Review Article

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.apjtb.org

doi: 10.4103/2221-1691.281139

Impact Factor: 1.59

Emerging mosquito-borne arboviral infection Zika - An epidemiological review

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ABSTRACT

The unprecedented resurgence and geographical expansion of arboviral infections such as dengue, chikungunya, yellow fever, and Zika have a significant impact on human health and pose a serious threat to public health globally in recent years. Zika virus is a *Flavivirus* and is transmitted to humans through an infected mosquito bite. The Zika virus has been identified in many countries in Africa, Asia, and Pacific islands and sporadic human cases have been reported since 1947. The non-specific clinical symptoms of Zika fever are often misdiagnosed with other arboviral infections, especially dengue and chikungunya. Till now, there is no vaccine or specific antiviral treatment for Zika infection. The recent emergence of Zika is alarming and highlights the need for arboviral research to develop an effective treatment. Here in this review, we discussed the epidemiology of Zika, which has re-emerged in the recent decade and caused international concern.

KEYWORDS: Arboviruses; Epidemiology; Mosquito; Zika

1. Introduction

Global health security is under threat for a decade with the recent epidemics of emerging and re-emerging infectious diseases. Mosquito-borne diseases including but not limited to dengue, chikungunya, malaria, and Japanese encephalitis are becoming a major threat to the living population. Recently, Zika infection has been added to mosquito-borne diseases, and has attracted the attention of the medical community as it causes severe birth defects and microcephaly[1]. Zika was declared as public health emergency of international concern by the World Health Organization in February 2016[2].

Zika virus (ZIKV) infection is caused by arthropod-borne *Flaviviruses*. ZIKV got its name as this virus was first isolated from a Rhesus monkey in the Zika forest of Uganda in April 1947[3]. The ZIKV was isolated from the *Aedes africanus* mosquitoes which were predominant in the same forests. *Aedes* mosquitoes are the transmitting vectors for ZIKV in equatorial and tropical zones. Zika infection has been reported in the Americas, the Pacific Islands, and many countries in Africa and Asia which made ZIKV a major global concern (Figure 1). The re-emergence of mosquito-borne diseases such as chikungunya and Zika in recent decades causes serious public health burden worldwide[4,5].

2. Virus structure

The ZIKV belongs to the family Flaviviridae and genus *Flavivirus*. It has the same genome organization like other *Flaviviruses* such as dengue virus, Japanese encephalitis, yellow fever virus and West Nile virus[6]. It is a spherical, enveloped virus and has icosahedral symmetry with a non-segmented, single-stranded positive-sense RNA genome containing 10 794 nucleotides[7]. The RNA is a single open reading frame with untranslated regions at 3' and 5' end. The diameter of the virus is 42-52 nm. The long polyprotein of Zika comprises of three structural proteins [precursor membrane protein (prM), envelope protein (E protein), capsid protein (C protein), and

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How to cite this article: Malla A, Shanmugaraj B, Ramalingam S. Emerging mosquito-borne arboviral infection Zika - An epidemiological review. Asian Pac J Trop Biomed 2020; 10(5): 193-200.

Article history: Received 13 October 2019; Revision 11 December 2019; Accepted 10 February 2020; Available online 6 April 2020

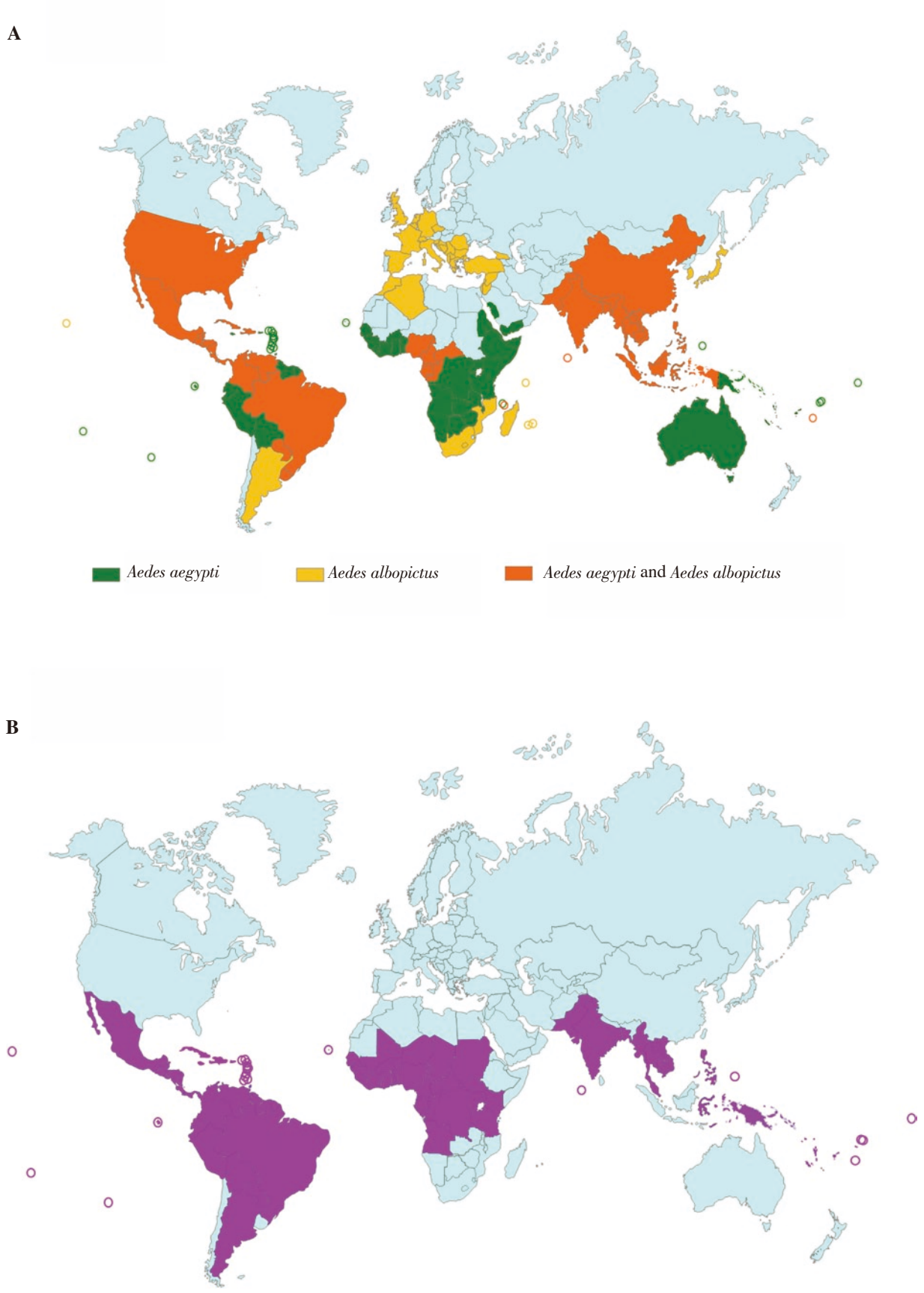

Figure 1. Occurrence and distribution of *Aedes* mosquito vectors and Zika virus. A: Geographic distribution of Zika virus mosquito vectors *Aedes aegypti* and *Aedes albopictus*; B: Countries with evidence of Zika virus reports/outbreaks[5].

seven non-structural (NS) proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5] (Figure 2)[8].

3. Structural proteins

3.1. C protein

The 122 amino acid C protein is seen in the cytoplasm of infected cells that forms the RNA- nucleocapsid complex in virions. The C proteins of virions are positively charged and assemble the homodimers after the polyprotein cleavage and its release into the cytoplasm. The two-sided domain of the capsid contains basic residues that bind with RNA genome and hydrophobic residues that co-operate with the lipid envelope of the virus. The C protein also acts as RNA chaperone and its dimer evades RNA sensors and nucleases from the host. It aids in the formation of nucleocapsid buds along with E and prM proteins in the lumen of the endoplasmic reticulum to release a complete virion[9].

3.2. prM protein

The prM protein, which is present beneath E protein contains 178 amino acids. The prM and E proteins are arranged in icosahedral symmetry with 60 repeating units[10].

3.3. E protein

The 500 amino acid E protein is the precursor encoding the envelope, C protein, and prM protein. E protein plays a vital role along with surface proteins in binding and membrane fusion and is also responsible for targeting the receptors of the host cell. The icosahedral shell of the ZIKV contains 180 copies of each E protein, glycoprotein and membrane proteins embedded in the viral lipid membrane through their transmembrane regions, thereby binds to a variety of cells receptors. The E protein plays a major role in receptor binding, membrane fusion and host recognition[11].

Out of the four domains of E protein, a stem-transmembrane domain helps in membrane anchorage. The remaining 3 domains (Domain Ⅰ, Ⅱ, Ⅲ) which are present outside of the membrane are responsible for host membrane fusion carrying the putative receptor binding site. ZIKV has longer '150 loops' residues with a single glycosylation site in the domain Ⅰ of E protein and varies with other flaviviruses suggesting that this difference influences virus transmission and disease[12].

3.4. NS proteins

The NS1 protein is 342 amino acids long with a molecular weight of 46-55 kDa. It is a highly conserved protein with significant levels of glycosylation that exists as a monomer, dimer, and hexamer. It plays a vital role in the replication of the virus and its secretion provokes immune response[13,14].

NS2A is a membrane-associated hydrophobic and multifunctional protein and aids in the replication of viral RNA. The 226 amino acid long protein binds to 3' untranslated region of RNA virus or to other replication complexes[15]. It controls the antiviral interferon response from the host and secretion of viral particles from cells. NS2B is a hydrophobic protein with 130 amino acids and unknown enzymatic motifs. The membrane-spanning regions present on this portion play a major role in virus replication on the endoplasmic reticular membrane[16]. It also forms the complex of serine protease by association with the C- terminal protease domain of NS3.

NS3 is a multi-dimensional protein and has 617 amino acids with a C terminal portion containing RNA triphosphatase and RNA helicase. The N terminal is involved in capping and viral RNA synthesis. The enzymes present in NS3 help in the unwinding of structured template regions and the processing of viral protein during viral RNA synthesis[14].

NS4A protein consists of 127 amino acids and acts as a determinant factor for the pathogenesis of the Zika virus[17]. NS4B is a poorly conserved protein with 252 amino acids. It contains multiple potential membrane-spanning hydrophobic regions and forms the membrane constituents in the viral replication complex along with its involvement in localization in membranes of NS3 protein[18].

NS5 is a two-domain protein with C terminal RNA dependent RNA polymerase and N terminal methyltransferase. It consists of 902 amino acids and is involved in the synthesis of the viral polypeptide by acting as template strands. The viral and cellular factors recognition, genome stabilization, translation, and RNA packaging

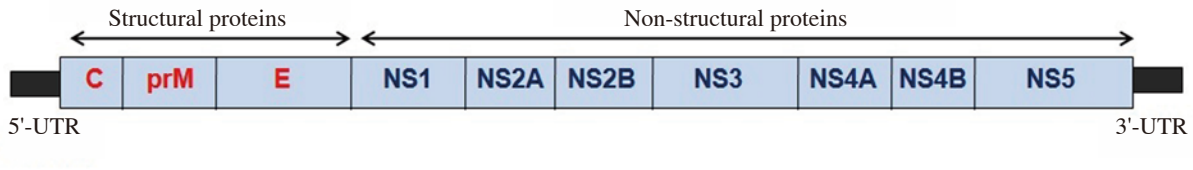

Figure 2. Genomic organization of Zika virus. The viral genome contains a single open-reading frame flanked with untranslated regions at 3' and 5' end. The long polyprotein of ZIKV comprises of three structural proteins (capsid protein, C; precursor membrane protein, prM; envelope protein, E; and seven non-structural proteins, NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5).

are controlled by the other genes in the 3' NCR region[19].

4. Replication and host immune response

The ZIKV can infect a variety of cells from different tissues, where its replication is nuclear in arthropod insects and cytoplasmic in humans and other primates[20]. Kidney cells, fibroblasts, keratinocytes, dendritic cells, brain cells, and astroglial cells are most susceptible to ZIKV infection and support its replication. The salivary glands and midgut are the sites of viral replication in *Aedes* mosquitoes[21]. The infection of Zika in epidermal keratocytes results in cell apoptosis where cytoplasmic vacuolation appears along with the presence of pyknotic nuclei in stratum granulosum, which prevents the antiviral immune response in host cells[22].

The structural proteins play a key role in the attachment and multiplication of the virus in host cells. ZIKV particle carries specific E proteins on its outer envelope that facilitates the attachment of the virus to host-specific receptors located on the cell membrane thereby internalizing the virus through endocytosis[23,24]. After the entry into the cell, the RNA genome of the virus is released into the cytoplasm, where it actively multiplies to synthesize a long polypeptide encoding for structural proteins to make new viral particles. The virus replication takes place on the endoplasmic reticulum surface, where the viral assembly is formed using a patch of ER membrane that constitutes the viral envelope[25]. The virions use the endosomal sorting complexes of the host for transportation to the Golgi apparatus. The virion is called as mature virus after the cleavage of prM protein and exits the cell *via* exocytosis[26,27].

The viral replication in host cells incites an innate antiviral response, stimulating the transcription of toll-like receptors-TLR3, TLR7, RIG-I and MDA5[28]. The increased levels of TLR3 were accompanied with strongly enhanced expression of interferon regulatory factor (IRF7) and production of IFNα, IFNβ. The levels of two chemokines- CXCL10 and CXCL11, which have crucial roles in innate and adaptive immunity in the host system have found to be increased during ZIKV infection. The Zika viral infection also triggers autophagy in infected fibroblasts. The cells infected with the ZIKV showed co-localization of autophagic marker LC3 along with viral proteins[29].

5. Geographical distribution and outbreaks

ZIKV is a re-emerging vector-borne virus that was first isolated from a Sentinel Rhesus Macaque monkey in 1947[3,30]. From 1947 to 2007, only 14 cases Zika infection were reported and were diagnosed by viral isolation or serology in Asia and Africa[31]. In the last decade, ZIKV infection has been widely spread to different geographical locations including East & West Africa, South Asia, Micronesia, French Polynesia and South America[32]. The *Aedes* species is the causative vector for the recent outbreak. Eggs of *Aedes albopictus* species could undergo suspended development for several months, thereby increasing its survival rate and multiplicity in temperate regions[33,34]. The changes in climatic factors and environmental conditions are the main causes that lead to the spread of mosquitoes causing Zika infection worldwide[35].

ZIKV was first isolated in a febrile Sentinel Rhesus monkey in Uganda, 1947; recovered in *Aedes africanus* mosquito in 1948 and was found circulating in the blood of a girl in Nigeria, 1954[3,36]. The virus was in circulation from 1954-2001 in African countries like Kenya, Fagbami, Sierra Leone, Uganda, Gabon, Central African Republic, Senegal and Ivory Coast with prevalence 1%-50%[28]. Recently in 2015-2016, approximately 7 500 cases of Zika were reported at Cabo Verde islands without any neurological complications[37].

The virus also spread to the South East Asian sub-continent where seroprevalence of ZIKV in humans was seen in countries like India, Malaysia, Philippines, Vietnam, and Thailand. Few positive cases were identified in travelers returning from Thailand, Maldives, and Cambodia from 2010 to 2015. ZIKV epidemic emergence was observed for the first time on the Yap Island of the Federal States of Micronesia infecting three-quarters of the residents in 2007. The transmission of the virus into Yap Island is still unknown and is suspected to be transmitted through an infected mosquito (*Aedes hensilli*) or by an asymptomatic person[38]. A large outbreak happened in French Polynesia, South Pacific in 2013 affecting 11% of the population showing Guillain-Barre syndrome[39,40]. The analysis revealed that probable vectors were *Aedes aegypti* and *Aedes polynesiensis*, that carried circulating virus closely related to the 2007 Yap and 2010 Camboya strains[41,42]. Subsequently, the outbreak spread to other Pacific Islands like New Caledonia, Cook Islands, Eastern Island, Vanuatu and the Solomon Islands epitomizing that the virus was imported from individuals travelling from French Polynesia[43].

Australia showed the first case of Zika infection in 2012 which was identified in a traveler returning from Indonesia[44] and later all the cases have been imported from countries affected with the Zika virus. Europe also showed a case of ZIKV infection that was diagnosed in a German traveler returning from Thailand[45]. In 2015, the first autochthonous transmission of ZIKV was reported in Brazil due to the large mobility of the population, favorable climatic conditions with a rapid disease spread affecting about 1.3 million cases[32,46]. Several countries of South and Central America were also prone to ZIKV infection with a quick spread of the disease in 2016[47]. A total of 49 countries and territories in the Americas showed ZIKV transmission in April 2017[48]. The viral strain in America showed genetical identity, and the strain isolated from patients in French Polynesia disclosed the extension of infection through the Pacific Islands[43]. The ZIKV outbreak was serious

during 2016 in the Americas and declined considerably in 2017 and 2018.

Zika-associated congenital malformations such as microcephaly and fetal death have been reported in some countries in Asia[49]. In 2016, the South East Asian countries like Vietnam, Singapore also reported that the local ZIKV transmission in some cases showed ZIKV associated microcephaly[50,51]. In 2018, there was an epidemic outbreak of ZIKV infection in India at Jaipur, a popular tourist destination, affecting around 130 people including pregnant women[52]. In July 2019, 87 countries and territories were affected with ZIKV with evidence of autochthonous mosquito-borne transmission[53].

6. Transmission and symptoms

ZIKV is primarily transmitted through the bite of infected female mosquito vectors of the genus *Aedes* (*Aedes aegypti* and *Aedes albopictus*) that also spread dengue and chikungunya viruses. The virus was also isolated from other species such as *Aedes furcifer*, *Aedes vittatus*, *Aedes africanus*, *Aedes luteocephalus*, *Aedes taylori*, *Aedes apicoargenteus* and *Aedes hirsutus*[31,54,55]. The ZIKV is transmitted through a mosquito bite, human to human transmission, blood transfusion and animal to human transmission[56]. There are two life cycles of ZIKV: urban and sylvatic. Humans are the primary amplification hosts for ZIKV in the urban cycle whereas non-human primates are the major reservoirs in the sylvatic cycle. The virus is acquired by the hematophagus mosquitoes *via* blood meal; and hosts it throughout their life span without being affected. The infected mosquitoes in their next bite or blood meal transmit the virus to the host where it replicates[57].

ZIKV can be transmitted from mother to fetus by the viral replication in placental macrophages and cytrophoblasts[58]. Impaired fetal brain development, microcephaly, and other congenital developmental defects have been reported due to the trans-placental virus infection[59]. The virus is also transmitted by the sexual route from an infected man to woman and *vice versa*[60]. ZIKV can also be transmitted passively by blood transfusion[61]. ZIKV RNA has been detected in blood, urine, semen, saliva, female genital tract secretions, cerebrospinal fluid, amniotic fluid and breast milk[62].

ZIKV causes severe fever and most of the cases are asymptomatic. The mild symptoms may be similar to that of dengue. The symptoms reported are fever, red eyes, joint pain, headache, muscle pain, fatigue, chills, loss of appetite and maculopapular rashes on the skin. The symptoms generally last less than seven days. Other commonly reported clinical symptoms include myalgia, retro-orbital pain, and asthenia. Zika infection in adults is associated with Guillain-Barre syndrome, autoimmune disease and other rare central nervous system pathologies[41,63]. The recent outbreaks of Zika showed direct effects on the nervous system within 6 days after the onset of virus symptoms[41]. ZIKV infection is also associated with severe outcomes such as microcephaly, congenital neurological symptoms and intrauterine growth defects due to vertical transmission of the virus during pregnancy[64]. The risk of infection varies with gestational age and could be highest in the first trimester of pregnancy and also few cases were observed in the third trimester[64,65]. Viremia is the adverse effect during pregnancy, as high viremia breaches the placental barrier and increases the risk of fetal growth abnormalities[58].

7. Diagnosis, treatment and control

As most of the arboviral infections have similar clinical symptoms, the detection of the ZIKV infection may be misdiagnosed with other flaviviruses. Zika, chikungunya, dengue, Japanese encephalitis, West Nile fever and yellow fever share similar symptoms which induces the production of cross-reactive antibodies in humans[66,67]. The cross-reactive antibodies limit the use of serological tests and viral culture for the detection of ZIKV antigens[41]. The diagnosis of ZIKV can be done by reverse transcription (RT)-PCR based detection of viral RNA in a patient's blood or urine samples[68,69]. "Pan flavivirus" amplification technique in combination with sequencing can be used as an alternative to RT-PCR[12,70,71]. Recently, commercial tests like IgM ELISA, immunofluorescence assays and plaque reduction neutralization tests are available for diagnosis of ZIKV infection[72].

Till now, there is no specific antiviral treatment, vaccines or therapeutics available for ZIKV infection. Research is in progress for the development of DNA based, live-attenuated, chimeric, subunit and purified inactivated vaccines. Symptomatic treatments include supporting treatment, rest, fluid intake and avoiding the mosquito bites. The intake of analgesics, antipyretics, and antihistamines can relieve body pains, fever, and pruritic rashes. The usage of analgesics and antipyretics must be cautious to prevent adverse effects especially in patients suffering from dengue. Usage of aspirin and non-steroidal anti-inflammatory drugs must be avoided if the patient has dengue virus infection also, as it may lead to complications like bleeding/ hemorrhages[73]. Acetaminophen can be given to treat pain and fever[74]. Cold bath and application of lotions containing calamine or menthol are recommended along with antihistamines that have sedative action on skin rashes[75,76]. People with suspected Guillain-Barre syndrome should be hospitalized due to the risk of respiratory muscle paralysis, and should be treated by plasmapheresis and hyperimmune intravenous immunoglobulin[77]. Development of many nucleoside inhibitors[78-81], interferons[82,83] and neutralizing antibodies[84,85] are in pipeline for inhibition of viral entry and replication in the host. Repurposing drugs like mycophenolic acid, bortezomib, PHA-690509, vermectin, sertraline, daptomycin, cyclosporine a, azathioprine, vinblastine, vincristine,

nocodazole, sunitinib, clemastine, colchicine, azithromycin, sinefungin, suramin, memantine, kitasamycin, 6-azauridine can be used as remedial measures to inhibit ZIKV infection[14].

The control measure for ZIKV is the prevention of mosquito bites and the control of mosquito vectors. The mosquito population can be controlled by spraying insecticides, neem leaf fumes and by bacterium *Wolbachia*[86]. Use of personal protective measures like wearing long-sleeved shirts, long pants, mosquito repellents, and sleeping under mosquito nets are recommended to avoid the mosquito bites. Other measures include the elimination of standing water, installation of window and door nets to prevent the contact of mosquito vectors with humans. Centers for Disease Control recommends the implementation of mosquito control programs along with the increase of awareness among the public on sexual transmission and blood transfusion[28].

8. Conclusion

The urbanization, increase in tourism, transportation, change in climatic conditions and vector resistance and adaptation are the key risk factors for the emergence and re-emergence of arboviral infections. The genus *Flavivirus* consists of more than 70 viruses which are mostly vector-borne with mosquitoes as primary transmitters. Zika is a mosquito-borne infection that primarily occurs in tropical and subtropical regions. The complications associated with ZIKV infection need an immediate and effective vaccine candidate to fight against this disease. The progressive occurrence of ZIKV infection and its epidemics has thrown a challenge to the scientific world for a complete understanding of the virus and disease. There is an urge to identify and study the molecular mechanisms underlying the ZIKV infection, which can open up an avenue for novel approaches to confer long-lasting protection against Zika. Advanced, efficient and cost reduction measures have to be implemented with the active involvement of the community for control of mosquito vectors and its larvae. Health departments should take initiatives to maintain local areas with proper sanitation, hygiene, and cleanliness by conducting regular awareness programs to prevent local transmission.

Conflict of interest statement

We declare that there is no conflict of interest.

Acknowledgments

The authors are very thankful to The Department of Biotechnology, Bharathiar University, Coimbatore, Tamil Nadu, India for supporting this research through DST-FIST, UGC-SAP and UGC-UKIERI.

Authors' contributions

SR supervised and critically reviewed the manuscript. AM and BMS carried out the literature search and drafted the manuscript. All the authors read and approved the final manuscript.

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