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Zika virus: A threat to public health and recent strategies developed to curb the menace

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Abstract
Zika virus infection has proved to be a concern for physicians worldwide because of its communicable nature and high prevalence rates in the areas of outbreak despite of low mortality rates. Zika virus is a positive sense single stranded RNA virus of flaviviridae family and a close relative of Spondweni virus. Phylogenetic analysis suggests that Zika virus has emerged from East Africa during the late 1800s or early 1900s. Clinical signs of zika virus infection are mild involving rashes, fever, dizziness, stomach ache, arthralgia, myaligia, ankle edema, malaise etc. It adversely affects the embryo development and results in a birth defect 'microcephaly'. The residents of tropical and subtropical countries are more susceptible to Zika virus infection owing to the higher population of *Aedes aegypti* and *Aedes albopictus* mosquitoes. It is mainly a mosquito born virus, *Aedes hensilli* being the most potential vector; various other modes of transmission have also been described though. Largest outbreak of zika virus has been reported in pacific islands in 2013 and 2014. India with lots of travelers from south America is at higher risk of ZIKV outbreak. Both molecular and serological tests are recommended for diagnosis of ZIKV infection.

Keywords: Zika virus, evolution, transmission, pathogenesis, recent developments

1. Introduction
Zika virus is a member of the flaviviridae family which also includes the Yellow fever virus (YFV), the Dengue virus (DENV) and the West Nile virus (WNV) [1]. It is also an arthropod borne virus known as arbovirus. It is (10,794 –nt genome) single stranded positive sense RNA virus and is closely related to Spondweni virus [1-4]. Zika Virus RNA has a biased nucleotide composition in being purine-rich and pyrimidine-poor and the preference for purines is a general characteristic of the mosquito-borne and tick-borne flaviviruses [2]. The virus was identified in a rhesus monkey (*Macaca mulata*) during sylvatic yellow fever surveillance in the Zika Forest in Uganda in 1947 from where it got its name and was reported in humans in 1952 [1,2,5,6]. The second isolation was made from *Aedes africanus* mosquitoes caught in the same forest in January 1948 [7]. Thus, ZIKV received its name from the geographical area where the initial isolations were made.

2. Objective of study
To aware the researchers, clinicians and scholars about the pathogenesis, clinical signs and various public health implications associated with Zika virus which has been considered as an emerging disease and also apprises the scientific community regarding the latest developments in the field of Zika virus research.

3. Course of outbreak
In 2007 there was an outbreak of the disease in Yap Island in the Federated States of Micronesia. It was the first time when the disease was reported outside Africa [1, 8, 9]. The largest outbreak of the disease was reported in the year 2013 and 2014 in French Polynesia which spread to Pacific islands (New Caledonia, Cook island, Easter island, Vanuantu, Soloman island etc.) [1, 9-12]. In Pacific islands, the outbreak coincided with dengue and chikungunya outbreak [13-14]. The next outbreak was reported in Brazil in 2015. Camacari was the city where the first cases of Zika virus infection in Brazil was identified [1]. Zika virus infection was detected in the serum samples of 24 patients in Santa Helena hospital through RT-PCR technique in 26th march, 2015 [1].

It has been predicted that the virus spread to Brazil from French Polynesia during the world cup soccer in 2014 [6]. Till date the virus has been isolated in several African countries (Uganda, Tanzania, Egypt, Central African Republic, Sierra Leone, and Gabon), Asian countries (India, Malaysia, the Philippines, Thailand, Vietnam and Indonesia) and in Micronesia [5]. Zika represents a real challenge for the medical and scientific community as well as for the world and possess a severe threat to the human health [15-16]. With an estimated 1 million cases in Brazil by the end of 2015 and continuing emergence of new cases in Central America most recently, the United States, assessing the full pandemic potential of the virus is an urgent task with major ramifications for global health policy [16, 17].

4. Molecular virology

Zika virus is a positive-sense single-stranded arbovirus in the family Flaviviridae. Flaviviruses are small enveloped single stranded positive RNA viruses that include important human and animal pathogens such as yellow fever virus (YFV), dengue virus (DENV), West Nile virus (WNV), St. Louis encephalitis virus (SLEV), Japanese encephalitis virus (JEV) or tick-borne encephalitis virus (TBEV) [18]. Its closest relative is Spondweni virus (SPOV) responsible for fever, chills, nausea malaise and headache [1, 4, 11]. SPOV is found in sub Saharan Africa and Papua New Guinea, the only other member of its clade. The sequence of the prototype strain of ZIKV MR766, which corresponds to a passaged virus derived from the initial ZIKV isolated by intracerebral inoculation of the serum of the febrile monkey (Rhesus 766) into mice in 1947 revealed that The Zika virus genome contains 10,794nt with single ORF encoding polyprotein of 3,400 amino acids which cleaves later in order to form mature virus proteins [7, 19]. Like other flaviviruses, Zika virus also has in a similar manner to cellular mRNAs, includes a cap structure at its 5´ end [20]. Proper methylation of this structure is important not only for efficient translation of viral genome, but also for evasion of immune response [21]. The single ORF of Zika virus genome is flanked by two untranslated regions (UTR) located at the 5´ and 3´ ends of the genome, which in the prototype ZIKV MR766 are of 106 and 428 nucleotides in length, respectively [19]. ZIKV lacks 30 poly (A) tract in contrast to other cellular mRNAs. The different isolates from the various outbreaks have the similar basic organization. The cyclization of flavivirus genome between 5´and 3´ terminal regions is important for the functionality of the genome, which is mediated by the interaction of complementary sequences located with genome regions termed conserved sequences (CSs). Nevertheless, it has to be remarked that the organization of the CS in the 3´end of ZIKV is different from that of other mosquito-borne flaviviruses thus lays emphasis on the fact that this virus behaves in a bit different manner than other flaviviruses [19]. In the case of ZIKV, there are differences among strains due to a 12 nucleotides deletion on the glycosylation motif located at position 154 in the E protein (E-154), which is present in many flaviviruses [22-24].

4.a. Molecular evolution of virus

Phylogenetic analysis shows that Zika virus can be classified into distinct African and Asian lineages both emerged from East Africa during the late 1800s or early 1900s [25]. The Asian lineage was first detected in Malaysia during its migration from Africa to Southeast Asia. From there, Zika virus spread to the Pacific Islands, separately to Yap and French Polynesia, and then to New Caledonia, Cook Islands, Easter Island, and the Americas. A study of Zika virus's molecular evolution, based on viral strains collected from 4 countries in West Africa during 1947–2007, identified several sites within the Zika viral genome that were under strong negative selection pressure. This finding suggests frequent purging of deleterious polymorphisms in functionally important genes and the possibility of recombination, which occurs rarely among flaviviruses.

4.b. Host cell-virus interaction

A broad range of cells are infected by ZIKV in different tissues and species. ZIKV replicates in the midgut and salivary glands of diverse Aedes mosquitoes and also in cultured mosquito cells C6/36 *in vitro* [26-28]. ZIKV also replicates in a wide variety of mammalian cell types. Experimental infection has revealed that the virus replicates mainly in the neurons and astroglial and other brain cells of mice [29, 30]. ZIKV can also replicate in cultured monkey cell lines such as LLC- MK2, or Vero, inducing cytopathic effect [31]. Few studies have investigated the pathogenesis of Zika virus infection. One study showed that human skin fibroblasts, keratinocytes and immature dendritic cells allow entry of Zika virus [32]. Several entry and adhesion factors (e.g., AXL receptor tyrosine kinase) facilitate infection and cellular autophagy, needed for flaviviral replication, enhances Zika virus replication in skin fibroblasts [32]. After cellular entry, flaviviruses typically replicate within endoplasmic reticulum-derived vesicles. However, Zika virus antigens were found exclusively in the nuclei of infected cells; this finding suggests a location for replication that differs from that of other flaviviruses and merits further investigation [15]. Many surface proteins facilitate flavivirus entry into cell but the precise mechanism remains largely unknown and additional factors may also contribute to infection [33]. Several of these proteins are sufficient to support ZIKV entry into HEK293T cells that normally have low infectivity, including DC-SIGN (encoded by CD209), TIM1 (encoded by HAVCR1), TYRO3 and AXL. However AXL which is known to mediate ZIKV and dengue virus entry in human skin cells showed particularly high expression in radial glia [28]. Several studies have indicated that flaviviruses make initial contact with the host cell by binding to glycosaminoglycans (GAGs), such as heparan-sulfate proteoglycans or syndecans. GAGs are long, unbranched, sulfated polysaccharides that are found linked to core proteins attached to cellular surfaces (proteoglycans). GAGs are prominently exposed on the cell surfaces of all tissues, providing an easily accessible receptor for viral adhesion. GAGs act mainly as attachment factors that concentrate flavivirus particles at the target cell surface before their interaction with primary receptors.

It has been speculated that the development of neurological disease and fetal abnormalities after Zika virus infection may be due to the presence of antibodies against other flaviviruses that enhance disease. In support of this hypothesis, it has been shown that antibodies to dengue virus enhance infection of cells by Zika virus.

5. Transmission

Several modes of transmission of the virus have been reported by various workers. The most important and widely accepted one is the transmission through mosquitoes [2, 3, 12, 15, 34]. The virus has been detected in several species of mosquitoes

including *Aedes aegypti* which is the same vector that spreads dengue (DENV), chikungunya (CHIKV) and yellow fever virus (YFV) [2, 5]. Because of the fact of concurrent transmission of the virus with dengue and chikungunya it has global public health threats [10, 16]. However, the abundance of *Aedes aegypti* and *Aedes albopictus* mosquitoes throughout tropical and subtropical regions of the world has increased the chances of spread of this disease in these areas to a much extent [10]. The other species of mosquitoes known to transmit the virus are *Aedes africanus, Aedes luteocephalus, Aedes hensilli, Aedes vittatus, Aedes apricoargenteus, Aedes furcifer, Aedes albopictus* etc [2, 5, 10]. Among these *Aedes hensilli* is considered as most potential vector of the virus [35]. There is also a possibility of transmission of the virus *by Culex sp*.[12, 36].

Zika virus has been isolated in 3% blood donors during outbreak in French Polynesia and hence blood transfusion may be another potential mode of transmission [5]. There may also be intrauterine and intrapartum transmission [37, 38]. A case of sexual transmission was detected in French Polynesia outbreak involving a 44 year old Tahitian man whose semen was contaminated with the virus but the virus was not reported in blood sample [5, 38]. Further studies have confirmed that sexual transmission of Zika virus is possible from male to female, male to male and female to male [4,39]. There are some evidence of laboratory exposure [38]. There is a theoretical concern that it could transmit through tissue transplantation [38]. Travel-related imported infections have thus been increasingly reported from the western Pacific and sporadically also in travelers to other regions of the world, including Thailand, Indonesia, and Senegal [6]. An acute Zika virus infection was reported in a 45 year old woman traveler returning from Malaysian Borneo who experienced bilateral hearing difficulties during the course of illness [6]. The virus has been isolated from blood, plasma, serum, saliva, semen, urine, cervical mucus, vaginal swab, fetal brain tissue, placenta, amniotic fluid and in breast milk (yet transmission by breast feeding has not been documented) [4, 11, 15, 37, 38, 40]. It has been detected in semen and urine respectively in a patient after 62 days of infection and another patient after 14 days of infection [15]. Zika virus has been detected for up to 6 months in semen, although the maximum duration of transmissibility remains unknown at this time [40]. Non human primates are considered as reservoir for the virus as the virus was initially isolated from a rhesus monkey (*Macaca mulatta*) [6, 15].This has also been recently reported that another emerging aspect of Zika virus zoonosis hasbeen the possible transmission through bites of monkeys and other non-human primates (USFDA, 2016) [41]. There is no evidence of non-primate reservoir but in one study its antibody was found in rodents [8] and experimentally in Swiss Albino mice [15].

5.1 Non human primates involved in viral transmission: In the case of non-human primates, it is known that epizootics occur in them [42] but it is unclear whether they are an obligatory reservoir in the transmission to humans. In Africa, ZIKV natural transmission cycle involves primarily *Cercopithecus aethiops* and *Erythrocebus patas* monkeys [43]. In Asia (Borneo), antibodies against ZIKV have been detected among semi-captive and wild orangutans [44]. However, this study reported a higher prevalence of anti-ZIKV antibodies in humans than in orangutans, suggesting a possible incidental infection of these animals through contact with mosquitoes infected by viremic people or from recently established sylvatic cycles. Nonetheless, it is also possible that sylvatic ZIKV transmitting mosquitoes in Borneo have a more narrow distribution or an ecology that does not lead to frequent exposure by orangutans. An acute symptomatic ZIKV infection case after a monkey bite has been recently described [45]. Monkey bite can also be considered as a plausible route of transmission (Leung *et al.*, 2015). Information regarding the possible susceptibility of animals other than human and non-human primates is limited. Antibodies directed against ZIKV have been found in several vertebrate species, such rodents, birds, reptiles, goats, sheep, and cattle in Kenya and in Pakistan, where some species of rodents were suggested as possible reservoirs of ZIKV [46, 47]. In addition, the rapid periodicity of amplification observed in Senegal along the 2011 outbreak could support that, besides primates, other vertebrates may also play a role in ZIKV circulation [48].

6. Pathogenesis

The virus is highly neurotropic and immature neurons are more prone to its attack [5, 49]. It has also been suggested that like undifferentiated neurons, replicating and regenerating neurons are also susceptible to Zika infection such as the olfactory and dentate gyrus of the adult human brain [49]. There are also the reports of relative resistance of mature neurons found in adult human brains to Zika virus [49]. After entering the body it replicates in the dendritic cells (may be in cytoplasm or in nucleus) near site of inoculation and then invades blood stream via lymphnodes [8]. An experiment involving mice model revealed that vaginal mucous membrane supports robust Zika virus replication which has direct negative effect on fetal brain cells. It has been confirmed that intra-vaginal route of inoculation causes more replicates as compared to intra-peritoneal route of inoculation [4]. At the same time humans are more susceptible to Zika virus infection as Zika virus antagonizes human STAT2 but not mouse STAT2 [4]. Zika fetal neuropathogenesis are analysed from a comparative pathology perspective, using the historic metaphor of “TORCH” (Toxoplasmosis, Rubella, Cytomegalovirus and Herpes simplex virus-2) viral pathogenesis [12]. When a pregnant woman is infected with the virus, it enters the fetal brain neurons and form viral fusion particles causing syncitial cells to form a giant cell formation with central chromatolysis [48]. The most vulnerable stage of infection for fetus is 17 weeks of pregnancy. ZIKV infection of neuroepithelial cells and radial glial cells causes centrosomal depletion and mitochondrial sequestration of phospho-TBK1 (phosphorylated TANK binding kinase 1) during mitosis. Microcephaly in baby is primarily caused by depletion of neural stem or progenitor cells due to centrosomal defects, premature differentiation, and/or cell death [49]. Zika virus efficiently infects induced pluripotent stem cell (iPSC) derived human neural progenitor cells (hNPCs), resulting in cell cycle abnormalities and apoptosis [50]. The expression of unique transcriptomic signatures in Zika virus infected human neural stem cells has been revealed through bio-informatic analysis [3]. Zika virus activates several inflammatory signals within infected human neural progenitor cells (hNPCs) that are implicated in innate and acquiredimmune responses [3]. Infected hNPCs can further release infectious ZIKV particles, supporting a spreading infection that can lead up to 90% of cells being Zika Virus positive [51].

7. Clinical Signs

The incubation period of disease is 3-12 days and symptoms last for about 2-7 days [49]. Zika virus conventionally presents as a mild infection, with 80% of cases estimated to be asymptomatic [3, 16, 49, 52].The most common sign reported in Zika virus infection is maculopapular rashes [49]. Other signs include chills, fever, headache, anorexia, vomiting, diarrhea, stomach ache, dizziness, hypotension, lymphadenopathy, leg pain, muscle pain, arthralgia, myalgia, ankle edema, malaise, conjunctivitis and periorbital pain etc but there are no cases of permanent damage to articulations [3, 52]. ZIKV was isolated from two icteric patients with no other disease during the outbreak and so icterus is a suspected symptom of the disease. Hence, the concept of considering Zika as mild cousin of dengue may not be adequate [5]. Neuronal degeneration, cellular infiltration and softening in the brain is seen in infected, young mice [5]. Ocular and ophthalmic lesions have also been reported. Infected Rhesus monkeys showed transient pyrexia. It has been reported that the virus is linked to Guillain -Barré syndrome (a syndrome that involves tetraparesis predominantly in the lower limbs, paresthesia of the extremities, diffuse myalgia, a bilateral but asymmetric facial palsy, with abolition of deep tendon reflexes) [2, 3, 5, 12, 15, 51, 53]. In the French Polynesian outbreak of Zika virus out of 74 infected patients presented with neurological symptoms, 47 were later diagnosed with Guillain -Barré syndrome in which there was inflammation of dentate gyrus of brain [49]. There were some cases of temporary bilateral hearing difficulty in Borneo [6]. During the outbreak in Brazil it was observed an increase of almost 20 times the number of cases of microcephaly in reported newborn babies [16, 54]. The possible link between Zika virus and microcephaly is studied using induced pleuropotent stem cells (IPS) [51]. There are strong evidence of association between Zika Virus infection and microcephaly [2, 55, 56]. Microcephaly is a birth defect where a baby's head is smaller than expected when compared to babies of the same sex and age. Microcephaly is defined anatomically as occipitofrontal circumference less than the third percentile based on standard growth charts (e.g., Fenton, Olsen, CDC, or WHO growth curves) for sex, age and gestational age at birth [40]. Among the affected population in different outbreaks most were females. Pregnant women at their first trimester (weeks 0-13) are more susceptible [52]. The reason behind this is the immature neurons or undifferentiated neurons are highly susceptible to zika virus where as mature ones are resistant as experimented on human neuroblastoma cell lines [5, 49]. However, studies of symptomatic pregnant women with Zika virus have found that infection even in the second or third trimesters has resulted in anomalies in the fetal brain and other serious outcomes, including stillbirth [39, 52]. Once microcephaly develops it's a lifelong condition and it cannot be treated. Hence, Centre for disease control and prevention (CDC) has told women to avoid getting pregnant at least for up to 2 years in disease prone areas [40].

8. Diagnosis

For diagnosis of Zika virus CDC has recommended both molecular and serological testing [38, 40]. This includes RT-PCR for viral RNA, and immunoglobulin (IgM) ELISA and plaque reduction neutralization test (PRNT) for Zika virus antibodies [8, 37, 38, 40]. It has been suggested that urine is more advantageous than blood and serum for molecular diagnosis [32]. Zika virus RT-PCR testing is performed on acute phase serum samples. IgM ELISA can give falsely positive results because of cross-reacting antibodies of ZIKV and DNV. However, PRNT possess improved specificity that can be performed to measure virus-specific neutralizing antibodies and to discriminate between cross-reacting antibodies from closely related flaviviruses. Immuno histochemical staining to detect Zika virus antigen on fixed placenta and umbilical cord tissues can be considered [40]. Spectrums of findings are formulated associated with congenital Zika virus infection in the IPESQ in northeastern Brazil and composed illustrations to aid the radiologist in identifying Zika virus infection by imaging [57]. No commercial tests for Zika virus are available [17, 39]. The mainstays of the routine diagnosis of Zika virus infection are the detection of viral nucleic acid by RT-PCR and the detection of IgM antibodies by IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA). The detection of viral nucleic acid in serum provides a definitive diagnosis; however, in most instances viremia is transient and diagnosis by RT-PCR has been most successful within 1 week after the onset of clinical illness.

9. Treatment

No specific treatment or approved drug is available for the treatment of this disease [54]. Some researchers suggest that broad spectrum antiviral drugs of nucleoside analogue class such as ribavirin, favipiravir, sofusbuvir etc posses some action against Zika virus but they are not being licensed because of their teratogenic effect on fetus [53, 54, 58]. Only supportive therapy is prescribed. Affected person should get plenty of rest and drink fluids to prevent dehydration. Antipyretics and pain killers may be taken. But aspirin or other NSAID are contraindiacted. It has been reported that the green tea polyphenol molecule (-) epigallocatechin gallate (EGCG) inhibits Zika virus entry [54]. Vero cells (African Green Monkey, adult kidney, epithelial) were used for determining ZIKV multiplication, for antiviral assays [17, 39]. A full length infectious c-DNA clone of Zika virus from the 2015 epidemic in Brazil was developed as a genetic platform for studies of virus-host interactions and vaccine development [39]. Recently, a vaccine has been developed against Zika virus as claimed by Bharat Biotech International Limited, Hyderabad. In Bharat Biotech there are two candidate vaccines in development. One of them is an inactivated vaccine that has reached the pre-clinical testing in animals. Bharat Biotech has an early mover advantage in developing the Zikavac and is emerging as the first in the world to file for global patent for Zika vaccine candidates [59]. Antiviral activity of 2′-C–methylated nucleosides suggesting that these compounds might represent promising lead candidates for further development of specific antivirals against Zika virus [17].

10. Preventive Measures

A person who is living in or traveling to an area where Zika virus is found and who has not already been infected with Zika virus is at risk for infection. As India has a good number of travellers from South America and other affected countries, it is at a higher risk. Bengaluru is considered as most susceptible city in the country based on its rapid travel and commerce link urban centres. Besides garbage menace in the city has put it on risk. Although the disease has not been reported in India, it cannot be said exactly that India is free of the virus. As the signs are mild, many cases may go unidentified easily. But it should not be taken easily because previously West Nile virus was also considered not so

dangerous but now it has proved to be dangerous [8]. However the association of the virus with microcephaly is a matter of concern. Preventive measures must be taken. Most importantly, complete health check up and screening for Zika virus should be done to all the travellers from areas with Zika transmission. Garbage management should be improved. At individual level people should avoid travelling to Zika prone countries. Moreover, mosquito bite can be prevented by wearing long sleeves and using mosquito bed nets. Using EPA registered insect repellants is a good choice [40]. Vero cell-adapted cDNA clone of zika virus was generated that can be used as a convenient platform for studies aimed at the development of Zika virus vaccines and therapeutics [39]. Food and Drug Administration of U.S. Department of Health and Human Services has recently (August 2016) [60] released revised recommendations for reducing the risk for Zika virus transmission by blood and blood components. It recommends the eligible blood donor must be in good health and free from transfusion-transmitted infections as can be determined by the processes in the subchapter as mentioned in the recommendations (USFDA, August 2016). However, a guideline released by U.S. Food and Drug Administration [61](February 2016) recommends that a blood donor with a history of Zika virus infection or exhibiting signs and symptoms of ZIKV infection within 2 weeks of departure from a ZIKV prone area should self-defer for 4 weeks after the resolution of symptoms (USFDA, February 2016).

11. Conclusion

The communicable nature and high prevalence rate has led to rapid spread of ZIKV infection from Africa to other areas like Micronesia, French Polynesia and to Brazil. It is a positive-sense single-stranded arbovirus in the family Flaviviridae. Microcephaly in babies is primary concern of ZIKV outbreak. Clinical signs include chills, fever, headache, anorexia, vomiting, diarrhoea, stomach ache, dizziness, hypotension, lymphadenopathy, leg pain, muscle pain, arthralgia, myalgia, ankle edema, malaise, conjunctivitis and periorbital pain etc but there are no cases of permanent damage to articulations. For diagnosis of Zika virus CDC has recommended both molecular and serological testing. India is at a higher risk owing to large number of travelers from affected countries and favourable climatic conditions for proliferation of the virus. The present scenario demands a worthy effort from the researchers around the world to develop a potent vaccine and preventive measures for the disease.

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