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REVIEW

Neurological manifestations of Zika virus infection

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Abstract

Zika virus (ZIKV) is a flavivirus (*Flaviviridae* family) transmitted mainly by *Aedes* mosquitoes. The virus was restricted to the African continent until its spread to south-east Asia in the 1980's, the Micronesia in 2007, the French Polynesia in 2013 and, more recently in the Americas in 2015, where, up to date, the World Health Organization (WHO) has estimated about 3-4 million total cases of ZIKV infection. During outbreaks in the French Polynesia and Brazil in 2013 and 2015, respectively, national health authorities reported potential neurological complications of ZIKV disease, chiefly an upsurge in Guillain-Barré syndrome, which coincided with ZIKV outbreaks. On the other hand, the emergence of ZIKV in Brazil has been associated with a striking increase in the number of reported cases of microcephaly in fetus and newborns, twenty times higher than in that reported in previous years. While investigations are currently assessing whether there is an actual association between neurological complications and ZIKV infections, the evidence was enough worrisome for WHO to declare a public health emergency of international concern. Here we present an updated review addressing what is currently known about the possible association between ZIKV infection and the development of severe neurological disorders.

Key words: Zika virus; Flavivirus; Microcephaly; Guillain-Barré syndrome; Transmission routes

Core tip: Zika virus (ZIKV), a mosquito-borne flavivirus, was restricted to Africa until its spread to south-east Asia, the Pacific, and, finally, to the Americas, where an estimated 4 million cases of ZIKV infection have been recorded, and where a worrisome possible association of ZIKV with the development of severe neurological disorders, such as Guillain-Barré Syndrome and microcephaly, have been reported. In this contribution we present an updated review addressing what is currently known about the possible association between ZIKV infection and the development of severe neurological disorders, remarking the urgent need for further investigations to clearly resolve this point.

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THE VIRUS

Zika virus (ZIKV) is a mosquito-borne *Flavivirus* classified into the *Flaviviridae* family. It is closely related to other important pathogens that affect human and animal health such as Japanese encephalitis virus, dengue virus (DENV), yellow fever virus (YFV), West Nile virus (WNV) or St. Louis encephalitis virus[1]. ZIKV was first isolated in 1947 from the serum of a febrile sentinel rhesus monkey in the Zika Forest (Uganda) during the investigations performed to study the enzootic cycle of YFV. The virus was isolated for the second time from *Aedes africanus* mosquitoes collected at the same site one year later. In both cases, the virus was isolated by intracranial inoculation into infant mice[2].

ZIKV genome is constituted by a positive polarity RNA molecule of about 11 kb in length, comprising two untranslated regions flanking an open reading frame coding for a polyprotein of about 3420 amino acids. Similar to other flaviviruses, the ZIKV single polyprotein is expected to be post-translationally cleaved by host and viral proteases into three structural proteins [capsid (C), pre-membrane (prM), and envelope (E)] and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A NS4B, and NS5)[3] (Figure 1). The structure of mature ZIKV particle has been recently described[4] (Figure 2), and the virus particle has been observed to be structurally stable even at 40 ℃[5].

Phylogenetic analyses of the virus confirm its inclusion within the mosquito-borne flavivirus cluster with the presence of two major lineages: One includes the African strains, which is divided into two groups, the East and the West African clusters, and the other gathers the Asian and American strains[1]. ZIKV life cycle, as any other arbovirus, has several barriers to accumulate mutations as a consequence of the intrinsic constraints associated with dual replication in mammalian and invertebrate hosts, thus driving to a relatively slow fixation of mutations[1]. For instance, ZIKV strains collected over a few years interval in Central African Republic show minimal changes on their sequences[6].

Even though ZIKV strains from different continents and outbreaks showed up to 99% identity[1], nonsynonymous nucleotide differences have been described among them that, in other flaviviruses, have been implicated in viral infectivity. For instance, a full-length ZIKV genome amplified from fetal tissues obtained during the Brazilian outbreak presented five nonsynonymous mutations when compared with the French Polynesian isolate[7]. Three of these amino acid changes were found in NS1, implicated in immune evasion in the case of DENV[8], one in NS4B, related to the inhibition of type I interferon signaling in other flaviviruses[9,10], and one in a NS5 domain which has been shown to mask the viral RNAs from host recognition in the case of WNV[11,12]. In this line, it has been hypothesized the possible adaptation of the ZIKV virus to the human host by changes in non-structural proteins[13]. Thereby, Asian strains of ZIKV differ significantly from the African ones in codon usage in the NS1 region of the genome[14]. Codon usage by the pandemic strain is optimized for adaptation to human housekeeping cells, which could facilitate viral replication in human cells. In fact, codon optimization could result in higher viral titers and increased infectivity for mosquito vectors, as seen in other viruses[15].

Analysis of the polyprotein sequence predicted the presence of potential N-glycosylation sites in the ZIKV proteins prM, E and NS1[4,16-18]. Noteworthy, a 4 amino acid deletion corresponding to the envelope protein 154 glycosylation motif was found in several ZIKV strains, in a similar way to many other flaviviruses, such as West Nile virus strains[6]. Glycosylation has been associated in some instances with virulence[19,20], even though the functional importance of the N-glycosylations is not clear in related flaviviruses, since flaviviruses presenting or not this N-glycosylation can maintain the same antigenicity[21]. Additionally, glycosylation could play a role in replication and maturation[22]. In fact, it has been suggested that extensive mouse brain or cell culture passage could lead to the deletion of the potential glycosylation site, since there are differences on this site even between ZIKV isolates with different passage history, such as those of the prototypic strain ZIKV MR766[23,24]. Even more, it has been suggested that ZIKV may have experienced recombination in nature and that a loss of the N154 glycosylation site in the envelope protein was a possible adaptive response to the vector[25]. Therefore, a detailed analysis of whether and how these differences are directly related to virulence and pathogenicity has to be clearly elucidated for a better control of ZIKV infection.

TRANSMISSION

ZIKV is transmitted by mosquitoes of the genus *Aedes,* mainly of *Aedes aegypti* and *Aedes albopictus*, although the virus has been isolated from other genus such as *Anopheles, Culex,* and *Mansonia spp*[1]. Both *Ae. aegypti* and *Ae. albopictus* have a history of global expansion associated with trade and travel and are widely distributed[26].

Non-human primates are considered to serve as reservoir hosts for ZIKV, although the primary species have not been identified. ZIKV natural transmission cycle has been described to involve *Cercopithecus aethiops* and *Erythrocebus patas* monkeys in Africa[27], while ZIKV antibodies have been found among semi-captive and wild orangutans in Asia[28] (Figure 3). There is no current evidence of other animals than humans and non-human primates acting as amplifying hosts for ZIKV[29]. However, antibodies against ZIKV have been

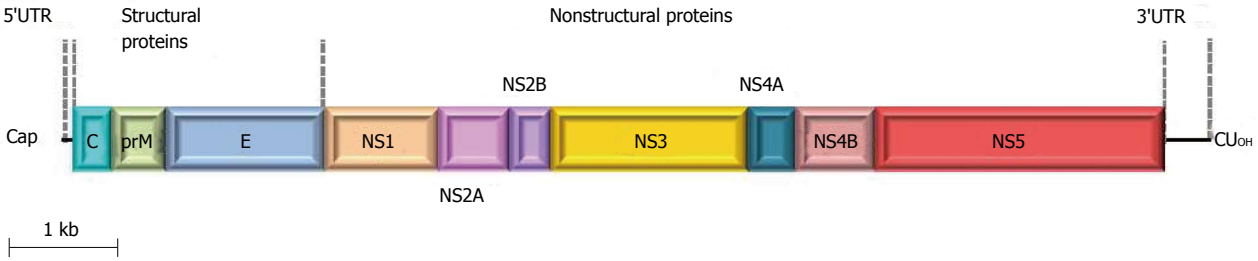

Figure 1 Schematic representation of Zika virus genome organization. The single open reading fram (boxes) that encodes both structural and non-structural proteins is flanked by two untranslated regions.

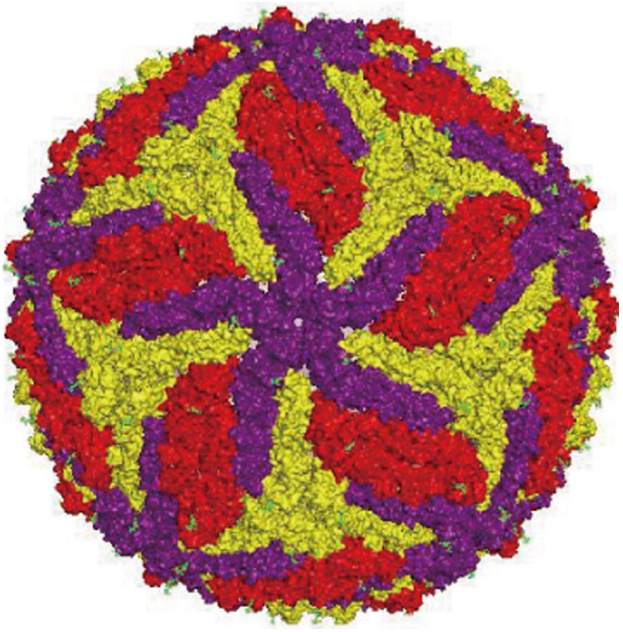

Figure 2 Schematic representation of Zika virus particle based on cryo-electron microscopy data[4].

found in many other vertebrate species, such as sheep, goats, cattle birds, rodents and even reptiles[1].

Even though mosquito transmission is the main cause of ZIKV outbreaks, other additional routes of transmission have been proposed: Breastfeeding, perinatal, sexual or by blood transfusion (Figure 3).

Horizontal transmission

The potential for viral transmission through blood transfusion was first suggested during the French Polynesia outbreak. Almost 3% of blood donors, who were asymptomatic at the time of donation, were found positive for acute ZIKV infection by specific reverse transcriptase polymerase chain reaction (RT-PCR)[30]. Moreover, in a very recent prospective study carried out in 72 pregnant women in Brazil, 26 tested positive for ZIKV RNA in blood samples[31]. These data point to the need for implementation of measures to prevent this way of infection in endemic areas, and, in other zones free of ZIKV, to advice people coming back from affected areas to delay blood donations[1].

Besides blood transfusion, sexual activity could be another risk factor for horizontal transmission. In this regard, ZIKV RNA and replicative virus have been found in semen[32-34]. In 2008, a case of sexual transmission was suspected to occur from an American scientist, who contracted ZIKV infection in Senegal, to his wife. Even though she had not left the United States during the previous year, she also developed clinical symptoms related to ZIKV infection. Even though, ZIKV was not investigated in the semen of the patient, virus infection was serologically confirmed in both[35]. A recent retrospective study in Italy detected ZIKV specific neutralizing antibodies in the sera of a couple with a suspected DENV infection, of which the female had not travelled to tropical areas during the previous year[36]. Later on, in early February 2016, the case of a ZIKV infected person after sexual contact in the United States has been reported[37]. In this line of investigations, the CDC received reports of 14 cases of suspected sexual transmission of ZIKV during February 2016, of which only two were laboratory-confirmed and four classified as probable cases of Zika disease. All reported cases belonged to women which only known risk factor was to have had sexual intercourse with symptomatic partners recently returned from an area with ongoing ZIKV circulation[38]. Up to date, and according to WHO, five countries have reported locally acquired infection in the absence of any known mosquito vectors, probably through sexual transmission (Argentina, France, Italy, New Zealand and the United States). Additionally, ZIKV RNA and infectious ZIKV in urine[39] and saliva[40] have been reported. All these data suggest that sexual transmission could play a role on ZIKV infection and transmission, even though this route seems unlikely to play a major role in ZIKV spread. In any case, the CDC have considered that ZIKV sexual transmission is of particular concern and, consequently, have published an interim guideline for prevention of sexual transmission of ZIKV[41].

Vertical transmission

ZIKV RNA in breast milk was first detected during the outbreak in the French Polynesia[42] and, more recently, the presence of infective ZIKV particles, with substantial viral loads, in breast milk has also been described[43]. Nevertheless, since there is no evidence supporting viral transmission to babies by lactation, the CDC

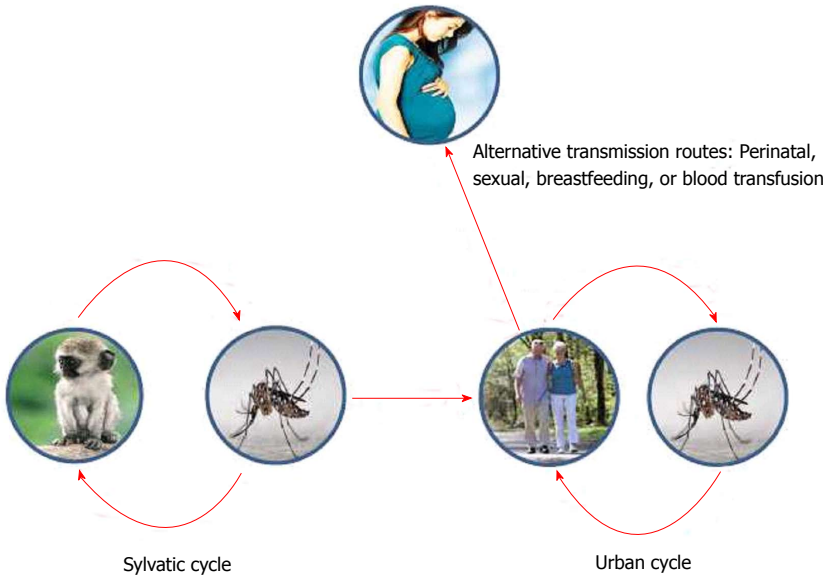

Figure 3 Schematic representation of Zika virus transmission cycle, with a sylvatic natural cycle between mosquitoes and monkeys, and an urban cycle between mosquitoes and human population.

encourage mothers to breastfeed their children, arguing that the benefits of it outweigh the risk of transmission (http://www.cdc.gov/zika/transmission/), as so do the Pan American Health Organization (PAHO/WHO) (http://www.paho.org), and several national health authorities. However, it should be noted that breast milk transmission has been previously documented in humans and experimentation animal models in other flaviviruses, such as DENV or WNV[44,45].

In any case, the most worrying aspect of recent ZIKV outbreaks is the increasing evidence pointing to mother-to-child viral transmission, which can lead to infants neurological disorders. As mentioned early, perinatal transmission was documented for the first time during the French Polynesia outbreak[42]. Sera from two mothers and their newborns were RT-PCR tested positive for ZIKV, although contamination during delivery could not be discarded. Later on, during the outbreak in Brazil, RT-PCR detection and histopathologic findings in tissue samples from two newborns with microcephaly who died within 20 h of birth and two miscarriages showed the presence of ZIKV. All four mothers had clinical signs of ZIKV infection during the first trimester of pregnancy, but not at the time of delivery or miscarriage[46]. Further reports in Brazil have described the presence of ZIKV RNA in fetuses and amniotic fluids[31,47,48]. Even though sporadic vertical transmission in humans has been previously reported in other members of the *Flaviviridae* family, such DENV[49] or YFV[50], the surprisingly high number of infants born with microcephaly in Brazil during the current outbreak, which could probably be the result of a possible vertical transmission, has urged the WHO to publish some advice for women who are pregnant, or planning to become pregnant, to take extra care to protect themselves from the bites of the mosquitoes that transmits ZIKV (http://www.who.int/features/qa/zika-pregnancy/en/).

Clinical features of the disease

ZIKV infection has been described to be symptomatic only in around 18% of the cases[51], causing a mild, self-limiting illness with an incubation period of up to 10 d[52]. Signs and symptoms generally include an onset of fever, maculopapular rash, arthralgia, myalgia, and conjunctivitis, and can be often mistaken with other arboviral infections, like dengue or chikungunya (Table 1). However, severe disease with hospitalization has not been commonly needed until now[1]. However, and even though a causal link has not been yet established, there seem to be growing evidences linking ZIKV infection to Guillain-Barré syndrome (GBS) and microcephaly in newborns. So that, due to this unexpectedly upsurge of severe neuronal complications, a case definition for ZIKV disease has been established by the WHO (http://www.who.int/csr/disease/zika/case-definition/en/) for the purpose of providing global standardization for classification and reporting of ZIKV cases. These interim guidelines distinguish between suspected cases, probable cases, and confirmed cases of ZIKV disease, showing the essential requirements for each of them[12] (Table 2).

GBS is a clinical syndrome of multiple autoimmune etiologies, which involve idiopathic peripheral neuropathy manifested as a progressive paralysis over 1-3 wk, with a 5% death rate and up to 20% of patients left with a significant disability[53-55]. Severe manifestation of GBS with respiratory failure affects 20%-30% of cases[56]. GBS is the most common and severe acute paralytic neuropathy, with en estimate incidence ranging 0.8-1.9 cases per 100000 people per year, with a 70% of these cases associated with previous infectious diseases. The syndrome was also first associated with ZIKV infection

Table 1 Clinical features of Zika virus disease

Mild symptoms	Other complications of the disease
Fever	Guillain-Barré syndrome
Rash	Microcephaly in fetuses and newborns
Joint pain	
Conjunctivitis	
Muscle pain	
Headache	

Table 2 Zika virus disease interim case definitions according to World Health Organization

Suspected case	Probable case	Confirmed case
A person presenting with rash and/or fever and at least one of the following signs or symptoms: Arthralgia, or Arthritis, or Conjunctivitis (non-purulent/ hyperaemic)	A suspected case with presence of: IgM antibody against Zika virus (with no evidence of infection with other flaviviruses) and An epidemiological link (contact with a confirmed case, or a history of residing in or travelling to an area with local transmission of Zika virus within 2 wk prior to onset of symptoms)	A person with laboratory confirmation of recent Zika virus infection: Presence of Zika virus RNA or antigen in serum or other samples, or IgM antibody against Zika virus positive and PRNT90 for Zika virus with titre ⩾ 20 and Zika virus PRNT90 titre ratio ⩾ 4 compared to other tested flaviviruses, and Exclusion of other flaviviruses

Available from: URL: http://www.who.int/csr/disease/zika/case-definition/en.

during the French Polynesian outbreak in 2013[57], where the incidence rate of GBS cases was about 20-fold higher than expected[58]. Likewise, in Colombia, during the ongoing outbreak, a three times higher number of GBS cases than the averaged expected cases during the 6 previous years has been reported. An association between the increase of GBS cases and ZIKV infection has also been reported in Venezuela (http://www.who.int/csr/don/12-february-2016-gbs-colombia-venezuela/en/). Very recently, two cases of GBS with confirmed ZIKV infection have been notified from the United States to the PAHO/WHO (http://www.who.int/csr/don/21-march-2016-gbs-usa/en/). According to the WHO, and in the context of ZIKV circulation, twelve countries or territories have reported an increased incidence of GBS and/or laboratory confirmation of a ZIKV infection among GBS cases (http://www.who.int/emergencies/zika-virus/situation-report/17-march-2016/en/). These data point to an alarming increase in the potential clinical severity of ZIKV infection[59].

In a case-control study performed during the French Polynesia outbreak, 42 patients were diagnosed with GBS at the Centre Hospitalier de Polynésie Française (Papeete, Tahiti, French Polynesia). Study control cohorts were age-matched, sex-matched, and residence-matched patients who presented at the hospital with a non-febrile illness (control group 1; n = 98) and age-matched patients with acute ZIKV disease and no neurological symptoms (control group 2; n = 70). Up to 98% of the patients with GBS had anti-ZIKV IgM or IgG, compared with 56% in control group 1[60]. Even though in this study a history of past dengue virus infection seemed not to differ significantly between patients with GBS and those in the two control groups, other reports have suggested that the simultaneous increase in dengue and chikungunya infections in the region may have contribute to the registered increase in GBS incidence[61]. The 42 GBS cases reported in the French Polynesia between November 2013 and February 2014 contrasted with the less than ten cases per year recorded during the previous four years (http://ecdc.europa.eu/en/publications/Publications/Zika-virus-French-Polynesia-rapid-risk-assessment.pdf), and suggests a possible association between ZIKV and GBS[60]. GBS was also the first important ZIKV-associated condition documented in Brazil, with 121 cases during the first half of 2015 (http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/svs/noticias-svs/19139-evento-desaude-publica-relacionado-aos-casos-de-febre-do-zika).

Even though GBS has also been associated to other arboviral infections, such as DENV[62,63], WNV[64], or CHIKV[65], it is believed to be a rare event. The onset of GBS presumably involves an autoimmune process[66], and although the possible factors determining the association of GBS and ZIKV have not yet been established, it has been suggested that sequential arbovirus infections may exacerbate the immune response and trigger an immunopathogenic process attacking peripheral nerves, and thus leading to the onset of GBS[58].

No matter what, the most concerning manifestation of ZIKV infection is the dramatic increase of reported cases of microcephaly in Brazil. Microcephaly is a head size smaller than expected for age, and is associated to different genetic factors, maternal malnutrition, intrauterine infection (including toxoplasmosis, cytomegalovirus, or rubella), and exposure to toxins during gestation (http://www.cdc.gov/ncbddd/birthdefects/microcephaly.html). Microcephaly is defined as an occipitofrontal head circumference below the third centile, or more than 2 standard deviations (SD) below the mean for sex, age, and ethnicity[67]. Anyway, the possible link of microcephaly with ZIKV is not still clear among researchers. The Latin American Collaborative Study of Congenital Malformations (ECLAMC) suggested that this increase in reported cases of microcephaly might largely be due to the intense search for cases of the birth defect, and to misdiagnoses, that arose from heightened awareness in the wake of the possible link with ZIKV; and the WHO had also stated that the causal relation of these disorders with ZIKV infection had not yet been scientifically proven[68].

According to the WHO data, between October 2015 and January 2016, Brazil reported 4783 cases of microcephaly and/or central nervous system malformation, while during the fifteen previous years the average number of cases reported in the country was 163 per year[69]. Although most of the Brazilian cases have not yet been confirmed, as only a few studies have investigated in detail the possible link between ZIKV infection and fetus cerebral damage, an increase in microcephaly and other fetal malformations has been widely reported in Brazil[31,70,71] and the French Polynesia[72]. In a retrospective analysis of data performed from the ZIKV outbreak in French Polynesia, eight cases of microcephaly were identified between September 2013 and July 2015. Seven of them occurred in a 4-mo period around the end of the ZIKV outbreak. With the development of a mathematical model, the study estimated a prevalence of risk of microcephaly associated with ZIKV infection in the first trimester of pregnancy of 95 out of 10000 infected women (around 1%) *vs* a baseline prevalence of microcephaly of 2 out of 10000[73]. Two additional cases, linked to a stay in Brazil, were detected in the United States[74] and Slovenia[7]. Even though no such a high increase has been observed in ZIKV Brazil endemic neighboring countries, a very recent report has diagnosed, for the first time in Colombia, one newborn with microcephaly and two with congenital brain abnormalities, which tested positive for ZIKV[75], and Panama has recently reported to the WHO a newborn with microcephaly and occipital encephalocoele who died a few hours after birth and also tested positive for ZIKV by RT-PCR.

It is also noteworthy to mention that first experimental studies with ZIKV infection in two mouse model revealed that virus replication is mainly performed in brain cells, such as neurons and astroglial cells[76,77], which would be in line with a possible physiological mechanism linking ZIKV infection with microcephaly. Otherwise, a very recent study have showed that ZIKV infection of human cortical neural progenitors cells derived from induced pluripotent stem cell produced an attenuation of their growth, pointing to a possible mechanistic link between ZIKV and microcephaly[78]. On the other hand, it has been hypothesized that infection could damage the fetus either by evading the natural immunoprotective response of the placenta by direct transmission of the virus to the early embryo or fetus, or by the placenta itself provoking a response to the exposure, and thus contributing to, or causing, the brain defects[79]. In any case, the mechanism by which ZIKV may cause fetal microcephaly is still unknown and, thus, this point need to be clearly established.

Public health measures and future considerations

As in most flaviviral infections, there is no current specific antiviral treatment, vaccine or prophylaxis available for ZIKV. Treatment is generally symptomatic and based on analgesics, antipyretics, and antihistamines. This lack of specific measures against the virus emphasizes the importance of vector control strategies (Table 3). ZIKV is principally spread by mosquitoes, and not by person-to-person contact, although a limited number of cases of sexual transmission has been reported. Accordingly, vector control measures are analogous to those suggested in other mosquito-transmitted diseases[3], such as removing sources of standing water, insecticide application, avoidance of mosquito exposure, and implementation of accurate mosquito control programs. Besides these vector control approaches, development of effective ZIKV vaccines, and search for specific antiviral drugs are current challenges for Zika disease.

Table 3 Preventive measures

Vector control measures	Personal preventive measures
Removal of sources of standing water	Avoidance of mosquito exposure
Implementation of accurate mosquito control programs	Insecticide application
	Prevention of sexual transmission by use of preventive measures
	Travelling avoidance to risk countries during pregnancy

Since the WHO declared a public health emergency of international concern on the 1st of February of 2016, a list of preventive guidelines has been assessed, particularly during pregnancy. Recommendations for pregnant women considering travel to an area with ZIKV circulation and recommendations for screening, testing, and management of pregnant returning travelers are included in the CDC interim guidelines[80]. However, it should be taken into account that, even though ZIKV has been identified in a few cases in fetuses with microcephaly, this association does not demonstrate causality, and it will be necessary careful assessment to find the causal link between ZIKV infection and microcephaly[1,81]. Furthermore, in the case of newborns with microcephaly, the lack of data on short or long-term outcomes of neonatal or infant infection makes it difficult to take into consideration more subtle effects of ZIKV infection in the brain until later stages of childhood. Therefore, systematic and longer-term follow-up is mandatory to assess this point and to determine whether there are more fetal effects.

On the other hand, Zika's association with other viral infections in humans, such as dengue and chikungunya, has raised questions about the potential roles of these other viruses as cofactors for the more serious complications of ZIKV infection[82]. As the current ZIKV expansion is occurring in regions where dengue is endemic, pre-existing dengue immunity can cause increased ZIKV replication in patients, resulting in increased viremia and increased infectivity. In this sense, the possibility of immune enhancement by pre-existing heterologous anti-flavivirus antibodies, like DENV, has been hypothesized to increase viral replication[13]. Immune enhancement has been reported to play a major role in the pathogenesis of severe dengue infections[83]. In fact, ZIKV replication in cell culture were shown to be

enhanced by heterologous flavivirus antibodies[4]. In any case, the potential role of this immune enhancement by previous infection with other flaviviruses as cofactors for the more serious complications associated with ZIKV should be addressed in future research.

Beyond the considerable efforts exerted by the scientific community and the national and international health authorities focused on improving the knowledge on ZIKV infection, sufficient resources should be allocated to provide the necessary tools for assessing the potential mechanisms of ZIKV association to severe neurological diseases, such as GBS or microcephaly, as well as the development of more systematic diagnostic tools, vaccines, and design of antiviral therapies.

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