Chapter

Aedes aegypti: The Main Enemy of Public Health in Brazil - Challenges and Perspective for Public Health

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Abstract

Mosquitoes (Diptera: Culicidae) are important vectors responsible for transmission of many diseases and parasites. They are causing millions of deaths every year and are considered one of the deadliest animals in the world. The most common arboviruses, such as dengue, chikungunya and Zika, to which the Brazilian population is most exposed and that occur through the bites of the *Aedes aegypti* mosquito, which is the main aim of this study. These infections caused by these three arboviruses are widely distributed on the national territory and have severe consequence to population in some cases. Without effective vaccine and specific treatment, the maintenance and integration of a continuous entomological and epidemiological surveillance are important, besides the methods to control and to prevent these arboviruses in Brazil. This chapter discusses the role of Fiocruz (Oswaldo Cruz Foundation, the most prominent institution of science and technology in health in Latin America) for the development of new methodologies to diagnose and control mosquito-borne diseases through public health policies for the country.

Keywords: *Aedes aegypti*, dengue, Zika, chikungunya, surveillance, prevention

1. Introduction

The mosquitoes' ability of disease transmission is studied since the nineteenth century, although malaria has affected humanity for millennia. Oswaldo Cruz called it "Amazonian's elf," and in the 50th year, a new disease combat method became important worldwide, the medicated salt of Mario Pinotti. Since this, the efforts of the Oswaldo Cruz Foundation (Fiocruz) combated and prevented the diseases transmitted by mosquitoes in Brazil. Among these diseases, we can find malaria, dengue, Zika and chikungunya. Brazilian territory is an endemic area for their transmission, considering the tropical climate and the Brazilian population habits. In the last years, the country was affected by an outbreak caused by chikungunya virus and by the third arbovirus (Zika virus—ZIKV). These viruses were responsible for causing a large number of infections [1, 2].

1.1 *Aedes aegypti*

The first report about *Aedes aegypti* is dated from 1925 by Kirkpatrick, in Egypt [3]. *Aedes aegypti* is a small dark-colored mosquito with white stripes markings. Mosquito is considered domesticated animal as much as other animals, such as the pet dog or cat [3]. These mosquitoes can use natural locations or artificial containers with waters to lay their eggs, thus tree holes, plant axils and common household items that can accumulate rainwater, for example, are potential breeding sites, especially when these locations contain organic material. During their lifetime, the *A. aegypti* females are found around the houses and all day long they are capable of biting humans. Unlike most other mosquitoes, *Aedes* mosquitoes are active and bite only during the daytime, with peak activity during the early morning and in the evening before dusk. They are also capable of biting other animals, but without transmitting diseases to them. Thus, after feeding on human blood, they lay her eggs in the still water. These eggs are laid over a period of several days, and they are resistant to desiccation surviving for long periods of six or more months, until they have contact with water again, and the larvae are released [4, 5].

In America regions, *A. aegypti* is the only epidemiological important species transmitting the dengue virus. This species is originated from Africa where it was domesticated and adapted to the environment created by man, becoming anthropophilic. In the seventeenth century, these mosquitoes started spreading all over the world, to Mediterranean in the eighteenth century, to tropical Asia in the nineteenth century and to Pacific Island in the end of the nineteenth century and beginning of the twentieth century. These adaptive characteristics allowed them to become abundant in many cities and easily carried to other areas by means of transport, which increased their vectorial competence, that is, their ability to become infected by a virus, to replicate it and transmit it. Although *A. aegypti* eradication took place in the Mediterranean in the 1950s and between 1950s and 1960s in most countries of the Americas, there was a reinfestation in most of the areas from which it had been previously eradicated. Nowadays, this vector is considered a cosmotropical species due to the increasing adaptive capacity of the *A. aegypti* [6–10].

In the past, *Aedes albopictus* has its origin in the Asian jungles, but in consequence of an intense tire trade, by sea, this vector came to the Americas in the 1980s, firstly to the USA and then, in Brazil and in others countries of the Central and South America, in Africa, Europe but either in some Pacific Island [6]. *A. albopictus* also lays their eggs in tree holes, but differently of *A. aegypti*, that mosquito has their habits outside the household and bites both animals and humans (anthropophilic and zoophilic diurnal habits). In Asia, *A. albopictus* is responsible for the transmission of epidemic outbreaks of classical and hemorrhagic dengue fever [11].

1.2 Arboviruses: dengue, Zika and chikungunya

Arboviruses (an acronym of ARthropod-BOrne virus) have caused much concern in public health worldwide. Arboviruses have been emerging in different parts of the world due to genetic changes in the virus, alteration of the host and vector population dynamics or because of anthropogenic environmental factors. These viruses' capacity for adaptation is notable, as well as the likelihood of their emergence and establishment in new geographic areas [12]. Here, we highlight three important viruses such as dengue virus (DENV), chikungunya virus (CHIKV), and, lately, Zika virus (ZIKV).

Dengue is a flaviviruses infection transmitted by mosquitoes of *Aedes* genus, mainly *A. aegypti* and *A. albopictus*. The dengue virus (DENV) comprises five distinct serotypes, and this disease is a fast emerging pandemic-prone viral considered the major public health challenge worldwide [4, 13].

The first epidemic of dengue hemorrhagic fever occurred in Manila, Philippines, between 1953 and 1954, followed by Bangkok, Thailand and Malaysia in 1958 and Singapore and Vietnam in 1960. Due to economic growth and consequent increase of post-World War II urbanization, the epidemic of dengue and hemorrhagic dengue spread in the 1970s to other areas of the world, starting in Southeast Asia [10].

In Brazil, since the 1980s, there is an intense virus circulation with epidemic bursts affecting all the regions of the country [14].

The World Health Organization (WHO) estimates 100 million symptomatic cases per year and 2.5 billion people are at risk of infection worldwide. There are no available vaccines and no effective treatment for dengue, which reinforces the need for strategies to prevent virus transmission by the main vector *A. aegypti* (**Figure 1**).

ZIKV is also transmitted by *Aedes aegypti,* and it was first isolated from a rhesus macaque (*Macaca mulatta*) placed as sentinel during a study about yellow fever in the Zika Forest, Uganda, Africa in 1947 [15]. ZIKV had its first documented outbreak only in 2007 in Micronesia. Since then, the transmission area has spread to islands in the Pacific Ocean, especially during a great epidemic in Polynesia in October 2013. In 2015, some cases of humans infected by ZIKV were reported in Brazil, developing into an outbreak that spread throughout South America, the Caribbean islands and Central America. Originally adapted to a zoonotic cycle in Africa, ZIKV evolved into an urban cycle involving a human reservoir and domestic mosquito vectors [16].

Zika virus was first identified in Uganda in 1947. Before 2007, only sporadic human cases were reported from countries in Africa and Asia. In 2007, the first documented Zika virus disease outbreak was reported in the Federated States of Micronesia. In subsequent years, outbreaks of Zika virus disease were identified in countries in Southeast Asia and the Western Pacific. Zika virus was identified for the first time in the Western hemisphere in 2015, when large outbreaks were reported in Brazil. Since then, the virus spread throughout the Americas (**Figure 2**) [17].

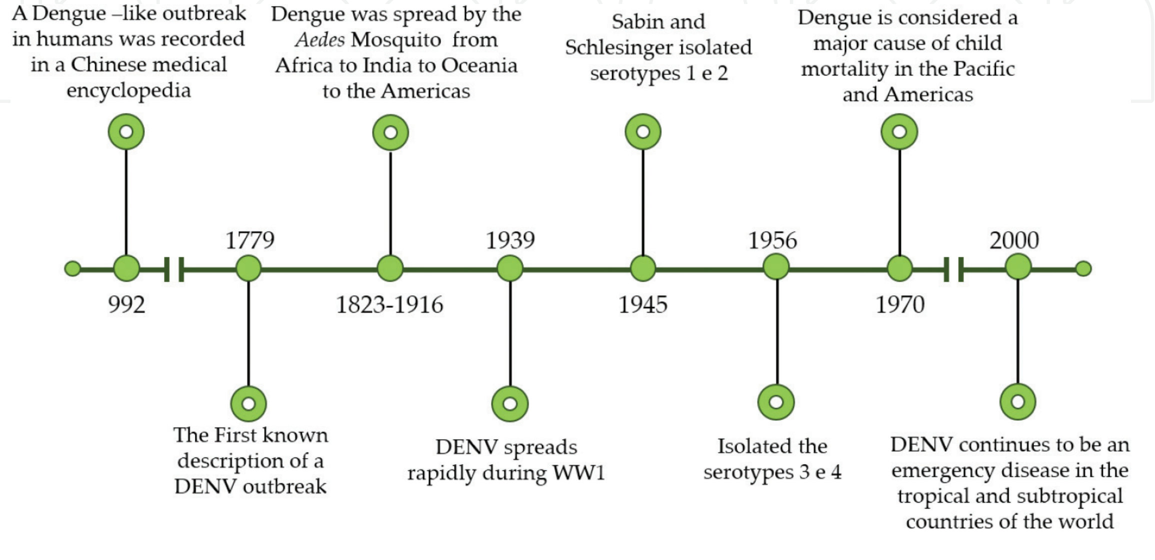


Figure 1.
Chronological spread of DENV (adapted from https://www.centralmosquitocontrol.com/resources/disease-information/dengue).

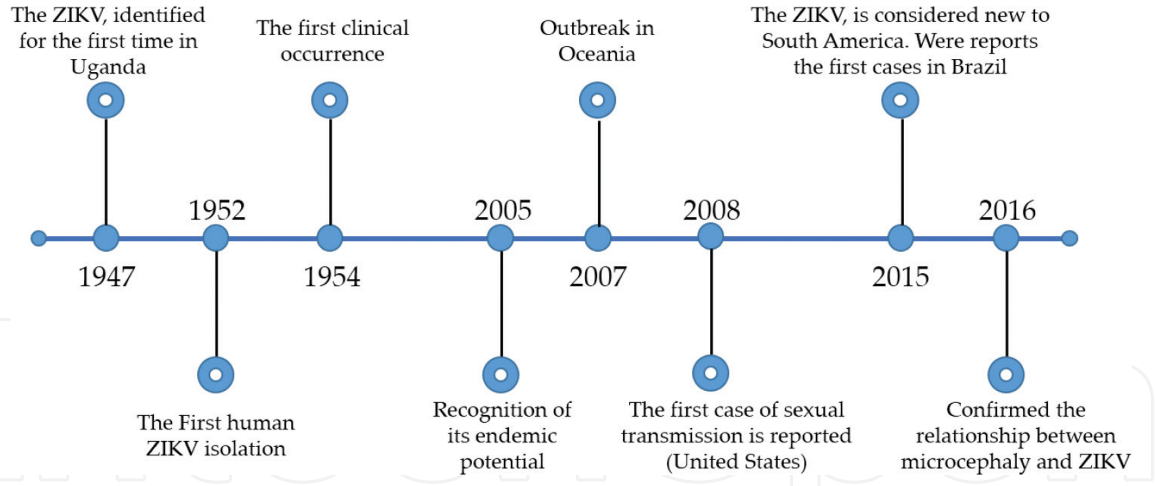


Figure 2.
Chronological spread of ZIKV (adapted from Ref. [18]).

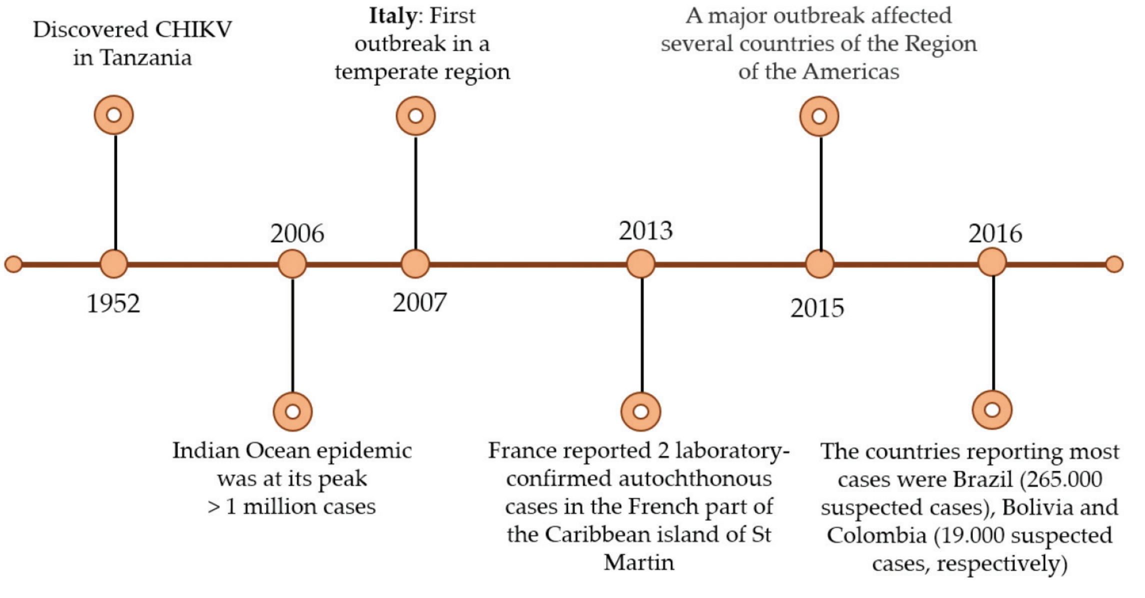


Figure 3.
Chronological spread of CHIKV.

Zika virus caused large outbreaks in previously unexposed populations, and from 2013 onward, outbreaks linked with neurological disorders including Guillain-Barré syndrome and congenital malformations, for reasons that are not yet known. The future transmission of Zika infection is likely to coincide with the global distribution of *Aedes* vectors [19].

A different arbovirus type, an alphavirus, is responsible for causing chikungunya. Differently than the other two diseases, dengue and Zika, chikungunya causes prolonged joint pain and persistent immune response.

Chikungunya is a mosquito-borne viral disease first described during an outbreak in southern Tanzania in 1952. It is an RNA virus that belongs to the alphavirus genus of the family Togaviridae. The name "chikungunya" derives from a word in the Kimakonde language, meaning "to become contorted" and describes the stooped appearance of sufferers with joint pain (arthralgia) (**Figure 3**) [20].

Both *A. aegypti* and *A. albopictus* have been implicated in large outbreaks of chikungunya, whereas *A. aegypti* is confined within the tropics and sub-tropics, *A. albopictus* also occurs in temperate and even cold temperate regions. In recent decades, *A. albopictus* has spread from Asia to become established in areas of Africa, Europe and the Americas [20].

The first report for *A. albopictus* in the Americas occurred in Houston (the United States) in 1985. In Brazil, it was detected for the first time in 1986 in the states of Rio de Janeiro and Minas Gerais [21, 22]. *A. albopictus* was essentially a species wilderness that bred and fed on of the forests and adapted outside houses and inside houses in the various urban and suburban areas of their distribution, according to records made by Gomes and Pessoa [23, 24]. This mosquito species is known as a secondary vector of chikungunya and dengue virus [25].

There is no specific antiviral drug treatment for chikungunya. The treatment is directed primarily at relieving the symptoms, including the joint pain using antipyretics, optimal analgesics and fluids. There is also no commercial chikungunya vaccine.

2. Clinical diagnosis and treatment for dengue, Zika and chikungunya fever

The greatest challenge is the differential clinical diagnosis between dengue, Zika and chikungunya. These three diseases have identical symptomatology and often the patient may present more than one disease at the same time or even having one of these diseases without the manifestation of symptoms. The clinical diagnosis can still occur after some days after the beginning of the infection, but mainly by laboratorial diagnosis [26–28].

Dengue, Zika and chikungunya infection are diagnosed based on clinical, laboratory and epidemiological criteria. It is an important recognition and differentiation of the clinical symptoms and signs to make the correct diagnosis, start proper treatment and prevent the associated complications [26–28].

Dengue is an exanthematic febrile disease, which is often accompanied by nausea, aches (especially frontal headache) and pains and responsible for high rates of morbidity and mortality in countless endemic areas around the world.

In dengue fever, the incubation period lasts for 4–10 days; after that, the disease has three phases: febrile (lasts 2–7 days with no specific signs and symptoms); critical (last 24–48 h) and convalescence. The progression to severe dengue infection (hemorrhagic fever) is variable and difficult to predict [29].

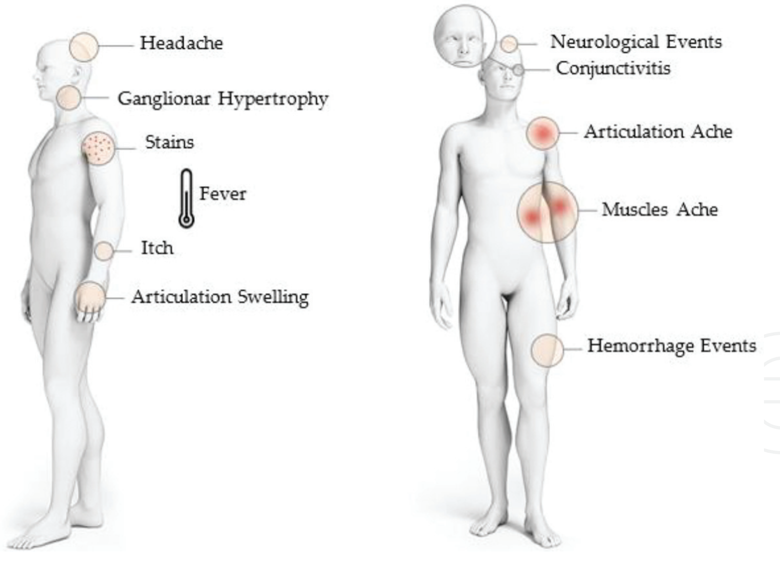
Zika fever and dengue are so similar, characterized by fever, exanthema, headache, conjunctivitis (nonpurulent), myalgia and arthralgia (notably small joints of hands and feet).

Unlike dengue, Zika presents low morbidity, but it is associated by diseases such as congenital microcephaly cases and Guillain-Barré syndrome (a neurological disorder that could lead to paralysis and death), myelitis and meningoencephalitis [30].

Zika fever is very analogous to dengue, symptom manifests in period of 3–12 days and lasts for 4–7 days. It is estimated that in five infected patients, only one develop them [31].

Chikungunya fever symptoms are sudden fever accompanied by headache, polyarthralgia (debilitating) or arthritis and maculopapular rash. The incubation period lasts for 2–12 days. Symptoms usually disappear in less than 2 weeks, but arthralgia may last even years. Severe chikungunya can manifest encephalitis, myocarditis, hepatitis and multiple organ failure that are fatal [32, 33] (**Table 1**).

Diagnosis of dengue, Zika and chikungunya is primarily clinical. In regions of epidemic, dengue is primordial, look for warning symptoms and a complete blood count and transaminases to determinate the phase and severity of the disease. The



Symptoms*	Arboviruses		
	DENV	CHIKV	ZIKV
Headache	Intense	Moderate	Moderate
Ganglionar hypertrophy	Mild	Moderate	Intense
Cutaneous rash (exantema)	From the 4th day (30–50% cases)	Appear from 2nd and 5th days (50% cases)	Appear from 1st or 2th day (90–100% cases)
Fever	Above 38°C (4–7 days)	Above 38°C (2–3 days)	without febrile and subfebrile 38 (1–2 days of subfebrile)
Itch	Mild	Mild	From moderate to intense
Articulation swelling	Rare	From moderate to intense	Mild
Neurological events	Rare	Rare	More frequently that DENV and CHIKV
Conjunctivitis	Rare	30% cases	50–90% cases
Joint pain	Mild	From moderate to intense	Moderate
Muscles pain	Intense	Intense	Moderate
Hemorrhage events	Moderate	Mild	—

**Adapted from: http://combateaedes.saude.gov.br/pt/sintomas*

Table 1.
The main symptoms of dengue, Zika and chikungunya.

methods for establishing a laboratory diagnosis of these arboviruses are as follows: (1) detection of the virus for example, cell culture or viral RNA real-time detection; (2) antibody detection for example, IgM or IgG detection and (3) antigen/antibody combined detection for example, NS1 and IgM/IgG [27, 28].

These diseases are usually self-limiting with no need for hospitalization except warning signs are observed, especially severe dengue. There are no specific treatments available. Only symptomatic treatment with nonsalicylic analgesics and nonsteroid anti-inflammatories drugs are administrated when dengue infection is discovered. Patients should be advised to drink plenty of fluids to replace fluid lost from sweating, vomiting and others.

3. Epidemiology

The Brazilian regions with the highest incidence and prevalence of these diseases (northeast and southeast region) present a favorable climate for the development of the *Aedes aegypti* (**Figure 4**) and the use of lighter clothes, which cover smaller areas of the body, favoring their exposure.

The number of suspected or confirmed dengue cases reported to the World Health Organization (WHO) is showed in **Figure 5** as well its distribution in the world.

In 2015, the incidence of probable cases of dengue fever (number of cases/ 100,000 inhabitants), according to Brazilian geographic regions, shows that the

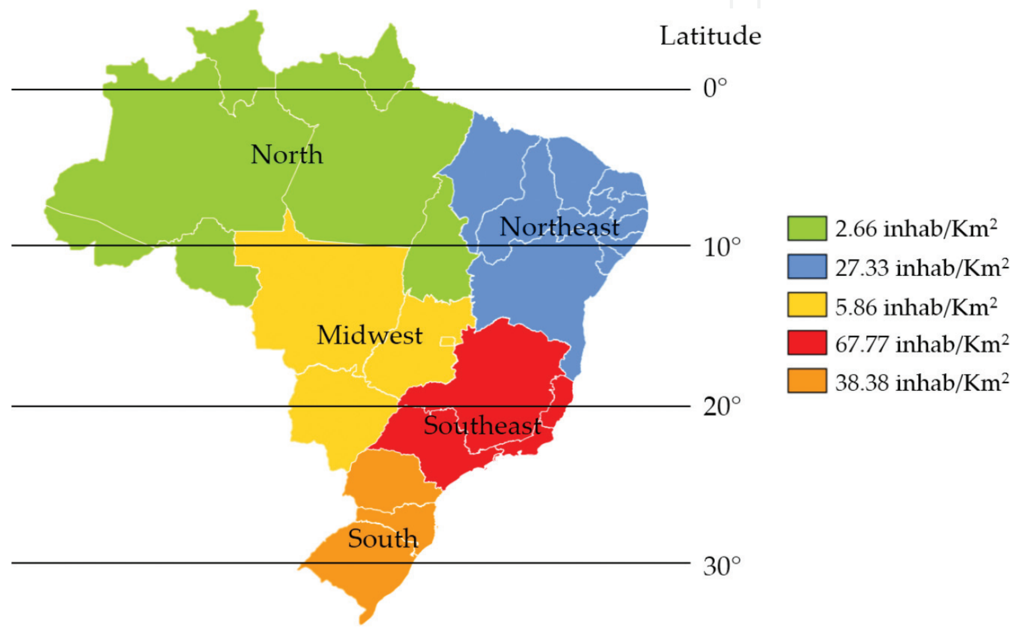


Figure 4.
Brazilian demographic density and latitude at geographic regions.

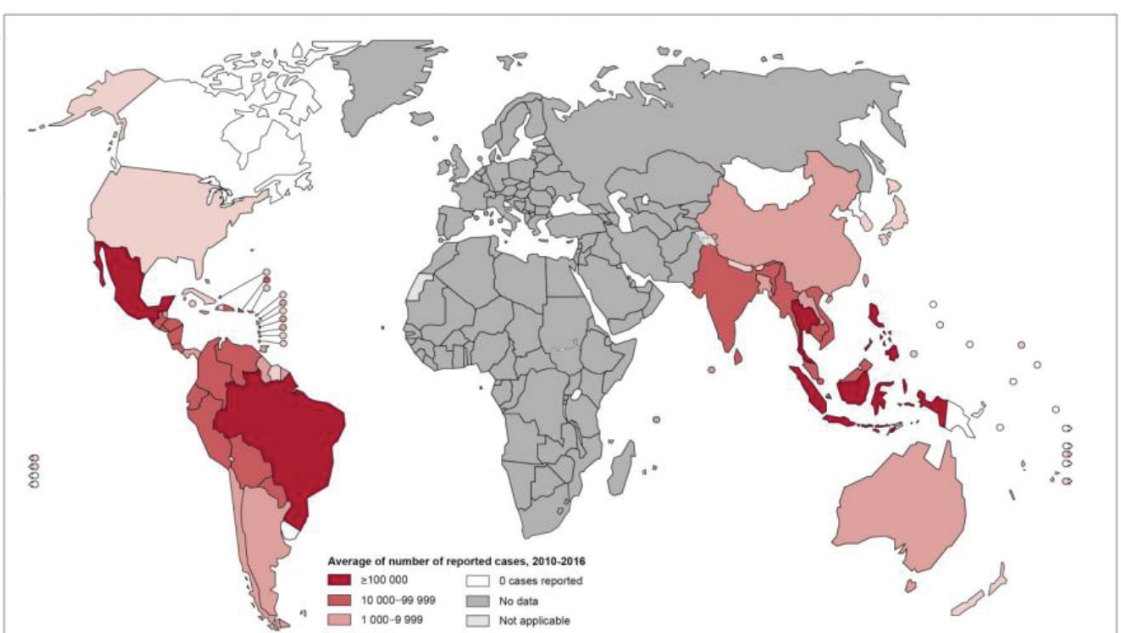


Figure 5.
Average number of suspected or confirmed dengue cases reported to WHO, 2010–2016.

Midwest and Southeast regions had the highest incidence: 1451.9 cases/100,000 inhabitants and 1205.7 cases/100,000 inhabitants, respectively. Among the states, Goiás (2500.6 cases/100,000 inhabitants) and São Paulo (1665.7 cases/100,000 inhabitants) have presented the most incidence numbers [34].

The dengue fever incidence rate was about 733.4 cases/100,000 inhabitants in all Brazilian States at 2016. During this year, the midwest (1322.0/100,000 inhabitants) and the southeast (1001.2/100,000 inhabitants) regions have presented bigger incidence numbers than the other geographic Brazilian regions [35].

In 2017, the midwest region had an incidence of 502.7 cases/100,000 inhabitants and the northeast region had 151.8 cases/100,000 inhabitants, most notably the states of Goiás with 947.3 cases/100.00 inhabitants, Ceará with 453.4/100,000 inhabitants and Tocantins with 331.2/100,000 inhabitants [36].

Figure 6 shows the total number cases of dengue in Brazilian regions during 2015–2017, mainly in the Southeast and Northeast regions, due to their characteristic climate aspects.

In 2015, 38,499 suspected chikungunya fever cases were registered in Brazil (**Figure 6**) which caused an incidence rate of 18.8 cases/100,000 inhabitants. These cases were distributed by 704 cities and 17,971 (46.7%) of them and 14 deaths were confirmed: 05 in Bahia, 02 in Sergipe and 07 in Pernambuco Brazilian states [35].

In 2016, the registered cases number increased significantly to 271,824 and the incidence rate was 133.0 cases/100,000 inhabitants. These cases were distributed in 2829 cities and 151,318 (55.7%) were confirmed. Once again, the northeast region had the highest incidence rate. Among the states were: Rio Grande do Norte (723.1 cases/100,000 inhabitants), Ceará (537.7 cases/100,000 inhabitants), Alagoas (514.8 cases/100,000 inhabitants) and Paraíba (503.0 cases/100,000 inhabitants). At the same year, 196 deaths caused by Chikungunya fever were confirmed [35].

In 2017, the registered cases number had a slight decrease with 185,737, and the incidence rate was 90.1 cases/100,000 inhabitants. However, there are 52,285 cases discarded. During this year, the Northeast region had the highest number of probable chikungunya fever cases (142,131 cases, 76.5%) in relation to the total of the country. Followed by the Southeast (22,984 cases, 12.4%), North (16,570 cases, 8.9%), Midwest (3679 cases, 2.0%) and South (373 cases, 0.2%) [36].

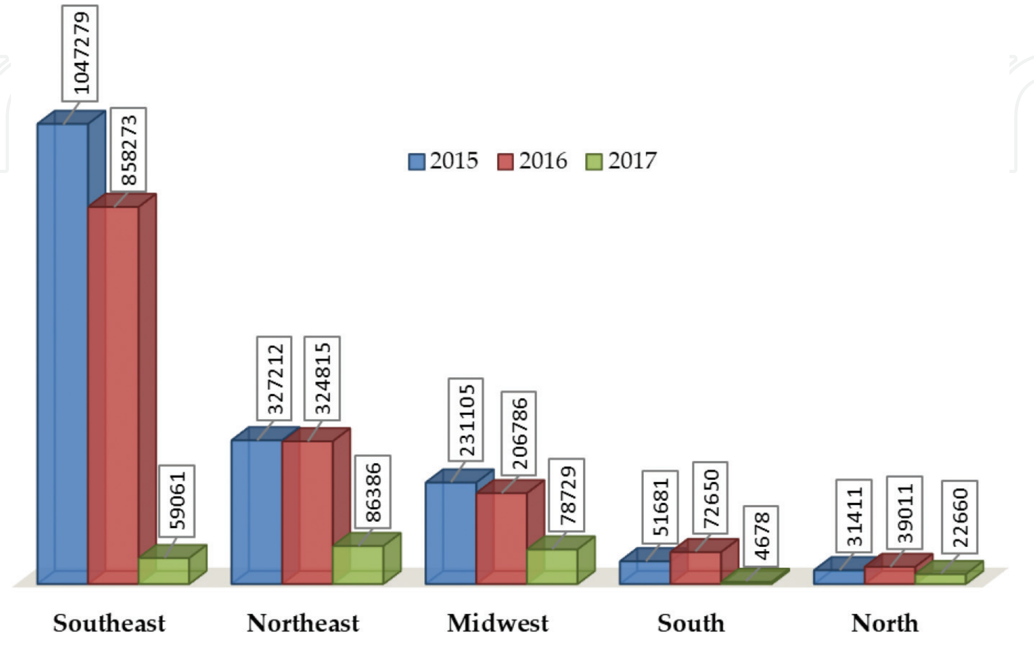


Figure 6.
Total dengue cases within Brazilian regions at the last 3 years.

The analysis of the incidence rate of probable cases of chikungunya fever (number of cases/100,000 inhabitants), according to geographic regions, shows that the Northeast presents the highest incidence rate: 249.7 cases/100,000 inhabitants. Among the Brazilian states, we highlight Ceará (1271.0 cases/100,000 inhabitants), Roraima (795.0 cases/100,000 inhabitants) and Tocantins (207.1 cases/100,000 inhabitants) [36].

The general objective of the Zika surveillance is to describe the epidemiology of the occurrence of microcephaly related to congenital infections in the national territory. Thus, from week 45/2015 until week 06/2016, there were 5280 registered cases of microcephaly occurrence, considering newborns, stillbirths, abortion and fetuses. Considering the year of notification, 60.1% (3174/5280) were recorded in 2015 and 39.9% (2106/5280) in 2016. [37]. Thus 3174 are confirmed, being 508 confirmed and 203 of these cases distributed in 13 Brazilian states, mainly in Northeast region (93.6%). Southeast region presented only five microcephaly notified cases. At least 27 of the confirmed cases evolved to death after birth or during pregnancy. At the end of 2016, the number of reported cases of the microcephaly increased to 10,867. Of these, 3183 (29.3%) remain under investigation and 7684 (70.7%) cases were investigated and classified, being 2366 confirmed, 49 probable and 5269 discarded. According to the geographical distribution, confirmed cases of the 10,867 reported are distributed in 751 Brazilian cities of the 27 Brazilian states, mainly in Northeast region (75.3%). The southeast region showed a large increase in the number of confirmed cases of microcephaly: 74 cases [38].

Due to this epidemiological situation of Zika viruses and its consequences, this disease is considered an Emergency in Public Health of National Importance (ESPIN). From week 45/2015 and until week 52/2017,there were 15,298 cases notified of suspected changes in growth and possibly related to infection with the Zika virus and other infectious etiologies, of which 2869 (18.8%) remained research until 2017, December. Of the total cases, 3071 (20.1%) were confirmed, 339 (2.2%) were classified as likely to be related to infection during pregnancy and 230 (1.5%) as inconclusive. The majority of cases reported is concentrated in the Northeast region of the country (60.6%), followed by the Southeast (23.9%) and Midwest region (7.3%). The five Brazilian states with the greatest number of reported cases are Pernambuco (16.8%), Bahia (16.3%), São Paulo (9.0%), Paraíba (7.3%) and Rio de Janeiro (7.3%) [39].

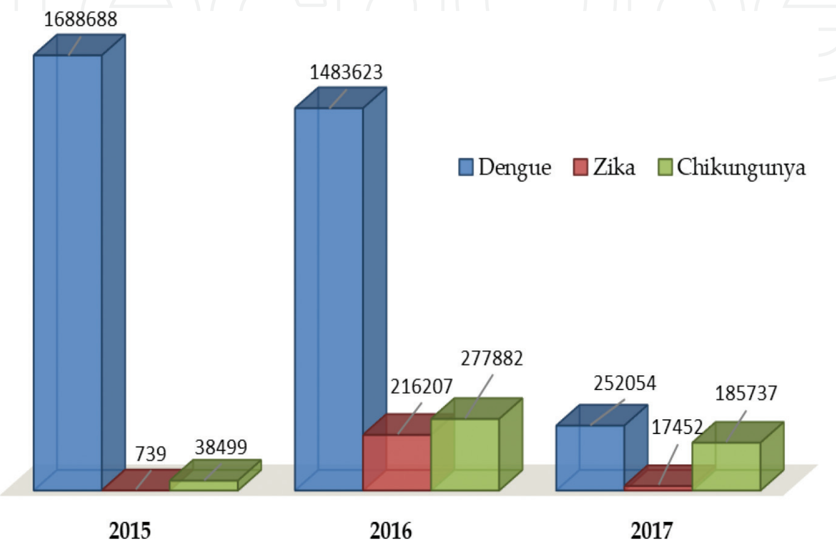


Figure 7.
Cases of dengue, chikungunya and Zika fever in Brazil during 2015, 2016 and 2017.

Nowadays, the 542 microcephaly cases confirmed in Brazil between weeks 1 and 52/2017, 204 (37.6%) received care in childcare. The confirmed children were concentrated in the Southeast (183 cases). Attending in precocious stimulation was performed in 100 of the 542 (18.5%) of confirmed cases, while care in specialized care occurred in 184 of the 542 (33.9%) confirmed cases [39].

Figure 7 shows the behavior of these three diseases in relation to the number of registered cases for the period 2015–2017.

These epidemiology data have demonstrated the incidence rates of the three arboviruses among 2015–2017. In 2016, the incidence of dengue cases has slightly decreased. In 2017, although the numbers of dengue have decreased, the cases of Zika and chikungunya increased, consequently the occurrence of accompany Zika diseases increases during the same period, mainly the microcephaly cases [35–39].

4. Control and prevention

For residents in areas populated by the *Aedes aegypti* species, the most important preventative measure they can take is to remove standing water wherever possible to eliminate breeding sites. This species can breed in as little as one tablespoon of water, so every effort should be made to eliminate standing water in buckets, old tires, gutters, birdbaths, flower pots and more. Additionally, residents should protect themselves indoors with the use of air conditioning and properly maintained window screens and outdoors with the use of mosquito repellents containing DEET (N,N-diethyl-meta-toluamide) and loose fitting clothing [40]. At present, the control of dengue disease is mainly hampered by the absence of antivirals or a vaccine, which results in an estimated half worldwide population at risk of infection.

Currently, antiviral treatment against dengue is available, and the development of an effective anti-dengue vaccine would represent a cornerstone in public health. An important aspect of dengue is that an effective immunity can be potentially impaired during heterologous infections (refers to the immunity that can develop to one pathogen after a host has had exposure to nonidentical pathogens), which may lead to severe manifestations of dengue and represents a great burden in the development of a vaccine against this pathogen.

Due to the absence of an effective vaccine for these arboviruses, the control is still accomplished through the prevention and elimination of potential mosquito-breeding habitats. Thus, the use of chemical insecticides is yet the main vector control component. Alternative products, with potential to be used in the control of *A. aegypti*, including the biolarvicide Bti (*Bacillus thuringiensis var. israelensis*) and some insect growth regulators are also being used recently [41].

4.1 Vaccination

It is widely recognized that passive vaccination is the most appropriate preventive and therapeutic option but till now no vaccine is available for Zika and chikungunya although some initiative to the development of a vaccine have been tested. Several vaccine approaches have been used such as inactivated viral vaccines, live-attenuated viruses, recombinant subunit vaccines, DNA vaccination and others. In Brazil, a live-attenuated viruses vaccine developed by Sanofi Pasteur laboratory has been available since 2016. It is sold in private clinics and is part of vaccination pilot public programs in Paraná state. The product requires three applications with an interval of 6 months between them. In the early studies, the efficacy in the population above 9 years old is approximately 66% against the four serotypes of dengue virus. In addition, it reduces severe cases—those that lead to death, such as hemorrhagic dengue—by 93% and hospitalization rates by 80%.

Pending vaccine development, the measures recommended to prevent against mosquito bites and vector control consist of individual protection or action. Mosquito control is the best available method for preventing arboviruses infection. Breeding sites must be removed, destroyed, cleaned and treated with insecticides.

4.2 Repellents and larvicides

About the intervention against mosquitoes, mainly *Aedes aegypti*, the use of new repellents and insecticides agents are investigated. Due to the development of resistance, biological magnification of toxic substances through the food chain, and others adverse effects on the environment and human health caused by the synthetic insecticides, eco-friendly agents control of mosquitoes vectors have a great importance to avoid dengue, Zika and chikungunya and others diseases transmitted by *A. aegypti*. By this way, so many natural products as plant extracts and essential oils have been evaluated against larval and pupal stages of *A. aegypti* as nanoparticles containing plant extracts and the essential oils from *Zingiber officinale, Curcuma longa, Ocimum basilicum,* and *Mentha piperita* which variety of types and levels of their actives constituents could be responsible for their potential to combat mosquitoes and have been shown to be promising and low-cost mosquitoes control strategies [42–45].

Other intervention, could be done such as using repellents with DEET, wear cloth which minimizes skin exposure to the day-biting vectors, stay in places with air conditioning, use domestic insecticides in aerosol form or in vaporizers within the home.

The conventional methods such as insecticides and larval biological used until now revealed that control have proven ineffective at halting disease spreading [46, 47]. A successful system controlling a broad spectrum of approaches should be mutually compatible and encompass including the development of novel insecticides, transgenic disease-resistant mosquitoes, the release of sterile insects to suppress vector populations and equipment for preventing mosquito bites is to be developed [48].

In Brazil, some new approaches to control mosquito have shown considerable promise in latest years are the biolarvicide Bti, the genetic control of *A. aegypti* mosquitoes and the development of mosquitoes that are resistant to arbovirus infection [47].

Brazil was among the pioneers in adopting Bti to control mosquitoes and black flies. Developed by research groups in Brazilian institutions, this bacterial larvicide is highly toxic at very low doses to target organisms (mosquito and black flies larvae) and safe to other nontarget organisms. Larvicidal activity is due to large amounts of crystal proteins produced during sporulation and transformed into toxins under specific conditions after ingestion by larvae. The structure of the proteins made by the bacterium strain and the presence of proteolytic enzymes and receptor in the host larvae midgut determined the selectivity observed. Brazilian product showed some advantages such as reduction in the number of applications, formulation with high storage stability, no environmental impact and high persistence in the environment and especially efficient in tropical climates [49].

4.3 Biological control of mosquitoes

One way to control mosquitoes is the genetic control strategy known as release of insects carrying dominant lethal genes (RIDL) which is an advancement of the environmentally benign sterile insect technique (SIT). The RIDL involves the insertion of a lethal gene into male mosquitoes that prevents them from being able to reproduce successfully. The insects are considered sterile because the vast majority dies before maturing. These genetically modified males will seek out females to mate with and the ensuing progeny will contain the lethal gene [50–52]. If an appropriate number of mosquitoes are released, the females will be more likely to find a modified male, and a substantial drop in population can be achieved in a remarkably short period. To control populations with this technique as "zones" of release should be established to ensure sufficient area coverage. The preliminary results in Brazil showed that successful approach achieved a 95% reduction in local mosquito populations [53].

Another alternative approach to *A. aegypti* control is the use of mosquitoes with the *Wolbachia pipientis* an endosymbiotic bacterium to prevent arboviruses replicating within the mosquito. The bacteria can hinder the fertility of their hosts and influence the sex of offspring. Besides, it can block viruses from reproducing in infected fruit flies and mosquitoes [50, 52, 53]. Mosquito control is an effective measure to prevent a dengue outbreak [54].

FIOCRUZ's initiative to produce, create and release adult mosquitoes infected by bacterium of *Wolbachia* genus in several districts of the city of Rio de Janeiro has been shown to be very effective in controlling the diseases transmitted by *Aedes aegypti*.

Other mosquitoes genetically modified (Moscamed™, created in 2005) are produced in large scale and released in different cities of Bahia states, reducing the mosquito population in 95% during 6 months. These strategies are being expanded throughout the Brazilian territory to combat *Aedes aegypti* [55, 56].

4.4 Control of mosquitoes by the Brazilian government

- Monthly/bimonthly inspection of households/population orientation by health agents;

- Application of larvicides in the houses (more than 300,000 nonmilitary health agents +220,000 soldiers fighting against potential mosquitoes breeding sites);

- Smoke dispersion containing neurotoxic agent to adult mosquitoes at epidemic locals;

- Biological control through the use of a bacterium naturally found in the environment, *Wolbachia*, which when present in *Aedes*, is able to prevent the transmission of the disease by the mosquitoes, and this characteristic is passed through on to their larvae.

5. The role of Fiocruz

In Brazil, dengue has a seasonal pattern, with a higher incidence of cases in the first 5 months of the year, a warmer and wetter period, typical of tropical climates. In the second half of the twentieth century, from 1986, dengue became epidemiologically important, when the epidemic broke out in the State of Rio de Janeiro and the circulation of serotype 1, which soon reached the Northeast Region. Thus, dengue became endemic in Brazil, interspersed with epidemics, usually associated with the introduction of new serotypes, in areas previously indene [14, 55–58].

The Oswaldo Cruz Foundation (Fiocruz), under the Ministry of Health have a mission to produce, disseminate and share knowledge and technologies aimed at the strengthening and consolidation of the Unified Health System (SUS) and contribute to the promotion of health and quality of life of the population [59].

Since 2003, in order to promote dengue control actions, Fiocruz has established the Fiocruz Dengue Network, through the allocation of resources to the Program for Development and Technological Innovation in Public Health in the field of research.

With the epidemiological cycles of the disease continuing, repeating itself and spreading throughout the country, more than 30,000 cases of dengue fever were reported in the city of Rio de Janeiro in 2008. Due to this epidemic, Fiocruz was called to assist the state and municipality in actions to combat the disease.

Thus, from 2009, Fiocruz redirected an integral focus to the issue with coverage in these three areas, without excluding the research. The Network Health Care of Integrated Actions for Health Care in Dengue Control originated from 2015 onwards and began to include in its scope the issues related to two emerging viruses in Brazil: chikungunya and Zika.

Aiming to reduce or even block the transmission of Zika, dengue and chikungunya Fiocruz has set up a factory for the large-scale release of *Aedes aegypti Wolbachia* bacterium in Rio de Janeiro. The plant has the capacity to produce 10 million eggs of the mosquito per week.

The initiative, officially called "Eliminating Dengue: Brazil Challenge," began in 2016 as a pilot project focused on the city of Niterói and the Tubiacanga neighborhood of Rio. According to the project's schedule, it will expand to North and South zones of Rio de Janeiro. The release of mosquitoes will be finalized by the end of 2018, at which time the project's coverage will have increased to a total area occupied by approximately 2.5 million people.

The Oswaldo Cruz Foundation (Fiocruz) developed a new test that will help drive public policies to fight the health emergency caused by the three infection diseases. The kit uses molecular diagnostics to detect and differentiate simultaneous RNA of the three viruses through real-time PCR technology, and the result is released on the same day. The kit can be used for laboratory diagnosis of all three viruses, two of them or each separately. The test allows diagnosis in the critical phase of the disease, at the beginning of clinical symptoms and an accurate laboratory diagnosis is essential. The opportunity or earlier diagnosis can also aid for epidemiological surveillance and prevention of new cases.

Fiocruz maintains investment in research, development and innovation because this is the only way to seek and find answers to the challenges due to triple Zika-dengue-chikungunya epidemic. Therefore, the goal is to search for cooperation with other institutions in Brazil and internationally to build projects that could offer new possibilities to generate knowledge and developing technologies.

6. Conclusion

Aedes aegypti is still a worldwide threat, since more than half of the world's population live in areas where these mosquitoes species are present. However, many efforts have been undertaken to combat and to control these mosquitoes and the diseases transmitted by them, such as vaccination, repellents and larvicides and the biological control of mosquitoes. Brazil has been continuously developing public policies to health education, alerting the population on the risks which can be avoided, with the purpose of decreasing the dengue, Zika and chikungunya diseases. The Brazilian government plays a role in continuing investment in research, development and innovation to find new ways with national and international cooperation to combat *Aedes aegypti*.

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Conflict of interest

The authors confirm that this chapter content has no conflict of interest.

Abbreviations

CDC	Centers for Disease Control and Prevention
CHIKV	Chikungunya virus
DENV	Dengue virus
DEET	N,N-diethyl-meta-toluamide
ESPIN	Emergency in Public Health of National Importance
FIOCRUZ	Oswaldo Cruz Foundation (A Brazilian Government Research Institute)
IgG	Immunoglobulin G
IgM	Immunoglobulin M
RIDL	release of insects carrying dominant lethal genes
SIT	sterile insect technique
SUS	Unified Health System
WHO	World Health Organization
ZIKV	Zika virus

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References

[1] Patterson J, Sammon M, Dengue GM. Zika and chikungunya: Emerging arboviruses in the new world. Western Journal of Emergency Medicine. 2016; **17**(6):671-679. DOI: 10.5811/westjem.2016.9.30904

[2] Cavalcanti LPG, Freitas ARR, Brasil P, Da Cunha RV. Surveillance of deaths caused by arboviruses in Brazil: From dengue to chikungunya. Memórias do Instituto Oswaldo Cruz. 2017;**112**(8): 583-585. DOI: 10.1590/0074-027601 60537

[3] Shoukry NM, Elwan NA, Morsy TA. *Aedes aegypti* (Linnaeus) re-emerging in southern Egypt. Journal of the Egyptian Society of Parasitology. 2012;**42**(1): 41-50. DOI: 10.12816/0006293

[4] World Health Organization (WHO). What is dengue? [Internet] 2017. Available from: http://www.who.int/de nguecontrol/disease/en/ [Accessed: 2017-12-12]

[5] Centers for Disease Control and Prevention (CDC). Dengue and the *Aedes aegypti* mosquito. [Internet]. 2015. Available from: https://www.cdc.gov/de ngue/resources/factSheets/factsheet_de ngue-what-you-need-to-know.pdf [Accessed: 2017-12-12]

[6] Rodhain F, Rosen L. Mosquito vectors and dengue virus-vector relations ships. In: Gubler DJ, Kuno G, editors. Dengue and Dengue Hemorragic Fever. New York: CAB International; 1997. pp. 45-60

[7] Silva AM, Dittus WPJ, Amerasinghe PH, Amerasinghe FP. Serologic evidence for an epizootic dengue virus infecting toque macaques (*Macaca Sinica*) at Polonnaruwa, Sri Lanka. The American Journal of Tropical Medicine and Hygiene. 1999;**60**(2):300-306. DOI: 10.1002/ajp.10105

[8] Dye C. The analysis of parasite transmission by bloodsuccking insects. Annual Review of Entomology. 1992;**37**: 1-19. DOI: 10.1146/annurev.en.37. 010192.000245

[9] Scott WT, Clark GG, Lorenz LH, Amerasinghe PH, Reiter P, Edman J. Detection of multiple blood feeding in *Aedes aegypti* (*Diptera: culicidae*) during a single gonotrophic cycle using a histologique technique. Journal of Medical Entomology. 1993;**30**(1):94-99. DOI: 10.1093/jmedent/30.1.94

[10] Gubler DJ. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. Trends in Microbiology. 2002;**10**(2):100-103. DOI: 10.1016/S0966-842X(01)02288-0

[11] Teixeira MG, Barreto ML, Guerra A. Epidemiologia e medidas de prevenção do Degue. Informe Epidemiológico do SUS. 1999;**8**:5-33

[12] Donalisio MR, Freitas ARR, Zuben V APB. Arboviruses emerging in Brazil: Challenges for clinic and implications for public health. Revista de Saúde Pública. 2017;**51**:30-36. DOI: 10.1590/S1518-8787.2017051006889

[13] Mustafa MS, Rasotgi V, Jain S, Gupta V. Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma in dengue control. Medical Journal Armed Forces India. 2015;**71**(1):67-70. DOI: 10.1016/j. mjafi.2014.09.011

[14] Braga IA, Valle D. *Aedes aegypti*: Histórico do controle no Brasil. Epidemiologia e Serviços de Saúde. 2007;**16**(2):113-118. DOI: 10.5123/S1679-49742007000200006

[15] Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological

specificity. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1952;**46**:509-520. DOI: 10.1016/0035-9203(52)90042-4

[16] Epelboin Y, Talaga S, Epelboin L, Dusfour I. Zika virus: An updated review of competent or naturally infected mosquitoes. PLoS Neglected Tropical Diseases. 2017; **11**(11):1-22. DOI: 10.1371/journal.pntd.0005933

[17] Tai-Ho Chen J, Staples E, Fischer M. Infectious diseases related to travel. [Internet]. Available from: https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/zika [Accessed: 2017-12-01]

[18] Dos Santos FB, Nunes PCG, De Sequeira PC, Machado LN, Lima MA, Gava RP. Zika. In: Dengue, Zika E Chikungunya: Diagnóstico, tratamento e prevenção. Organização Luiz José de Souza 1 ed. Rio de Janeiro: Rubio; 2016. 204 p

[19] Kindhauser MK, Allen T, Frank V, Santhanaa RS, Dyea C. Zika: The origin and spread of a mosquito-borne virus. Bulletin of the World Health Organization. 2016;**94**:675-686. DOI: 10.2471/BLT.16.171082

[20] World Health Organization (WHO). Chikungunya [Internet]. Available from: http://www.who.int/mediacentre/factsheeeets/fs327/en/ [Accessed: 2017-11-10]

[21] Forattini OP. Identificação de Aedes (Stegomyia) albopictus no Brasil. Revista de Saúde Pública. 1986;**20**(3): 244-245. DOI: 10.1590/S0034-89101986000300009

[22] Carvalho RG, De Oliveira, RL, Braga IA. Updating the geographical distribution and frequency of *Aedes albopictus* in Brazil with remarks regarding its range in the Americas. Memórias do Instituto Oswaldo Cruz. 2014;**109**(6):787-796. DOI: 10.1590/0074-0276140304

[23] Gomes AC, Souza JMP, Bergamaschi DP, Santos JLF, Andrade VR, Leite OF, et al. Atividade antropofílica de *Aedes aegypti* e Aedes albopictus em área sob controle e vigilância. Revista da Sociedade Brasileira de Medicina Tropical. 2005;**39**(2):206-210. DOI: 0.1590/S0034-89102005000200010

[24] Pessoa VEM, Silveira DA, Cavalcante ILR, Florindo MIG. Aedes albopictus no Brasil: Aspectos ecológicos e riscos de transmissão da dengue. Entomotropica. 2013;**28**(2):75-86

[25] Di Luca M, Severini F, Toma L, Boccolini D, Romi R, Remoli ME. Experimental studies of susceptibility of Italian *Aedes albopictus* to Zika virus. Euro Surveillance. 2016;**21**:30223. DOI: 10.2807/1560-7917.ES.2016.21.18.30223

[26] Beltrán-Silva SL, Chacón-Hernández SS, Moreno-Palacios E, Pereyra-Molina JA. Clinical and diferencial diagnosis: Dengue, chikungunya and zika. Revista Médica del Hospital General de México. 2016; **81**(3):146-153. DOI: 10.1016/j.hgmx.2016.09.011

[27] Tilak R, Ray SCS, Tilak VW, Mukherij S. Dengue, chikungunya and the missing entity—Zika fever: A new emerging threat. Medical Journal Armed Forces India. 2016;**72**:157-163. DOI: 10.106/j.mjafi.2016.02.017

[28] Moulin E, Selby K, Cherpillod P, Kaiser I, Boillat-Blanco N. Simultaneous outbreaks of dengue, chikungunya and zika virus infections: Diagnosis challenge in a returning traveler with nonspecific febrile illness. New Microbes and New infections. 2016;**11**: 6-7. DOI: 10.106/j.nnmi.2016.02.003

[29] Tang KF, Ooi EE. Diagnosis of dengue: An update. Expert Review of

Anti-Infective Therapy. 2012;**10**(8): 895-907. DOI: 10.1586/eri.12.76

[30] WHO. Zika virus and complications: Questions and answers. [Internet]. 2017. Available from: http://www.who.int/features/qa/zika/en/ [Accessed: 2018-15-01]

[31] Rather IA, Kumar S, Bajpaj VK, Lim J, Park Y-H. Prevention and control strategies to counter zika epidemic. Frontiers in Microbiology. 2017;**8**: 305-413. DOI: 10.3389/fmicb.2017.00305

[32] Galán-Huerta KA, Rivas-Estilla AM, Férnadez-Sala I, Farfan-Ale JA, Ramos-Jimenéz J. Chikungunya vírus: A general overview. Medicina Universitaria. 2015; **17**(68):175-183. DOI: 10.106/j.rmu.2015.06.001

[33] Caglioti C, Lalle E, Castilletti CF, Capobianchi MR, Bordi L. Chikungunya virus infection: An overview. The New Microbiologica. 2013;**36**:211-227

[34] Brasil, Ministério da Saúde (MS). Monitoramento dos casos de dengue, febre de chikungunya e febre pelo vírus Zika até a Semana Epidemiológica 52, 2015. Boletin epidemiológico. 2016; **47**(3):1-10. ISSN: 2358-9450

[35] Brasil, Ministério da Saúde (MS). Monitoramento dos casos de dengue, febre de chikungunya e febre pelo vírus Zika até a Semana Epidemiológica 52, 2016. Boletin epidemiológico. 2017; **48**(3):1-11. ISSN 2358-9450

[36] Brasil, Ministério da Saúde (MS). Monitoramento dos casos de dengue, febre de chikungunya e febre pelo vírus Zika até a Semana Epidemiológica 52, 2017. Boletin epidemiológico. 2018; **49**(2):1-13. ISSN 2358-9450

[37] Brasil, Ministério da Saúde (MS). Informe Epidemiológico N°13. Monitoramento dos casos de microcefalia no Brasil. [Internet]. 2017. Available from: http://portalarquivos2.saude.gov.br/images/pdf/2016/fevereiro/17/coes-microcefalia-inf-epi-13-se06-2016.pdf [Accessed: 2018-15-03]

[38] Brasil, Ministério da Saúde (MS). Informe Epidemiológico N°57. Monitoramento dos casos de microcefalia no Brasil. [Internet]. 2017. Available from: http://combateaedes.saude.gov.br/images/pdf/Informe-Epidemiologico-n57-SE-52_2016-09jan2017.pdf [Accessed: 2018-15-03]

[39] Brasil, Ministério da Saúde (MS). Monitoramento integrado de alterações no crescimento e desenvolvimento relacionadas à infecção pelo vírus Zika e outras etiologias infecciosas, até a Semana Epidemiológica 52 de 2017. Boletin epidemiológico. 2018;**49**(6): 1-10. ISSN 2358-9450

[40] Central Life Sciences. Dengue fever: What you need to know. [Internet]. Available from: https://www.centralmosquitocontrol.com/resources/disease-information/dengue [Accessed: 2017-11-10]

[41] Braga IA, Valle D. *Aedes aegypti*: Inseticidas, mecanismos de ação e resistência. Epidemiologia e Serviços de Saúde. 2007;**16**(4):279-293. DOI: 10.5123/S1679-49742007000400006

[42] Govindarajan M, Rajeswary M, Mutukumaran U, Hoti SL, Khater HF, Benelli G. Single-step biosynthesis and characterization of silver nanoparticles using *Zornia dphylla* leaves: A pontent eco-friendly tool against malaria and arbovirus vectors. Journal of Photochemistry and Photobiology. B. 2016;**161**:482-489. DOI: 10.1016/j.jphotobiol.2016.06.016

[43] Govindarajan M, Khater HF, Panneerslvan C, Benelli G. One-pot fabrication of silver nanocrystals using *Nicandra physalodes:* A novel route for mosquito vector control with moderate toxicity on non-target water bugs.

Research in Veterinary Science. 2016; **107**:95-101. DOI: 10.1016/j.rvsc.2016.05.017

[44] Roni M, Murugan K, Panneerselvam C, Subramaniam J, Nicoletti M, Madhiyazhagan P, et al. Characterization and biotoxicity of *Hypnea musciformis*-synthesized silver nanoparticles as potential eco-friendly control tool against *Aedes aegypti* and *Plutella xylostella*. Ecotoxicology and Environmental Safety. 2015;**121**:31-38. DOI: 10.1016/j.ecoenv.2015.07.005

[45] Khater HF. Bioactivity of essential oils as green. In: Govil JN, Bhattacharya S, editors. Recent Progress in Medicinal Plants, Vol. 37. Essential Oils II. 2013. pp. 153-220

[46] Maciel-de-Freitas R, Peres RC, Alves F, Brandolini MB. Mosquito traps designed to capture *Aedes aegypti* (Diptera: Culicidae) females: Preliminary comparison of Adultrap, MosquiTRAP and backpack aspirator efficiency in a dengue-endemic area of Brazil. Memórias do Instituto Oswaldo Cruz. 2008;**103**:602-605. DOI: 10.1590/S0074-02762008000600016

[47] Faucon F, Dusfour I, Gaude T, Navratil V, Boyer F, Chandre F, et al. Identifying genomic changes associated with insecticide resistance in the dengue mosquito *Aedes aegypti* by deep targeted sequencing. Genome Research. 2015; **25**(9):1347-1359. DOI: 10.1101/gr.189225.115

[48] Khater HF. Ecosmart biorational insecticides: Alternative insect control strategies. In: Perveen F, editor. Insecticides—Advances in Integrated Pest Management. InTech; 2012. DOI: 10.5772/27852. Available from: https://www.intechopen.com/books/insecticides-advances-in-integrated-pest-management/ecosmart-biorational-insecticides-alternative-insect-control-strategies

[49] Sanches EG, da Silva ACB, Campos FMA, Pinheiro RA, de Jesus FJ. Composição bioinseticida à base de *Bacillus thuringiensis* var israelensis e o respectivo processo de preparação. Patente: PI0003314-6. Concedida em 24 de maio de 2000

[50] Yakob L, Walker T. Zika virus outbreak in the Americas: The need for novel mosquito control methods. The Lancet Global Health. 2016;**4**(3): e148-e149. DOI: 10.1016/S2214-109X(16)00048-6

[51] Alphey L. Genetic control of mosquitoes. Annual Review of Entomology. 2014;**59**(1):205-224. DOI: 10.1146/annurev-ento-011613-162002

[52] McGraw EA, O'Neill SL. Beyond insecticides: New thinking on an ancient problem. Microbiology. 2013;**11**:181-193. DOI: 10.1038/nrmicro2968

[53] Dutra HLC, Rocha MN, Stehling FB, Mansur SB, Caragata, EP, Moreira L. Wolbachia blocks currently circulating zika virus isolates in Brazilian *Aedes aegypti* mosquitoes. Cell Host & Microbe. 2016;**19**(6):771-774. DOI: 10.1016/j.chom.2016.04.021

[54] Pang T, Mak TK, Gubler DJ. Prevention and control of dengue—The light at the end of the tunnel. The Lancet Infectious Diseases. 2017;**17**:79-87

[55] Ministry of Health. Secretariat of Social Communication—International Area Presidency of the Federative Republic of Brazil. 2016

[56] Carvalho DO, McKemey AR, Garziera L, Lacroix R, Donnelly CA, Alphey L, et al. Suppression of a field population of *Aedes aegypti* in Brazil by sustained release of transgenic male mosquitoes. PLoS Neglected Tropical Diseases. 2015;**9**:e0003864. DOI: 10.1371/journal.pntd.0003864

[57] Schatzmayr HG. Dengue situation by year 2000. Memórias do Instituto Oswaldo Cruz. 2000;**95**:179-181. DOI: 10.1590/S0074-02762000000700030

[58] Silva JB Jr, Siqueira JB Jr, Coelho GE, Vilarinhos PT, Pimenta FG Jr. Dengue in Brazil: Current situation and control activities. Epidemiological Bulletin. 2002;**23**(1):3-6

[59] FIOCRUZ The Foundation [Internet]. Available from: https://portal.fiocruz.br/en/content/foundation [Accessed: 2017-11-10]