Chapter 11

Transmission of Major Arboviruses in Brazil: The Role of *Aedes aegypti* and *Aedes albopictus* Vectors

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Additional information is available at the end of the chapter

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Abstract

Arthropod-borne viruses (arboviruses) are transmitted to a mammalian host by an infected arthropod vector. More than 130 types of arboviruses are known to cause disease in susceptible vertebrate hosts and are responsible for some of the most explosive epidemics of emerging infectious diseases in recent decades. The transmission cycle requires three essential components: virus, vector and vertebrate. Understanding the role of the vector in the arboviruses transmission is critical to improve emerging arbovirus disease control strategies. Since 2015, Brazil is faced with the challenge of three co-circulating arboviruses of major public health importance. Dengue virus (DENV) infection has been a public health for 30 years, which has suffered several epidemics caused by all four serotypes. The emergence of Chikungunya virus (CHIKV) and Zika virus (ZIKV) in Brazil poses new challenges to clinicians and public health authorities. In urban and suburban areas, those arboviruses are transmitted between people by *Aedes* mosquitoes in the subgenus *Stegomyia*, especially *Ae. aegypti* (the main vector) and potentially *Ae. albopictus*. Factors relating to the environment and the vector-virus interactions can influence the dynamics of arboviruses transmission. This chapter describes the main biology aspects of the *Ae. aegypti* and *Ae. albopictus* that can influence the success of the transmission of main arboviruses in Brazil and provide information to understand the role of those factors in this dynamic relations

Keywords: *Aedes aegypti*, *Aedes albopitcus*, Arboviruses, virus-vector interactions, transmission

1. Introduction

A critical premise of epidemiology is that disease and other health events do not occur randomly in a population but are more likely to occur in some members of the population than others because of risk factors that may not be distributed randomly in the population.

As noted earlier, one important use of epidemiology is to identify the factors that place some members at greater risk than others. Agent, host and environmental factors interrelate in a variety of complex ways to produce disease. Different diseases require different balances and interactions of those components. In the case of many communicable diseases, such as Dengue, Chikungunya and Zika, the agent can only reach the host via a third party, the vector. Infectious diseases transmitted by insects have long been associated with significant human illness and death. Vector-borne diseases account for more than 17% of all infectious diseases, causing more than 1 million deaths annually [1].

Development of appropriate, practical and effective public health measures to control or prevent vector-borne diseases usually requires assessment of all components and their interactions, and much remains to be elucidated, in particular about the complex biological and ecological relationships that exist among pathogens, vectors, hosts and their environments, **Figure 1**.

Arbovirus or arthropod-borne virus is the ecological term used to define viruses maintained in nature by biological transmission between a susceptible vertebrate host and a hematophagous arthropod, such as mosquitoes, the best known disease vector [1]. More than 130 types of arboviruses are known to cause disease in susceptible vertebrate hosts, being responsible for some of the most explosive epidemics of emerging infectious diseases in recent decades. Moreover, the global expansion of these arboviruses was preceded by the global spread of their vectors [2].

1.1. Major arboviruses currently affecting Brazil: Dengue, Zika and Chikungunya

Descriptions of a dengue-like disease were reported in China during the Chin Dynasty (265–420 A.D); however, the first well-documented cases believed to be dengue occurred in 1779–1780 on Asia, Africa and North America [3], and the first viruses were isolated by the Japanese [4] and American investigators [5] during World War II [6].

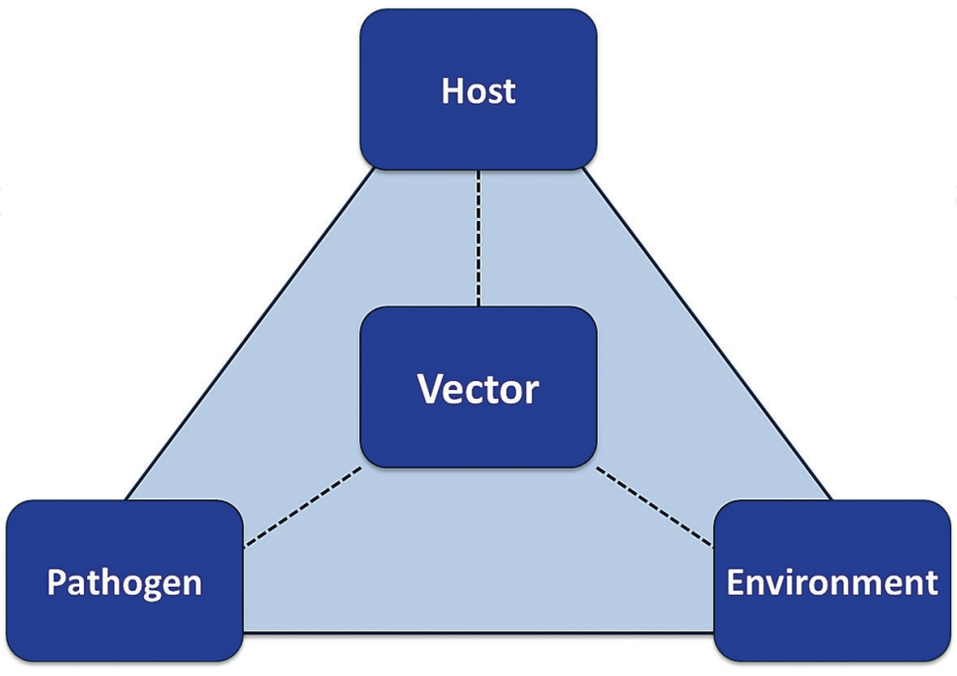

Figure 1. Epidemiological triad of vector-borne diseases.

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Dengue viruses (DENV) exist in either sylvatic or human transmission cycles, most prevalently in tropical and subtropical areas in the world, and due to its impact poses relevant social and economical effect related to the increased geographic extension, number of cases and disease severity [7]. The four serotypes (DENV-1 to DENV-4) that belong to the family *Flaviviridae* and the genus *Flavivirus* show only 62–67% homology based on amino acid sequences [8], and despite they could have been classified as separate viral groups, the four serotypes are classified as belonging to a single group. Within each serotype, distinct genotypes are characterized based on a nucleotide divergence ≥6% for a given region of the genome [9, 10].

In the last 50 years, the disease has gradually reached the status of a pandemic, hospitalizing more than 5 million children and resulting in more than 70,000 deaths [11]. In Brazil, DENV has become a major public health problem of significant social and economic impact after DENV-1 introduction in 1986 [12]. In 1990, DENV-2 was also introduced in Rio de Janeiro and led to the first severe cases and increase in the number of hospitalizations [13]. DENV-3 was first detected in December of 2000, again in Rio de Janeiro, and caused one of the most severe epidemics in 2002. In 2007–2008, an epidemic caused by the reemergence of DENV-2 led to severe cases and deaths on children 15 years-old and under. DENV-1 reemergence in 2009–2010 caused explosive epidemics throughout the country, and severe cases on patients with comorbidities were reported. Despite its detection in 1982 in Boa Vista, Roraima, North of Brazil, DENV-4 emerged and caused epidemics, after its introduction in 2010. Currently, the four DENV serotypes are circulating in the country in a hyperendemic scenario, with increased number of cases occurring year after year. Only in the first semester of 2016, a total of 1,399,480 probable dengue cases were reported in Brazil [14].

Chikungunya virus (CHIKV), *Togaviridae* family, genus *Alphavirus*, was first isolated from human serum during a febrile illness outbreak in Tanzania in 1953 [15]. It is an Old World alphavirus belonging to the Semliki Forest antigenic complex, which also includes Bebaru virus, Mayaro virus, O'nyong nyong virus, Ross River virus, Getah virus, Semliki Forest virus, and Una vírus. It has four genetically distinct genotypes characterized as West African, East-Central-South African (ECSA), Asian and Indian Ocean [16].

As another emerging arbovirus, CHIKV represents nowadays a global risk. Since the 60s, chikungunya outbreaks were reported in Southeast Asian countries. After years of its isolation, the virus caused epidemics in Congo in 1999–2000 [17] and Indonesia from 2001 to 2003 [18]. Until then, chikungunya cases were restricted to Asia and Africa; however, in 2005–2006, epidemics were reported in several Indian Ocean Islands [19]. In October of 2013, the CHIKV Asian genotype was first reported in the island of Saint Martin in the Caribbean, and the increased occurrence of cases in the Caribbean and its spread to other Latin American countries led to the introduction of this arbovirus also in Brazil. First autochthonous CHIKV infections in the country were reported in Oiapoque, Amapá, bordering French Guiana in North region and Feira de Santana, Bahia [20, 21], and viral genome sequencing characterized the Asian genotype circulating in the North of the country and the ECSA genotype in Bahia, suggesting this genotype introduction in the Americas for the first time. Despite the susceptible population, CHIKV infections were restricted to four Brazilian states (Bahia, Amapá, Mato Grosso do Sul and Roraima) and Distrito Federal in 2014. In 2015 and 2016, the virus

spreads to other Brazilian states, and in the first half of 2016, Brazil reported 170,000 cases, 10 times the number reported in the same period of 2015 and the country accounts for 94% of confirmed cases in the Americas [22].

Zika virus (ZIKV), member of the *Flaviviridae* family, genus *Flavivirus*, also related to Ilheus virus, Rocio virus, St. Louis Encephalitis viruses, Yellow Fever virus and DENV, was first isolated in 1947 from a rhesus monkey in the Zika forest in Uganda; however, the first human case was reported in Uganda in 1964. Since then, sporadic human cases were reported in countries of Asia and Africa. The first reported large outbreak of ZIKV human infection occurred at the Federated States of Micronesia in 2007 [23], when 73% of the local population became infected [24]. The first laboratory testings performed at the time suggested that patients were infected by DENV, what proved to be untrue after ZIKV was later confirmed as the causative agent of the epidemic [23]. More recently, epidemics due to ZIKV were reported in French Polynesia, New Caledonia, Easter Island and the Cook Islands and imported cases to Australia and Germany [25–27]. The potential emergence and spread of ZIKV outside Africa, such as to the Pacific Islands and Americas, were stressed previously [28].

ZIKV was previously believed to cause only a mild and self-limiting illness; however, it has emerged as a new public health threat since the outbreak in French Polynesia in 2013–2014 and the explosive epidemic in Brazil in 2015. In Brazil, the virus was introduced in Bahia and Rio Grande do Norte, in March [29, 30], and an increase in severe congenital malformations (microcephaly) and neurological complications, mainly Guillain-Barré Syndrome (GBS), was reported in the country. Moreover, ZIKV has been associated with fetal microcephay and other birth defects in both humans [31–35] and mice [36–38]. By December 2015, all regions of the country had already reported autochthonous transmission, and estimates were that zika suspected cases ranged from 440,000 to 1,300,000 [39]. A recent study reports that the introduction and rapid spread of ZIKV in the Americas resemble that of CHIKV, after its introduction and spread by and from the Caribbean. Furthermore, it was estimated that it took approximately 5–6 months for the virus to spread from the northeastern coast to the southeastern coast and western border of Brazil [40]. In 2016, a total of 174,003 probable cases of zika were reported in Brazil [14]. Following its spread to other American countries, the World Health Organization declared the zika epidemic, a Public Health Emergency of International Concern, on February 1, 2016.

2. *Aedes aegypti* and *Aedes albopictus* vectors

Aedes (Ae.) aegypti and *Ae. albopictus* are the most important vectors for arboviruses transmission to humans. Both are exotic species and took advantage of trade developments to spread throughout the tropics from their native area: *Ae. aegypti* from Africa and *Ae. albopictus* from Southeast Asia. With the presence of the two species in the American Continent, the transmission of arboviruses among humans occurs, but factors relating to the environment and the vector-virus interactions can influence the dynamics of that transmission.

Ae. aegypti most likely originated in Africa; since then, the mosquitoes spread globally and adapted easily in tropical and subtropical areas, and parts of the temperate world. Their

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distribution is associated to urban areas, specifically to human dwellings, feeding preferentially on human blood. *Ae. albopictus* originated in Asia and is considered one of the most important invasive species worldwide. Its colonization of temperate regions such as North America and Europe as well as tropical and subtropical regions such as South America and Africa was facilitated by the species' strong biological and behavioral plasticity. Currently, both *Ae. aegypti* and *Ae. albopictus* are present in most Asian cities and large parts of the Americas [41].

Ae. aegypti adults are relatively small and range in size from 4 to 7 mm and could be mistaken with *Ae. albopictus*. However, lyre-shaped white scales on the dorsal surface of the thorax are a marked characteristic. White basal bands that appear as stripes are present on each tarsal segment of the hind legs. Its abdomens are generally dark brown and may also present white scales [42]. Females are larger than males and are distinguished by minute palps with silver or white scales present on their tips. Females also differ from males by short, sparse hairs whereas males have plumose antennae.

2.1. *Aedes* mosquitoes' life cycle

The mosquitoes' species have a complex life cycle with dramatic changes in shape, function and habitat. They have four distinct stages during their life cycle: egg, larva (L1, L2, L3 and L4), pupa and the adult insect (**Figure 2**). Both male and females mosquitoes are nectar feeders, but females are adapted for blood feeding, and sucking blood of vertebrate animals to mature her eggs. Generally, about 3–4 days after the blood meal, the females produce on average 100–200 eggs per batch.

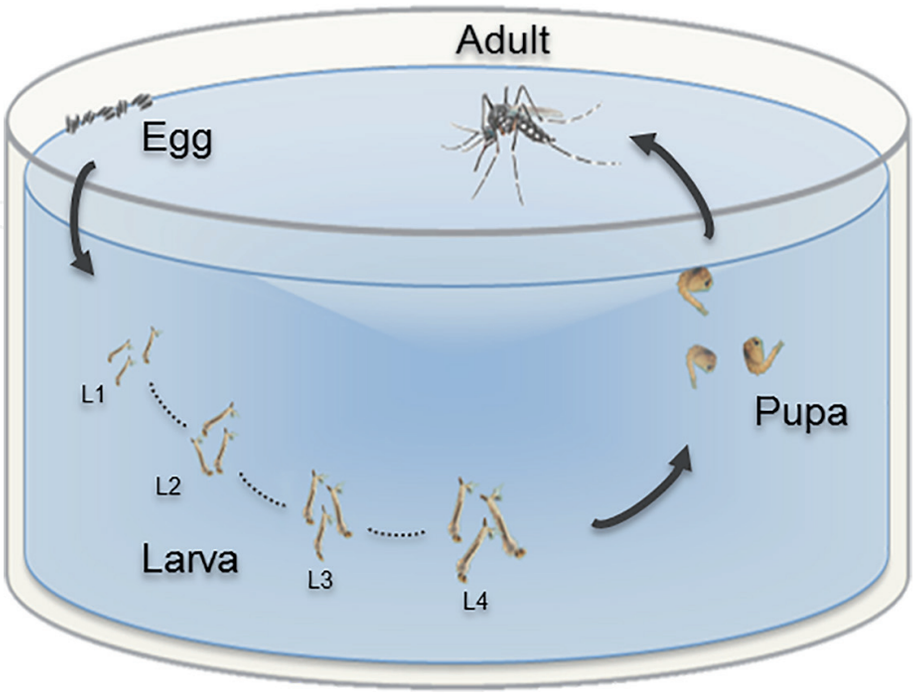

Figure 2. The Aedes mosquitoes' four life stages: egg, larva, pupa and adult.

Both species lays their eggs in internal and damp surfaces of containers that, permanently or intermittently, contain water. When first laid, eggs appear white but within minutes turn a shiny black. The embryogenesis is complete in 2–3 days after layer but can be variable depending on ambient temperature. In warm climates, eggs may develop in 2–3 days, whereas in cooler temperate climates, this time can extend and the development can take up to a week [43]. Laid eggs can survive for very long periods in a dry state, often for more than a year. However, the proportion of eggs hatched from the same batch varies according to the ambient temperature, relative humidity and the time of exposure to desiccation [44]. This desiccation peculiarity enables the eggs are transported over long distances in dry containers, allowing the dispersion of the vector.

When in contact with the water, triggering the process of hatching of the larvae and the cycle of larval development begins [45]. The larval phase is the period of feeding and growth of immature stage. The larvae feed on suspended particulate matter (i.e., detritus, bacteria, diatoms, algae and other microorganisms) by filtering water with modified mouth parts often referred to as "mouth brushes," shedding their skins three times to be able to grow from first to fourth instars. When the larva has acquired enough energy and size and is in the fourth instar, metamorphosis is triggered, changing the larva into a pupa. Strongly dependent on food availability and water temperature, the larvae can develop from first instar to pupae within several days to a few weeks [46]. In optimal conditions, the period between hatching of the egg and the formation of the pupa may not exceed 5 days, or in most adverse conditions such as low temperatures, insufficient nutrients and high larval density, it can extend for several weeks [47]. In fact, males develop faster than females, so males generally pupate earlier, and consequently, they are the first ones to appear on refuges.

The pupa is the last immature stage. Mosquitoes' pupae are mobile, do not feed and expend almost all the time breathing near the surface. They just change in form until the body of the adult, flying mosquito is formed. This stage lasts for 2–3 days, depending mainly on the temperature. Unlike the larval stage, which is influenced by many other environmental conditions, the mortality rate of the pupae is practically null. For this reason, it is suggested that the number of pupae found in one location corresponds directly to the number of adults that will emerge and occupied the houses in brief [48].

The adult emerges slowly through the longitudinal opening in the pupal case and remains at rest for a few minutes about water, due to the surface tension. The terrestrial phase has an essential function to reproduction and dispersion.

2.2. *Aedes* mosquitoes′ reproduction and feed behavior

The males are attracted to the females due to the sound that is made by their wing beat 2.5 h after emergence [49, 50]. The attracted male clasps the tip of the female abdomen with his genitalia and inserts his aedeagus into the female genital chamber. The duration of the copulation is brief and lasts less than a minute [49]. Older and larger males as well as larger females have greatest mating success. Density and ambient environmental conditions are influential factors of mating biology of mosquitoes [51].

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During copulation, sperm and seminal fluid are transferred from the male into the female's bursa copulatrix [52], and the males' seminal fluid of male contains a large number of proteins that are transferred to females during mating, possibly affecting the female biology and behavior [53]. The seminal fluid is thought to be responsible for female refractoriness to mating in both species. However, there are indications, especially in *Ae. albopictus*, that multiple inseminations occur in the field species and also that the fertilization of eggs could be done by the sperm issued from several males [54], and in *Ae. aegypti*, there are evidence that polyandrous behavior depends on the postmating interval [55]. Mating errors between biologically incompatible species may result in varying degrees of reproductive loss that decreases fitness [56].

The feeding behavior of females includes the intake of blood to provide energy for the maturation of eggs at every cycle of ovarian development, called gonotrophic cycle. Many females blood-sucking insects will develop and lay a batch of eggs each time a sufficient blood meal is taken gonotrophic concordance. However, *Ae. albopictus* and *Ae. aegypti* often take multiple blood meals in different individuals or not, in each gonotrophic cycle, a phenomenon that has high epidemiological importance, once maximize the chances of viral transmission.

Apparently, in nature, sugar intake by *Ae. albopictus* occurs more often than by *Ae. aegypti*. Moreover, *Ae. aegypti* and *Ae. albopictus* females can also feed in other animals; however, the *Ae. aegypti* feeds preferentially on humans, which increases its fitness, and synthesis of energy reserves, therefore, an effective disseminator of human pathogens. *Ae. albopictus* has also been shown to exhibit strongly anthropophilic behavior similar to *Ae. aegypti* in specific contexts [57, 58].

The females of both mosquitoes may bite at any time of the day, although the biting peak periods are early in the morning and before dark in the evening [59]. Host finding by mosquitoes is largely driven by olfactory cues that are given off by individual hosts. Mosquitoes use the wind direction and odors, such as carbon dioxide, emitted by the hosts in order to locate a host to bite [60].The bites can occur in any part of the body but are more frequent in feet and lower parts of the legs, where normally concentrate CO_2 molecules and sweat components that are attractive to anthropophilic species, and variation in sweat composition may cause differential attractiveness within and between individuals and also between humans and other mammals [61].

The *Culicidae* family females may enhance the development and survival of their immature forms by obeying some specific preferences, determined by physical and chemical characteristics of the water, by the degree of exposure to sunlight or shade, the location and the size of the site, among other factors [62]. In general, female mosquitoes laid her eggs at once in a single focus of reproduction. However, the skip oviposition behavior is clearly observed in *Ae. aegypti* females and is also observed in *Ae. albopitcus* ones. The females choose to oviposit a few eggs in several different sites. "Skip oviposition" behavior may ensure the greater distribution of progeny from an individual female which, in turn, tends to increase the genetic diversity of populations and reduces sibling competition, that may maximize the survival of their offspring, and even if one site are destroyed, some of their eggs have the possibility to become adult mosquitoes in another site, neglected by the control [63, 64]. It is possible that

the transovarial transmission represents a way of maintenance of the virus in nature, because the virus can persist until the seventh generation in the mosquitoes' tissues [65–67]. Even at this low rate, transovarial transmission may allow virus survival in unhatched eggs during dry or cool periods [68, 69].

2.3. *Aedes* mosquitoes′ breeding sites

For mosquitoes, location of suitable sites for oviposition requires a set of visual, tactile and olfactory cues that influence females before laying their eggs. The ability of gravid females to distinguish among potential oviposition sites that will or will not support the growth, development and survival of their progeny is critical [70].

Ae. aegypti and *Ae. albopictus* are sympatric species that tend to breed in similar sites, most commonly in artificial containers [71]. Interspecific competition between these species has been documented. Both prefer breeding sites that contain stagnant, clean and unpolluted water. The containers with dark background and kept in locations shaded are the breeding sites hotspots.

Ae. aegypti is highly endophilic and anthropophilic, therefore frequently found in urban and suburban environments, with high concentrations of humans and houses. The immature stages are found in water-filled habitats, mostly in artificial containers or objects for domestic use, closely associated with human dwellings and often indoors. Water storage containers, such as wells, tanks, cisterns, barrels, jars, buckets, should be kept clean and sealed so mosquitoes cannot use them as aquatic habitats. Such breeding sites are, as a rule, which ensures the development of immature forms with adequate space and less competition inter- and intraspecific and must be strategically inspected and mitigated [46]. In addition to these, plant pots and dishes, plastic pools, tires, damaged appliances, animal drinking pans whose water is not changed periodically, gutters clogged and traps of drains are also frequently used as breeding sites for this species.

The urban landscape has several implication characteristics for the life parameters of *Ae. aegypti* females. The organization and structure of the modified environment, the lack of infrastructure, sewage and drainage systems, as well as the cultural habits of human populations pose direct influence on the presence and density of the *Ae. aegypti* [72, 73]. *Ae. albopictus*, on the other hand, inhabits at the edges of forests and breeds in natural habitats (e.g., tree holes, bamboo stumps and bromeliads), and it was previously considered a rural vector [74]. However, this species has adapted well to urban environments with larvae also breeding in artificial containers. In some opportunities, it has become the most important and sometimes sole vector in urban areas [75, 76]. Due to its considerable ecological valence, easily adapting to the rural, urban and periurban environments, it is presumed that *Ae. albopictus* may serve as a bridge between the urban and sylvatic cycles.

Both species showed seasonal variation in their larval densities. The rainfall and the ambient temperature have direct influence in the adults' population density. Overall, larval densities are greater during the wet seasons. However, in tropical climate, its proliferation is continuous, even though during that period and lower precipitation and lower temperatures, the population density tends to decrease significantly. The temperature increases above 20°C in temperate

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areas, or 22–24°C in tropical areas in South America, is strongly associated with the increase in the *Ae. aegypti* density and, consequently, the risk of transmission of arboviruses [48].

2.4. Vector-virus interactions

In the arboviruses transmission cycle, the arthropod is exposed to and becomes infected when ingesting blood from the viremic host. The arbovirus cycle requires replication in the cellular environment of the arthropod vector. The extrinsic incubation period (EIP) comprises the time between the ingestion of an infectious blood meal by susceptible mosquito and the presence of infective viral particles in the salivary secretion. After this period, the insect becomes able to transmit the virus to a new vertebrate host [77–79]. This period in the vector is required for viral replication and dissemination and is conditioned by the kinetics and tropisms of virus replication in the vector. The EIP is an important epidemiological factor, as it is a temporal process. The life span of a mosquito is intimately tied to this period, and thus, potential transmission of those viruses cause transmission is only permitted when the longevity of the vector exceeds the EIP. To be transmitted by a susceptible vector, the viral particles must adhere to cell receptors on target cells in the midgut epithelium of the insect for establishing infection [80]. Virions need to enter epithelial cells through the microvilli before the blood meal is surrounded by the peritrophic matrix, which will prevent the virus to infect the midgut. The pore size of the peritrophic matrix is smaller (20–30 nm) than all arboviruses [81]. In the *Ae. aegypti*, the peritrophic matrix becomes evident at 4–8 h after blood feeding and attains mature thickness and texture by 12 h [82]. Infection patterns of midgut epithelial cells vary according to virus-mosquito species combinations. In order for productive infection of a mosquito, enough virus must be ingested to infect the midgut, and thus, only vertebrate hosts that manifest sufficient titers can contribute to the transmission cycle. The blood meals containing high concentrations of DENV enhance the probability of disseminating the virus for secondary tissues, increasing the chances of virus being found in the salivary gland of *Ae. aegypti* and the prevalence of infectious mosquitoes after the blood feeding [83, 84].

After the penetration into the midgut epithelial cells, the virus begins the replication process. The virions need to pass through the basal lamina of the midgut epithelium to enter the hemocoel. The hemocoel is the mosquito's body cavity, which contains the organs and muscles and is an open circulatory system that contains hemolymph fluid. Following escape from the midgut into the hemocoel, arboviruses typically disseminate to secondary tissues and organs such as fat body, ovaries, hemocytes and nerve tissue, occurring the viral dissemination in the body of the insect. In non-susceptible mosquitoes, the dissemination does not occur, and the infection is confined to the midgut, in general, in low titers [85].

Finally, it is necessary to establish the infection in salivary glands. Mosquito salivary glands are laterally paired organs located in the thorax. Each gland consists of three lobes or acini, two lateral lobes and one medial (shorter median lobe), connected to a main salivary duct [86]. The lateral lobes can be divided into proximal and distal regions. The glands are made of a single layer of epithelial cells, which are surrounded by a basal lamina and different regions of the glands excrete different proteins. Arboviruses' infection of salivary glands typically begins in the distal lateral lobes [85, 87]. DENV-2 and CHIKV, for instance, infect the proximal

lateral and median lobes of *Ae. aegypti*. The distal lateral lobes of salivary glands in *Aedes* mosquitoes are speculated the site containing receptors to enable endocytosis of arboviruses [85].

Following replication, the virus is released into salivary ducts for horizontal transmission to an uninfected vertebrate host [88] (**Figure 3**). Once the salivary glands of the mosquito become infected, the mosquito transmits the virus throughout his life [89]. The arthropods' saliva is known to facilitate transmission and modulate host responses to virus replication by injecting a variety of substances, which contains complex protein peptide mixtures such as glycosidases, antimicrobials, antihemostatics, proteins with angiogenic or anti-inflammatory properties, and immune modulators [90].

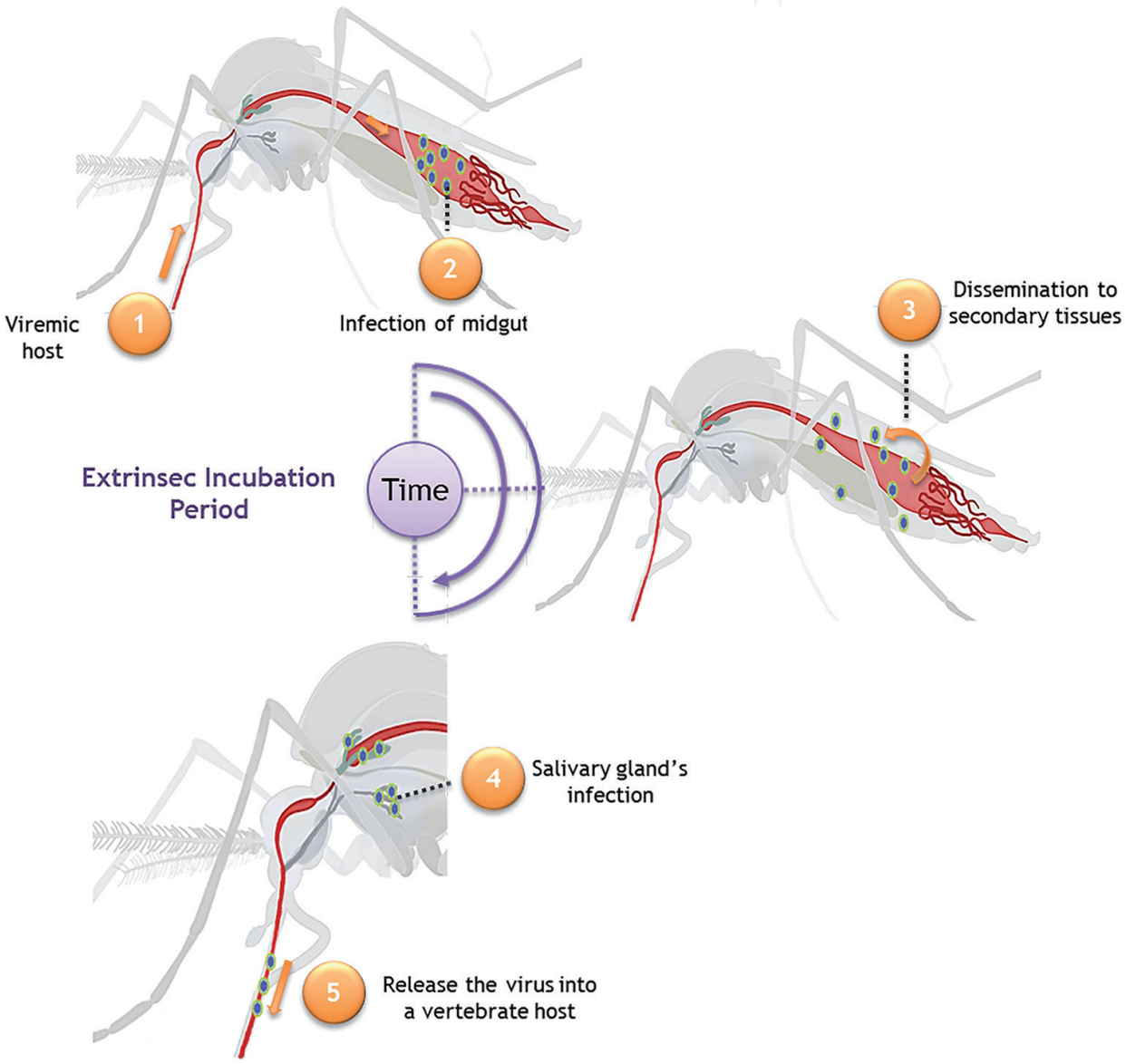

Figure 3. The main steps for an arbovirus infection in the vector: (1) the arthropod is exposed to and becomes infected when ingesting blood from the viremic host; (2) epithelial cells' infection of the midgut by the ingested viral particles, thus occurs viral replication and spread within the midgut epithelium; (3) viral dissemination and amplification from the midgut to secondary tissues; (4) infection of salivary glands; and (5) release of the virus into salivary ducts for horizontal transmission, which can lead to inoculation into a uninfected vertebrate host upon refeeding.

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The extrinsic incubation period is dependent on the genetic characteristics of the virus, the viral titer and the amount of blood that the insect feeds [89]. In addition, environmental factors, mainly temperature, humidity and intrinsic factors of the vector competence and the viral genotype involved, may influence the spread of the virus to the salivary glands of the mosquito, affecting the EIP [85, 91–93].

The biological transmission of an arbovirus by a mosquito vector implies overcoming a series of physical and physiological barriers to allow the virus to be transmitted in a new blood meal along with the saliva and a subsequent gonotrophic cycle. Barriers to the insect able to prevent the virus to replicate and spread to the salivary glands, such as the innate immunity, the midgut infection barrier (MIB), midgut escape barrier (MEB), salivary gland infection barrier (SGIB) and salivary gland escape barrier (SGEB), can significantly affect the vector competence.

It is known that a close combination between genotypes of the mosquitoes and viral genotypes is imperative in determining these phenotypes [83, 94]. Intraspecific genetic variations in populations of the mosquito vector influence the various systems of barriers mentioned above, preventing or allowing the infection of various cells and tissues and the spread of the virus. These barriers are genetically controlled and can be expressed in various proportions in a population of mosquitoes, affecting the arboviruses epidemiology [77].

Genetic variation among mosquito's populations contributes significantly to the transmission potential and length of EIP, affecting the nature of human outbreaks [95]. Different samples of the DENV serotypes can replicate with different intensities and spread with distinct efficiencies, until the salivary gland in a same population exhibiting a wide variation in vector competence to transmit dengue [96, 97]. After feeding on a viremic individual, the mosquito Ae. aegypti becomes infected, and then a reported EIP of 7–14 days is required before the mosquitoes can transmit the virus to a new host [85]. Coinfections with different DENV serotypes in a single mosquito demonstrate competition between serotypes leading to a different transmission potential [98, 99].

In addition to vector competence, several other entomological parameters contribute to vector capacity, which reflects the overall contribution of the vector population to pathogen transmission [100], that is, the vector biting rate, vector density and vector survival.

Experimental infection and transmission of DENV in *Ae. aegypti* and *Ae. albopictus* have been extensively performed since the 1970s. Currently, the *Ae. aegypti* is the main vector for all four DENV serotypes, although *Ae. albopictus* has been incriminated in small-scale dengue epidemics and it is considered a minor vector compared to *Ae. aegypti* [101]. The potential role of *Ae. albopictus* as a dengue vector has become a major concern in dengue-free temperate regions where this mosquito has been established in the absence of *Ae. aegypti.*

In Brazil, the presence of *Ae. aegypti* is found in all regions and federal units of the country [102]. *Ae. albopictus* was detected for the first time in 1986, and by 2014, the mosquito was identified in 25 out of the 27 Brazilian states [103, 104]. It inhabits suburban and rural vegetated areas in Brazil whereas *Ae. aegypti,* more urban areas. Under resource-limited conditions, *Ae. albopictus* demonstrated to be a superior competitor than *Ae. aegypti* [105]. Coexistence of both

species in vegetated areas in Brazil is likely affected by seasonal environmental differences, such as detrital resource levels or egg desiccation [106].

Some ecological aspects of the interaction between DENV and *Ae. aegypti* have been explored. It was observed a negative impact on mosquito fecundity, since infected females laid fewer eggs per clutch than uninfected controls in the third and subsequent oviposition cycles [107]. Moreover, it was observed that infected mosquitoes spent more time ingesting blood [108], and *Ae. aegypti* females infected intrathoracically with DENV-2 had an increase of up to 50% in their locomotor activity when compared to uninfected control [109]. In DENV-infected mosquitoes, increased locomotor activity could potentially increase the chances to find a host [110]. However, a recent study shown that, vertical or horizontal viral transmission has no reproductive cost on *Ae. aegypti* females, suggesting why both types of transmission are sustained evolutionary [111]. Despite the existence of DENV vertical transmission was recently report that asymptomatic infections in human host and infected individuals' movement are more important determinants of DENV's persistence [112].

CHIKV is also transmitted by *Ae. aegypti* and *Ae. albopictus*, and occasional coinfection has been reported [113]. The extrinsic incubation period (EIP) ranges from 2 to 9 days, with an average of 3 days [114]. A number of studies have focused on identifying particular viral genetic determinants that could be driving successful infection of mosquitoes as hosts.

In the CHIKV outbreak occurred in La Reunion island in 2005–2006, a single viral mutation at the position 226 on the E1 glycoprotein in ECSA genotype (E1-A226V) was associated with an enhanced ability of the *Ae. albopictus* significantly infect and disseminate the virus [115]. This viral variant was selected after passing through the midgut barrier, the first step in mosquito infection [116].

American populations of *Ae. aegypti* and *Ae. albopictus* are responsible and highly efficient in transmitting the Asian and ECSA CHIKV genotypes (with and without the E1-A226V mutation [117]. Interestingly, several positions in the CHIKV genome were later discovered to exert strong epistatic effects on the E1-A226V substitution [118, 119]. Recently, a double mutant virus containing E1:K211E and E2:V264A mutations in background of E1:226A revealed remarkably higher fitness for *Ae. aegypti*, as indicated by significant increase in virus infectivity, dissemination and transmission compared to parental E1:226A virus [120]. Therefore, CHIKV represents a threat to the public health in infested areas or in the process of infestation by both *Ae. aegypti* and *Ae. albopictus*. In Brazil, the CHIKV ECSA genotype was detected in 2014; however, the isolates did not contain the A226V mutation on the viral genome [20, 121].

Currently, only *Ae. aegypti* has been implicated in CHIKV transmission in the Americas and Brazil [122, 123]; however, experimental infection of *Ae. albopictus* by Asian strains of CHIKV has been reported [117]. In fact, the current chikungunya epidemic in the Americas could potentially spread on regions infested by both vectors, but with low risk to regions in Europe infested by *Ae. albopictus* [124]. Actually, it has been shown that CHIKV potential transmission by *Ae. albopictus* strong relied on the combination of the mosquito population, virus strain and temperature [125].

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The ZIKV emerged in the Pacific Ocean and subsequently caused a dramatic Pan-American epidemic after its first appearance in Brazil in 2015 [24, 30, 126, 127]. By October 2016, 60 American countries or territories have already reported active ZIKV transmission [128]. Although the virus can be transmitted between humans, it is believed that the most common mode of biological transmission in epidemic and endemic zones is by vector transmission [129, 130].

Although the virus has been discovered in Uganda for almost 70 years, little is known about natural ZIKV vectors. *Aedes* mosquitoes are considered the primary vectors of ZIKV in Africa with reported viral isolations from several species, especially from *Ae. africanus* [130, 131]. More recently, natural infections screened by molecular methods in sylvatic African mosquitoes were again predominantly found in *Aedes*, but also in other species [132, 133]. Nevertheless, ZIKV transmission in the wild has remained poorly understood. In laboratory assays, only two sylvatic species (*Ae. vittatus* and *Ae. luteocephalus*) proved to be able to transmit ZIKV [134].

The domestic mosquito *Ae. aegypti* was early shown to be competent to experimentally transmit ZIKV [135]. Due to its high anthropophilic and domestic behaviors and virus detection in field caught specimens [136, 137], this mosquito has been incriminated as the urban and periurban vector in Africa and Asia [130].

ZIKV has only recently emerged outside of its natural distribution in Africa and Asia and has caused a series of epidemics in urban and periurban sites on Pacific islands [24, 138, 139] before reaching the Americas, probably in 2013 [140]. The spreading virus belonged to the Asian genotype. Despite multiple efforts, the mosquito vectors involved in the ZIKV outbreaks across the Pacific Ocean from 2007 to 2015 were not identified. Experience with ZIKV in the Pacific confirmed that the virus may be transmitted by different vectors during outbreaks, that is, by *Ae. hensilii* in Yap State, *Ae. aegypti* in New Caledonia and *Ae. aegypti* and/or *Ae. polynesiensis* in French Polynesia. In Gabon, *Ae. albopictus* introduced into an environment where the *Ae. aegypti* level was low was the vector for ZIKV [141]. Further experimental studies supported the role for Asian populations of *Ae. albopictus* as vectors of ZIKV transmission concomitantly with *Ae. aegypti* [142, 143].

The global number of zika cases, either suspected or confirmed in the Americas, reached levels never seen before [144, 145]. The virus proved to have a high potential for geographic expansion in regions where *Ae. aegypti* mosquitoes are present and concomitantly with DENV 1–4 and CHIKV, as it has occurred in Brazil and other American tropical and subtropical countries [128, 145].

It has been shown that American *Ae. aegypti* and *Ae. albopictus* populations showed to be competent to transmit the ZIKV belonging to the circulating genotype but displayed heterogeneous infection, dissemination and transmission rates in laboratory assays [146]. Currently, our knowledge of the ZIKV vectors in all reported studies from Africa, Asia, the Pacific region and the Americas is pointing the *Aedes* mosquitoes as the main vectors [147]. Furthermore, the identification of those potential vectors has important implications for the disease outbreak control, especially with the rapid disease spread in the world.

3. Conclusion

Anthropogenic environmental modifications, climate change, global transport network expansion, disordered urban growth are some factors that influence the emergence or reemergence and transmission of vector-borne diseases. The Brazilian population is exposed to infections caused by arboviruses previously described and transmitted by mosquito vectors with anthropophilic habits, widely distributed on the national territory.

The characterization of behavioral patterns allows a better understanding of the transmission dynamics and the design of more effective vector control strategies. No vaccine or specific treatments are available to most arboviruses diseases; therefore, the emergences and epidemics rely mostly on vector control and personal protection. Furthermore, the cocirculation of distinct arboviruses in a same region leads to a complicated clinical and laboratorial diagnosis, as signs and symptoms are similar, and much diagnostic tests are difficult due to cross-reactions.

The transmission' cycles are dynamic with ecological and molecular interactions, between the vector and the pathogen. Many of the steps of those interactions are now seen as of potential use in the control of endemic diseases, through strategies that have targeted the vector, the pathogen transmitted or the transmission' mechanism. In that scenario, understanding the mechanisms of viral-vectors' interactions, as well behavioral characteristics contributing to their competence in transmitting the viruses, is still in need.

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