Expansion of Zika virus circulation from Africa to the Americas, 1947-2018: a literature review*

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Abstract

Objective: to describe the temporal and geographical expansion of Zika virus (ZIKV) circulation in countries and territories, from the time it was first isolated until 2018. Methods: This was a non-systematic literature review covering the period from 1947 to 2018 using the MEDLINE database and World Health Organization estimates. Results: Since its isolation in 1947, ZIKV circulation spread through Africa, Asia and the Pacific before reaching the Americas in 2013, causing serious clinical manifestations; the highest seroprevalence rates were recorded in Yap (74%) and in Brazil (63%); genetic mutations, absence of immunity and high vector susceptibility may have influenced ZIKV transmissibility and help to explain the magnitude of its expansion. Conclusion: The spread of ZIKV circulation in the Americas was the most extensive recorded thus far, possibly as a result of population and geographical characteristics of the sites where the virus circulated.

Keywords: Zika Virus, Flavivirus; Epidemiology; Epidemics; Congenital Abnormalities; Review Literature as Topic.

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Introduction

Following its discovery in 1947, Zika virus (ZIKV) was responsible for sporadic cases of mild infections that were not cause for great concern and were limited to the African and Asian continents. This scenario changed with effect from 2007, when the virus began to be considered a pathogen capable of causing large epidemics after having produced two large-scale outbreaks in the Pacific Islands and in French Polynesia. ZIKV circulation continued to expand (Figure 1A). Within a short time, the virus was considered to be a Public Health concern associated with a large number of microcephaly cases that occurred in Brazil.

Concern as to the severity of the consequences of infection led the Ministry of Health to declare a state of Public Health Emergency of National Concern on November 11th 2015. Following this declaration, the Pan American Health Organization (PAHO) issued an alert about the increased number of microcephaly cases in Brazil’s Northeast region. Just days afterwards, on November 28th 2015, despite there being little evidence, the Ministry of Health confirmed the link between ZIKV and the microcephaly outbreak. On December 1st 2015, the World Health Organization (WHO) and PAHO issued an alert suggesting possible association between ZIKV and the increase in cases of congenital syndrome and Guillain-Barré syndrome. On February 1st 2016, WHO declared a Public Health Emergency of International Concern. The agility with which health authorities and researchers acted enabled rapid proof of the causal relationship between ZIKV infection and the occurrence of microcephaly and other central nervous system alterations. This position was endorsed by WHO at a meeting of the Emergency Committee held in June 2016 (Figure 1B).

The potential of the virus to give rise to a broad spectrum of clinical manifestations was confirmed, ranging from non-specific symptoms, easily confused with other virus diseases, to neurological manifestations and congenital malformations. By the end of 2016, 2,366 Zika virus-associated congenital abnormalities had been confirmed in Brazil. The emergence of ZIKV in the Americas and the potential for its circulation to expand require better comprehension of its epidemiological profile, in order to facilitate understanding of the changes in infection detected over time.

The objective of this literature review was to describe the temporal and geographic expansion of ZIKV circulation in countries and territories, from the time it was isolated up until 2018.

Methods

This is a narrative review of ZIKV circulation expansion over the years in countries and territories on diverse continents. We searched the MEDLINE database (via PubMed), using the following keywords retrieved from the Health Sciences Descriptors (DeCS) virtual library: ‘zika’, ‘zika virus’, ‘flavivirus’ and ‘arbovirus’. Eligible articles were those that provided microbiological evidence of ZIKV infection in humans and non-humans published between 1947 and 2018, in any region of the world, and which contained complete information on how the study was conducted: period, place, sample, type of test used for diagnosis and test result. We excluded articles that did not present positive laboratory test results for the virus in humans or where virus isolation in non-humans was not conducted. No restriction was made as to language or whether the publication was free of charge or not.

We also used estimates, available on the official website of the PAHO-WHO, of confirmed Zika cases or confirmed cases of Zika infection-associated congenital syndrome, occurring in countries or territories in the Americas up until January 2018. In order to demonstrate the magnitude of infection in different places, ZIKA infection seroprevalence in the samples examined was calculated as follows: firstly we totaled the positive test results and then divided the total number of tests by the total number of samples in each study.

Global expansion of ZIKV circulation

1940s and 1950s

ZIKV is believed to have emerged in around 1920, although it was only isolated in 1947 in a study on yellow fever in *Rhesus* monkeys conducted by researchers from the Virus Research Institute. The term ‘Zika’ was borrowed from the name of the
Emergence of the virus around 1920

Virus isolated in Aedes

First records of infection on the Asian continent, in Malaysia

Emergence of the virus in the Pacific, on the Micronesian island of Yap


Virus isolated in rhesus monkeys in Uganda

First cases of human infection recorded in Africa

First cases of infection by Aedes aegypti recorded in Malaysia

Virus emerges in French Polynesia

Records of Guillain-Barré syndrome cases

Ministry of Health declares Public Health Emergency of National Concern

Ministry of Health confirms relationship between Zika virus and microcephaly

WHO declares Public Health Emergency of International Concern

WHO declares end of Public Health Emergency of International Concern

11/11/15 12/11/15 01/12/15 01/02/16 06/16 11/16 05/17

PAHO issues alert about increased microcephaly cases in Northeast Brazil

WHO issues alert about possible association between Zika Virus and increased number of microcephaly and Guillain-Barré syndrome cases

WHO confirms association between Zika virus and microcephaly

Ministry of Health declares end of Public Health Emergency of National Concern

Notes:
A) Timeline of Zika virus circulation expansion up until 2015.
B) Measures adopted by health authorities (Brazilian Ministry of Health, Pan American Health Organization [PAHO], and World Health Organization [WHO]) in the face of the increased number of microcephaly Guillain-Barré syndrome cases in Brazil.

Figure 1 – Timeline of Zika virus circulation expansion and measures adopted by health authorities

Zika forest, in Entebbe, Uganda, where the Institute was based. Despite the study mentioned above being focused on yellow fever and dengue, researchers found evidence of Zika virus being a new pathogen.22

In 1948, less than a year after its discovery, ZIKV was isolated in the Aedes (Stegomyia) africanus vector,22-24 even though at that time it was not known that it was a ZIKV vector.

ZIKV spread following its original lineage, referred to as African lineage Zika, and expanded over part of the African continent.1 In West Africa it was introduced twice, at different times, and gave origin to two African lineages.14

The first human ZIKV infections were recorded in 1952, on the African continent, and were confirmed by its presence in serum of ZIKA neutralizing antibodies.25,26 At that time there was no other way of demonstrating ZIKV infection, since test results could be biased because of a possible immune response to yellow fever vaccination.24
studies identified the presence of these antibodies in people living in North Africa, West Africa, East Africa and Central Africa, as well as in South Asia and Southeast Asia (Figure 2 and Figure 3A). The highest seroprevalence rates were recorded in Malaysia and the Philippines: 50% and 36%, respectively (Table 1).

Jaundice was found in the three human cases identified in 1954, indicating that the virus could also be viscerotropic. Another characteristics described was its affinity for nerve tissues, found in mice that developed neurological diseases after being infected. \( Aedes aegypti \) was found to be a ZIKV vector in 1956.

### 1960s to 1990s

The third ZIKV lineage, i.e. the Asian lineage, originated from a strain isolated in Malaysia in around 1966. It was here that the first Zika virus infection attributed to the \( Aedes aegypti \) vector was recorded. At that time, serological and virological evidence indicated that it was circulating in almost all of Africa, in its Northern, Central, Western and Eastern regions (Figure 2 and Figure 3B). The majority of the countries in these regions are located in latitudes where the climate is tropical and this is propitious for vector development. Joint circulation of yellow fever virus and Zika virus was found in a region of Ethiopia in 1968. Studies indicate that ZIKV antibodies can attenuate yellow fever virus infection but do not interfere with its transmission. In the decades in question, the highest seroprevalence rates were recorded in Burkina Faso (53%), Mali (52%) and Benin (44%).

### 2000s

For more than half a century, ZIKV remained confined to the African and Asian continents, before emerging in the Pacific Islands in the late 2000s. Between April and July 2007, the first large epidemic caused by the virus occurred in Yap, an island in Micronesia (Figure 2). Infection incidence was high in this outbreak at around 74% (95% confidence interval: 68-77). Despite affecting the majority of the population, only around 20% of total cases were symptomatic and reported having exanthema, conjunctivitis and pain in their joints. The serum samples of the inhabitants of Yap were tested by means of the enzyme-linked immunosorbent assay (ELISA), the virus neutralization test to detect antibodies (NT) and reverse transcription polymerase chain reaction (RT-PCR). Phylogenetic analyses showed that a strain of the Asian lineage of the virus was responsible for this outbreak.

By the end of the 2000s, ZIKV had been isolated in \( A. aegypti \), \( A. africanus \), \( A. apicoargenteus \), \( A. luteocephalus \), \( A. vitattus \), \( A. Furticifer \) and \( A. Hensillii \) species vectors, whereby the latter was the most frequent species in the Yap outbreak. For a long time it was believed that the only form of Zika virus transmission was by the bite of mosquitoes of the \( Aedes \) genus. In 2008, however, two researchers were infected in Senegal and one of them transmitted ZIKV to his wife, possibly through sexual intercourse. Other studies have corroborated this hypothesis by indicating the possibility of this form of transmission.

### 2010s

The 2010s were marked by important discoveries, such as the possibility of mother-to-child Zika virus transmission and clinical manifestations with unprecedented association with Zika virus infection, such as congenital abnormalities and Guillain-Barré syndrome. At that time the virus caused a new epidemic that affected a considerable part of the population of French Polynesia with effect from 2013, with approximately thirty thousand people infected and 42 patients with Guillain-Barré syndrome. That epidemic was the consequence of a new strain that appeared in the same year and was genetically related to the strains isolated in Yap in 2007 and in Cambodia in 2010. It is likely that its magnitude was the result of a population with low levels of immunity, high vector density and genetic mutations in which important amino acids were modified, increasing the capacity of Zika virus transmission by the \( Aedes aegypti \) vector.

ZIKV continued to expand to other Pacific Ocean Islands and through Southeast Asia until it was identified in the Americas in May 2015. Between 2015 and 2016, seroprevalence in Brazil was 63% (Table 1). The timeline of Zika virus circulation expansion is shown in Figure 1A, while its geographic expansion is shown in Figure 3, highlighted by period to demonstrate its swiftness and extent.
<table>
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<th>Country or territory</th>
<th>Type of test used</th>
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Legend:
- NT: virus neutralization test to detect antibodies.
- ELISA: enzyme-linked immunosorbent assay.
- CF: complement fixation test.
- HI: hemagglutination inhibition test.
- IMT: intracerebrally inoculated mice test.
- VI: virus isolation.
- PCR: polymerase chain reaction.
- RT-PCR: reverse transcription polymerase chain reaction.

Figure 2 – Countries or territories recording Zika virus circulation between 1947 and 2018, listed by continent and decade of occurrence

Continued on next page
The seroprevalence tests used in the various studies we consulted differ as to the method of laboratory diagnosis used and, therefore, have differing levels of sensitivity and specificity, thus compromising the comparability of the results of the different methods applied.

RT-PCR was used in 31 studies and was the most used test, followed by the hemagglutination inhibition test (HI) in 24 studies, ELISA in 17 studies, NT in 13 studies and the complement fixation test (CF) in 4 studies. Some studies used more than one diagnostic method. Cross-reactivity between ZIKV antibodies and those of other flaviviruses may also have compromised correct estimation of infection prevalence.

**ZIKV in the Americas**

The first genetic studies of the strain causing the ZIKV epidemic on the American continent suggest that it originated from a unique Asian genotype lineage, introduced in Brazil between late 2013 and early 2014 and having come from French Polynesia. Four hypotheses have been raised regarding the introduction
of the virus in Brazil. Initially it was thought that it had happened in 2014, during the FIFA World Cup,\textsuperscript{74} despite there being no Pacific countries among the participating soccer teams. A second possibility was that the virus was introduced during the Canoe Sprint World Championship, held in August 2014 in Rio de Janeiro, as there were teams from four Pacific countries with registered Zika cases: French Polynesia, New Caledonia, the Cook Islands and Easter Island.\textsuperscript{84} However, the hypothesis of the virus having entered Brazil via Rio de Janeiro does not help to explain why such a high number of cases were concentrated in the country’s Northeast region. The third hypothesis is that the virus was introduced one year earlier, between July and August 2013, during the Confederations Cup.\textsuperscript{81} According to the fourth and final hypothesis, the virus circulated in Oceania and Easter Island, spreading to Central America and the Caribbean before arriving in Brazil at the end of that year.\textsuperscript{85} The only ancestor of the cases studied was a strain from Haiti, indicating that ZIKV could have been introduced in Brazil by immigrants or Brazilian troops returning from that country. However, recent studies indicate that the virus followed a different route, namely from Brazil to Central America, entering via Honduras, between July and September 2014.\textsuperscript{86} Phylogeographic analysis has estimated that the virus arrived in Honduras from Brazil and later spread to Guatemala, Nicaragua and southern Mexico by early 2015. Another study corroborates the hypothesis that the introduction of ZIKV in South America occurred prior to its introduction in Central America, possibly in the first half of 2013.\textsuperscript{80}

In October 2014, some municipalities of the Brazilian states of Rio Grande do Norte, Paraíba and Maranhão reported suspected cases of a viral disease with presence of exanthema, mild fever, itching and painful joints, these being symptoms not in keeping with suspected cases of other exanthematous viral infections, such as measles and dengue. Before long a further six states reported exanthematous syndrome cases between October 2014 and March 2015.\textsuperscript{75} The intense and concomitant circulation of other flaviviruses, together with similar clinical presentation, low specificity of ELISA diagnostic tests for dengue\textsuperscript{76} as well as the fact of the presence of the pathogen in Brazil still being unknown, led to ZIKV not being indicated as the main suspect.

In March 2015, samples from the states of Rio Grande do Norte and Bahia had positive ZIKV results confirmed by RT-PCR.\textsuperscript{73,74} It spread well beyond Brazil’s borders. By late 2015, ten Central and Southern American countries had recorded autochthonous
Table 1 – Zika virus seroprevalence in humans by affected country and period of infection, 1947-2016

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<tr>
<th>Period</th>
<th>Country/reference</th>
<th>Type of test used</th>
<th>No. of cases</th>
<th>Total</th>
<th>Seroprevalence (%)</th>
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<td>1964-1965</td>
<td>Guiné-Bissau&lt;sup&gt;45&lt;/sup&gt;</td>
<td>HI</td>
<td>122</td>
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<td>1964-1966</td>
<td>Togo&lt;sup&gt;46&lt;/sup&gt;</td>
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<td>1964-2010&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Camarões&lt;sup&gt;43,542&lt;/sup&gt;</td>
<td>HI, CF</td>
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<td>1,232</td>
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<td>55</td>
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<td>Somalía&lt;sup&gt;98&lt;/sup&gt;</td>
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<td>3</td>
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<td>1966-1968</td>
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<td>509</td>
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<td>108</td>
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<td>1967</td>
<td>Gabão&lt;sup&gt;42&lt;/sup&gt;</td>
<td>HI</td>
<td>50</td>
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<td>1972</td>
<td>Serra Leoa&lt;sup&gt;132&lt;/sup&gt;</td>
<td>HI</td>
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<td>CF</td>
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<td>1983</td>
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<td>HI</td>
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<td>2007</td>
<td>Ilha de Yap, Micronésia&lt;sup&gt;3&lt;/sup&gt;</td>
<td>ELISA</td>
<td>414</td>
<td>557</td>
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<td>2011-2013&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>ELISA</td>
<td>319</td>
<td>1,069</td>
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<td>ELISA</td>
<td>217</td>
<td>3,625</td>
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<tr>
<td>2015-2016</td>
<td>Brasil&lt;sup&gt;123&lt;/sup&gt;</td>
<td>ELISA, PRNT</td>
<td>401</td>
<td>633</td>
<td>63</td>
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Legend:
NT: virus neutralization test to detect antibodies.
ELISA: enzyme-linked immunosorbent assay.
CF: complement fixation test.
HI: hemagglutination inhibition test.
IMT: intracerebrally inoculated mice test.
PRNT: plaque reduction neutralization test.
and by the beginning of the next year this number had increased rapidly to 48 countries (Figure 2 and Figure 3D). Only Canada and Bermuda, both located in North America, and Chile and Uruguay, in South America, did not have autochthonous cases. Figure 4 shows the geographic and temporal spread of ZIKV in the Americas, from the first recorded case on the continent up until 2017.

Of all these countries, Brazil had the highest number of ZIKV infections, totaling 137,288 confirmed cases between 2015 and January 2018, followed by Puerto Rico and Mexico, with 40,562 and 11,805 confirmed cases, respectively. In 2016 the total number of cases reduced by more than 95% compared to the previous year and on November 18th 2016 WHO stopped considering the virus as a Public Health Emergency of International Concern. In May 2017, the Brazilian Health Ministry also declared the end of the emergency.

In the first semester of 2015, a change was noted in the pattern of the occurrence of Guillain-Barré syndrome in two states of Brazil’s Northeast region, namely Pernambuco and Bahia: in the former state the number of cases tripled compared to the previous year, with a peak in April, while Bahia recorded a peak in occurrence of the syndrome between June and July. In the same period, four patients undergoing solid organ transplantation were infected with ZIKV, diagnosed by RT-PCR between June 2015 and January 2016. In October of the same year, a change was detected in the epidemiological pattern of microcephaly occurrence, when Pernambuco state health authorities informed the Ministry of Health about a significant increase in the number of cases. In late November 2015, the Evandro Chagas Institute in the state of Pará, a body linked to the Health Ministry’s Health Surveillance Secretariat (IEC/SVS/MS), sent the result of tests performed on a baby with microcephaly to the Ministry: presence of ZIKV in blood and tissues. This resulted in the Ministry of Health confirming the relationship between ZIKV and microcephaly.

By the end of 2016, 22 countries had registered cases of congenital syndrome associated with ZIKV infection: a total of 2,525 reported cases, 2,289 (90%) of which related to Brazil. By December 2017, the 27 Brazilian states together recorded 3,071 microcephaly cases, 2,004 (65%) of which occurred in the Northeast region. This number reduced significantly to 123 new cases between January and May 2018. In all, there was a total of 3,194 records possibly associated with ZIKV infection since these began to be counted in 2015. Zika virus, the cause of this pandemic, had become a potential Public Health threat owing to its association with neurological complications and congenital malformations, which have been widely documented.

The epidemics caused by the virus brought to light a broad range of clinical manifestations; although it is not possible to know the magnitude of the complications related to ZIKV infection, which may possibly be greater than those found so far. Little is known about issues such as the severity of clinical presentation of ZIKV infection or its viral load, nor about its influence on the clinical spectrum found in different places and populations.

A descriptive study assessed 1,950 confirmed microcephaly cases in Brazil, 1,373 of which were in the country’s Northeast region, using secondary data obtained from the Health Ministry’s Notifiable Diseases Information System (SINAN) relating to the period between January 1st 2015 and November 12th 2016. Its results revealed two waves of ZIKV infection: during the first wave, in 2015, there was a monthly peak of microcephaly occurrence estimated at 50 cases per 10,000 live births, most of them (70% of the total) living in the Northeast region; during the second wave, occurrence was much lower, with monthly peaks estimated as varying between 3 and 15 cases per 10,000 live births. The number of microcephaly cases related to ZIKV infection following both outbreaks, or waves, showed temporal variation according to the region of the country; the reasons for these differences have, however, yet to be enlightened.

A possible explanation for the result of these estimates is the fact that, during the second wave of infection, the relationship between ZIKV infection and the microcephaly cases in question was already suspected and even supported by evidence, leading the government to broadcast campaigns with the aim of keeping the population informed. Pregnant women began to take prevention measures in order to avoid contact with the vector, such as using insect repellent, bug screens and even delaying planned pregnancy.

Little is known about genetic variations between ZIKV lineages and their ability to interfere with ZIKV pathogenicity. One experimental study that used trophoblasts derived from human embryonic stem...
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1:180.934.416

2014-2015
2016
2017
No cases reported

Notes:
A) Countries or territories registering Zika virus circulation between 2014 and 2015.
B) Countries or territories registering Zika virus circulation in 2016.
C) Countries or territories registering Zika virus circulation in 2017.

Figure 4 – Geographic and temporal expansion of Zika virus in the Americas, 2015-2017

Discussion

The factors that led to large-scale and rapid emergence, spread and apparent increase in Zika virus pathogenicity in the Pacific and the Americas are not yet totally understood. It is possible that there are various mechanisms in operation, including virus mutations that might increase transmission from humans to mosquitoes, modulating the host immune response. Another factor lacking explanation is the absence of large epidemics in Africa and Asia. A hypothesis given for this fact is that it possibly reflects higher levels of immunity provided by cross-protection against other Zika-related flaviviruses or that epidemics that in fact existed may have been associated with dengue due to the clinical similarity between the two viruses dengue and due to their antibody cross-reactivity. Another study corroborated the hypothesis that large outbreaks have not happened in Africa because Aedes aegypti of African origin may be less susceptible to virus strains than Aedes aegypti that is not of African origin. Notwithstanding, this characteristic has not helped to explain why there have not been large outbreaks in Asia, different to the Americas, given that the populations of both regions had similar levels of susceptibility.

Intensity of Zika dissemination, viremia and clinical symptoms in the Americas, including microcephaly,
could have intensified owing to dengue virus immunity existing in endemic regions.\textsuperscript{110} However, a pediatric cohort study conducted in Nicaragua between January and February 2017 monitored 3,700 children aged 2 to 14 years and concluded that the opposite may occur, i.e. ZIKV infection symptoms may be reduced owing to prior dengue virus immunization.\textsuperscript{111} This hypothesis is corroborated by research involving an experiment with mice that demonstrated the effect of dengue infection on CD8+ T-cells in guaranteeing cross-protection against ZIKV during pregnancy.\textsuperscript{112} Another factor capable of intensifying dissemination was a slight genetic alteration in ZIKV polyprotein which happened before the 2013 outbreak and was sufficient to permanently increase its infectivity in human nerve cells.\textsuperscript{105} This fact would help to explain why microcephaly cases have been so numerous in the Americas in comparison to other continents.

Other aspects to be considered are related to \textit{Aedes aegypti} and \textit{Aedes albopictus} susceptibility, as well as that of ZIKV strains, due to genetic differences that influence vector response levels to infection and consequent ZIKV transmission capacity.\textsuperscript{113-120} The American strain is more easily transmitted than the Asian strain from which it is derived, this being an hypothesis confirmed by analysis of vector saliva: only the virus in the sample containing the American strain remained viable after three days of infection, in addition to having a higher infection rate in \textit{Aedes aegypti}.\textsuperscript{121} The highest number of Zika and microcephaly cases was recorded in Northeast Brazil. Some reasons indicated for this were presented in an ecological analysis study: joint circulation of the virus that causes Chikungunya feber, which exists in this region, could increase the risk of other communicable diseases being transmitted.\textsuperscript{122} Another study found higher ZIKA prevalence infection in poorer social classes.\textsuperscript{123} The fact that the first notifications of infections occurred in Northeast Brazil, along with the massive media alerts that followed, helped measures to be taken that may possibly have contained greater spread of the virus in other regions. The same reasoning could be applied to Brazil, where the first infections were recorded, and to the other Latin American countries where cases were not numerous.

The Brazilian epidemic showed a sharp decline in recorded infections with effect from 2017. A possible cause of this may have been high seroprevalence in the population, leading to immunity against ZIKV.\textsuperscript{123,124} A study conducted in Bahia, a Northeastern Brazilian state, assessed 633 individuals based on their serum samples collected between 2015 and 2016. The results of the analyses showed a rapid increase in ZIKV infection seroprevalence in the population, reaching 63% in 2016.\textsuperscript{123} It is possible that population and geographic characteristics may have directly influenced the pace of propagation, and the possible reasons for this would be the variations in vector density, immunity and changes in routine habits, as well as high population mobility.\textsuperscript{100,120,125}

The outbreak in the Americas has ended. Notwithstanding, a study supported by a stochastic spatial model has indicated the possibility of the emergence of new epidemics approximately every ten years, this being the time needed for a new generation of the population to become susceptible once more.\textsuperscript{124} In conclusion, the spread of ZIKV circulation seen in the last decade was the swiftest and largest recorded thus far. Possible factors contributing to this include genetic changes that increased its transmission potential, together with favorable population and geographic characteristics in the regions where the virus circulated. Large numbers of microcephaly cases were expected to occur in most countries in the Americas,\textsuperscript{99} but in the end this expectation was not confirmed. Similarly, the reasons why Brazil recorded such a higher number of cases in comparison to other Latin American countries has not been totally explained. Nor have the reasons why most of the infections recorded in Brazil were concentrated in its Northeastern region. This gives rise to several unanswered questions as to increased virus circulation and pathogenicity. Another limitation of this literature review relates to the different methods adopted in the studies consulted, thus hindering precise seroprevalence rates from being obtained. Cross-reactivity, caused by other flavivirus antibodies, was a limiting impediment to the accuracy of the results presented.\textsuperscript{76}

Further research is needed to overcome gaps in knowledge about ZIKV pathogenesis and to assess local risks; seroprevalence studies to identify regions vulnerable to infection so as to foresee the potential of future epidemics. A benefit of this work is that the efforts of health authorities would be better directed, so as to contribute to the development of effective Zika virus infection control measures.
Vaccine development also needs to be encouraged, in order to interrupt the transmission chain and avoid future outbreaks and epidemics.

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References


Authors’ contributions

Netto EM, Sampaio GS, Brites C, Moreira-Soto A and Drexler JF took part in the conception and planning of the study and writing and critical revision of the manuscript contents. Sampaio GS and Miranda FL collected and analyzed the study data. All the authors approved the version to be published and take on responsibility for all aspects of the work, including its accuracy and integrity.

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