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Review Article

Zika Virus: A Literature Review

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Abstract: Zika virus is a mosquito-borne arbovirus first isolated in the Zika forest in 1947. After a period of obscurity, it emerged in 2007 with an outbreak in the Yap Island, Federated States of Micronesia followed by another outbreak in 2013 in French Polynesia. During the French Polynesian outbreak, Zika virus was found to be associated with neurological complications like Guillain-Barre Syndrome. The current epidemic in Brazil also demonstrated an increased incidence of congenital malformations and neurological complications forcing the World Health Organization to declare Zika fever as a Public Health Emergency of International Concern (PHEIC). This review attempts to compile the current knowledge available on the virology, clinical features, complications, diagnosis, treatment and control of Zika virus infection.
Keywords: Zika virus, Arbovirus, Flavivirus, Guillain-Barre Syndrome, Microcephaly, *Aedes aegypti*

INTRODUCTION

Zika virus, an emerging arthropod borne virus, was first isolated incidentally from the serum of a sentinel febrile rhesus monkey which was held captive on wooden platforms in the canopy of forested areas in April 1947, in a study originally planned to recover Yellow Fever virus in the Zika forest of Entebbe area in Uganda. It is named after the Zika forest. Subsequently in January 1948, the virus was isolated from a batch of *Aedes africanus* mosquitoes raising the suspicion of the probable role of *Aedes africanus* mosquito in the transmission of Zika virus [1].

The evidence for human infection with Zika virus was put forth by Smithburn *et al*., when they demonstrated neutralizing antibodies to Zika virus in the sera of humans from East Africa in 1952 [2].The virus was first isolated from a human case in 1952 by Macnamara when he was investigating an outbreak of suspected Yellow Fever in Eastern Nigeria [3].

Subsequently the virus remained relatively quiescent for more than half a century with only a few sporadic cases documented [4]. During this period serological evidence of human infection have been demonstrated from various African countries and also from parts of Asia including Malaysia, the Philippines, Thailand, Vietnam, Indonesia and others [5].

Zika virus came to limelight in April 2007 when the first documented outbreak of Zika fever occurred in Yap Island, Federated States of Micronesia in Southwestern Pacific Ocean infecting approximately three quarters of Yap residents with more than 900 cases of illness attributed to Zika virus [4]. This outbreak indicated that Zika virus was an emerging viral disease with epidemic potential.

In October 2013, it emerged again with an outbreak in French Polynesia, South pacific and this was dubbed as the biggest outbreak till then, with an estimated 28,000 Zika virus infections affecting 11% of the population and 396 laboratory confirmed cases [6-8]. This was followed by outbreaks in the Pacific Islands of New Caledonia, Cook Island and first identified in America in Easter Island [9, 10]. The first autochthonous case of Zika fever in Brazil was reported in May 2015 [11].

Zika fever was considered a mild self-limiting viral infection until increasing incidence of neurological complications like Guillain-Barre Syndrome (GBS) and congenital malformations in infants of infected pregnant women were reported in French Polynesia and America [12].

As of 20th July 2016, 65 countries and territories have reported mosquito borne transmission of Zika virus with 13 countries and territories reporting microcephaly and other CNS malformations potentially associated with congenital Zika virus infection and 15 countries and territories reporting increased incidence of Guillain-Barre Syndrome [13].

Based on the advice of the Emergency Committee of the International Health Regulations, the Director General of World Health Organization declared, on 1st of February 2016, that the reported increase in microcephaly and other neurological disorders associated with Zika fever was a Public Health Emergency of International Concern (PHEIC) [14].

VIROLOGY

Zika virus virion is an enveloped, icosahedral particle with a single stranded, non-segmented, positive sense Ribonucleic Acid (RNA) genome belonging to the family *Flaviviridae*, genus *Flavivirus* and is a member of the Spondweni virus group, closely related to Dengue virus [15-19]. Zika virus RNA is 10794kb in length with two flanking non-coding regions (5' and 3' NCR) and a single long open reading frame consisting of a capsid (C), precursor of membrane (prM), envelope (E) and seven non-structural proteins (NS) [20]. Zika virus strains belong to two clades: African and Asiatic, with a nucleotide divergence of less than 11.7%. The African clade consists of the MR766 prototype cluster and the Nigerian cluster. The Asiatic clade is comprised of the Micronesian strains and the Malaysian strains [18]. Studies on Zika virus genome sequences sampled in Americas and Brazil show that both have a common ancestor belonging to the Asian lineage and shows 99% identity with a sequence of Zika virus isolated from French Polynesia and that the virus spread from Brazil to the rest of the Americas [21, 22].

Similar to other mosquito-borne flaviviruses, it is believed that Zika virus infection is initiated by multiplication in dendritic cells near the site of inoculation followed by spread to lymph nodes and blood stream [5]. It has been shown that, the initial target cells after inoculation are the skin fibroblasts, epidermal keratinocytes and dendritic cells. Similar to Dengue virus, infection of epidermal keratinocytes by Zika virus induces apoptosis which helps the virus to divert antiviral immune responses by increasing their dissemination from dying cells [23].

The virus has been found to have a high mutation rate of 12 to 25 mutations a year which is equivalent to 0.12% to 0.25% of RNA mutating each year [24]. Its genome has undergone several recombination events over the years in the envelope (E) and the NS5 sequences. In addition, loss of N-linked glycosylation site in the E protein have been detected which could be related to mosquito cell infectivity and may enable greater adaptation to Aedes mosquitoes [20].

EPIDEMIOLOGY

Zika virus is an arbovirus transmitted by the bite of female mosquitoes of the genus Aedes . The natural transmission of Zika virus is maintained between the Aedes mosquito and monkeys in the sylvatic cycle, man being occasionally involved in the urban cycle [25, 26]. The virus has been demonstrated in old-world non-human primates like African Green Monkey, Red-tailed monkey, etc. which are the possible natural Zika virus reservoirs [18].

Aedes africanus is considered as the major vector in the sylvatic cycle and *Aedes aegypti* and potentially *Aedes albopictus* are the vectors in the human cycle of Zika virus transmission [27-29]. In addition the virus has been isolated from various mosquitoes of Aedes species like *Aedes apicoargenteus, Aedes luteocephalus, Aedes vittatus, Aedes furcifer, Aedes hensilii, Aedes dalzieli, Aedes apok, Aedes jamoti, Aedes flavicolis, Aedes grahamii, Aedes taeniarotris, Aedes tarshis, Aedes fowleri, Aedes metallicus, Aedes minutus, Aedes neoafricanus*and also mosquitoes belonging to Culex, Mansonia and Anopheles species but their significance in Zika fever transmission is unclear [18, 30, 31]. The extrinsic incubation period in the mosquito is found to be up to 10 days [5, 32].

During heavy rains proliferation of the mosquitoes leads to their spread from the forest to nearby villages thus infecting the local inhabitants. Increased human activity in the forest also facilitates the initiation of the urban cycle [18]. Studies have suggested that Zika infections peak towards the end of the rainy season [33].

Reasons for the emergence of Zika virus infection have been speculated. Zhu *et al.* have found genomic changes in the epidemic strain from the pre-epidemic strain, the significance of which needs to be explored [34]. *Aedes aegypti* and *Aedes albopictus* have been shown to be low competent vectors of Zika virus and it is suggested that large number of susceptible population and their close contact with *Aedes* mosquito have contributed to the rapid spread of Zika virus [35]. In addition, factors like globalization, urbanization, climatic changes, increased awareness of Zika virus disease and improved diagnostic capacity have led to increased detection of Zika virus cases [34].

Aedes aegypti is a day-biting mosquito and typically rests indoors [36]. It lays eggs in artificial collections of water like domestic water storage

including overhead tanks, ground water storage tank and septic tanks as well as rain-filled habitats like used tires, discarded food and beverage containers and non-household cryptic breeding sites like blocked gutters and storm drains [36-38].

Zika virus disease has not yet been reported in India though the mosquito vector *Aedes aegypti* and *Aedes albopictus* are widely prevalent [39, 40]. Once infection is transmitted, there is a possibility of establishment of Zika virus disease in India [41]. Hence countries like India have to be on the look out to prevent introduction of cases into the country.

MODES OF TRANSMISSION

Zika virus is most frequently transmitted to humans by the bite of the female *Aedes aegypti* mosquito which also transmits Dengue and Chikungunya [42]. It can also be transmitted vertically from infected pregnant mothers to their fetuses leading to congenital malformations like microcephaly [7].

Sexual transmission of Zika virus has also been reported. Replicative Zika virus particles were demonstrated in the semen sample of a patient with Zika virus infection and haematospermia [43]. In a study by Barry Atkinson *et al.*, semen samples were positive for Zika virus by rRT-PCR (real time reverse transcriptase polymerase Chain Reaction) up to 62 days after onset of febrile illness [44]. It has also been shown that the viral load in the semen was roughly 100,000 times that of his blood or urine, tested more than 2 weeks after symptom onset, which could facilitate potential sexual transmission of the virus [45]. B.D. Foy*et al.*, have reported a case of an American scientist who acquired Zika fever in Bandafassi in Southeastern Senegal and after returning transmitted it to his wife who had not travelled outside USA during the previous year [46]. As of June 15, 2016, 11 countries have reported person to person transmission of Zika virus, probably via sexual route [13]. The first documented case of female to male transmission of Zika virus infection was reported in United States of America on 15th July 2016 [13].

Due to the high rate of asymptomatic infections caused by Zika virus, there is a potential for Zika virus transmission by blood transfusion [47]. Hence blood donation should be deferred from donors returning from areas with an outbreak of Zika virus infection [47]. Presence of infective Zika virus particle in breast milk with substantial viral loads (850000 copies per mL) has been reported [48]. The significance of this finding in transmitting the virus from the infected breast feeding mother to her child needs to be explored. Monkey bite has also been suggested as a potential route of transmission based on the case of an American traveller who developed Zika virus infection 5 days after a monkey bite in Indonesia [5].

CLINICAL PRESENTATION

This infection was a neglected tropical disease before 2015 and its natural history is still understudied [45]. The first systematic study of the clinical presentation of Zika virus infection was published by Bancroft, when he inoculated the Eastern Nigerian strain of Zika virus in a human volunteer. The volunteer developed a mild, short-lived febrile illness with headache after 82 hours of inoculation [49]. Clinical features can be indistinguishable from Dengue and Chikungunya making diagnosis difficult in areas where these infections co-exist [50]. Majority (around 80%) of infections are asymptomatic [50]. Incubation period of Zika fever is unknown, but it has been shown that symptoms appear 3–12 days after mosquito bite and resolve within 7 days [51]. The most common symptom seen with Zika virus infection are low grade fever, an often pruritic maculopapular rash that spreads from face to limbs, arthralgia and non-purulent conjunctivitis. Other symptoms include frontal headache, myalgia, retro-orbital pain, peri-articular edema& vomiting [4, 11, 52]. Cervical and retroauricular lymphadenopathy were also frequent findings [51]. Moderate thrombocytopenia has also been occasionally associated with Zika virus infection [53]. Mortality rate with Zika virus is very low [54].

Though Zika fever is a mild self-limiting disease, it has gained importance due to the increasing incidence of neurological complications following Zika fever like Guillain-Barre Syndrome and congenital malformations like microcephaly in infants born to infected mothers.Based on current research, there is scientific consensus that Zika virus is one of the causes of congenital central nervous system malformations and Guillain-Barre Syndrome [13]. The pathogenesis of these two conditions vary, with fetal abnormalities possibly being the result of direct fetal invasion and Guillain-Barre syndrome occurring possibly due to exaggerated autoimmune response [24].

Congenital Zika virus infection

An association has been found between Zika virus infection in early pregnancy, especially in the first trimester and risk of development of microcephaly [55]. Neurological involvement has been described following intrauterine infection with other Flaviviruses also like West Nile virus and Chikungunya virus [56]. According to Brazil Ministry of Health, between 22nd October 2015 to 9th July 2016, a total of 8,451 suspected cases of microcephaly and congenital malformations of central nervous system have been reported in newborns of which 1687 cases were confirmed due to Zika virus in accordance with Brazil's surveillance and response

protocol and 3622 cases discarded due to other causes and 3142 remain under investigation [57].

Microcephaly is defined as neonatal head circumference measured 24 hours after birth and within the first week of life, of greater than or equal to 2 Standard Deviations below the mean forgestational age and sex of the infant; with severe microcephaly being defined as head circumference more than 3 Standard Deviations below the mean for gestational age [58, 59]. It is estimated that the risk of microcephaly in the child was about 1% with infection of the mother with Zika virus during the first trimester of pregnancy [56]. The CT and MRI brain imaging features most commonly found in case of congenital Zika virus infection include calcification, cortical hypergyration, ventriculomegaly, enlarged cisterna magna, corpus callosum abnormalities (hypoplasia or hypogenesis), delayed myelination and cerebellum and brainstem hypoplasia suggesting that ZiKA virus is associated with disruption in brain development [60].

Presence of Zika virus envelope protein and nonstructural protein 5 in brain tissues of newborns with microcephaly indicates that brain is the main target organ of viral replication in the foetus, highlighting a strong neurotropism [61, 62]. Zika virus has also been isolated from the brain of fetus with congenital Zika virus infection providing further evidence for its association with fetal brain damage [23]. In addition, studies have also demonstrated Zika virus genome by Real Time – quantitative Polymerase Chain Reaction (RT-qPCR) and anti-Zika virus IgM antibodies by ELISA in the amniotic fluid of pregnant women whose foetuses had been diagnosed with microcephaly [63]. Zika virus RNA has been identified in the amniotic fluid of women whose fetuses had been found to have microcephaly by prenatal ultrasound [58].

The temporal and spatial relationship between outbreaks of Zika virus disease and increased detection of microcephaly, suggests a presumptive link between these two epidemiological events [55]. This is further substantiated by the fact that Zika virus can directly infect human Neural Progenitor cells (hNPCs) leading to attenuated population growth through virally induced caspase-3 mediated apoptosis and cell-cycle dysregulation [64]. Damage of placental barrier by Zika virus facilitates fetal infections [61].

Ocular examination of children with microcephaly due to Zika virus have shown several abnormalities [65]. Optic nerve findings consists of hypoplasia with double ring sign, pallor and increased cup-to-disk ratio and the macular abnormalities were foveal reflex loss, mild to gross pigment mottling and sharply demarcated circular areas of chorioretinal atrophy [65]. In addition intra-uterine Zika virus infection has also shown to cause hydranencephaly, hydropsfetalis and fetal demise [66].

GuillainBarre Syndrome (GBS)

Guillain-Barre syndrome is an acute paralytic neuropathy, preceded by infection or other forms of immune stimulation leading to an aberrant autoimmune response that targets peripheral nerves and their spinal roots [67].

The first case of Guillain-Barresyndrome occurring 7 days after Zika virus infection was reported in French Polynesia in December 2013 [68]. During the outbreak in French Polynesia, the incidence of GBS has escalated 20 times [68]. 42 patients were admitted to the hospital with GBS. 88% of these cases reported having Zika virus symptoms roughly 6 days preceding the onset of neurological symptoms [69]. Serological investigations performed on these 42 patients confirmed that all patients had experienced Zika virus infection [70]. Incidence of GBS has been estimated to be 0.24 per 1000 Zika virus infections during the French Polynesian outbreak [70].

In 2015, Brazil registered 1708 cases of GBS demonstrating a 19% surge in comparison to previous year [71]. Zika virus has been demonstrated by Reverse Transcriptase PCR in urine of patients with GBS, with viruria lasting for more than 15 days after symptom onset [72].

Other neurological complications following Zika virus infection like acute myelitis and meningoencephalitis have also been reported [34, 73].

LABORATORY DIAGNOSIS

Due to the similarity in clinical presentation with Dengue and Chikungunya, laboratory diagnosis is essential for confirming Zika virus infection. A Biosafety level 2 containment is required for handling suspected samples [74, 75].

Nucleic Acid Testing

Zika virus can be diagnosed in the first week by performing real time Reverse Transcriptase Polymerase Chain Reaction (rRT-PCR) on serum targeting the non-structural protein – 5 genomic region [41, 76, 77]. However, a negative rRT-PCR result does not exclude Zika virus infection, and in such cases serum IgM antibody testing for Zika and Dengue virus infection should be performed [78]. WHO recommends whole blood, serum or urine sample for nucleic acid testing (NAT) [79].

After first week of symptom onset, urine is the ideal sample for PCR for Zika virus as levels of viremia among Zika infected patients are relatively low lasting only 3-5 days. Viremia decreases rapidly after

appearance of rash which occurs 2-3 days after disease onset [80-82]. Studies have shown that viral RNA can be detected in urine as early as 4 days after symptom onset to up to more than 2 weeks, while viral RNA was detectable in plasma up to day 10 after symptom onset [83, 84]. Hence urine samples can be used as an alternative to serum or plasma for detection of Zika virus RNA because of a longer period of RNA detection, higher RNA levels than serum and less invasive sample collection [84].

Detection of Zika virus RNA in saliva has also been reported with a higher viral load than plasma [83, 85].Though some studies have reported persistent shedding of virus in saliva, it is believed that the use of saliva only improved the ability to detect Zika virus RNA within the first week from symptom onset without increasing the duration of window of detection in contrast to what is reported for urine [85].

In India the Reverse Transcriptase Polymerase Chain Reaction is available in National Institute of Virology, Pune and National Centre for Disease Control, Delhi for testing Zika virus from serum sample during the acute stage of illness [86].

Virus isolation

Zika virus can be isolated by intracerebral inoculation into newborn mice or isolated in mosquito derived cell lines (AP-61: *Aedes pseudoscutellaris* and C6/36: *Aedes albopictus*) and non-human primate cell lines (VERO cell line and Baby Hamster Kidney cell line) [18]. Viral growth on cell lines can be confirmed by an indirect immunofluorescence assay (IFA)[20]. Though viral isolation is considered as the 'gold standard' for viral diagnosis, it is not the preferred method as it is labor intensive, time consumingand is cumbersome for routine use [20].

Serology

According to WHO, for patients presenting after 7 days of symptom onset, serology is the preferred method [79]. WHO recommended serological assays include Enzyme Immunoassays (EIAs) and Immunofluorescence assays (IFA) detecting IgM antibodies as well as neutralization assays such as Plaque-Reduction Neutralization Tests (PRNTs) [79]. WHO also recommends testing for Dengue and Chikungunya along with Zika virus due to presence of co-infection in flavivirus endemic areas [79].This not only increases the cost, but also limits the diagnosis of Zika virus to be performed by ruling out related Flavivirusinfections[87].

Serological testing focuses on detecting IgM antibodies in serum or Cerebrospinal fluid using IgM antibody capture Enzyme-Linked Immunosorbent Assay (Zika Mac-ELISA) [78]. Serological assays can be false positive due to cross reacting antibodies to other Flaviviruses like Dengue virus [88]. Studies have shown that cross reactions with Dengue virus IgM assay can occur in Zika virus infected patients especially if Zika virus is a secondary flavivirusinfection. This phenomenon described as 'original antigenic sin' will lead to the erroneous conclusion of Dengue virus infection in a patient with Zika fever due to cross reacting antibodies in sera of patients previously infected with Dengue [80]. This can be differentiated by Plaque Reduction Neutralization testing which provides higher specificity[88]. A four-fold rise in neutralizing antibody titres in the absence of a rise in antibody titre to other flaviviruses is further evidence of recent Zika virus infection, though these results might not discriminate between anti-Zika virus antibodies and cross-reacting antibodies due to secondary flavivirus infections [79]. Hence the Centre for Disease Control and Prevention recommends a more conservative approach to interpret results of Plaque Reduction Neutralization Test (PRNT)[78]. A PRNT using plaque reduction cut-off value of 90% with a titre of $\geq$10 against Zika virus and negative PRNTs against other flaviviruses is confirmatory for recent Zika virus infection [78]. There is a strong and urgent need for the development of quality assured, safe, simple, rapid and specific universally available in vitro diagnostic test for Zika virus diagnosis at or near the point of care facility [79].

TREATMENT

Due to lack of an approved antiviral agent, treatment of Zika fever is symptomatic involving adequate fluid intake, rest, antipyretics like Paracetamol, preventing mosquito bites to hinder further spread to others and in pregnant patients monitoring for birth defects and appropriate counselling [89]. Several drugs have shown antiviral activity against Zika virus like Azathioprine, Bortezomib, Daptomycin, Ivermectin, Mefloquine, Mycophenolic acid, etc [90]. These drugs have to be further evaluated for use in treatment of Zika fever. Drug target sites like Zika virus helicase and RNA-dependent RNA polymerase (NS5) have also been proposed for discovering of new drugs with anti-Zika activity [91, 92].

CONTROL

There is currently no approved vaccine for the treatment or prevention of Zika virus disease though a few candidate vaccines are being tested [39]. 15 research groups including an Indian firm, Bharath Biotech are in the race for vaccine development [89].

Control of Zika virus disease aims at preventing virus transmission using acomprehensive approach by way of vector surveillance by larval and adult surveys and by integrated management of Aedes mosquitoes [37].

Mosquito control

Aedes mosquitoes can breed in extremely small amounts of water and their eggs are very sturdy, making vector control difficult [93]. Mosquito control involves control of breeding sites and destruction of adult mosquitoes. The mosquito eggs, larvae and pupae population can be controlled by eliminating mosquito breeding sites by community clean-up campaigns, use of larvicides like Temephos, larvivorous fish and other larvivorous aquatic insects, mosquito proofing of overhead tanks, cisterns or underground reservoirs, improved drainage, introducing efficient irrigation practices like weekly flushing, etc. [36, 37]. Endotoxin-producing bacteria, Bacillus thuringensis serotype H-14 (Bt H-14) has been found an effective mosquito control agent [37]. Adult mosquitoes can be controlled by targeted residual spraying applied selectively to areas known to be resting sites for Aedes mosquito and space spraying techniques like cold fogging or thermal fogging which targets adult mosquitoes while they are in flight and has no residual effect [36].

Two innovative approaches that have shown considerable promise in the recent years is genetic control of *Aedes aegypti* mosquitoes like RIDL (Release of Insects carrying Dominant Lethal genes) which involves releasing male mosquitoes provided with dietary supplement not present in nature like Tetracyclin which repress the lethal gene activation [10]. Offspring of such mosquitoes do not survive to the adult stage because they do not receive the dietary additive in the wild [10]. The alternative approach is use of endosymbiotic bacteria to prevent arbovirus replicating within the mosquito, for example by releasing Wolbachia infected mosquitoes into the wild [10]. Laboratory results have shown that Wolbachia infection reduces replication of Dengue virus, Chikungunya virus and Zika virus in Aedes mosquito and eliminates or markedly delays appearance of virus in mosquito saliva, thus reducing competence of mosquito to transmit viruses [36].

Personal protection

Personal protective measures include application of repellents to exposed skin, wearing clothes that minimizes skin exposure, using window, door screens, safe repellents, avoidance of unprotected sexual activity with a possibly infected partner, using insecticidal mosquito nets when sleeping during the day, avoiding travel to affected areas and avoidance of pregnancy in women residing in affected areas [36, 89, 94]**.** It has been suggested that men returning from countries with ongoing virus transmission should abstain from sexual activity or use condom for 28 days after return and if infected they should use a condom for 6 months after recovery [95].

Community education

Persistent Behavior Change Campaign (BCC) is essential to educate the community about the mode of transmission, vector control options, availability of services including appropriate treatment, so that timely and appropriate action is taken [37].

Surveillance

Integrated surveillance at various levels involving both private and public sector is essential for the prompt detection and control of outbreaks of Zika fever [89].

CONCLUSION

Zika fever, once considered a mild self-limiting arboviral disease has emerged as an important public health concern due to increased incidence of congenital malformations and neurological complications like Guillain-Barre Syndrome associated with it. It has also transpired as a disease with pandemic potential. Various factors like globalization, urbanization, climatic changes and large number of susceptible population and their close contact with Aedes mosquito has facilitated the rapid spread of this virus [34, 35]. Diagnosis of Zika fever can be confounded due to the presence of cross-reacting antibodies in the sera of patients residing in areas where other flavi viruses are co-circulating [80]. Ongoing active surveillance and vector control measures are essential to curb the menace of Zika virus and to prevent it from becoming a universal health problem.

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