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Review

Zika virus – an overview

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Abstract

Zika virus (ZIKV) is currently one of the most important emerging viruses in the world. Recently, it has caused outbreaks and epidemics, and has been associated with severe clinical manifestations and congenital malformations. However to date, little is known about the pathogenicity of the virus and the consequences of ZIKV infection. In this paper, we provide an overview of the current knowledge on ZIKV.

Keywords: Zika virus; Flavivirus; Arthropod-borne virus; Viral emergence

1. Introduction

Zika virus (ZIKV) is an arthropod-born virus (arbovirus) belonging to the genus *Flavivirus* and the family Flaviviridae [1]. The virus carries the name of the forest where it was first identified [2], a name that means "overgrown" in the Luganda language [3].

Beyond ZIKV, the genus *Flavivirus* comprises 52 other viral species, including the dengue, yellow fever, Saint Louis encephalitis and West Nile viruses [1]. Flavivirus virions are small, spherical particles that contain a single-stranded, non-segmented RNA of positive-sense and approximately 11 kb in length. The genomic RNA has one open reading frame (ORF) that is flanked by 5′ and 3′ non-coding regions. The genome is translated into a single polyprotein that is subsequently cleaved by both viral and host cell enzymes, resulting in three structural proteins that form the virion (capsid, pre-membrane/membrane and envelope) and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5) [4].

2. Epidemiology

Zika virus was first isolated in 1947 from the serum of a sentinel *Rhesus* monkey from the Zika Forest (Uganda) during a study on the transmission of yellow fever. The second isolation was made from a pool of *Aedes* (*Stegomyia*) *africanus* mosquitoes from the same forest in 1948 [2]. The occurrence of human infection was first evidenced by the presence of neutralising antibodies in the sera of east African residents [5].

Since then, ZIKV has been described as causing sporadic human infections in Africa and Asia. Serological and entomological studies have suggested that ZIKV is widespread throughout these continents. The virus was detected in Thailand [6], Malaysia [7], Uganda [8], Nigeria [9], Indonesia [10], Senegal [11], and Cote d'Ivoire [12]. In other studies, antibodies against ZIKV were detected in healthy people from India [13], Egypt [14], Vietnam [6], Kenya [15], Sierra Leone [16], and Pakistan [17]. Because there exists only serological evidence of ZIKV circulation in these countries and considering that there is high cross-reactivity between related flaviviruses, these data should be analysed carefully.

In 2007, however, an outbreak of illness characterised by rash, conjunctivitis, fever, arthralgia, and arthritis was reported

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on Yap Island, Micronesia. This was the first documented outbreak of ZIKV disease outside of Africa and Asia. Although this outbreak was initially suspected to be caused by dengue virus (DENV), the serological and molecular findings indicated that ZIKV was the causative agent. It was estimated that over 70% of Yap residents were affected. However, no deaths or hospitalisations were associated with ZIKV during this outbreak [18,19]. A genetic characterisation suggested that the ZIKV that emerged in Micronesia is from Southeast Asia [20].

Subsequent infections were reported in Cambodia in 2010 [21], Philippines in 2012 [22] and Thailand in 2012–2014 [23]. The extent of infection in these countries is unknown.

Another outbreak of ZIKV disease in the Pacific islands initiated in 2013 in French Polynesia. Approximately 29,000 people (~10% of the population) have sought medical care for a ZIKV infection, and 72 cases have been severe presentations, including neurological or autoimmune complications. This was the first time that ZIKV was associated with severe disease, although no deaths were reported [24,25]. The outbreak in French Polynesia occurred concomitantly with DENV-1 and DENV-3 outbreaks [26]. An investigation was carried out to determine both the direct involvement of ZIKV in the severe clinical presentations and the possible association between these complications and co-infection or secondary infection with other flaviviruses, especially DENV.

This outbreak spread to other islands in Oceania: New Caledonia, the Cook Islands, Vanuatu, and the Solomon Islands [27,28].

In 2013, the first imported case of ZIKV infection in Europe was reported, occurring in a German traveller returning from Thailand. The case was confirmed by the presence of anti-ZIKV IgM and IgG and of ZIKV neutralising antibodies in the patient's blood [29]. Imported cases were also described in other countries such as Canada, the United States, Australia, Japan, Norway and Italy [30–35].

In early 2014, Chilean public health authorities confirmed the autochthonous transmission of ZIKV on Easter Island. Easter Island, or “Isla de Pascua”, is a Chilean island located in the South Pacific, approximately 3800 km away from the American continent. Fifty-one cases were confirmed from January to May 2014, and phylogenetic analysis revealed that the virus was most closely related to those from French Polynesia [36]. It was the first autochthonous outbreak of ZIKV within a territory of the Americas.

In early 2015, the Brazilian Ministry of Health confirmed the autochthonous transmission of ZIKV in the country. The first cases were identified in the northeast region of the country, where cases of an exanthematic illness associated with fever, conjunctivitis and arthralgia were reported [37,38]. By February 2016, 22 Brazilian states had confirmed autochthonous ZIKV transmission. In addition, ZIKV has been associated with foetal malformations and death. Brazilian health authorities received reports of more than 5600 suspected cases of microcephaly in newborns (an increase of more than 20 times that of the historical average over the past five years) and 120 deaths due to congenital malformations supposedly related to the Zika virus; these reports are under investigation [39]. Moreover, two other deaths appear to be related to ZIKV infection.[1]

As of February 2016, the public health authorities of another 30 countries and territories in the Americas also reported the autochthonous circulation of ZIKV. This is the largest ZIKV outbreak ever recorded [39]. The relevant information is constantly being updated and is available on the Pan American Health Organization website (http://www.paho.org/HQ/index.php?option=com_topics&view=article&id=427&Itemid=41484&lang=en).

Phylogenetic studies showed that ZIKV that emerged in the Pacific islands and in South America belongs to the Asian lineage [22,26,37,40].

The high potential for the spreading of this virus is evidenced by several factors: the recent outbreaks, the increasing speed by which the virus is spreading in the Americas, the detection of imported cases in different regions of the world, and the probable association of the virus with severe cases, foetal malformations and death. On 1st February 2016, the World Health Organization (WHO) declared a global public health emergency due to the ZIKV threat [41].

3. Phylogeny

ZIKV belongs to the Spondweni serocomplex, and phylogenetic analyses revealed the existence of two main virus lineages (African and Asian). The results from Berthet et al. [42] suggest that a different ZIKV subtype of the West African circulated in the *Aedes* species in Central Africa.

Molecular evolution studies indicated that ZIKV might have undergone several natural recombination events, which is an unusual feature among members of genus *Flavivirus*. A specific adaptive genetic change, the recurrent loss and gain of the N-linked glycosylation site in the E protein, was observed, and it has been suggested that this genetic alteration could be related to mosquito-cell infectivity [43].

During the current epidemics in the Americas, a growing number of ZIKV genome sequences are being determined and their phylogenetic relationship with other members of the flavivirus genus revisited [44,45].

4. Transmission cycles, vector and reservoirs

In Africa and Asia, ZIKV is maintained in a sylvatic environment, in a zoonotic cycle between mosquitoes (*Aedes* spp. and other species) and non-human primates. ZIKV antibodies have been detected in large mammals and in rodents, but the role of these animals as virus reservoirs, if any, remains to be determined [24].

The first vector ZIKV isolate was obtained in 1948 from *Ae. africanus* [46]. Since then, ZIKV has been isolated from several different mosquito species in nature: *Ae. africanus*, *Aedes furcifer*, *Aedes luteocephalus*, *Aedes vittatus*, *Aedes*

[1] Available in http://www.brasil.gov.br/saude/2015/11/ministerio-da-saude-confirma-relacao-entre-virus-zika-e-microcefalia.

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dalzieli, *Aedes hirsutus*, *Aedes metalicus*, *Aedes taylori*, *Aedes aegypti*, *Aedes unilineatus*, *Anopheles coustani*, *Culex perfuscus*, and *Mansonia uniformis* in Africa. *Ae. aegypti* was suspected to have an important role in the urban transmission (mosquito-human-mosquito) of ZIKV in Nigeria due to the high prevalence of ZIKV antibodies in the urban population of Nigeria [9]. In Gabon, a retrospective study of sera samples from patients with febrile syndrome and of mosquito pools collected from 2007 to 2010 showed ZIKV RNA-positive pools of *Aedes albopictus* when these samples were screened by molecular techniques [47]. In Asia, further evidence incriminated *Ae. aegypti* as the urban vector after ZIKV was identified in a mosquito pool collected in Malaysia [7]; furthermore, in Indonesia, the peak in human ZIKV infections coincided with a peak in the *Ae. aegypti* population [10]. The virus is transmitted from life-long infected female mosquitoes to humans during a blood meal. Because some male mosquitoes have been found to be positive for ZIKV, vertical transmission might also occur [48].

Despite the recent ZIKV-related human epidemics observed in the Yap Islands, French Polynesia and the Americas, little is known about the mosquito vectors implicated in these events and their competence in transmitting ZIKV to humans. During the Yap Island epidemic, *Aedes hensilli* was implicated as the potential vector because it was the predominant species identified in local water-holding containers, although ZIKV has never been isolated from this mosquito species or from any other less abundant mosquito pools [19,49]. Because *Ae. aegypti* and *Aedes polynesiensis* are highly prevalent in French Polynesia, by association, the former species was incriminated as the urban ZIKV vector throughout the 2013 epidemics [26].

Laboratory infection assays have demonstrated the susceptibility of several *Aedes* spp. to ZIKV infection, with variable rates of virus dissemination in the insects' tissues. Nevertheless, the competence to transmit ZIKV has been demonstrated for few species and should be better evaluated [50,51].

Boorman et al. demonstrated that *Ae. aegypti* mosquitoes that were artificially fed ZIKV were able to transmit the virus to both mice and monkeys under laboratory conditions [52].

Presently, South and Central American countries are experiencing an enormous ZIKV epidemic [39]. Brazil displays high infestation rates of both the widely distributed *Ae. aegypti* and *Ae. albopictus.* The former species is the principal vector for DENV [53], and the latter has been demonstrated to be competent to transmit CHIKV [54]; both of these viruses co-circulate simultaneously with ZIKV within Brazilian territory [39,53,55]. *Ae. aegypti* populations are susceptible to ZIKV infection *in vitro* [56], and their role as the ZIKV primary vector in nature is being investigated. It remains to be determined whether mosquito species other than *Aedes* spp., and with different ecological behaviours, could be involved in urban ZIKV transmission in Brazil.

5. Transmission

The transmission of ZIKV typically occurs through the bite of an infected female mosquito during its blood feeding. In addition to the arthropod vector bite, perinatal ZIKV transmission has been described, and viral RNA has been detected in breast milk in two cases [57]. Caution should also be taken regarding the risk of contamination by blood transfusion for ZIKV and other arboviruses that co-circulate in the American continent, such as DENV and CHIKV [58].

ZIKV was isolated from the semen of a patient several weeks after the acute phase of the disease [59], and a case of sexual transmission has been reported [60]. Since the risk of sexual transmission of ZIKV exists, there is a recommendation that men who reside in or have travelled to an area of active ZIKV transmission might consider the sexual abstinence or condom use during sexual intercourse, especially if his partner is a pregnant woman [61].

ZIKV RNA and/or protein has also been detected in urine [62], saliva [63], amniotic fluid [64] and placental tissues [65], highlighting the possibility of other modes of transmission. More recently, infective viral particles have been detected in the saliva of two individuals who tested positive for ZIKV, opening the possibility of another mode of person-to-person transmission (Bonaldo et al., unpublished data).

6. Clinical manifestations

Until recently, ZIKV disease was generally reported to result in a mild clinical presentation and a self-limiting course of infection. The symptoms range from asymptomatic to a dengue-like illness. The most frequently reported symptoms are a maculopapular rash (frequently pruritic), fever, arthritis or arthralgia, headaches and non-purulent conjunctivitis. Other symptoms include chills, asthenia, malaise, edema of the extremities, retro-orbital pain, vertigo, myalgia, digestive disorders and cervical lymphadenopathy [10,19,37,60,66]. Haematuria and haematospermia have also been reported [10,59,60].

It is estimated that most cases of this disease are asymptomatic or subclinical. In most symptomatic cases, ZIKV infection is self-limiting and lasts a few days, although arthralgia may persist for up to a month [19,31,60]. Haemorrhagic signs have not been observed, but other severe manifestations have been reported, including neurological (Guillain-Barré syndrome and meningoencephalitis) and autoimmune (thrombocytopenic purpura and leukopenia) complications and possibly microcephaly, other foetal malformations, and optical lesions [24,25,64,67]. Deaths were not reported until last year, when Brazilian health authorities confirmed two deaths, those of a 35-year-old man and a 16-year-old girl, in addition to the foetal and newborn deaths in cases of suspected ZIKV-related microcephaly.[1]

7. Pathogenesis

To date, there exists little information about the pathogenesis of ZIKV. The symptoms of ZIKV infection usually appear three to eleven days after the mosquito bite occurs [60,68]. Although the viremic period still has not been established, it is expected to be shorter than that of other flaviviruses. Viral RNA has been detected in serum samples from

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days 0−11 (mostly in samples from <6 days) after the onset of symptoms [18,31].

Experimental studies demonstrated that mice are susceptible to intracerebral inoculation with ZIKV regardless of animal age, whereas infection via the intraperitoneal route occurs more frequently in mice that are younger than two weeks of age. Intracerebral-inoculated mice exhibited encephalitis with neuronal degeneration, cellular infiltration and areas of softening [69]. Further study revealed an enlargement of astroglial cells and the destruction of the pyriform cells of Ammon's horn in the brains of mice that had been infected intracerebrally [70]. As in the case of other flaviviruses, ZIKV appears to be formed within the endoplasmic reticulum network, in close association with host cell membranes [70,71]. Another study, however, suggested that ZIKV antigens could be found in the nuclei of infected cells [72].

In vitro and *ex vivo* experiments demonstrated the permissibility of human skin cells, including dermal fibroblasts, epidermal keratinocytes and immature dendritic cells, to ZIKV infection. In this study, ZIKV induced an antiviral state in the infected fibroblast skin cells, with enhancement of IFN-α and IFN-β gene expression and upregulation of the expression of several IFN-stimulated genes (ISGs), including OAS2, ISG15 and MX1. Both type I and type II IFN inhibited ZIKV replication. Moreover, ZIKV induced an upregulation in the expression of Toll-like receptor 3 (TLR-3), retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene-5 (MDA-5), which have been previously described as involved in the detection of other flaviviruses. Finally, autophagosomes and autophagy were associated with the enhancement of viral replication in skin fibroblast cells [71].

8. ZIKV, microcephaly and other birth defects

After the introduction of ZIKV in northeastern Brazil in early 2015, and the subsequent spread of this virus throughout the country, unusually high incidences of microcephaly and other birth defects have been observed (from September 2015 onwards). There is a temporal association between the increase in cases of microcephaly in areas affected by the ZIKV outbreak and the increase in pregnant women presenting ZIKV-compatible clinical symptoms during early pregnancy.

ZIKV RNA has been detected in the amniotic fluid samples from two women who were pregnant with foetuses that were diagnosed with microcephaly [64], and viral RNA and antigens have been found in placental tissue from miscarriages and in foetal brain tissues from foetus/infants with microcephaly [65,73]. ZIKV has also been implicated in 67 cases of microcephaly in Brazil [39].

However, much remains to be revealed regarding both the association of ZIKV with microcephaly and other foetal malformations and the mechanism by which transmission occurs.

9. Diagnosis

The diagnosis of infection by Zika virus is based on clinical, epidemiological and laboratorial criteria. Because the symptoms of ZIKV disease are nonspecific and can easily be confused with those of other arbovirus-induced diseases, such as dengue and chikungunya, in regions where those viruses co-circulate, ZIKV infection can be misdiagnosed; thus, the differential laboratory diagnosis is important.

Laboratorial diagnosis of ZIKV can be realised by the detection of virus, viral nucleic acid, viral antigen, or antibody or by a combination of these techniques. The choice of method depends on the purpose for which the test is performed (clinical, epidemiological study, or vaccine development), the type of laboratory facilities and expertise available, and the sample collection time.

When the sample is collected in the first few days after the onset of symptoms, a test detecting virus or viral nucleic acid may be performed. The virus detection is based on isolation from cell culture (using mosquito or mammalian cell lines), directly from mosquitoes, or intracerebrally from newborn mice [2,23,31,42]. However, virus isolation is restricted to specialised laboratories and is rarely successful. The low levels of viremia may explain this difficulty with the isolations [18]. For the detection of viral RNA, molecular techniques, such as conventional or real-time RT-PCR, have been developed [18,74−76]. These molecular techniques are the most widely used methods for ZIKV diagnosis, particularly because of the extensive antigenic cross-reactivity between flaviviruses [18,77]. RNA loads have been detected up to approximately 7.3×10^6 copies/ml in serum [18,34,35,57], 2.2×10^8 copies/ml in urine [57,59,62], 2.9×10^7 copies/ml in semen [59], and 2.0×10^6 copies/ml in breast milk samples [57].

In addition, viral antigens can be detected in other tissues by immunohistochemistry [65].

Anti-ZIKV IgM and IgG antibodies can be detected by serological tests. Usually, IgM can be detected by ELISA or immunofluorescence from day five or six after the onset of symptoms, although it has been detected as early as the third day of symptomatic illness [18,77]. The presence of ZIKV-specific IgM in a single sample during the acute phase is suggestive of an acute infection. However, it is recommended to demonstrate seroconversion (negative to positive) or an antibody titre increase of at least four-fold in paired (acute and convalescent) serum samples [77]. The haemagglutination inhibition test, plaque-reduction neutralisation test (PRNT), complement-fixation test, and IgM and/or IgG ELISA could be used for these purposes [20,60].

The results of serological tests should be analysed carefully because false-positive results can occur due to the cross-reactivity with other flaviviruses. It has been demonstrated that when a patient has had no previous infection by another flavivirus, the cross-reactivity is minimal. In contrast, when ZIKV infection occurs as a secondary infection with another flavivirus, the cross-reactivity is extensive. Even in the case of PRNT, which offers greater specificity, some patients with probable previous infection by another flavivirus exhibit a four-fold or higher rise in neutralising antibody titres against other flaviviruses [18]. This cross-reactivity was also observed in a laboratory ZIKV infection following vaccination against yellow fever virus [78].

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10. Treatment and prevention

There is no specific treatment for ZIKV infection, and medical care is based upon personal symptoms [39]. The use of fluids and acetaminophen (paracetamol) or dipyrone is recommended to control fever and provide pain management. In the case of an itchy rash, antihistamines may be considered. However, aspirin and other anti-inflammatory drugs are not recommended due to the increased risk of bleeding complications.

There are no vaccines or other prevention strategies for ZIKV, and control measures rely on the elimination of mosquito vector breeding foci. Historically, *Ae. aegypti* eradication strategies have proved to be inefficient, and the mosquito infestation index in the Americas is very high. The uses of the bacterium *Wolbachia* and of transgenic *Ae. aegypti* are alternative strategies that can be implemented along with insecticide spraying to control the mosquito population. It is also recommended that individuals avoid mosquito bites through the use of personal protection measures including long sleeves and pants to limit skin exposure and the use of repellents. Other measures, such as window and door nets and the elimination of potential breeding sites, would help reduce human contact with the mosquito vector.

In the case of pregnant women, some recommendations have been made: the evaluation for symptoms of ZIKV disease; the laboratorial diagnosis during the prenatal care; a careful evaluation of the foetus for brain anomalies, including microcephaly and intracranial calcifications, during the ultrasound; special attention on the prevention of mosquito bites and possibility to sexual transmission of ZIKV [79].

11. Conclusion

There are several open questions: Are there modes of transmission other than through the vector? Are mosquito species other than *Aedes* involved in the urban cycle? Can person-to-person contamination occur through saliva? Can congenital or sexual transmission occur? What is the rate of transmission by blood transfusions? Is ZIKV capable of establishing a chronic infection? Is there the generation of a long-lived protective immune response? Is there the possibility of re-infection?

These questions must be urgently answered to allow the effective design of strategies to prevent and/or treat ZIKV transmission and infection and will demand a collective and coordinate basic research initiative to address these issues.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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