

Dengue in Brazil: Past, Present and Future Perspective

by

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Abstract

Brazil is the largest country in South America, with 165 million inhabitants largely exposed to dengue outbreaks in the last 16 years. *Aedes aegypti* was reintroduced in Brazil approximately 25 years ago. Following that, DEN-1, DEN-2 and DEN-3 outbreaks occurred in 1986, 1991 and 2001, respectively. These outbreaks started in Rio de Janeiro and spread to all regions of Brazil. With the continuous circulation of multi-serotypes, more than 2 million cases of dengue have been reported in Brazil in the last 16 years and more than 3,000 of these were cases of DHF/DSS. Vector control activities have not been able to control dengue transmission in the country. Thus, DHF has become a major public health problem in Brazil.

Keywords: Dengue outbreaks, DHF/DSS, major public health problem, Brazil.

Introduction

Brazil is the largest country in South America, with an area of 8,512,000 km², mostly tropical, extensively covered by rain forests such as the Amazon, as well as by forests in the eastern and south-eastern coastal areas. The climate in most of the country is tropical with a large diversity of flora and fauna, suitable enough for the dissemination of zoonosis caused by arthropod-borne viruses. Brazil has a population of 165 million, most of them living in urban areas of large cities in the south-east and north-east regions. These

areas are infested by the mosquito *Aedes aegypti* and dengue has become an endemic disease in these urban centres.

Brazilian flaviviruses

Presently, 11 flaviviruses are known to exist in Brazil: Bussuquara (BUS), Cacipacoré (CPC), dengue serotypes (DEN-1, DEN-2, DEN-3 and DEN-4), Iguape (IGU), Ilhéus (ILH), Rocio (ROC), Saint Louis encephalitis (SLE), and yellow fever (YF), including the wild virus and the 17DD vaccine strain⁽¹⁾. All flaviviruses are 60nm spherical enveloped

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viruses, with surface glycoprotein projections, possessing a single stranded RNA (+) genome, with approximately 11,000 nucleotides. The *Flavivirus* RNA contains a single open reading frame that encodes 10 proteins, as follows: 5'-C-preM-E-NS1-ns2a-ns2b-NS3-ns4a-ns4b-NS5-3'⁽²⁾. A phylogenetic study based on 124 nucleotides of NS5 gene and 145 nucleotides of the 3'non-coding region showed that most of the Brazilian flaviviruses are included into two clades, one containing the dengue viruses and another including the Asiatic Japanese encephalitis virus and the related ILH, ROC, SLE and CPC. YF and IGU are still ungrouped and BUS was not included in this study⁽³⁾.

Most of the Brazilian flaviviruses are maintained in nature as sylvatic zoonosis that only occasionally can attack man and domestic animals that come in contact with ecosystems where such viruses circulate⁽¹⁾. Dengue viruses constitute exceptions to this scenario, causing large urban epidemics⁽⁴⁾. Likewise, there is a permanent risk of yellow fever re-urbanization into these cities, caused by the constant arrival of viremic patients from sylvatic areas⁽⁵⁾.

History of dengue in Brazil

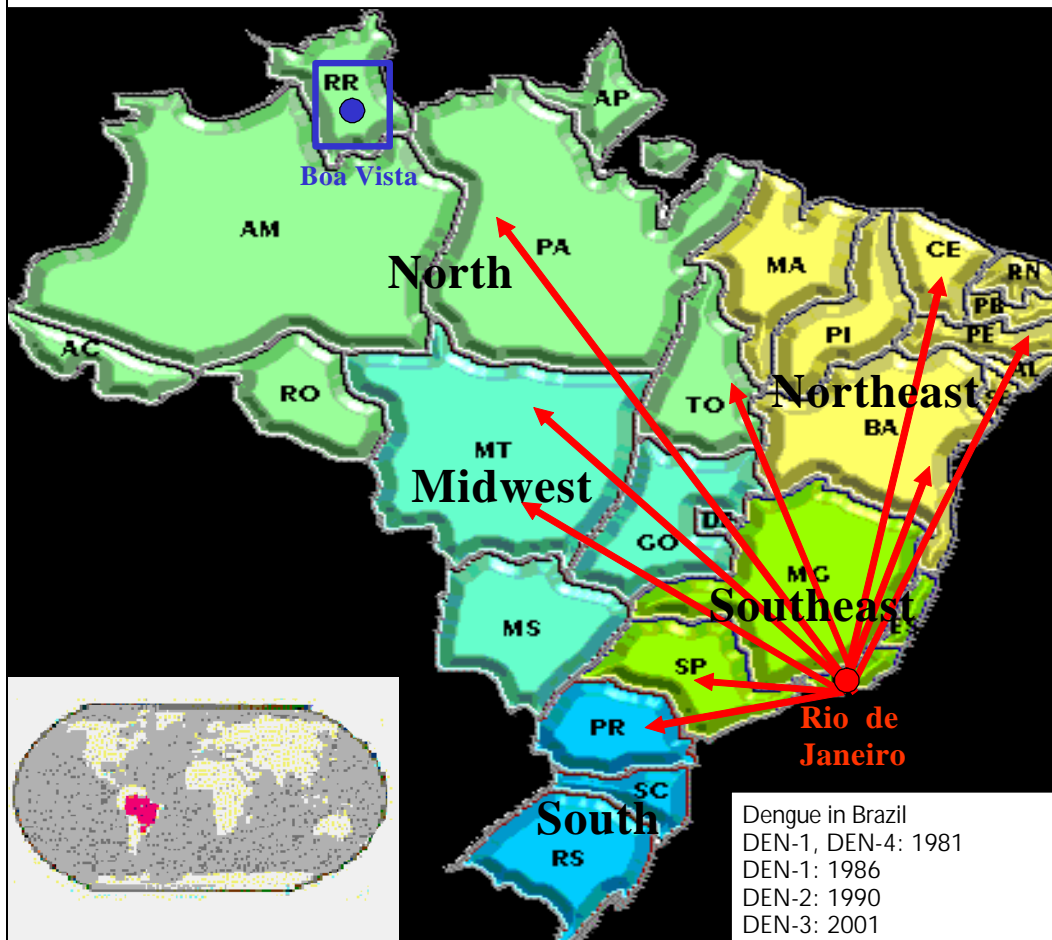
Reports on dengue outbreaks in Brazil started in the 19th century. Mariano, in 1917⁽⁶⁾, mentioned that an epidemic occurred in Rio de Janeiro in 1846. The disease was named *polka* because of the twitches that are characteristic of that dance, caused by myalgia and arthralgia in sick people. It is possible that dengue epidemics occurred in Rio de Janeiro more than once during the 19th

Century⁽⁷⁾. Dengue outbreaks probably also occurred in the north-east and south regions of Brazil during the 19th century. Reis, in 1896⁽⁸⁾, described the clinical picture of dengue cases that occurred during an outbreak in Curitiba, in south Brazil. Furthermore, in 1917, Mariano⁽⁶⁾ reported an outbreak of dengue fever in the state of Rio Grande do Sul. Also, in 1923, Pedro⁽⁹⁾ made an accurate description of the clinical manifestations of dengue fever on the basis of cases studied during the epidemic of 1922/1923, in Rio de Janeiro city.

In July 1981, following the spread of the dengue epidemics in Central America and the Caribbean, an outbreak occurred in Boa Vista, state of Roraima, Amazon region. It is presumed that 11,000 people were infected by DEN-1 or DEN-4; these two viruses were isolated from patients and from *Aedes aegypti*. The clinical presentation of the disease was a benign, non-specific viral fever and cases were reported until August 1982⁽¹⁰⁾. The location where this outbreak occurred is shown in Figure 1.

During the last 16 years, Brazil suffered many dengue epidemics. The virus and the vector spread throughout the country and dengue outbreaks occurred in all regions including the most populated areas of Brazil. The first outbreak in the south-east of Brazil started in a town near Rio de Janeiro in March of 1986. Later, the virus spread into the metropolitan area of Rio de Janeiro. It was the beginning of a large epidemic caused by DEN-1⁽¹¹⁾. Approximately 95,000 cases of dengue were reported until 1987, and an estimated 3 million people became infected by dengue virus during this outbreak⁽¹²⁾.

Figure 1. Map of Brazil showing regions, sights where dengue outbreaks started and dengue viruses spreading



The majority of the patients presented with either a benign undifferentiated febrile illness or the classic dengue fever, including severe headache, retro-bulbar pain, body aches, malaise, skin rash and pruritus. Haemorrhagic phenomena (epistaxis, intestinal bleeding) were rare⁽¹³⁾. The epidemic spread toward the north-east of Brazil, with outbreaks in the states of Alagoas, in June 1986, and Ceará, in September 1986⁽¹⁴⁾. Approximately 50,000

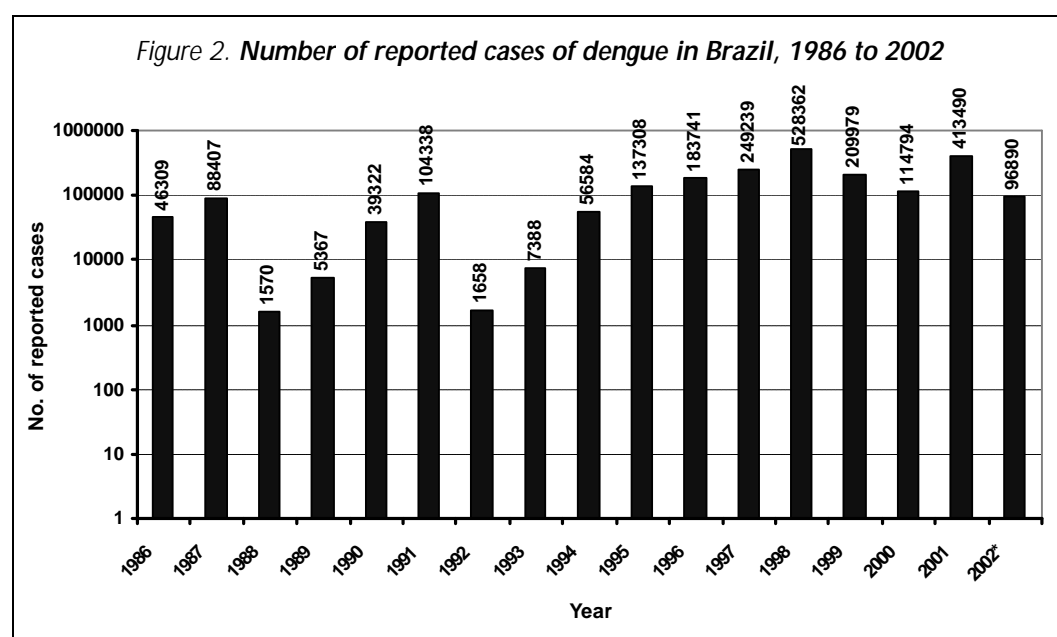
cases of dengue were reported in Ceará between 1986 and 1993⁽¹⁵⁾. In the mid-west region of Brazil, DEN-1 caused an outbreak in 1987. From 1990 to 2002, DEN-1 outbreaks were reported in practically all regions of the country⁽¹⁴⁾.

In April 1990, a new dengue epidemic started in the Rio de Janeiro metropolitan area. DEN-2 was then isolated for the first

time in Brazil⁽¹⁶⁾. DHF/DSS represented 2% of the 17,000 total reported cases, with an uncertain number of fatalities⁽¹⁷⁾. DHF/DSS cases were probably related to sequential infections. DEN-1 and DEN-2 have been circulating simultaneously in Rio de Janeiro in the last 12 years, and DEN-2 reached and caused outbreaks also in the northern region^(18,19). DEN-2 spread and caused outbreaks in the Amazon region⁽²⁰⁾. This virus was introduced in north-east Brazil in 1994 and in the state of Ceará 27,000 cases were reported in three months. The occurrence of 26 DHF/DSS cases was confirmed and 14 patients died. DEN-1 was also isolated during the same outbreak⁽¹⁵⁾. DEN-2 outbreaks have been reported in practically all regions of Brazil, in many cases associated to DEN-1, and at least one case of simultaneous infection by DEN-1 and DEN-2 has been described^(14,21).

DEN-3 virus was isolated in Brazil for the first time in 1999, from a patient returning from Nicaragua (personal communication from Rocco IM, Adolfo Lutz Institute, 1999). This suggested that DEN-3 which circulated in Central America and in northern South America, could reach Brazil soon. In fact, in January 2001, the first reported Brazilian DEN-3 outbreak started in Rio de Janeiro⁽²²⁾. A massive outbreak has been in progress in Rio de Janeiro in 2002, with rapid spread to the north, north-east and south-east of Brazil⁽¹⁴⁾. At the time of writing this paper in April 2002, hundreds of dengue cases are being reported daily in Brazil.

The spread of DEN-1, DEN-2 and DEN-3 in Brazil is shown in Figure 1.



Source: Data from the Ministry of Health, Brazil

* Denotes reported cases and deaths of dengue in January and February 2002

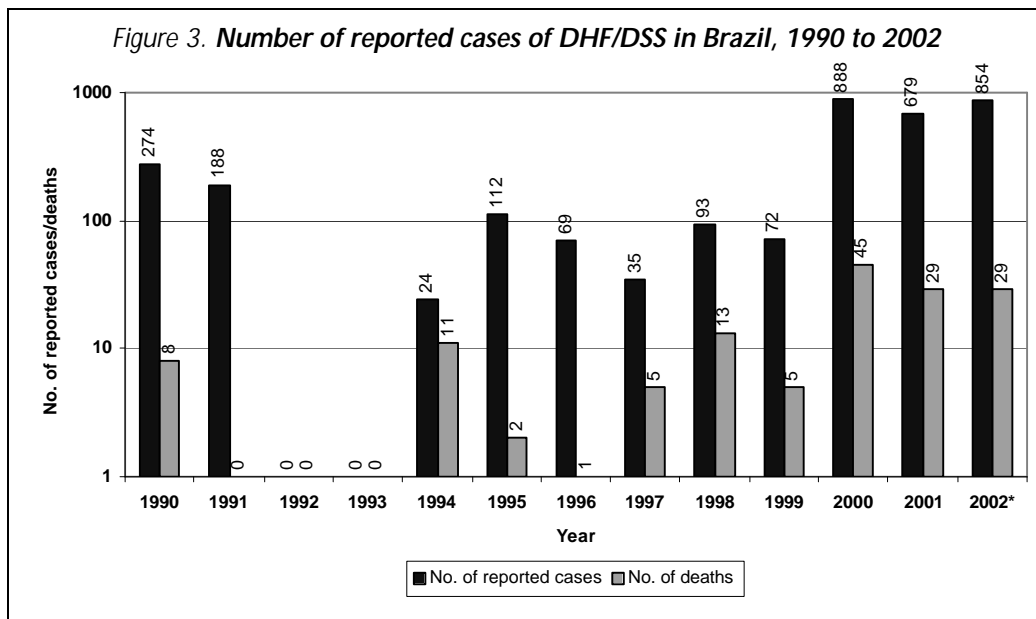
In short, a total of 2,420,105 cases of dengue were reported in Brazil in the last 16 years⁽¹⁴⁾. Figure 2 shows the annual number of reported cases and these numbers clearly indicate the seriousness of the problem in Brazil.

DHF/DSS in Brazil

In spite of the fact that the majority of dengue cases in Brazil have been benign, 795 cases of DHF/DSS were reported until 1998, with a fatality rate of 5% (unpublished, Brasil - Ministério da Saúde, Situação do dengue no Brasil desde 1982, 1999). DHF/DSS cases were mostly associated with secondary infections that occurred during successive outbreaks caused by more than one virus type, and especially during DEN-2 epidemics after previous DEN-1 outbreaks. However, DHF/DSS cases associated with primary infections have also been reported⁽²³⁾. DHF/DSS cases occurred in the populated regions of the northeast and

south-east. Most of the DHF/DSS fatal cases occurred in adults and had started with classic dengue symptoms. After 2 or 3 days of the onset of the disease, they presented haemorrhagic disorders such as petechiae, gastrointestinal bleeding, low platelet count (less than 100,000 platelets/mm³), and a 45% or higher haematocrit level, suggesting that they had a capillary leak syndrome^(17,19). It was also observed that patients who did not receive immediate treatment died.

A total of 3,288 DHF/DSS cases were reported in Brazil until February 2002, showing that this number has increased four times in the last three years, as shown in Figure 3. The fatality rate of Brazilian DHF/DSS cases is 4.3%. In January/February 2002, the DEN-3 outbreak in Rio de Janeiro claimed 854 cases of DHF/DSS, with 29 deaths, and, probably, many of them were not associated with secondary infection (personal communication from Schatzmayr H, 2002)⁽¹⁴⁾.



Source: Data from the Ministry of Health, Brazil

* Denotes reported cases and deaths of dengue in January and February 2002

In order to detect DHF/DSS early and to start disease management as soon as possible, the Brazilian Ministry of Public Health recommends that suspected dengue cases should undergo careful medical observation during the first 48 to 72 hours of the onset. Dengue patients and/or their families should be warned about the appearing of symptoms and signs of DHF/DSS⁽²⁴⁾. In some medical centres the routine evaluation of dengue patients includes tourniquet test and haematocrit level determination.

During dengue outbreaks in Brazil at least eight fatal cases presented with an unusual and severe involvement of the central nervous system^(25,26). In addition, one case of severe bilateral retinal occlusive vasculopathy was reported⁽²⁷⁾. A prospective study of 10 children whose mothers had dengue during pregnancy did not confirm congenital disease⁽²⁸⁾.

Genotypes of Brazilian dengue viruses

The origins of Brazilian dengue viruses were determined in phylogenetic studies based on the entire E gene or the E/NS1 junction nucleotide sequences. DEN-1 strains isolated between 1986 and 2000 from different regions of Brazil were shown to belong to the same genotype II, the Caribbean one (personal communication from Pires Neto RJ and Fonseca BAL, 2002)⁽²⁹⁾. Likewise, DEN-2 isolates from different Brazilian regions showed to belong to the genotype III, the Puerto Rican topotype (personal communication from Pires Neto RJ and Fonseca BAL, 2002)^(30,31). Probably, there was no introduction of new genotypes of DEN-1

in Brazil since 1986 and of DEN-2 since 1990. DEN-3 viruses, recently isolated in Brazil, were shown to belong to genotype III, Sri Lanka (personal communication from Miagostovitch M, 2001). All these viruses were probably introduced in Brazil from the Caribbean, Central America or northern South America, where they caused previous outbreaks.

Aedes aegypti and *Aedes albopictus*

Aedes aegypti, an anthropagic mosquito, is the major vector of dengue as well as of yellow fever virus. It is possible that *Aedes aegypti* was introduced from Africa into Brazil in the 16th century with the slave trade. It probably happened many years before the arrival of dengue virus in the American continent⁽³²⁾.

The Brazilian *Aedes aegypti* eradication campaign was started by Oswaldo Cruz in 1904 to fight yellow fever. After 1920, with the technical assistance and financial support of the Rockefeller Foundation, the campaign was successful in eradicating the mosquito from Brazil, as confirmed in 1955⁽³²⁾. That campaign was probably the reason for the absence of dengue outbreaks in Brazil between 1923 and 1981. The reappearance of *Aedes aegypti* in Brazil after its eradication could be related to the beginning of dengue outbreaks. Firstly, *Aedes aegypti* infested the north of Brazil, reaching the state of Pará in the seventies, and in the following years expanding into the north-east⁽³³⁾. Between 1978 and 1984, almost all states in the north-east, south-east and mid-west of Brazil were infested by *Aedes aegypti*⁽³⁴⁾.

Aedes albopictus, a mosquito from South-East Asia, and a known dengue vector, was introduced in the American continent after 1980. In 1986, it was observed in three different locations in Brazil. However, dengue transmission by *Aedes albopictus* has been reported only once during a Brazilian outbreak⁽³⁵⁾.

In 1998, all Brazilian states were infested by *Aedes aegypti* and dengue transmission was occurring in 22 of the 26 states⁽³⁶⁾.

The most important tool for dengue prevention so far is vector control. Since the beginning of dengue outbreaks, the Brazilian Ministry of Public Health, helped by state and county health agencies, monitored mosquito infestation levels and community clean-up programmes as well as mosquito control with insecticides were carried out⁽³⁴⁾. Innovative vector control programmes have been carried out in Brazil such as vertically structured programmes emphasizing destruction and/or treatment of larval habitats; education of schoolchildren resulting in the removal of large amounts of trash in community clean-up campaigns; cholinesterase level measurements in order to evaluate undesirable effects of the use of organophosphorate insecticides, and biological control of *Aedes aegypti* using copepods⁽⁴⁾.

Evidence that vector control interrupts dengue transmission during dengue outbreaks was shown by the results of a dengue serological survey carried out in Ribeirão Preto city, Brazil, one year after the first DEN-1 outbreak that had led to an intensive *Aedes aegypti* control campaign

with destruction and/or treatment of larval habitats and removal of large amounts of trash in community clean-ups. It was estimated that 23,000 people had dengue infection during the outbreak and that most of the infected people lived in the district of Ipiranga in the north of Ribeirão Preto City⁽³⁷⁾. It is highly probable that the *Aedes aegypti* control campaigns limited the outbreak to that part of the city.

An *Aedes aegypti* eradication programme was submitted to the Brazilian community in 1996 in order to eliminate dengue transmission, to prevent the occurrence of DF/DHF/DSS, and to prevent vector spread to non-infected areas; and to prevent re-urbanization of yellow fever⁽³⁸⁾. However, this expensive and ambitious programme was not implemented.

Presently, the programme for the control of dengue in Brazil aims at lowering the *Aedes aegypti* infestation to under 5% of the houses. However, there has been a deficient infrastructure required to fight *Aedes aegypti*. After DEN-3 isolation in Rio de Janeiro in January 2001, a large outbreak was expected but the federal and state public health authorities were not able to put in place an effective vector control strategy, resulting in a serious DEN-3 outbreak in Rio de Janeiro in 2002.

Conclusion

The successive dengue epidemics in Brazil, caused by DEN-1, DEN-2 and DEN-3, led to the occurrence of DHF/DSS. The continuous circulation of three dengue types, with millions of reported dengue fever cases and

with DHF/DSS, is becoming an endemic disease that is posing a serious public health threat. This situation is similar to what is found in South-East Asia⁽³⁹⁾. This scenario is worrisome because Brazil faces a severe

hospital management crisis and the system cannot support a sudden demand for the care of thousands of DHF/DSS cases requiring hospitalization.

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