnancy has been briefed in Table 2.

Table 2: Complications of Zika virus disease in pregnancy.

Maternal	Fetal and neonatal
1.Abortion 2.Preterm birth 3.Fetal growth restriction 4.Intrauterine fetal death 5. Placental insufficiency. 6. Polyhydramnios.	1. Congenital infection Neurological manifestation: Microcephaly, hydranencephaly, intracranial calcification, cerebral atrophy, polymalformative syndromes, brainstem dysfunction, and absence of swallowing. Ocular involvement- macular atrophy and optic nerve abnormalities (hypoplasia with double-ring sign, pallor, increased cup-to-disk ratio), iris coloboma, intraocular calcifications, lens subluxation Others- arthrogryposis. 2. Low birth weight 3. Increases Perinatal morbidity

Ultrasound abnormalities include cerebral atrophy, intracranial calcifications (frontal lobes, caudate, lenticular vessels, cerebellum, around lateral and fourth ventricles), corpus callosum dysgenesis, vermian and thalamic dysgenesis, enlarged cisterna magna, asymmetric cerebral hemispheres, and unilateral ventriculomegaly.^{39,55,56}

Effect of pregnancy on Zika virus disease

Pregnancy is not known to increase the severity of the illness. The clinical manifestations are same as those in non-pregnant state.

DIAGNOSIS

Acute Zika virus disease in pregnant women is suspected in the presence of its typical manifestations with positive history of exposure (residence in or travel to Zika virus affected area or unprotected sexual contact with an infected male partner.) The laboratory confirmation of Zika virus infection is done either by RT-PCR or serological tests. The viral assays can be performed on maternal serum, plasma, amniotic fluid or cord blood.^{41, 44, 45, 57-59}

RT-PCR

Reverse-transcriptase polymerase chain reaction: It is the laboratory test of choice during the first week of symptom onset. Detection of viral RNA in serum is done with the help of RT-PCR during the first 7 days of infection. RT-PCR may not detect Zika virus RNA in a woman after the period of viremia.

Serological tests

Detection of Zika virus specific IgM antibody is done with the help of ELISA or PRNT (Plaque-reduction neutralization test). Zika specific IgM and neutralizing antibodies start developing towards the end of the first week of infection. Cross-reactivity with other flavivirus like dengue and yellow fever viruses may alter test results. PRNT can be used to quantify the level of

neutralizing antibodies to differentiate Zika infection from other flavivirus infections or previous vaccination for other flavivirus diseases like yellow fever or Japanese encephalitis. Zika virus IgM with neutralizing antibody titers in serum ≥ 4 -fold higher than that for dengue virus by PRNT confirms Zika disease. There is no FDA approved test for detection of Zika specific IgG antibody. Histopathological examination and immunohistochemical staining of placenta and cord can also be used to diagnose this infection. CDC diagnostic algorithms for suspected Zika infections are available (Figures 1 and 2).^{41,58}

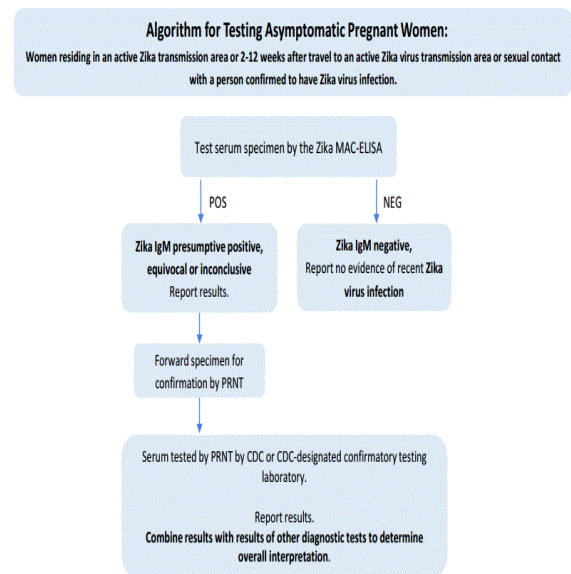


Figure 1: Algorithm for testing asymptomatic pregnant women.

MANAGEMENT

Preconception counselling

Women residing in an area with active Zika virus transmission

The health care provider should counsel both women and men who are planning to conceive regarding the possible

effects of Zika virus on the fetus. The final decision regarding the timing of pregnancy should be decided by the couple.

- Women and men with Zika virus disease: They should not conceive for at least 8 weeks and 6 months respectively after symptom onset.
- Women and men with possible exposure to Zika virus but without clinical illness: Possible exposure includes travel to or residence in an area of active Zika virus transmission or sex without a condom with a man who travelled to or resided in an area of active transmission.

The risk of exposure to Zika virus should be assessed by evaluating the environmental conditions near the house, use of protective measures and level of active transmission of Zika. The chances of exposure at any time during pregnancy are high in such an area so some authorities have even recommended not to conceive at all until control of the outbreak. It is better to avoid conception for at least 8 weeks after exposure. The final call should be taken by the couple after proper counselling regarding the pros and cons of the condition. The health care provider should provide effective contraceptive for those opting not to conceive to prevent unintended pregnancy. Prevention of sexual transmission by correct use of condom should also be encouraged.⁶⁰⁻⁶²

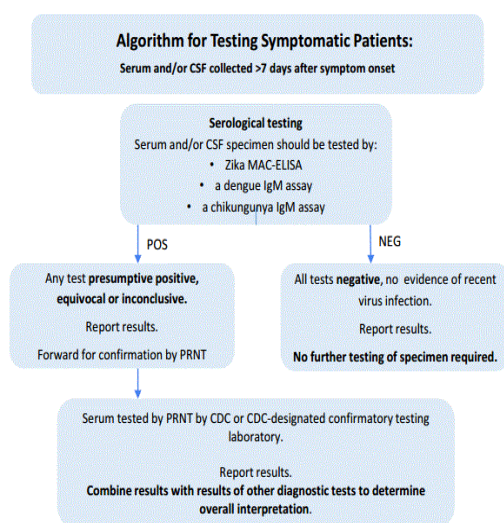


Figure 2: Algorithm for testing symptomatic patients.

Women with possible exposure to Zika virus who do not reside in an area with active Zika virus transmission

Asymptomatic women and men with history of exposure should not conceive for at least 8 weeks from exposure. They should be counselled about use of effective contraceptives to prevent unintended pregnancies. Additional information should also be provided regarding prevention of sexual transmission by condom. The virus may persist longer in semen for as long as two months.

The CDC took the known longest periods of sexual transmission and multiplied them by three to come up with this guideline.⁶⁰⁻⁶²

Pregnant women developing fever-like symptoms during or within 2 weeks of travel to areas with ZIKV transmission should be offered virological testing. Serial foetal ultrasound examinations should be performed every 3-4 weeks in these cases. Seropositive women with history of travel to affected areas should also be offered foetal USG and/or amniocentesis. Serum collected from the umbilical cord after delivery or from the neonate within 2 days of birth should be tested for RT-PCR, IgM and/or neutralizing antibodies against ZIKV. An affected child would need long term follow up.⁶³

TRAVEL RECOMMENDATIONS

The CDC notes that there was minimal likelihood for mosquito borne ZIKV transmission at elevations above 2000 meters. Accordingly, the CDC recommends that women postpone travel to areas <2000m above sea level with ongoing ZIKV transmission. Travel entirely limited to elevations >2000m are considered to pose minimal likelihood for ZIKV transmission by mosquito bites.²³

The MOHFW, India recommends deferral or cancellation of non-essential travel to affected countries. Pregnant women or women trying to become pregnant should defer/cancel their travel to these areas. At the same time, all travelers to the affected areas should follow strict mosquito protective measures especially during day time, including repellent creams, bed nets, clothing, and electronic mosquito repellents. Any traveler developing febrile illness within two weeks of return from an affected country should report to the nearest health facility.⁶⁴

TREATMENT

Prevention of the disease by strict mosquito control measures is most important as there is no vaccine, immunoglobulin or drug effective against Zika virus. Asymptomatic or uncomplicated infections do not require treatment. There is no specific antiviral agent directed at ZIKV at present. Mainstay of treatment is supportive.

- Arthralgias/fever: Acetaminophen may be used. Aspirin avoided due to risk of bleeding and Reye's syndrome. NSAIDs contra-indicated.
- Pruritus: Anti-histaminics
- Fluid loss: Adequate hydration.
- Neurological complications like Guillain-Barre syndrome need early use of intravenous immunoglobulin or plasmapheresis.

Rest, monitoring of vital signs, and watching for coagulopathy or multiorgan failure are important goals of care. Although rare, intensive care may be warranted for very sick patients. People infected with Zika,

chikungunya, or dengue virus should be protected from further mosquito exposure during the first few days of illness to prevent other mosquitoes from becoming infected and reduce the risk of local transmission.^{41,65-67}

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