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REVIEW

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Zika virus: A public health threat

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The resurgence of Zika virus as public health emergency of an international concern with increased incidence of microcephaly has drawn attention of scientific community for its detailed understanding with regard to virus evolution, epidemiology, geographical spread, pathogenesis, etc. The scope of the present review is to discuss the detailed updated information in respect of Zika virus evolution since its inception.

KEYWORDS
emergence, microcephaly, phylogeny, vector, zika virus

1 | INTRODUCTION

Zika virus is a flavivirus that is associated with zika febrile illness. The virus was first identified in 1952 in humans from Uganda and the United Republic of Tanzania. Zika virus disease outbreaks after that recorded in Africa, the Americas, Asia, and the Pacific. From the 1960s to 1980s, human infections were found across Africa and Asia, typically accompanied by mild illness.[1] The highest peak of Zika infection was reported from Yap Island in 2007.[2] In July 2015 association of Zika virus infection with Guillain-Barré syndrome was reported from Brazil. Similarly first association of Zika virus infection and microcephaly was reported in October 2015.[3,4,5]

2 | THE VIRUS

Zikavirus (ZIKV) is an arbovirus belong to family *Flaviviridae*, genus *Flavivirus*. The name of the virus came from a forest in Uganda. The ZIKV is found to belong the family harbor closely related viruses like Yellow Fever, West Nile, St Louis Encephalitis, Dengue, and Japanese Encephalitis viruses, etc. Zika virus is an emerging and current global public health important agent already affected more than 30 countries in Asia, Africa and America. Initially ZIKV was found to circulating in African and Southeast Asian countries in 20th century. Further global evolution access various viral migration events led to spread to other continents including Oceania (2007), French Polynesia (2013), and America (2014). ZIKV is a positive sense RNA virus of 10 794 nucleotide genomic length containing single ORF flanked with 3419 amino acids.[6] The ORF of viral genome encodes a polyprotein precursor which is further responsible for formation of three structural proteins (capsid [C], pre-membrane [prM], and envelope [E]) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Zika virus is maintained in a sylvatic cycle naturally. Zoonotic cycle is maintained between non-human primates (*Aedes* mainly) and mosquitoes.[7]

For the first time zika virus isolated in 1948 from mosquito (*Ae. africanus*).[8,9] After that, isolation from different mosquito pools from species that is commonly present in nature like: *Ae. africanus*, *Aedes furcifer*, *Aedes luteocephalus*, *Aedes vittatus*, *Aedes dalzieli*, *Aedes hirsutus*, *Aedes metalicus*, *Aedes taylori*, *Aedes aegypti*, *Aedes unilineatus*, *Anopheles coustani*, *Culex perfuscus*, and *Mansonia uniformis* in Africa was reported. In a retrospective study 2007-2010 from Gabon sera samples from patients with febrile illness and mosquito pools collected reported presence of ZIKV RNA in *Aedes albopictus* screening performed through molecular techniques.[10,11]

In Asia, further evidence incriminated *Ae. aegypti* as the urban vector in a mosquito pool collected in Malaysia after indentification of ZIKV; furthermore, in Indonesia, the peak in human ZIKV infections coincided with a peak in the *Ae. aegypti* population.[12,13] The virus transmission takes place to humans during a blood meal from life-long infected female mosquitoes. Presence of zika virus reported in male mosquito pool reported suggest vertical transmission may also occur. Research conducted in this area suggested that vertical transmission may have a potential for better survival of virus during adverse condition. It was also reported that nine other flaviviruses can vertical transmit the viruses.[14] *Aedes hensilli* was implicated as the most potential vector during the Yap Island epidemic due its predominant presence in the area, although ZIKV has never been isolated from this mosquito species.[15] The former species was incriminated as the urban

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ZIKV vector throughout the 2013 epidemics because *Ae. aegypti* and *Ae polynesiensis* are highly prevalent in French Polynesia, by association.[16]

3 | EPIDEMIOLOGY

Zika virus (ZIKV) firstly reported in 1947 in Uganda identified from rhesus monkeys during yellow fever surveillance programme.[17] Further first human cases were reported from Uganda and Tanzania in 1952. After that, sporadic cases were reported from different parts of Asian and African continents. But association of ZIKV with a major epidemic were again observed in 2007 (French Polynesia) and 2013/2014(New Caledonia).[18,19]

Attempts were also made for ZIKV isolation from an *Aedes* (*Stegomyia*) *africanus* mosquito pool in 1948 in Uganda. Further serological and entomological investigations revealed ZIKV widespread circulation among continents. The reports available for virus detection shows circulation of ZIKV in many countries of Africa and Asia (Thailand, Malaysia, Uganda, Nigeria, Indonesia, Senegal, and Cote d'Ivoire).[20–23]

In 2007 for the first time outside Africa and Asia ZIKV association with an outbreak of dengue like illness on Yap Island, Micronesia was reported.[2,24,25] Further genetic characterization of this outbreak suggested emergence of this strain of ZIKV from Southeast Asia. Subsequently virus was also reported from Cambodia (2010), Philippines (2012), Thailand (2012), Pacific Islands (2013).[26] In 2013 first time ZIKV association with severe complications (neurological/autoimmune complications) was observed. Imported case of ZIKV infection were reported in 2013 from Canada, Europe, the United States, Japan, Australia, Italy, and Norway.[27]

Autochthonous transmission of ZIKV was confirmed in early 2014, from Chile, Easter Island.[28,29] French Polynesian strains of ZIKV revealed as an etiology during phylogenetic analysis.[30] Autochthonous transmission of ZIKV was reported in early 2015, from northeast regions of Brazil, which was further expanded to 22 states in 2016.[6] Along with dengue like illness, ZIKV association with foetal malformations and death was observed for the first time. Brazilian health authorities also reported more than 5600 suspected cases of microcephaly in newborns and 120 deaths due to congenital malformations. Autochthonous circulation of ZIKV in 30 countries and territories in the Americas also reported up to February 2016.

This is the largest ZIKV outbreak ever recorded and also a more than twenty times increase of ZIKV cases over the past years.[31] Zika virus is a member of Spondweni serocomplex, and two main virus lineages African and Asian revealed during phylogenetic analyses.[32,33] Phylogenetic studies carried out in recent studies have shown emergence of Asian lineage ZIKV in the Pacific islands and South America. Recent molecular evolution analysis have shown virus have undergone several natural selection phases, rarely seen among members of genus *Flavivirus*.[34,35]

To understand the evolutionary dynamics of zika virus molecular epidemiological analysis carried out. All available complete genome sequences of ZIKV strains as of 10th June 2016 were retrieved from GenBank. Multiple sequence alignment and phylogenetic analysis were performed using MEGA 6 and a maximum likelihood tree was constructed by Tamura-Nei model. The results demonstrated that all the 2015 ZIKV isolates in American and Asian countries including Brazil, Suriname, Puerto Rico, Guatemala, and China clustered closely within the Asian lineage, forming a new American clade (Fig. 1).

4 | GEOGRAPHIC DISTRIBUTION

Different virological studies, and seroprevalence surveys, further led to identification of virus in Asia (Cambodia, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, Thailand, and Vietnam) Africa (Uganda, Nigeria, Senegal, Egypt, Tanzania, Sierra Leone, Gabon, Central African Republic, Ivory Coast, etc.) and in Oceania, in the Pacific (Cook islands, French Polynasia, Micronesia/Yap, and New Caledonia).[36]

Recently, a large increase was observed in the circulation of ZIKV worldwide, which initially was endemic only in Africa and Asia. Cases have been reported in countries of Europe, Oceania, and the Americas, particularly in Latin America where it is rapidly spreading to new areas (Fig. 2). From places with established autochthonous transmission, such as Brazil, viremic travellers have the capacity to introduce ZIKV into new countries, where *Aedes* mosquitoes would become infected

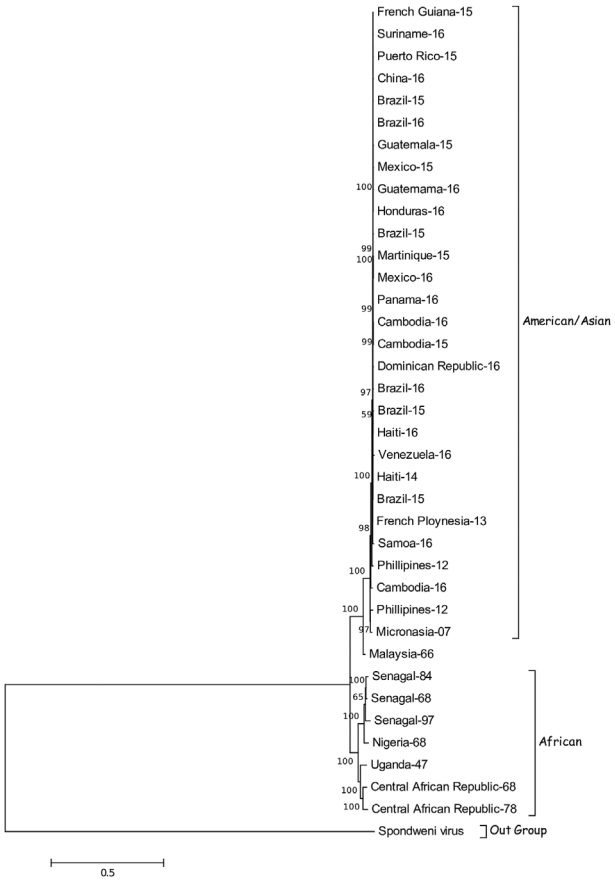

FIGURE 1 Maximum likelihood-based phylogenetic analysis for globally circulating Zikavirus. Circulating zikavirus was found to belong American cluster

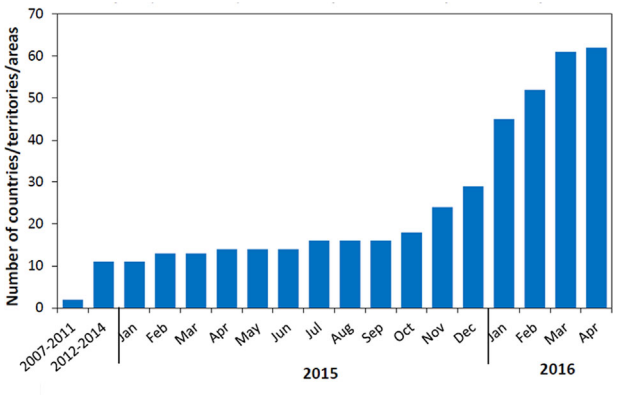

FIGURE 2 Zikavirus cases from 2007 to 2016 Cases have been reported in countries of the Americas, Oceania, and Europe, it is spread to new areas

and perpetuate local transmission cycles. In South America, Brazil had large concentration of cases of Zika, especially in the Northeast region, and serious complications occurred simultaneously with the outbreak of this arbovirus.

5 | CLINICAL FEATURES

Unlike in Dengue fever, zika virus fever is more sporadic and frequently milder. As Clinical symptoms of Zika fever (ZF) easily be confused with dengue fever (DF), Therefore, mild manifestation of fever and symptoms in a patient presenting similar to dengue fever (ie, rash, headache, musculo-skeletal complaints, conjunctivitis) should raise the concern of a ZIKV infection.

The clinical presentation of zika virus infected patients includes a low grade fever, headache, conjunctivitis, a maculopapular rash, retro-orbital pain, arthralgias, and/or myalgias. Symptom duration is generally 2-7 days, but the rash and arthralgias may last 2 weeks or longer. Peripheral edema, conjunctivitis, and are reported to be more common in ZIKV infections compared to DENV and CHIKV. A total of 80% of patients with a ZIKV infection remains asymptomatic or with mild clinical manifestations.[37]

Zika virus disease and an increased association of Guillain-Barré syndrome and autoimmune neurologic disorders has been reported from French Polynesia and Brazil.[38] An increased number of infants born with microcephaly and association with Zika virus have been reported. Imaging studies of these patients have demonstrated intracranial calcifications.

6 | MODE OF TRANSMISSION

The source of zika virus in transmission to humans is the bite of an infected *Aedes* mosquito. The virus life cycle is maintained between mosquito vector and a human as a reservoir host.

Rare modes transmission includes blood transfusion or sexual intercourse.[39] Zika virus presence was also detected in semen, saliva, breast milk, and urine.[40,41] Zika virus maternal transmission was reported in recent studies either through an infected mother to her fetus or newborn during pregnancy or at the time of delivery.[42,43] However, transmission of Zika virus through breast milk is not reported till now.

Transmission through laboratory exposure have also been reported. However, Zika virus presence in breast milk was reported, yet virus isolation from the same was unsuccessful.[44]

7 | SEXUAL TRANSMISSION

Till now multiple cases of zika virus transmission through sexual contact have been reported. The transmission from male to female through human semen was reported. In case study of infected male to his partner after sexual intercourse who returned from Senegal to US.[25] Both were found positive for Zika virus RNA. In an another study a confirmed zika virus infection was detected in a female who had sexual intercourses 13-14 day before from a positive confirmed zika infected male returned from Carribean.[45,46] Three other cases also reported consecutive findings by same authors.[25,42,44] In July 2016 first female to male sexual transmission case reported.[47,48]

Zika virus RNA persistence in semen was reported up to 188 days, after onset of symptoms. This was shown in a recent study even after the patient recovery.[49,50] This prolonged persistence in semen warrant the high potential of sexual transmission of disease.[25,51,52,53]

8 | PATHOGENESIS

The studies have shown that mosquito-borne flaviviruses replicate initially in dendritic cells. The available information in this area have shown presence of Zika virus antigens in infected cell nuclei.[54,55] The infectious Zika virus detection in human blood was reported as early as the day from onset of symptoms to as late day 11.[56] The study conducted have also shown the virus presence in neurons and glial cells, hence showing the ability to pass blood brain barrier. Along with this the presence of virus in intracytoplasmic inclusions (generally known as virus factories), is as virus hijacking the process of autophagy for their own replication.[56] Researchers also suggested virus involved in amplification of centrosome is a cause of neurodisorder anamolies due to involvement of autophagy proteins and stability of centrosomes.[57] Experiments conducted in mice, have shown increased numbers of centrosomes which causes mitosis delay, an increase in apoptosis, disorientation of neural stem cells, differentiation of premature neurons, and decrease in the number of progenitor cells—all of this events further lead to microcephaly.[46,52]

9 | MICROCEPHALY AND BIRTH DEFECTS

Microcephaly is a condition of neonate's head size smaller than expected healthy one. Although detection of congenital microcephaly is possible prenatally, but most commonly it is detected after birth.

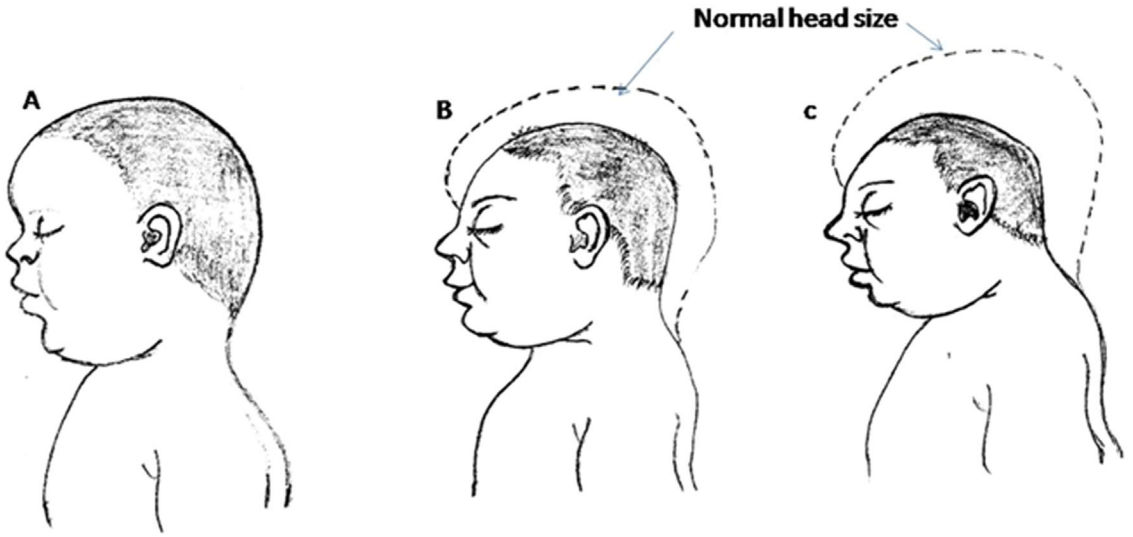

FIGURE 3 Zikavirus-induced microcephaly showing difference in head size. A head circumference difference than normal comes under microcephaly

Microcephaly is clinically a condition where circumference of head is three or more standard deviations below the mean (Fig. 3). Severe microcephaly has been reported in Brazil due to ZIKV infections.[58]

This presence of maternal-fetal transmission is a unique feature of zika virus infection as of other flaviviruses (ie, Japanese Encephalitis, Dengue, Yellow Fever virus, and West Nile virus) where its very rarely reported; the available reports have shown any association with congenital defects. This is a very important differential diagnosis criteria for ZIKV detection.

A recent report highlighted the differential development response of primary human fetal brain derived stem cells due to zika virus infection.[59]

Microcephalic children's generally shown symptoms like seizures, partial, or total impairment in vision or hearing, cognitive impairment. These manifestations can vary depending on the disease severity.

World Health Organization confirmed human transmission of Zika virus in May 2015 from Brazil.[60] By the end of 2015 virus spread was reported throughout the country; estimated cases between 440 000 and 1 300 000 due to disease. Increased number in cases from microcephaly of newborn more than 3500 case was also reported in October 2015 by Brazilian health ministry.

10 | ZIKV RISK DURING PREGNANCY

Zika virus infection can occur in any trimester of pregnancy and the infected women does not show any specific symptoms for the disease. Researchers also not found any susceptibility variance among the pregnant one for the virus.

It has been observed the transmission of zika virus through placenta throughout the pregnancy. The severe complications include microcephaly, brain atrophy, ventricular enlargement, and intracranial calcifications have been reported in neonates who have tested positive for Zika virus infection. Zika virus RNA was also detected in of fetal losses has shown there association with brain abnormalities of neonates.

The laboratory-confirmed cases of Zika virus infection during pregnancy tested by a amniocentesis followed by Zika virus RNA detection by RT-PCR after 15 weeks of gestation. Maternal Zika virus disease, generally monitored through serial ultrasound examinations of fetal anatomy and growth of fetus in every 3-4 weeks. In case of congenital Zika virus infections, delivery under well equipped facility is recommended.[61] Amniotic fluid have also shown the presence of viral RNA by molecular analysis.[5] The research conducted have shown fetal loss, where virus was detected from fetal and placental tissues by molecular and histochemical localization.[62]

11 | DIAGNOSIS

As of disease consequences a generalized disease symtoms as of other flaviviruses led to confusion.[36] In main endemic areas have more concern about misdiagnosis; therefore, the differential laboratory diagnosis is very much essential for appropriate health care. The diagnosis of ZIKV is based on clinical disease symptoms, their correlation with epidemiological details like presence of vector population and disease prevalence in the region and also through molecular or serological analysis in laboratory.

Zika virus laboratory diagnosis includes virus propagation in cell culture, viral nucleic acid detection by rapid and real time-based molecular assays like qRT-PCR, LAMP, genome sequencing. Similarly a battery of assay performed for detection of viral antigen and, antibody will give better clearance. The choice of method depends on the type of sample, samples collection time, the type of laboratory facilities and expertise available.

Sample collection is also an important consideration during disease diagnosis of zika virus illness. The sample collected immediately after onset of symptoms in the first few days after the onset of symptoms, a test either virus culture or molecular rapid diagnostic assays should perform.

The virus isolation in cell culture includes (use of mosquito or mammalian cell lines), or intracerebral inoculation in newborn suckling mice also be performed. Due to limitations of, virus isolation methods that is specialized laboratories are required and also these methods are time consuming and need expertise. Viral RNA, is generally detected through molecular techniques, such as conventional or rapid real-time RT-PCR.

Zika virus diagnosis is generally performed by using these molecular assays, particularly because of the extensive antigenic cross-reactivity between *flaviviruses*. Serological investigation by presence of IgM and IgG antibody based on plate ELISA/ICT generally performed for zikavirus antibody detection. Zika virus antigen presence in placenta and umbilical cord tissues detected by Immunohistological analysis. The limitations of these serological platform is of interpretations of false positive signals due to cross-reactivity with other *flaviviruses*.

It was observed with extensive cross-reactivity with presence of other flavivirus infections. Similarly in case of Plaque reduction and neutralization assay, which has greater specificity, some previous infection carrying persons have shown fourfold or higher rise in neutralising antibody titres.[63] This type of cross reactivity also have been observed in a experiment conducted for zika virus infection previously vaccinated against Yellow Fever virus. This rate of cross-reactivity with other *flaviviruses* is the reason for need of a differential diagnostic assays.

WHO-CDC has recently come up with an ELISA technique to detect specific anti-Zika IgM during the epidemic in Yap, in 2007. However, the limitation again in this case is the rate of very low antibody titre during early phase of infection may lead to misdiagnosis of samples. Till date no commercial kit is available for the detection of antibodies specifically related to ZIKV.

Therefore, the molecular detection-based laboratory diagnosis of acute ZIKV infection is only method of choice of rapid detection and characterization ZIKV in patient specimens. CDC has developed RT-PCR as well one-step real-time RTPCR targeted against ZIKV pre-membrane (prM), NS5, and Envelope (E) genes.[64,65]

A recent advance in molecular assay for differential diagnosis of zika virus is the development of taqman real time RT-PCR based multiplex assay for rapid identification and simultaneous detection of three flavivirus commonly misdiagnosed with zika virus, that is, dengue and Chikungunya.[66]

12 | TREATMENT AND PREVENTION

As of the common symptoms with other hemorrhagic fevers no specific treatment for ZIKV infection is available. Generally rest, intake of plenty fluids to prevent rehydration, and administration of acetaminophen (paracetamol) or dipyrone to control fever and for pain relief is suggested. Currently no vaccines are available as to prevent Zika virus infection. Prevention measures includes control of vector population using vector management and control plans. This includes use of insecticide personal care includes use of personal protection against the mosquito bites, like including cloths to cover the full body or the maximum area, also the use of mosquito repellents. Other measures, using the net on doors and windows and also the elimination of potential breeding sites by removing most of the stored rain water near by the home area, this would further help to reduce human contacts with the disease vector. In the case of pregnant women, some recommendations have been made: the 20 evaluation for symptoms of ZIKV disease; the laboratorial diagnosis during the prenatal care; foetus evaluation for brain anomalies, includes microcephaly and intracranial calcifications.

Sexual transmission risk can be minimized by avoiding sexual contact during period or use of appropriate protection during sexual contacts.

13 | SUMMARY AND FUTURE PERSPECTIVE

ZIKV is a *flavivirus* belong to Spondweni serocomplex and transmitted through mosquito vector. After firstly reporting of virus it was found endemic in Asia and Africa until 2007. In 2007 an emergence of ZIKV was reported first time outside its known endemic boundaries and caused an epidemic on Yap island.[67,68] Still the infection caused by virus was reported with mild human disease. In 2015 a sudden emergence of ZIKV in Brazil was reported and for the first time virus association was observed with disease severity, that is, potential to cause neurological complications (ie, Guillain-Barré syndrome and microcephaly). In 2015, ZIKV outbreak in America fist time reported many fold increase of microcephaly cases in newborns, and the retrospective study have shown etiology of the French Polynesia strains. WHO has declared a public health emergency of international concern, and women were warned to avoid pregnancy in the most affected regions. Another point of concern is that ZIKV infections were found usually asymptomatic, and non-specific symptoms such as fever and rash, similar to other arboviral infections mainly Dengue, Chikungunya. So it is very difficult to characterize the disease based on symptoms until any severe complication appears. Molecular evolution-based phylogenetic analysis revealed that the circulating viruses are changed a lot from 1947 to 2015. Which has played a major role in disease severity in 2015.

The presence of vectors (mosquitoes of the *Aedes* genus) has a high potential for spreading across the globe. This in depth study at viral genome level, vector host interactions, and diagnostic and therapeutic interventions should be focused in near future.

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