Zika virus: An emerging challenge to public health worldwide.

<table>
<thead>
<tr>
<th>Journal:</th>
<th>Canadian Journal of Microbiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>cjm-2019-0331.R2</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Review</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>19-Oct-2019</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Sharma, Vikrant; Maharshi Dayanand University Rohtak, Centre for Biotechnology Sharma, Manisha; Himachal Pradesh University, Department of Biotechnology Dhull, Divya; Maharshi Dayanand University Rohtak, Centre for Biotechnology Sharma, Yashika; Maharshi Dayanand University Rohtak, Centre for Biotechnology Kaushik, Sulochana; Maharshi Dayanand University Rohtak, Department of Genetics Kaushik, Samander; Maharshi Dayanand University Rohtak, Centre for Biotechnology</td>
</tr>
<tr>
<td>Keyword:</td>
<td>Emerging infection, flaviviruses, microcephaly, Zika virus, ZIKV</td>
</tr>
<tr>
<td>Is the invited manuscript for consideration in a Special Issue?:</td>
<td>Not applicable (regular submission)</td>
</tr>
</tbody>
</table>

https://mc06.manuscriptcentral.com/cjm-pubs
Title: Zika virus: An emerging challenge to public health worldwide.

Running Title: Emerging threat of Zika virus.

Authors: Vikrant Sharma¹, Manisha Sharma², Divya Dhull¹, Yashika Sharma¹, Sulochana Kaushik³ and Samander Kaushik¹*

¹Centre for Biotechnology, Maharshi Dayanand University, Rohtak-124001, Haryana, India.
²Department of Biotechnology, Himachal Pradesh University, Shimla-171005, Himachal Pradesh, India.
³Department of Genetics, Maharshi Dayanand University, Rohtak-124001, Haryana, India.

*Correspondence: Samander Kaushik, Centre for Biotechnology, Maharshi Dayanand University, Rohtak-124001, Haryana, India. Email: samanderkaushik@gmail.com; Phone: +91-9017733717

ORCID: 0000-0003-4835-6383
Abstract

Zika virus (ZIKV) is a mosquito-borne virus which was first isolated from Zika forest, Uganda in 1947. Since its inception, major and minor outbreaks have been documented from several parts of the world. *Aedes* spp. mosquitoes are the primary vectors of ZIKV but the virus can also be transmitted through sexual practices, materno-fetal transmission and through blood transfusion. The clinical presentations of symptomatic ZIKV infections are similar to dengue and chikungunya, including fever, headache, arthralgia, retro-orbital pain, conjunctivitis and rash. ZIKV often causes mild illness in the majority of cases but in some instances it is linked with congenital microcephaly and autoimmune disorders like Guillain-Barré syndrome (GBS). The recent Indian ZIKV outbreak suggests that the virus is circulating in the South East Asian region and may cause new outbreaks in the future. At present, no specific vaccines or antivirals are available to treat Zika virus and the management and control of ZIKV infections relies mostly on preventive measures.

**Key Words:** Emerging infection; flaviviruses; microcephaly; Zika virus; ZIKV
1. Introduction

Zika virus (ZIKV) is an important arbovirus belonging to the genus *Flavivirus* of the family *Flaviviridae*. It was firstly isolated in 1947 from a rhesus monkey in the Zika forest of Kampala, Uganda (Dick et al. 1952). The first seropositive cases of human infection were reported from Tanzania and Uganda in 1952 while the first human isolation of ZIKV was reported from a ten years old female from Nigeria in 1953 (MacNamara 1954). Since then, ZIKV expanded its geographic range to various countries of Africa, Asia, Oceania and Americas. Sporadic cases of self-limited illness continue to appear in human populations from these areas. The genus *Flavivirus* contains 53 different virus species, the majority of which are transmitted by mosquitoes (https://talk.ictvonline.org/taxonomy/). ZIKV is closely related to other mosquito-borne flaviviruses like dengue virus, Japanese encephalitis virus, yellow fever virus and West Nile virus which are responsible for a large number of human infections. All these viruses including ZIKV are known for their ability to propagate to new areas and are grouped as emerging or reemerging pathogens (Weaver et al. 2016). The genomic and phylogenetic analysis of ZIKV isolates indicated the presence of two distinct lineages; African and Asian, both originated from East Africa (Gatherer and Kohl 2016). *Aedes* spp. mosquitoes (*Ae. aegypti*, *Ae. albopictus*, *Ae. hensilli*, *Ae. africanus* and *Ae. polynesiensis*) are primarily responsible for the spread of ZIKV infection in humans (Boyer et al. 2018).

The infection can also be transferred by uncommon means like transfusion of infected blood products, sexual transmission and materno-fetal transmission (Petersen et al. 2016). Most of ZIKV infections are asymptomatic or represent a self-limiting febrile illness similar to chikungunya and dengue infections. In ZIKV endemic regions, most of the infections are not reported due to their self-limiting nature and therefore it is difficult to estimate the exact disease burden. The association of virus infection with neurological complications like congenital microcephaly and Guillain-Barré Syndrome (GBS) has been supported by studies performed during ZIKV outbreaks of Brazil and French Polynesia (Oehler et al. 2014; Schuler-Faccini et al. 2016; de Araújo et al. 2016). The complex transmission cycle of ZIKV and asymptomatic infections which are difficult to differentiate from that of other flaviviruses, further contribute to rapid spread of the disease. Thus in the present review we emphasize on important aspects of...
ZIKV including its virology, transmission, clinical manifestations, diagnosis, treatment and prevention strategies for better management and control of ZIKV related outbreaks.

2. Virology

The virion is about 40-60 nm in diameter, enveloped and has an icosahedral shell embedded with surface projections. The genome of ZIKV contains a non-segmented, positive-sense, single stranded RNA of about 11 kb which encodes around 3500 amino acids. Genome of ZIKV has a single long open reading frame (5’-C-prM-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-3’) with flanking untranslated regions at both ends (Cox et al. 2015). The genome encodes a single polypeptide which is cleaved by host-cell proteases into three structural proteins (capsid-C, envelope-E and precursor membrane-prM/membrane-M) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) (Cox et al. 2015; Lei et al. 2016; Wang et al. 2017).

The replication cycle of ZIKV is very similar to other flaviviruses starting with the binding of virus particles to one or more cellular receptors through surface spikes. The bound virion is then endocytosed into the host cell cytoplasm. The viral E protein plays key role in host surface binding and membrane fusion. Inside the host cytoplasm, endosomal lumen containing ZIKV becomes acidic, activating surface glycoproteins to undergo conformational changes (Heinz and Stiasny 2017). These changes lead to fusion of the viral envelope glycoproteins with the endosomal membrane releasing the viral genome from the capsid. The genome is translated into single polypeptide which is processed further to generate viral proteins. The positive-sense RNA genome of ZIKV is replicated via negative-strand RNA intermediate (Cortese et al. 2017). The viral C protein helps in packaging of new RNA genomes into progeny virions which are secreted from the endoplasmic reticulum lumen as enveloped viruses. After acquiring posttranslational processing of E protein and prM protein, matured infectious virus particles are released from the host cell by exocytosis (Pierson and Diamond 2012).

3. Epidemiology and Global expansion

The first isolation of ZIKV was from rhesus monkey in 1947 from Uganda and later it was isolated from Ae. africanus mosquitoes in 1948 from the same area (Dick et al. 1952). After its detection in humans in
1952, the serosurveillance studies showed a much wider distribution of ZIKV in many African and Asian countries (MacNamara 1954; Weaver et al. 2016). Seroprevalence of ZIKV-antibodies were reported from the human population in most of the African countries including Central Africa, Egypt, Gabon, Nigeria, Sierra Leone, Tanzania and Uganda (Smithburn 1952; Dick 1953; Smithburn et al. 1954a; Moore et al. 1975; Weaver et al. 2016). First reports of ZIKV outside Africa were from Malaysia, where it was isolated from *Ae. aegypti* mosquitoes and cases of human infection were reported from Indonesia (Marchette et al. 1969; Olson et al. 1981). In 1950s-1980s, serological evidence of ZIKV infection was reported from different Asian countries including India, Indonesia, Malaysia, Pakistan, Philippines, Thailand and Vietnam (Table 1) (Smithburn et al. 1954b; Smithburn 1954; Hammon et al. 1958; Pond 1963; Darwish et al. 1983).

For six decades since its discovery, ZIKV remained confined to Africa and Asia causing sporadic outbreaks. In 2007, the first major ZIKV outbreak was reported from Yap Islands, Federated States of Micronesia in Western Pacific, causing infection in approximately 75% of the total population (Duffy et al. 2009). The Asian lineage of ZIKV was thought to be responsible for this epidemic (Lanciotti et al. 2007). After this episode, ZIKV is considered as a potential emerging infection worldwide. The virus later spread over Pacific and caused outbreak in French Polynesia in 2013-2014 (Cao-Lormeau et al. 2013). Similar outbreaks were reported from other Pacific islands including Cook Islands, Easter Islands, New Caledonia and Solomon Islands (Dupont-Rouzeyrol et al. 2014; Musso et al. 2014a; Roth et al. 2016; Tognarelli et al. 2016). The outbreak of French Polynesia resulted in over 30,000 cases of illness however the precise number of infections is difficult to predict due to probability of silent infections. It is estimated that over 11% of the total population were infected in outbreak of French Polynesia (ECDC 2014; Musso and Gubler 2016). ZIKV was introduced into Easter Island, Chile by people traveling from French Polynesia and about fifty confirmed cases were reported by Public Health Institute Chile during 2014 (Tognarelli et al. 2016). The virus arrived to Americas between 2013 and 2015, most likely from Pacific and caused explosive outbreak in Brazil. The first infection cases were reported from Rio Grande do Norte in early months of 2015 (Zanluca et al. 2015). In May 2015, first case of autochthonous
transmission was reported from Bahia and till December 2015, 18 states of Brazil have reported autochthonous ZIKV transmission. This outbreak accounted for 440,000 to 1,300,000 suspected infection cases (Hennessey et al. 2016; Musso and Gubler 2016). Mosquito vectors for ZIKV have widespread distribution in Brazil where *Ae. aegypti* is distributed in mainly Northern, North Eastern and Central Eastern region while *Ae. albopictus* is found mostly in Southern region. ZIKV infections were also confirmed from Columbia, Mexico, Venezuela, Paraguay, Panama, El Salvador, Guatemala and different Caribbean countries (Hennessey et al. 2016; Musso and Gubler 2016). The researchers found rise in number of microcephaly cases from Zika infected areas in Brazil, and more than 4300 cases of fetal abnormalities including microcephaly have been reported till February 2016 (de Araújo et al. 2016; Victora et al. 2016). In 2016, ZIKV cases were reported from Florida and Texas which marked the entry of the virus in continental USA (McCarthy 2016).

ZIKV continues to develop and spread silently throughout the world in the form of asymptomatic infections. In May 2017, Ministry of Health and Family Welfare (MoHFW), India reported three RT-PCR positive cases for ZIKV from Gujarat, India. One more confirmed case was reported from Tamil Nadu, India (WHO 2017; Bhardwaj et al. 2017). These cases were the first confirmation of the presence of ZIKV in Indian population (Sapkal et al. 2018). No travel history to ZIKV endemic areas was noticed in any of these cases suggesting that the virus is endemic to the country. However, the virus showed a very low level of transmission in the community as evident by the number of confirmed infections. During September-November 2018, biggest Indian ZIKV outbreak is reported from Rajasthan and Madhya Pradesh states of India. A total of 159 individuals including 64 pregnant women have been confirmed as ZIKV positive by RT-PCR from Rajasthan state whereas Madhya Pradesh state has reported 130 confirmed cases of Zika infection (IDSP 2018). Fig. 1 shows geographic distribution of ZIKV since its discovery to recent outbreak in 2018.

4. Transmission

4.1. Vector-borne transmission
Like most of the flaviviruses, the main route of transmission for ZIKV is through the bite of infected mosquito. But other modes of transmission like, infected blood transfusion, sexual transmission and materno-fetal transmission are also reported. Two distinct life cycles have been reported for ZIKV; enzootic or sylvatic cycle and epidemic or urban cycle (Petersen et al. 2016; Weaver et al. 2016) (Fig. 2). ZIKV is maintained in nature through enzootic or sylvatic cycle occurring between \textit{Aedes} mosquitoes and non-human primates including apes and monkeys. Sylvatic cycle is thought to be the reason behind the maintenance of ZIKV lineage in Africa whereas sylvatic transmission has not been proved in Asia. The major forest-dwelling \textit{Aedes} mosquitoes are \textit{Ae. africanus}, \textit{Ae. furcifer}, \textit{Ae. taylori} and \textit{Ae. luteocephalus} which act as enzootic vectors in Africa (Diallo et al. 2014; Petersen et al. 2016). Humans are the incidental host in such transmission cycle and further carry the virus to epidemic or urban cycle in which human-mosquito-human transmission of ZIKV is observed (Fig. 2). In urban cycle, humans are the main host and serve as amplifier and carrier of infection to uninfected mosquitoes. \textit{Ae. aegypti} and \textit{Ae. albopictus} are principle species involved in such transmissions and have been noted in the majority of ZIKV outbreaks. \textit{Ae. aegypti} is mostly confined to tropical and sub-tropical regions but \textit{Ae. albopictus} is found in temperate areas along with tropical and subtropical regions, increasing the outreach of ZIKV. The other \textit{Aedes} species reported to act as vectors in epidemic cycles were, \textit{Ae. hensilli} and \textit{Ae. polynesiensis} during outbreaks of Yap and French Polynesia, respectively (Ledermann et al. 2014; Musso et al. 2014b).

\textbf{4.2. Non-vector-borne transmission}

Majority of ZIKV transmissions are vector-borne but it can also spread through non-vector borne mode including sexual transmission, materno-fetal transmission and blood transfusion. Sexual transmission is reported in different cases especially in travelers returning from ZIKV endemic areas (Foy et al. 2011; Hills et al. 2016; Musso et al. 2015a). ZIKV is the first arbovirus to be detected in the semen and high viral loads has been reported from semen samples of infected individuals indicating potential for sexual transmission (Atkinson et al. 2016). The viral RNA has also been detected in the saliva and urine samples of infected individuals (Gourinat et al. 2015; Barzon et al. 2016). Sexual transmission may enable limited
sub-critical transmission in areas without *Aedes* spp. In most of the cases, sexual transmission has been observed from infected males to their sex partners but female-to-male transmission is also reported in some instances (Davidson et al. 2016).

Blood transfusion is another potential novel route for ZIKV transmission and was suspected during the French Polynesian outbreak in 2013-2014. The viral RNA was detected among 2.8% asymptomatic blood donors in the region during ZIKV outbreak (Musso et al. 2014). In 2016, confirmed cases of viral transmission by blood transfusion were reported from Brazil (PAHO 2016). Likewise sexual transmission, the numbers of blood transfusion related transmissions are difficult to predict in ZIKV endemic areas. For safe blood transfusions, molecular diagnostic tools should be used for screening blood donors especially those who recently visited ZIKV endemic areas.

Prenatal transmission of ZIKV has been detected in neonates born to mothers with a history of infection. These transmissions were observed during the French Polynesian outbreak in 2013-2014 (Bensnard et al. 2014). ZIKV infection during pregnancy may be associated with microcephaly and miscarriages (Oehler et al. 2014; de Araújo et al. 2016; Schuler-Faccini et al. 2016; van der Eijk et al. 2016). Vertical transmission of ZIKV from an infected pregnant mother to her developing fetus via placenta can cause neurological damage to developing fetus (Mlakar et al. 2016). Experimental evidence of trans-placental transmission was provided in a study on mouse models however, the exact mechanism of ZIKV crossing the placental barrier is not understood yet (Bayer et al. 2016; Miner et al. 2016). ZIKV RNA has been recovered from amniotic fluid, placental tissue and fetal brain tissue, and electron microscopy has shown the presence of virus particles in fetal brain tissue (Calvet et al. 2016; Oliveira et al. 2016). The viral RNA has been detected in the breast milk but no definitive evidence has been reported (Colt et al. 2017). The other reported instances of non-vector-borne transmission are through bite of infected monkey and accidental exposure in laboratory environment (Simpson 1964; Leung et al. 2015).

5. **Clinical features, complications and mechanism of neuropathogenesis**

Clinical presentations of ZIKV infections are not specific and often mistaken for other flaviviral infections like dengue and chikungunya. In symptomatic ZIKV infections, the symptoms appear within 3-
12 days post-infection, however, 80% of estimated cases are asymptomatic (Duffy et al. 2009). Symptomatic cases represent low-grade fever, headache, joint pain, body rash, conjunctivitis and gastrointestinal disturbance (Basarab et al. 2016). Acute infection is mild, self-limiting and the patients recover within a week without any specific damage. The association of chronic ZIKV infections with neonatal complication is a matter of serious concern. It was recognized in late 2015 when the number of neonatal microcephaly cases was increased during ZIKV outbreak in Brazil (Kleber de Oliveira et al. 2016). However, in 20% of the cases of congenital Zika syndrome, microcephaly was not observed therefore, it can’t be used as the only symptom for screening congenital Zika cases (França et al. 2016). Presence of viral mRNA in amniotic fluids and placenta strongly suggests the association of congenital Zika syndrome with neonatal complications. Such complications include congenital microcephaly, optic neuropathy, congenital glaucoma, ventriculomegaly and lissencephaly (de Araújo et al. 2016; Baud et al. 2017). Investigations on neonatal pathogenesis by in-vitro and in-vivo models indicate destruction of neuroprogenitors, neural cells by the presence of inflammatory molecules (Hussain et al. 2018).

Apart from neonatal complications, infected adults have shown ZIKV related complications. Guillain-Barré syndrome (GBS) is thought to be strongly associated with ZIKV infections in adult population. It is an autoimmune condition, where the cell-mediated immunity attacks myelinated neural cells and leads to gradual muscle weakness, reduced nerve function or even paralysis. Evidence of strong association between GBS and ZIKV infection is provided by studies of outbreaks in French Polynesia and Americas. In French Polynesia, the incidence rate of GBS was increased twenty-fold during the outbreak of 2013-2014. Similar observations were recorded in various countries in the Americas during the outbreak of 2015-2016 (Cao-Lormeau et al. 2016; Dos Santos et al. 2016). Other associated complications in adults include arthralgia and cardiovascular problems however a more evidence-oriented research is needed to establish the exact link between Zika infections and cardiovascular anomalies (Edupuganti et al. 2017; Minhas et al. 2017).

The molecular mechanism of ZIKV neuropathogenesis involves the role of various cellular receptors like DC-SGN, heat shock proteins and phosphatidylserine receptor proteins (TIM-1, TIM-4, AXL and
TYRO3). ZIKV interacts with TLR3 receptors of cutaneous fibroblasts resulting in an interferon response. The AXL receptors protein, help the virus infect cutaneous fibroblasts and keratinocytes (Hamel et al. 2015). In a previous study on developing fetal brain cells in humans, it has been observed that these cells are highly enriched with AXL receptors making them susceptible to ZIKV infection (Nowakowski et al. 2016). For a successful infection, the innate immune barrier must be overcome, which is achieved by ZIKV through degradation of the IFN-regulated transcriptional activator STAT2 (Grant et al. 2016). In materno-fetal transmission of ZIKV, human neural progenitor cells (hNPCs) of the developing fetus are infected efficiently by ZIKV and this has been established in different in-vitro neuropathogenesis studies (Bhagat et al. 2016; Garcez et al. 2016; Tang et al. 2016). The ZIKV infected hNPCs may show cytopathic effects and cell death or consistent virus replication with restricted cytopathic effects thus making hNPCs, a target of ZIKV leading to brain abnormalities including microcephaly (Tang et al. 2016). The development of neurospheres and brain organoids mark the early phases of neurogenesis during the first trimester of fetal brain development. The ZIKV infected hNPCs have been shown to generate very few numbers of neurospheres in comparison to their healthy counterparts, suggesting significant damage to the developing fetal brain during this time period (Garcez et al. 2016; Tang et al. 2016).

**Diagnosis**

Rapid transmission of ZIKV infections has a severe impact on public health and a rapid, sensitive, specific and cost-effective diagnostic method is required for better management of the disease. Clinical symptoms such as rash, fever, conjunctivitis and patient history could be helpful in initial screening of symptomatic infections. But confirmation of infection solely based on clinical presentation is difficult as the symptoms overlap with other arboviral infections like chikungunya, dengue, yellow fever etc. Therefore, World Health Organization (WHO) has recommended the use of RT-PCR and serological tools for confirmations of suspected cases of Zika infection (PAHO 2017). Virus isolation is considered as the ‘gold standard’ method and can be used to generate large virus titre, but its lengthy and laborious nature limits its use in routine diagnosis (Bonaldo et al. 2016). Different commercial diagnostic kits based
on serology and nucleic acid detection, have been developed after the severe ZIKV outbreak of Americas in 2015-2016. The Food and Drug Administration (FDA) has fast tracked the commercial kits approval system by providing Emergency Use Authorisations (EUA) facility (FDA 2019). This enables manufactures to bypass the traditional FDA approval system and to provide relevant assay protocols for clinical diagnosis during an outbreak emergency. The present commercial diagnostic kits for ZIKV are EUA approved and are based on either serology or molecular detection (Table 2).

The blood serum is usually preferred specimen choice for detection of ZIKV through either antibody-based serological methods or molecular diagnosis of viral RNA. But low-level viremia cases and the serum collected 10 days after the onset of symptoms, may limit the sensitivity of molecular methods (St George et al. 2017; Theel and Hata 2018). However, the comparative analysis of different specimen types showed higher viral loads in urine samples (St George et al. 2017). Other than serum and urine; body fluids like amniotic fluid, saliva, cerebrospinal fluid (CSF), semen and placental tissue can also be used as specimen for ZIKV detection (Gourinat et al. 2015; Musso et al. 2015b; Atkinson et al. 2016; Staples et al. 2016). Most of the serological assays rely on detection of IgM antibodies by IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA). Serological analysis of anti-ZIKV IgM antibodies may help in diagnosis of infections which are not detected by RT-PCR due to low viremia. These assays may produce cross-reactive results similar to other flaviviruses, therefore a more specific confirmatory test like plaque reduction neutralization test (PRNT) is required (Rabe et al. 2016). Commercial assay kits with EUA approval such as Centers for Disease Control and Prevention (CDC) ZIKV MAC-ELISA; ZIKV Detect IgM capture ELISA; Liaison XL Zika capture IgM assay; ADVIA Centaur Zika test and DPP Zika IgM system have significantly aided the diagnostic facility especially in Zika endemic regions (Table 2).

Molecular detection of ZIKV RNA through the RT-PCR remains preferred choice of diagnosis during acute phase of infection. Most of the developed commercial kits for ZIKV detection are based on RT-PCR. The first molecular detection based commercial assay to get FDA EUA approval was CDC Trioplex Real-Time RT-PCR assay. It can detect ZIKV, dengue virus and chikungunya virus in different specimen
types including serum, whole blood, urine, CSF and amniotic fluid (Theel and Hata 2018). Non-PCR based amplification tools like reverse transcription loop-mediated isothermal amplification (RT-LAMP) has been used successfully to detect RNA viruses including dengue, influenza and ZIKV (Parida et al. 2005; Song et al. 2016; Calvert et al. 2017; Sharma et al. 2018). Molecular based methods like Real-Time RT-PCR could give more specific results if applied within the first week of illness. However, in the pregnant women having congenital fetal infections, the viral RNA could be detected in serum up to 10 weeks post illness (Driggers et al. 2016).

6. Management, treatment and prophylaxis

Currently, no specific antiviral or vaccine is available against ZIKV infection and the management of Zika cases relies on symptomatic care which includes resting, fluid intake, analgesics and antipyretics. Suspected Zika cases should not be given non-steroidal anti-inflammatory drugs unless likelihood of hemorrhagic dengue fever is annulled (Chan et al. 2016).

Significant research is being carried out in ZIKV vaccine development and different types of vaccines including DNA-based, live-attenuated, inactivated and subunit vaccines are at various stages of clinical development (Poland et al. 2018). In the absence of specific treatment, prevention is the best way of protection against ZIKV. For all the mosquito-borne diseases, preventive measures are same including protection from mosquito bites and control of vector population (Chen and Hamer 2016).

In ZIKV endemic areas, systematic mosquito control programs should be carried out by public health organizations. Mosquito-bites should be avoided by using mosquito repellent, permethrin cream for treating cloths or skin, using bed-nets and window screens (Chen and Hamer 2016; Petersen et al. 2016). People travelling from ZIKV endemic areas to non-affected regions, should use mosquito repellent for 2-3 weeks to stop the transmission to non-infected mosquito population of those areas. Mosquito repellents like N,N-Diethyl-m-toluamide (DEET) has been reported as safe for use in pregnant and nursing women, and in the children above the age of two months (Hennessey et al. 2016; Staples et al. 2016). In the present scenario, integrated vector management is the most effective approach to prevent and control arboviral disease like Zika. The population of mosquitoes should be controlled by using environment
management practices like destroying their breeding sites, removing stagnant water bodies, spraying larvicides and insecticides. In the areas with autochthonous ZIKV transmission, insecticides should be used to remove infected adult mosquitoes. Community sanitation programs should be carried out in high-risk areas such as landfill sites, construction sites, dumping grounds and wastewater treatment plants (Gubler 2011; WHO 2018). Novel biological control measures such as using Wolbachia bacteria for suppressing viral transmission within the mosquito population should be evaluated (Aliota et al. 2016). Sexual transmission of ZIKV infections has been reported during past outbreaks and hence safe sex practice should be followed after visiting high-risk areas (Musso et al. 2015a; Hills et al. 2016). Pregnant women are at a higher risk of getting infected therefore they should follow safety precautions during their stay in high-risk areas. The travellers returning from ZIKV endemic areas should follow safe sex practice with their pregnant partners. The public health should be monitored for any potential neurological and autoimmune complications in the high-risk areas. The healthcare workers and laboratory personnel should take precautionary measures while dealing with ZIKV infected patients or samples and they should follow safe hygienic practices to reduce the risk of ZIKV transmission (Rather et al. 2017).

7. Conclusion

With expanding global outbreaks, Zika infection has emerged as a significant threat to public health and epidemiological similarities of ZIKV with chikungunya and dengue makes it a suitable candidate for becoming a global health problem. The explosive outbreak in Brazil and the recent Indian outbreak have already highlighted ZIKV’s potential for rapid population spread. Public health authorities should make effective policies to prevent non-vector-borne transmissions along with conventional vector control measures. Detailed research using animal models is much needed to clearly understand the pathogenesis and association of ZIKV with neurological and autoimmune complexities. Factors such as climate change, increasing urbanization, global travel and growth in the human population are behind the increase in the geographical range of mosquitoes and leading burden of various arboviral diseases. It is difficult to predict the next ZIKV epidemic, but with the help of effective surveillance studies integrated with
accurate and rapid diagnosis and the development of specific antivirals and vaccines, we could prepare ourselves for better management and control of this emerging infection.

**Conflicts of interest**

The authors declare no conflict of interest.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Animal and Human Rights Statement**

This article does not contain any studies with human or animal subjects performed by any of the authors.

**References**

Aliota, M.T., Peinado, S.A., Velez, I.D., and Osorio, J.E. 2016. The wMel strain of *Wolbachia* reduces transmission of Zika virus by *Aedes aegypti*. Sci. Rep. 6: 28792. [https://doi.org/10.1038/srep28792](https://doi.org/10.1038/srep28792)


Basarab, M., Bowman, C., Aarons, E.J., and Cropley, I. 2016. Zika virus. BMJ. 352: i1049. [https://doi.org/10.1136/bmj.i1049](https://doi.org/10.1136/bmj.i1049)


https://mc06.manuscriptcentral.com/cjm-pubs


McCarthy, M. 2016. Four in Florida are infected with Zika from local mosquitoes. BMJ. 354: i4235. https://doi.org/10.1136/bmj.i4235


Oliveira Melo, A.S., Malinger, G., Ximenes, R., Szejnfeld, P.O., Alves Sampaio, S., and Bispo de Filippis, A.M. 2016. Zika virus intrauterine infection causes fetal brain abnormality and


Figure captions

Fig. 1 Global distribution of Zika virus infection in humans including major outbreaks till 2018

Fig. 2 Transmission cycle of Zika Virus
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Area or country</th>
<th>No. of infected cases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>Discovery of ZIKV in Rhesus Monkey</td>
<td>Zika forest, Uganda</td>
<td>--</td>
<td>Dick et al. 1952</td>
</tr>
<tr>
<td>1948</td>
<td>Isolation of ZIKV from <em>Aedes</em> mosquito</td>
<td>Zika forest, Uganda</td>
<td>--</td>
<td>Dick et al. 1952</td>
</tr>
<tr>
<td>1953</td>
<td>First isolation of ZIKV from human</td>
<td>Nigeria, Tanzania, Uganda</td>
<td>3</td>
<td>MacNamara 1954</td>
</tr>
<tr>
<td>1950s-1980s</td>
<td>Sporadic mild cases reported from Asian countries</td>
<td>Indonesia, India, Malaysia, Pakistan, Philippines, Thailand</td>
<td>-</td>
<td>Smithburn 1954; Smithburn et al. 1954b; Hammon et al. 1958; Pond 1963; Marchette et al. 1969; Olson et al. 1981; Darwish et al. 1983</td>
</tr>
<tr>
<td>2007</td>
<td>First large outbreak of ZIKV</td>
<td>Yap Island in the Federated States of Micronesia</td>
<td>49 confirmed and 7391 suspected cases</td>
<td>Duffy et al. 2009</td>
</tr>
<tr>
<td>2013-2014</td>
<td>French Polynesia ZIKV Outbreak, Evidence of the Guillaine Barrie syndrome(GBS); Sexual transmission</td>
<td>French Polynesia, Easter Island, Cook Islands, and New Caledonia</td>
<td>28,000-30,000 cases in French Polynesia; 1400 confirmed cases in New Caledonia</td>
<td>Cao-Lormeau et al. 2014; Musso et al. 2014; Roth et al. 2014; Tognarelli et al. 2014; Dupont-Rouzeyrol et al. 2015</td>
</tr>
<tr>
<td>2015-2016</td>
<td>ZIKV Outbreak in Americas</td>
<td>Brazil, Columbia, El Salvador, Mexico, Paraguay, Venezuela, Caribbean countries</td>
<td>440,000-1,300,000 estimated cases in Brazil; 51,473 suspected cases in Colombia</td>
<td>Zanluca et al. 2015; Hennessey et al. 2016</td>
</tr>
<tr>
<td>2016</td>
<td>ZIKV in Continental USA</td>
<td>Florida and Texas</td>
<td>4 cases in Florida</td>
<td>McCarthy 2016</td>
</tr>
<tr>
<td>2017</td>
<td>First confirmed ZIKV outbreak in India</td>
<td>Gujarat, Tamil Nadu</td>
<td>3 cases in Gujarat; 1 in Tamil Nadu</td>
<td>Bhardwaj et al. 2017; WHO 2017</td>
</tr>
<tr>
<td>2018</td>
<td>Biggest ZIKV Outbreak of India</td>
<td>Rajasthan, Madhya Pradesh</td>
<td>159 confirmed cases including 64 pregnant women in Rajasthan; 130 cases in Madhya Pradesh</td>
<td>IDSP 2018</td>
</tr>
</tbody>
</table>
## Table 2 Summary of various available detection methods for ZIKV

<table>
<thead>
<tr>
<th>Method</th>
<th>Commercial kits</th>
<th>Sample type</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus isolation</td>
<td>---</td>
<td>Serum, Urine, Plasma, CSF, Saliva</td>
<td>Produces high titre of virus; Time and labour intensive; Requires expertise and biosafety standards.</td>
<td>Bonaldo et al. 2016</td>
</tr>
<tr>
<td>Serological assays</td>
<td>ZIKV MAC-ELISA; ZIKV Detect IgM capture ELISA; Liaison XL Zika capture IgM assay; ADVIA Centaur Zika test; DPP Zika IgM system</td>
<td>Serum</td>
<td>ZIKV MAC-ELISA (CDC) is the first commercial serological assay to receive FDA approval for Zika diagnosis; All these kits are highly sensitive but lack specificity due to cross reactivity.</td>
<td>Staples et al. 2016; Sloan et al. 2018; Theel and Hata 2018</td>
</tr>
<tr>
<td>Molecular assays based on Real-Time PCR</td>
<td>Trioplex rRT-PCR; Zika Virus RNA Qualitative Real-Time RT-PCR; RealStar Zika Virus RT-PCR Kit; Zika ELITe MGB kit U.S.; Sentosa SA ZIKV RT-PCR test; TaqPath Zika Virus Kit; Versant Zika RNA 1.0 assay (kPCR); xMAP MultiFLEX Zika RNA assay</td>
<td>Serum, Whole blood, Urine, Saliva, CSF, Amniotic fluid</td>
<td>Trioplex rRT-PCR (CDC) is the first commercial molecular assay to get FDA authorisation; In this assay ZIKV envelope gene is targeted; Sensitivity of these kits is very high but varies with type of specimen.</td>
<td>Musso et al. 2015b; Staples et al. 2016; L’Huillier et al. 2017; Theel and Hata 2018</td>
</tr>
<tr>
<td>Transcription-mediated amplification (TMA)</td>
<td>Aptima® Zika Virus Assay</td>
<td>Serum, Plasma, Urine, Saliva</td>
<td>Rapid and high-throughput method; targets NS1 and NS4/NS5 genes.</td>
<td>Ren et al. 2017</td>
</tr>
<tr>
<td>Reverse transcription loop-mediated isothermal amplification (RT-LAMP)</td>
<td>---</td>
<td>Serum, Urine, Saliva, Whole blood</td>
<td>Rapid, reliable, specific and sensitive assay; can be performed in clinical settings</td>
<td>Calvert et al. 2017</td>
</tr>
<tr>
<td>Lateral flow assay</td>
<td>---</td>
<td>Whole blood, Serum, Plasma</td>
<td>No cross-reactivity with other flaviviruses but costly.</td>
<td>Lee et al. 2016</td>
</tr>
<tr>
<td>Plaque Reduction and Neutralization Test (PRNT)</td>
<td>---</td>
<td>Serum</td>
<td>Time consuming and requires expertise; Highly specific; positive results of serology must be confirmed using PRNT.</td>
<td>Rabe et al. 2016; Theel and Hata 2018</td>
</tr>
</tbody>
</table>
Fig. 1 Global distribution of Zika virus infection in humans including major outbreaks till 2018
Fig. 2 Transmission cycle of Zika Virus

592x291mm (96 x 96 DPI)