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Zika Virus (ZIKV): A New Emerging Pathogen Transmitted by *Aedes* Mosquitoes (Diptera: Culicidae) in the Latin American Subcontinent

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Abstract

Aedes aegypti and *Aedes albopictus* (Diptera: Culicidae) are two species of synanthropic mosquitoes that are common in outdoor and indoor domiciliary environments in tropical countries. Their vectorial competence and vectorial capacity make them excellent biological vectors for the main arboviruses that affect human beings. Both *Aedes* species are listed as the primary vectors of dengue (DENV) and chikungunya (CHIKV) viruses, which circulate in many American countries. The recent introduction of Zika virus (ZIKV) into the Latin American subcontinent and its association with microcephaly and Guillain-Barre syndrome has alerted health authorities about the sanitary emergency that the presence of this new virus in the American territory represents. The emergence of this pathogen raises the necessity to improve the epidemiologic and entomologic surveillance systems and to develop new strategies of prevention and control. This review aims to provide an overview of ZIKV and the role of *Ae. aegypti* and *Ae. albopictus* in its transmission.

Keywords

Zika; Arbovirus; Flavivirus; *Aedes aegypti*; *Aedes albopictus*

Introduction

Aedes aegypti and *Aedes albopictus* (Diptera: Culicidae) are two species of mosquitoes commonly found in urban and periurban environments in the Latin American subcontinent. *Ae. aegypti* was introduced around the seventeenth or eighteenth centuries, when the trade of slaves between Africa and America was intense [1]. The introduction of *Ae. albopictus* into the Latin American subcontinent occurred between the years 1985 and 1986, when this vector was detected in the United States and Brazil for the first time [2]. It is believed that this introduction was related to the importation of bamboo plants (*Dracaena* sp.) or used tires from Southeast-Asia [2]. Both *Ae. aegypti* and *Ae. albopictus* are biological vectors of viral diseases that affect human beings. *Ae. aegypti* is recognized as the world's most important vector in the transmission of dengue virus (DENV). Additionally, it can also transmit chikungunya (CHIKV), yellow fever (YFV) and Venezuela equine encephalitis (VEE) viruses [3,4]. On the other hand, *Ae. albopictus* is a known vector of viruses like DENV, CHIKV, Japanese encephalitis, La Crosse, among others [3,5]. Regarding Zika virus (ZIKV), both species of *Aedes* have been implicated in its transmission [6]. The infection by ZIKV usually generates a less severe clinical picture compared to DENV and CHIKV, but the association of this virosis with neurological syndromes such as Guillain-Barre, and with congenital problems such as microcephaly, represents a new point of interest in public health [7]. Thus, the presence of this emerging disease in the Latin American subcontinent constitutes a new challenge for local health systems [8,9]. This territory has environmental and urban conditions that are very appropriate for the dissemination of ZIKV. The absence of ZIKV immunity in the population and the high levels of *Ae. aegypti* and *Ae. albopictus* infestation make efficient circulation of ZIKV likely, along with DENV and CHIKV [10]. The aim of this review is to analyze the role of *Ae. aegypti* and *Ae. albopictus* in ZIKV transmission and to provide a brief overview of this virosis.

The etiologic agent

ZIKV was isolated for the first time in the Zika forest, Uganda in 1947 from a Rhesus monkey (*Macaca mulatta*) that served as sentinel animal for detection of YFV in a surveillance investigation [6]. The primate presented fever, and a blood sample was taken because of this. This sample was inoculated in the brain of a mouse and a new virus, different from YFV, was isolated [6]. Early in 1948, the same virus was identified in mosquitoes of the species *Aedes africanus* collected in the same forest in Uganda [6], but it was not characterized and designated as "Zika virus" (ZIKV) until 1952 [11]. The first report of human infection by ZIKV occurred in 1964 [12], and the first isolations from human beings were documented in Nigeria in 1968 [6,9]. Although there are several studies based on serological evidence that demonstrate the continuous circulation of ZIKV in human populations of Asia and Africa, it was not until 2007 that the first important outbreak was documented. This outbreak occurred in Yap Island in Micronesia; 49 cases were confirmed and 59 of them were classified as probable [13]. In 2013, another important outbreak occurred in French Polynesia, in which around 10,000 cases of ZIKV were reported and 70 of them presented neurological and autoimmune complications [8,14]. ZIKV is a flavivirus, similar to the Spondweni virus, and it is related to other viruses transmitted by mosquitoes such as DENV, YFV, West Nile virus (WNV), St. Louis encephalitis virus (SLE), and Japanese encephalitis virus (JE). The viral particle contains a positive-strand RNA-genome comprising 10,794 nucleotides, and it encodes for 3,419 amino acids [15]. The gene organization is similar to other flaviviruses. The genome encodes for several proteins, including the capsid (C), premembrane (prM), envelope (E), and seven nonstructural proteins denominated as NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [15] Molecular biology studies have recognized the existence of two lineages, the African and the Asian one [16].

Pathology and Clinical Picture

There is still scarce knowledge about the pathophysiology of ZIKV. As in other flaviviruses, it is thought that this virus initiates its

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replication in peripheral dendritic cells located in the skin, near the site where the vector bites. The replication in dermic fibroblasts and keratinocytes has also been demonstrated [17]. After this, the virus reaches the lymph nodes and then the bloodstream [4]. Clinically, the infection by ZIKV resembles that of DENV. Only 1 in 4 people infected show some form of clinical picture. The ZIKV incubation period ranges from 3 to 12 days and viremia occurs between days 3 and 5 after the onset of symptoms [4]. The clinical picture is characterized by a fever that usually does not exceed 38.5°C; other possible symptoms are headache, malaise, arthritis or arthralgia, back pain, and non-purulent conjunctivitis [4]. In most cases, a maculopapular rash that spreads from the face to the body can be observed. When arthritis or arthralgia is present, the phalanges of hands and feet may be the most affected [18].

The presence of the virus in other body fluids such as saliva, urine, and semen has also been documented [20-26], and there is recent evidence of cases that support sexual transmission of this virus [21,24-26]. Recently, the presence of viral RNA in amniotic fluid and fetal tissues of mothers that suffered ZIKV during pregnancy was reported [7]. These findings demonstrate that ZIKV is capable of vertical transmission between human beings [7].

ZIKV transmission during pregnancy may be responsible for microcephaly, as has been suggested by the epidemiological associations observed between microcephaly and virus circulation during the epidemics in French Polynesia and Brazil [27]. Studies of cell biology have demonstrated the increase of autophagy and proliferation of centrosomes in glial and fibroblast cells infected with ZIKV [28]. Coincidentally, the same events have been observed in nerve cells of patients that suffer microcephaly [28]. A case report was published recently of an expectant mother who showed a clinical picture compatible with Zika during the first trimester of pregnancy while she was living in Brazil; ultrasonography performed at 29 weeks of gestation revealed microcephaly with calcifications in the fetal brain and placenta [29]. The pregnancy was interrupted and the fetal autopsy corroborated the microcephaly. There were also agyria, hydrocephalus, and multifocal dystrophic calcifications in the cortex and subcortical white matter, with associated cortical displacement and mild focal inflammation. The presence of ZIKV RNA was evidenced by RT-PCT and electron microscopy in the fetal brain-tissue [29]. This finding demonstrates the pathological potential of ZIKV on fetal nerve-tissue in humans during the first trimester of pregnancy. Other reports of congenital abnormalities with presence of ZIKA virus RNA include cases of microcephaly and early spontaneous pregnancy losses, which have been associated with ZIKV infection during the first trimester of pregnancy [30]. However, more epidemiological studies are necessary in order to establish the risk of congenital infection and the incidence of severe outcomes.

Although it has been suggested that the infection by ZIKV could be related to neurological manifestations such Guillain-Barre syndrome, there is not enough scientific evidence yet to support this association [4,19]. However, an increased number of patients with Guillain-Barré syndrome were documented during the recent epidemic in Brazil, after suffering a clinical picture that resembles ZIKV [18].

Viral transmission

In Southeast Asia, *Aedes hensilli* was proposed as the main vector of ZIKV because it was the predominant mosquito during the outbreak in the State of Yap, Federated States of Micronesia, and its vector competence has been demonstrated in experimental studies [6,31]. In Africa, several species of *Aedes* that inhabit forest habitats were found to be naturally infected with the virus. Some of those species are *Aedes africanus*, *Ae. apicoargenteus*, *Ae. luteocephalus*, *Ae. vittatus*, *Ae. aegypti,* and *Ae. furcifer* [6]. A study conducted in Senegal in 2011 also showed natural infection in *Ae. taylori, Ae. dalzieli, Ae. hirsutus, Ae. metallicus, Ae. unilinaetus, Mansonia uniformis, Culex perfuscus*, and *Anopheles coustani* (32). It is very likely that primates that live in forest areas where those species of mosquitoes are prevalent can serve as feeding hosts for them and amplifier hosts for ZIKV. Those primates can suffer infection by ZIKV generating enzootic and epizootic transmission cycles [33]. Thus, it is clear that this virus can circulate between animals and mosquitoes, and like CHIKV, this transmission can affect people living in rural villages located near the forest where sylvatic transmission occurs. In urban environments, *Ae. aegypti* and *Ae. albopictus* are listed as the main vectors. Other probable transmission mechanisms of the virus that have been mentioned are perinatal, trans placental, blood transfusions, and sexual [26,34,35].

Aedes aegypti and *Ae. albopictus* in the transmission of ZIKV

The relationship between *Ae. aegypti* and ZIKV transmission was established for the first time in 1956 when the transmission of ZIKV to mice and monkeys from artificially infected mosquitoes was demonstrated in experimental models [36].Other studies have reported the isolation of this virus from *Ae. aegypti* collected during ZIKV outbreaks in Africa and Asia [6,37]. Although it is estimated that the extrinsic viral cycle lasts around 10 days, a recent study performed in Singapore showed that half of the sampled *Ae. aegypti*, which were artificially infected, presented viral particles in salivary glands just 5 days after infection [38]. By day 10, all the infected mosquitoes showed the presence of virus in saliva [38].These data suggest that the extrinsic cycle could be shorter than the previously established average. In another recent study performed in Senegal, the rates of infection with ZIKV in orally infected *Ae. aegypti* were 50 to 56%. These rates were reached between days 5 and 10 post-infection [39]. In the same study, the rates of virus spreading in the mosquitoes were 0-50%, determined 15 days post-infection [39]. These studies confirm that *Ae. aegypti* is susceptible to infection by ZIKV, and its vector competence may vary according to the characteristics of the vector population and viral genotypes [39].

The vectorial relationship between *Ae. albopictus* and ZIKV has been demonstrated more recently. The epidemiological link has been the initial criterion to consider the role of this mosquito species as a ZIKV vector. *Ae. albopictus* was reported as the most abundant species in urban environments during ZIKV outbreaks in Singapore [40]. Recent studies in Gabon have suggested an important role of *Ae. albopictus* in the epidemic transmission of ZIKV; these studies have demonstrated the natural infection of this virus in *Ae. albopictus* collected during Zika outbreaks, while *Ae. aegypti* collected in the same outbreaks resulted negative for the virus [41]. From a biological perspective, recent studies have confirmed the vector competence of *Ae. albopictus* for ZIKV [40]. In one of these studies a strain of *Ae. albopcitus* from Singapore was orally infected with a strain of ZIKV from Uganda. At day 7 post infection, 73% of the infected mosquitoes showed viral particles in salivary glands, and at day 10 all the mosquitoes showed viral particles in saliva [40].

The transmission of ZIKV by *Ae. aegypti* and *Ae. albopictus* represents a serious health problem for the countries of the Latin

American subcontinent that show a high endemicity for DENV and CHIKV. *Ae. aegypti* and *Ae. albopictus* are markedly anthropophilic, synantropic, and very common in urban and suburban environments. In these environments, many conditions are advantageous for their reproduction, oviposition, and development of immature forms. Countries of the Latin American subcontinent are located mainly in tropical latitudes and exhibit relatively low fluctuations in weather conditions during most of the year, which promotes the continuous presence of the vectors. For these reasons, outbreaks of DENV, CHIKV, and ZIKV are likely to occur throughout the year, with the possibility of co-circulation of all these viruses [41,42]. From a social point of view, the proliferation of informal urban settings with high population density and problems with water supply and garbage management may increases the proliferation of vectors [43]. In these places, it is common to find poor indoor and outdoor sanitation conditions, with the accumulation of many types of objects that can serve as breeding sites for the vectors. Some of those are barrels, buckets, tanks, and many other miscellaneous objects that can be filled with water and serve as sites for oviposition and development of immature forms of the mosquito vectors [43,44].

Epidemic of ZIKV in the Latin American subcontinent

The Easter Island (Chile) was the first territory in the Latin American Subcontinent that reported indigenous transmission of ZIKV on February 2014. This occurred simultaneously to the outbreak in French Polynesia [8]. After this, no more cases were reported until early 2015, when patients of Natal, Rio Grande do Norte, Brazil, showed a dengue-like syndrome that did not correspond to dengue or chikungunya [45]. Analyses carried out at the Institute Ozwaldo Cruz (State of Parana, Brazil) demonstrated the presence of ZIKV RNA in 8 of 21 samples of serum from patients with this syndrome. The RT-PCR and the sequence analysis corresponded to the Asian lineage of the virus, and this led to the hypothesis that suggests a possible introduction of the virus during the Soccer World Cup in 2014 [45]. Further phylogenetic studies showed that the circulating genotype is similar to the isolates from French Polynesia, and its introduction may have occurred during the world championship "Va'a World Canoe Sprint", held in Rio de Janeiro [14]. In that championship, four teams of the Pacific islands competed, unlike in the Soccer World Cup where no teams from that region participated. Reports from October 2015 documented ZIKV transmission in 14 states in Brazil (Alagoas, Bahia, Ceara, Maranhao, Mato Grosso, Pará, Paraíba, Paraná, Pernambuco, Piauí, Rio de Janeiro, Rio Grande do Norte, Roraima, and São Paulo) [46]. By October 2015, the presence of ZIKV was also reported in Colombia; health authorities documented the virus circulation in the state of Bolivar, describing nine confirmed cases [47]. In early November 2015, the media reported 239 additional cases in Bolivar, Antioquia, San Andres, North of Santander, and Sucre [48]. By January 2016, indigenous transmission of ZIKV in the Latin American subcontinent has been confirmed in several countries including Brazil, Barbados, Colombia, Ecuador, El Salvador, Guatemala, Guyana, French Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, San Martin, and Suriname [27]. The rapid spread of this virus may be the result of frequent movement of people within the region and the presence of favorable conditions for the establishment of the transmission cycle, as well as a high abundance of potential vectors (especially *Ae. aegypti* and *Ae. albopictus*) coexisting closely with people. Also, a recent report demonstrated a genetic mutation in the gene that codes for the NS1 protein, in the Asiatic lineage of ZIKV. This mutation gives this virus higher adaptability to mosquitoes and humans, which could also explain the rapid spread of the ZIKV in the American continent [49].

Laboratory diagnosis

The laboratory diagnosis of viral RNA is performed by RT-PCR techniques using serum of the viremic patient. This test detects the gene that codifies for the NS5 viral protein. The period of viremia has not yet been fully established and there are reports of detection of viral RNA in serum around 10 days after the beginning of the clinical picture, but it is recommended to take the samples for diagnosis during the first 5 days after the start of the symptoms [50]. The diagnosis can also be done by serology. There is an ELISA test that detects the presence of IgG or IgM about six days after the onset of symptoms. The results of this serological test have to be analyzed carefully, because there is important cross-reactivity with other flaviviruses such as DENV, and to a lesser degree with YF, WNV, and JE [4]. Other diagnostic alternatives include the evaluation of body fluids such as urine and saliva using RT-PCR and real-time PCR [51].

Perspectives on prevention and control

Similar to what happens with DENV and CHIKV, ZIKV does not have an available vaccine or an antiviral drug treatment [10]. For this reason the main control activities should be directed to minimizing vector populations. For this purpose, communities need to identify the problem and seek alternatives in order to eliminate the mosquito breeding sites. The use of agents with larvicide effect is also recommended. Specifically, the proper use of the organophosphate insecticide temephos, or the use of biological control systems such as *Bacillus thuringiensis* var. *israelensis* (BTI) or spinosad have been previously suggested [52]. The use of juvenoids such as methoprene or pyriproxyfen, and molting inhibitors like difluobenzuron can be considered as well [52]. Similar to what is recommended for DENV and CHIKV, the use of organophosphates and pyrethroid insecticides for the control of adult mosquitoes should be applied only in the case of outbreaks. Recently, other alternatives have been proposed such as the use of genetically modified mosquitoes (RIDL technology) or the use of the endosymbiont *Wolbachia*, but these options must be carefully analyzed and studied prior to a possible inclusion in control programs. At the government level, surveillance systems should make efforts to identify high risk areas for epidemic events and optimize the protocols for entomological, viral and serological diagnosis. On the other hand, entomological surveillance systems should be monitoring the effectiveness of insecticides used in the focal and spatial insecticide treatments.

Conclusions

ZIKV infection, as a new emerging infectious disease, has suffered a fast spread in most of the territories of the Latin American subcontinent during the last months of 2015 and the beginning of 2016. The immunological susceptibility of the majority of the human population makes it very likely to have outbreaks of this virus in the many areas where *Ae. aegypti* and *Ae. albopictus* are abundant. The presence of ZIKV represents a big challenge for the health systems because DENV and CHIKV viruses are also prevalent in the same areas where ZIKV can circulate.

The presence of ZIKV in the Latin American subcontinent raises many questions that need to be addressed. Topics include the new ecology of the virus, its potential vectors and reservoirs, as well as virus-mosquito interactions. It will also be necessary to generate more knowledge on the effects of infection in the human host, especially concerning pathology

and cellular biology. In addition, alternatives of antiviral therapy should be investigated, as well as the development of vaccines.

In terms of vector approaches, efforts are needed to develop new and more efficient tools for entomological surveillance in order to optimize and apply actions of control. The regular use of adult traps and ovitraps can be a feasible option for this purpose. Other aspect that the health systems must consider is to improve the process of case notifications. It is also necessary to improve the active and passive epidemiological surveillance systems in order to detect the exact areas of circulation of the virus.

The national and regional politics of prevention and control must be directed towards a preventive elimination and treatment of potential breeding sites for the vectors, and the correct application of adulticide control measures in the case of outbreaks. Also, the continuous monitoring of the vector resistance to insecticides is required in order to warrant the effectiveness of the focal and spatial treatments. Finally, it is important and necessary to educate the population regarding this disease and have an active participation of the community to ensure the success of the actions for prevention and control.

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