## REVIEW ARTICLE

# Zika Virus: An Emerging Public Health Challenge

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**Abstract:**

Emerging infectious diseases comprise a substantial proportion of global morbidity and mortality. The world has been hit by Zika virus (ZIKV) after it was able to surmount an effective public health response for its control. ZIKV disease is an emerging mosquito-borne disease which occurred as large outbreaks in Yap since 2007, Polynesia in 2013 and Brazil in 2015. ZIKV infection in pregnant women has been observed to be associated with congenital microcephaly with neurological and autoimmune sequelae in general population of Brazil. The incubation period of ZIKV varies from few days to weeks. Only 20% of infected cases have symptoms like any other arboviral illness. ZIKV is diagnosed using RT-PCR (reverse transcriptase-polymerase chain reaction) and virus isolation from blood samples. The treatment comprises of relief of symptoms by conservative management with no specific vaccine being available. The prevention and control of ZIKV is based on reduction of vector density by Integrated Vector Management and personal protection measures. As per Indian scenario, Ministry of Health had issued guidelines based on effective surveillance, risk communication, laboratory and travel regulations. Approaches to such a potential global health security threat should be consistent, proactive, and should involve coordinated, multi-pronged, multilateral collaborative efforts since the concern is at the highest and immediate because of Global epidemic, Rio de Janeiro Olympic Games starting from Aug 5-21, 2016 and strong association with microcephaly. Most importantly the need of the hour is the development of vaccine for protection especially the young women who are in the reproductive age groups. The research for which is ongoing as far as the current situation of global epidemic response is concerned.

**Keywords:** Zika virus (ZIKV), congenital microcephaly, Integrated Vector Management (IVM)

## Introduction:

Infectious diseases keep emerging and re-emerging. They are, indeed, responsible for one-third of global mortality. Emerging infectious diseases are the ones whose incidence has increased recently or is expected to rise in the near future. On the other hand, re-emerging diseases includes previously unknown or known diseases appearing and increasing abruptly in new geographical regions. It also comprises of diseases that are re-emerging after a quiescent period. The changing nature of our interactions with each other and with environment modifies the dynamics of disease epidemiology and exposes us to new threats. It is, therefore, imperative that while efforts for the prevention and control of communicable diseases must continue persistently, a regular awareness must be maintained on the behaviour of emerging and re-emerging infectious diseases.

The world has been on tenterhooks ever since the extent of Ebola crisis became known in 2016. As a result, the global health community was able to surmount an effective emergency response to control the spread of Ebola virus in West Africa. Subsequently, the world has been hit by another public health challenge with the spread of Zika virus (ZKV) in South and Central America.

ZIKV is an emerging mosquito-borne pathogen first identified in 1952 [1], after being isolated from sentinel rhesus macaque monkey in 1947 by Alexander Haddow and George Dick. The same virus was also isolated from a pool of *Aedes africanus* mosquitoes in 1948 from the Zika forest in Uganda. Since it was first reported, isolated cases were observed in Pakistan, Malaysia and Indonesia between 1977 and 1978 but the disease weaned off without any major public health interventions. The first large outbreak of ZIKV occurred in 2007 on Yap Island in the Federated States of Micronesia [2]. In October 2013, ZIKV was detected in French Polynesia affecting~10% of the total population [3]. In May 2015, ZIKV was observed as the causative organism for a dengue like disease in northern and eastern parts of Brazil. Subsequently, outbreaks occurred in many countries including Barbados, Bolivia, Brazil, Cape Verde, Chile, Colombia, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Haiti, Honduras, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin and Guyana, Venezuela, as well as Samoa in the South Pacific [4-7].

As per WHO, 23 countries in the Americas have reported cases as of 28th January 2016. Due to widespread international travel, there is risk of spread of outbreak across the world. Cases are being reported among travellers from other continents including Europe. The situation becomes more concerned and tense due to forecoming **2016 Summer Olympics**, the **Rio 2016**, which is a major international multi-sportic event that will take place in Rio de Janeiro, Brazil from August 5 to August 21, 2016. Many countries are participating in a record number of sports with more than 10,500 athletes from 206 National Olympic committees (NOCs) across the world.

**Agent ZIKAV**

Zika virus is an 11-kb single-stranded, positive sense Ribonucleic Acid (RNA) virus from the Flaviviridae family. Two major lineages, African and Asian, have been identified through phylogenetic analyses [8-9].

ZIKV disease is an evolving viral disease transmitted through the bite of an infected Aedes mosquito, that also transmits dengue, chikungunya and yellow fever [10]. Non-vector transmission includes potential modes like sexual transmission and monkey bite. Mother to child transmission during pregnancy or during delivery is also a potential route of spread of ZIKV. The incubation period of ZIKV disease is not clear, but is likely to be of few days. About 20% people infected with Zika virus are symptomatic. Symptoms typically begin 2 to 7 days after being bitten by an infected mosquito. The symptoms are similar to other arboviral diseases like dengue and include fever, malaise, headache, skin rashes, conjunctivitis, muscle and joint pain. The symptoms are usually mild and last for 2-7 days [8]. Zika virus infection in pregnant women has been observed to be associated with congenital microcephaly, with Brazil reporting maximum number of such cases.

ZIKV is diagnosed using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and virus isolation from blood samples. Its diagnosis by serology can be challenging as the virus can cross-react with other flaviviruses such as Dengue, West Nile and Yellow fever (WHO) [10].

Globally, ZIKV has been highly suspected to be associated with intrauterine transmission, newborn microcephaly as well as Guillan Barre syndrome [11-13].

Due to a rapid increase in the incidence of microcephaly, the United States Centers for Disease Control and Prevention (CDC) advised pregnant women to consider postponing travel to areas with ongoing ZIKV transmission [12-14].

According to the World Health Organization (WHO), ZIKV spread was considered to be of high concern [14]. This was followed by the declaration of ZIKV spread as Public Health Emergency of International Concern (PHEIC) on February 1, 2016 [15]. The possibility of ZIKV adaptation to life cycles based in urban areas coupled with human amplification via *A. aegypti* and other Stegomyia subgenus mosquito vectors poses a significant local and global health security risk [15]. Hence, for effective ZIKV containment and control, an effective public health surveillance system should be put into place by global health authorities. Such systems can be derived from arboviral diseases like dengue, chikungunya and other viral illnesses [17-20].

As per the recommendations of PAHO/WHO, (20-21) ZIKV surveillance system should comprise of two-pronged strategy:

(1) Determining whether the virus has originated or has been introduced to an area, and,

(2) Monitoring ZIKV cases for clinical and neurological progression and/or autoimmune sequelae [18-22].

Considering a wide circulation of *Aedes* mosquito in the America, Asia and Africa and huge number of migrants, recommendations for public health authorities in countries without autochthonous transmission of ZIKV include: (1) ZIKV testing of patients presenting with fever and arthralgia of unknown etiology, provided other arboviral infections are ruled out (2) Epidemiological mapping of clusters of febrile syndrome of unknown etiology involving rash, provided dengue, chikungunya, measles, rubella, and parvovirus B19 been ruled out; and (3) Augmenting early detection capabilities for identifying viral strains in circulation to enhance the outbreak response [9,22-23].

The countries with autochthonous transmission of ZIKV should closely monitor the observed temporal trends and geographical spread of the virus with the impact of viral spread on public health. Moreover, health systems for consistent assessment of pertinent risk factors, congenital anomalies, clinical severity and potential neurological and autoimmune complications [22-26].

**Prevention:**

The prevention and control of ZIKV should be based on reduction of vector density by Integrated Vector Management and personal protection measures [27-29].

Since *A. aegypti* uses a wide range of man-made and natural larval habitats, it is critical to consistently and continuously promote Integrated Vector Management (IVM) which aims to improve the cost-effectiveness and overall sustainability of the strategy [28]. Environmental management encompasses water supply management, acceptable maintenance and cleaning of water storage systems, rigorous solid waste management approaches and modifications

in human behavior and habitation (maintenance of buildings and structures such as installing mosquito screens on windows and doors and mosquito-proofing of storage containers) [10,21-22,30-32].

On the other hand, personal prevention measures are crucial in the setting of a known ZIKV outbreak. The infected patients must minimize any probable contact with the vector in order to prevent the spread of ZIKV. To prevent viral spread, a ZIKV-infected person should avoid being bitten by the Aedes mosquitoes during the 1 st week of illness. The community must be well informed about the risk of communicability and should be encouraged to use insecticide treated bed nets,clothing, repellants, coils and mosquito repellant creams. Insect repellants like N, N-diethyl-3-methylbenzamide, 3-(N-butyl-N-acetyl) amino propionic acid ethyl-ester or icaridin have been approved by WHO [33]. Pregnant women living or traveling to areas of ZIKV transmission are recommended to avoid travel to regions where ZIKV spread is imminent. They should also avoid the mosquito bites using bed-nets and proper clothing. Due to suspected reports of ZIKV transmission via sexual intercourse, parallel patient education must be provided.

The introduction of bacterial species *Wolbachia* into *A. Aegypti* mosquitoes, by virtue of "*Wolbachia* effect", has been successful for dengue virus and therefore, may also be effective for ZIKV [34-36].

A relatively new progress in ZIKV research is the use of Genetically Modified (GM) mosquitoes, especially *A. aegypti* OX513A that has been observed as highly effective against dengue, and thus hopefully against ZIKV [37]. Despite the prospective benefits of GM of mosquitoes,

scientific organization should be aware of the fact that transgenic technologies involve a number of environmental and safety concerns.

WHO has set up interim guidance on 25 Feb 2016 for those countries who are affected with ZIKAV and have been produced under emergency procedures and will remain valid until August 2016, or until recommendations informed by a systematic review of evidence are produced. Detailed recommendations can be read under referenced documents quoted in below paras :-

**(a) WHO Interim guidance on Breastfeeding in the context of Zika virus**

Based upon the facts, that currently no documented reports of Zika virus is being transmitted to infants through breastfeeding and in light of available evidence, WHO recommends the benefits of breastfeeding for the infant and mother outweigh any potential risk of Zika virus transmission through breast milk [37]. Therefore current WHO breastfeeding recommendations remain valid in the current context of Zika virus transmission.

**(b) WHO Interim guidance on Identification and management of Guillain-Barré syndrome in the context of Zika virus**

WHO recommends that Health care providers should be trained in the recognition, evaluation and management of patients with GBS [38]. Specifically, neurological examination skills and training in the acute management of GBS should be strengthened and the Brighton criteria should be used for the case definition of GBS. The risk of death in patients with GBS is associated with complications including respiratory failure, cardiac arrhythmias, and blood clots. Optimal

supportive care including frequent neurological assessments, vital sign and respiratory function monitoring should be provided to patients with GBS and Intravenous immunoglobulin therapy or therapeutic plasma exchange should be provided to GBS patients who are unable to walk or who have rapidly progressive symptoms.

**( c ) WHO Interim guidance on Assessment of infants with microcephaly in the context of Zika virus**

As per WHO [39], neonates with a head circumference of less than -2 SD i.e. more than 2 standard deviations below the mean should be considered to have microcephaly. Neonates with a head circumference less than -3 SD i.e. more than 3 standard deviations below the mean should be considered to have severe microcephaly. While Neonates with a head circumference between -2 SD and -3 SD should have a clinical assessment and subsequent regular follow up during infancy. A proportion of these infants will have normal neurological development. Neonates with a head circumference less than -3 SD should have neuroimaging (CT scan or MRI. Ultrasound may perhaps be performed if the fontanelle is of a sufficient size) to detect structural brain malformations. In addition, they should also have a clinical assessment and subsequent regular follow-up during infancy. Neonates with microcephaly and structural brain abnormalities diagnosed by neuroimaging, or neurological or developmental abnormalities should be considered to have microcephaly with a brain abnormality.

**Zika virus: Indian Context**

Due to extensive global travel and migration of population, Indian subcontinent is at an imminent risk of ZIKV spread. Hence, extensive preparedness for dealing with this epidemic is therefore crucial. As India harbors the vector mosquito, *Aedes aegyptii* and *Aedes albopictus*, there is a higher chance of disease transmission. Moreover, availability of several Viral and Rickettsial Disease Laboratories (VRDLs) favours the training of laboratory staff and helping in establishing a diagnostic facility for ZIKV, with National Institute of Virology being the nodal apex centre.

In the light of current disease trends, the Directorate General of Health Services, Ministry of Health and Family Welfare advises enhanced surveillance that encompasses community based surveillance based on Integrated Disease Surveillance Project (IDSP) and collaboration with Maternal and Child Health division of National Health Mission. It also directs Airport and Port Health Organizations to display signages on Zika virus disease for travelers and reporting to immigration authorities in case of febrile illness. It also directs the latter to strictly comply with aircraft disinfection guidelines. In accordance with IDSP, it also envisages formation of rapid response teams for early investigation of suspected outbreaks. National Centre for Disease Control (NCDC) and National Institute of Virology (NIV) have been designated as nodal agencies for laboratory diagnosis of ZIKV. RT-PCR is the gold standard test for diagnosis of ZIKV. Risk communication remains the cornerstone where all the concerned stakeholders are made aware of ZIKV disease and its grave outcomes. In Indian scenario, enhanced vector management of arboviral diseases along with

extensive vector surveillance is the methodology of choice for prevention and control of ZIKV. The communication and coordination with international agencies will definitely prove helpful in controlling the disease globally. Travel guidelines as recommended by WHO had been issued for Indian population as well. The outbreak situation will be monitored by Joint Monitoring Group under Directorate General of Health Services (DGHS).

Vaccination is the most effective community based intervention which holds definite potential for prevention and control of the disease. As vaccines for other arboviral diseases like dengue, Japanese Encephalitis (JE), yellow fever had been crucial in generating a global response, WHO suggests to develop inactivated ZIKV vaccines and other non-live vaccines, which are safe to use in pregnant women and those of childbearing age [41-43].

**Global response**

Currently there are 15 new countries and territories in the Americas where ZIKV has been detected from November 2015 to February 2016. In 2014, Ebola was designated a PHEIC (44). The highly suspected association between ZIKV and newborn microcephaly and the resultant public outcry has certainly been important factors in the recent WHO decision to declare PHEIC [14]. Creation of national and/or regional emergency ethics review boards should be aggressively pursued. Such boards need to be given sufficient resources so as to eliminate any undue delays pertaining to the "drug - trial - intervention" evaluation, revision, and approval process. Efforts should be made by the international community to create ethics review committees in every country. If this is not immediately feasible, an effort to

create regional ethics review committees encompassing multiple countries should be undertaken [16].

The full extent of the ZIKV outbreak has yet to be determined. Regional mobilization of economic and medical resources is currently taking place. Previous experiences of the international public health community with Severe Acute Respiratory Syndrome (SARS) and Ebola will hopefully facilitate an appropriate and healthy concern in the medical and public health communities, which should be sufficient to trigger a heightened awareness and lead to quicker and more effective channeling of resources needed to combat the ZIKV outbreak at all key stakeholder levels (e.g., government, industry, health care institutions, and research [44-45].

**Conclusion:**

Following the declaration of PHEIC, the experiences of the international public health community with SARS and Ebola should create an appropriate and healthy tension in both medical and public health communities to trigger a heightened awareness and targeted investment in research infrastructure. Approaches to such a potential global health security threat should be consistent, proactive, and should involve coordinated, multi-pronged, multilateral collaborative efforts since the concern is at the highest and immediate because of Global epidemic, Rio de Janeiro Olympic Games starting from Aug 5-21, 2016 and strong association with microcephaly. Most importantly the need of the hour is the development of vaccine for protection especially the young women who are in the reproductive age groups.

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