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## Review

## Mosquito-transmitted viruses – the great Brazilian challenge

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## ABSTRACT

Arboviruses pose a serious threat to public health worldwide, overloading the healthcare system and causing economic losses. These viruses form a very diverse group, and in Brazil, arboviruses belonging to the families *Flaviviridae* and *Togaviridae* are predominant. Unfortunately, the number of arboviruses increases in proportion with factors such as deforestation, poor sanitation, climate changes, and introduction of new viruses like Chikungunya virus and Zika virus.

In Brazil, dengue is endemic, along with the presence of other arboviruses. The situation is complicated by the scarcity of diagnostic infrastructure and the absence of approved vaccines for these diseases. Disease control, thus, relies solely on vector control. Therefore, enhanced clinical knowledge and improved general awareness about these arboviruses are indispensable to tackle diagnostic inadequacies.

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### Introduction

Arboviruses (arthropod-borne viruses) pose a serious threat to public health worldwide, especially in the tropical and subtropical countries, overloading the public healthcare system and causing economic losses. Despite these huge risks, the number of cases tends to increase because of diverse concomitant factors. Deforestation, migration, disordered occupation of urban areas, and poor sanitation as well as ongoing climate changes, which further aids the vectors of these diseases to

colonize new areas, will significantly increase the strength of population at risk.

These arboviruses form a very diverse group. In Brazil, the main arbovirus causing epidemics belongs to the families *Flaviviridae* and *Togaviridae*.<sup>1</sup> In addition to the endemic arboviruses such as dengue virus (DENV), other neglected arboviruses also cause epidemics, such as Mayaro virus (MAYV). This situation, coupled with the introduction of Chikungunya virus (CHIKV), followed by Zika virus (ZIKV), in the Brazilian territory highlights the importance of continuous survey and research about these viruses. Improved awareness

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about these viruses among physicians, healthcare personnel, and concerned authorities as well as general public in the affected areas is indispensable for disease control. This review will focus on the endemic DENV, the neglected MAYV, and the newcomers CHIKV and ZIKV.

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## Dengue fever

### Background

DENV are the most important human arboviruses found worldwide, transmitted by mosquitoes of the genus *Aedes*, the main vector being *Aedes aegypti*, and are responsible for morbidity and mortality. This group is the etiological agent of dengue fever (DF). DENV activity in Brazil, during its trajectory, is demonstrated by the high number of cases reported as well as the number of states involved in the epidemics. *Ae. aegypti* is observed in ~80% of the country, and the difficulties of implementing successful vector control are well known. Explosive epidemics have become a socially and politically significant public health problem, with great economic impact.<sup>2</sup>

The DENV species includes four genetically and antigenically different serotypes (DENV-1, -2, -3, and -4). DENV are members of the family *Flaviviridae*, genus *Flavivirus*. Like other flaviviruses, DENV have a single-stranded positive-sense RNA genome, 10,700-nucleotide-long, that is translated as a single polyprotein and post-translationally cleaved into three structural proteins: capsid, premembrane and envelope; and seven nonstructural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5.<sup>3</sup>

DENV-1 was the most predominant serotype in Brazil in the 1980s, and DENV-2 replaced it in the 1990s; subsequently, DENV-3 took the position in 2000, followed by DENV-4 in 2007.<sup>4,5</sup>

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### DENV-1

DENV-1 was first observed in the eighties. Phylogenetic studies classified DENV-1 into five genotypes, namely, I, II, III, IV, and V, on the basis of their genetic diversity.<sup>6</sup> The genotypes I, IV, and V were observed in the country, unlike II and III.<sup>7,8</sup>

Nucleotide sequencing subdivided the genotype V into three lineages.<sup>9</sup> The authors suggested that it was introduced by four different events: the first in 1984–1985, second in 1997–1999, and third and fourth in 2004–2007. Two distinct lineages were reported for viruses belonging to genotype V<sup>10</sup>; these lineages were introduced at different time-points in Goiás state. Genotype V was reported in Manaus<sup>11</sup> and Minas Gerais<sup>12</sup> states.

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### DENV-2

Co-circulation of DENV-1 and DENV-2 in Brazil began in 1990, initially in Rio de Janeiro, and subsequently in other states.<sup>13–16</sup> Similar to other countries in the Americas, the introduction of this strain coincided with that of the Southeast Asian genotype DENV-2 into the continent. Two

additional DENV-2 epidemics occurred in 1998 and 2007–2008 in Brazil. In 2001, a large outbreak of DENV-2 occurred in Manaus.<sup>17</sup>

Two lineages of DENV-2 have been reported in Brazil.<sup>18</sup> Phylogenetic analyses of DENV-2 showed that genotype III (Southeast Asian/American) was the only one that circulated over the past 19 years in Brazil, from 1991 to 2008.<sup>19</sup> Sequencing of samples collected in 2011 showed the presence of DENV-2 of the Asian/American genotype in Manaus.<sup>11</sup> Salvador et al. later isolated an American genotype strain in Brazil.<sup>20</sup>

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### DENV-3

Phylogenetic studies have classified DENV-3 into five genotypes, namely, I, II, III, IV, and V, on the basis of their genetic diversity.<sup>21</sup> In Brazil, DENV-3 was first isolated from an autochthonous case in December 2000, in the state of Rio de Janeiro. A large DENV epidemic occurred in 2001–2002 and DENV-3 was assigned to genotype III.<sup>22,23</sup> These DENV-3 isolates appeared to arise from single introduction of GIII.<sup>24</sup>

Co-circulation of DENV-3 genotypes I and III was later observed in Minas Gerais, Brazil. The genotype I was identified in outbreaks occurring during 2002–2004.<sup>25,26</sup> Analysis of the gene sequences of mosquitoes naturally infected with DENV-3 confirmed the circulation of genotype I in Minas Gerais.<sup>27</sup>

DENV-3 genotype III is prevalent in Brazil and has also been observed in Manaus, Amazonas state<sup>11</sup> and in São José do Rio Preto, São Paulo State.<sup>28</sup> Phylogenetic analysis of the DENV-3 genotype III isolated from 107 samples collected between 2001 and 2009 showed that four instances of genotype introduction might have occurred in Brazil because of the detection of four phylogenetically distinct lineages. Three lineages were probably imported from the Antilles and Caribbean, while the fourth one was probably introduced through Colombia or Venezuela.<sup>29</sup>

A gap of eight years between two instances of introduction has been suggested.<sup>30</sup> Both lineages seem to be co-circulating simultaneously, although lineage II is predominant in South and Northeast Brazil, indicating that periodic DENV serotype-specific peaks in incidence coincide with the introduction of new lineages in Brazil every 7–10 years.

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### DENV-4

DENV-4 was first reported in Roraima State during 1981 and 1982.<sup>31</sup> DENV-4 reemerged in Manaus, Amazonas State in 2007.<sup>25</sup> The virus was subsequently identified in the northern Brazilian states of Amazonas and Pará.<sup>32</sup> In the Southeast region, the first episode occurred in the states of Rio de Janeiro and São Paulo in 2011.<sup>33,34</sup>

Partial genomic studies have confirmed that the predominant virus in Brazil is directly associated to the Caribbean strains, and belongs to genotype II. Phylogenetic analyses of different strains demonstrated the presence of two distinct genotypes I and II in Brazil.<sup>11,32,34–40</sup>

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