

Dengue in Brazil during 1999–2009: A review

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Abstract

Over the period 1999 through 2009, the incidence of dengue in Brazil has shown an upward trend with more than 700 000 cases per year reported during 2002 and 2008. Despite efforts to control *Aedes aegypti*, a hyper-endemic situation has remained with large outbreaks involving all the four dengue serotypes (DENV-1 to 4). The average age of DHF/DSS cases has decreased, making it a disease affecting children. The number of fatalities has also increased. While other countries in the Americas have also witnessed an upward trend in case numbers, Brazil has been subject to more extreme peaks. Other arboviruses also cause sporadic human cases which are commonly confused with dengue and remain undiagnosed.

Keywords: Dengue outbreaks; DHF/DSS; burden of dengue; Brazil; arbovirus.

Introduction

Brazil, the largest country in South America (area of 8 512 000 sq. km.), has a population of 192.9 million,^[1] most of them living in urban areas of large cities infested by the mosquito *Aedes aegypti* and having frequent dengue outbreaks. The first outbreak occurred in the north-west Amazon region in the state of Roraima caused by DENV-1 in 1982.^[2] Since then Brazil has become hyper-endemic for dengue and all the four serotypes (DENV-1 to 4) are circulating in the country. DENV are 60nm spherical enveloped viruses with surface glycoprotein projections, possessing a single-stranded RNA(+) genome of approximately 11 000 nucleotides. Viruses of the genus

Flavivirus contain a single open reading frame RNA that encodes the 10 viral proteins, C-preM-E-NS1-ns2a-ns2b-NS3-ns4a-ns4b-NS5.^[3]

Epidemiological data

Dengue viruses and the vector *Aedes aegypti* have spread throughout the country leading to outbreaks in all regions, including the most populated areas of Brazil, as shown in Figure 1. A sequence of outbreaks has followed the introduction into the country of DENV-1 genotype II in 1986, DENV-2 genotype I in 1990, and DENV-3 genotype III in 2000.^[4] Recently, DENV-4 has been reported as causing acute febrile illness in Manaus city in the north of the country.

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Figure 1: Map of Brazil showing the circulation of dengue virus serotypes by macro-region in 2008

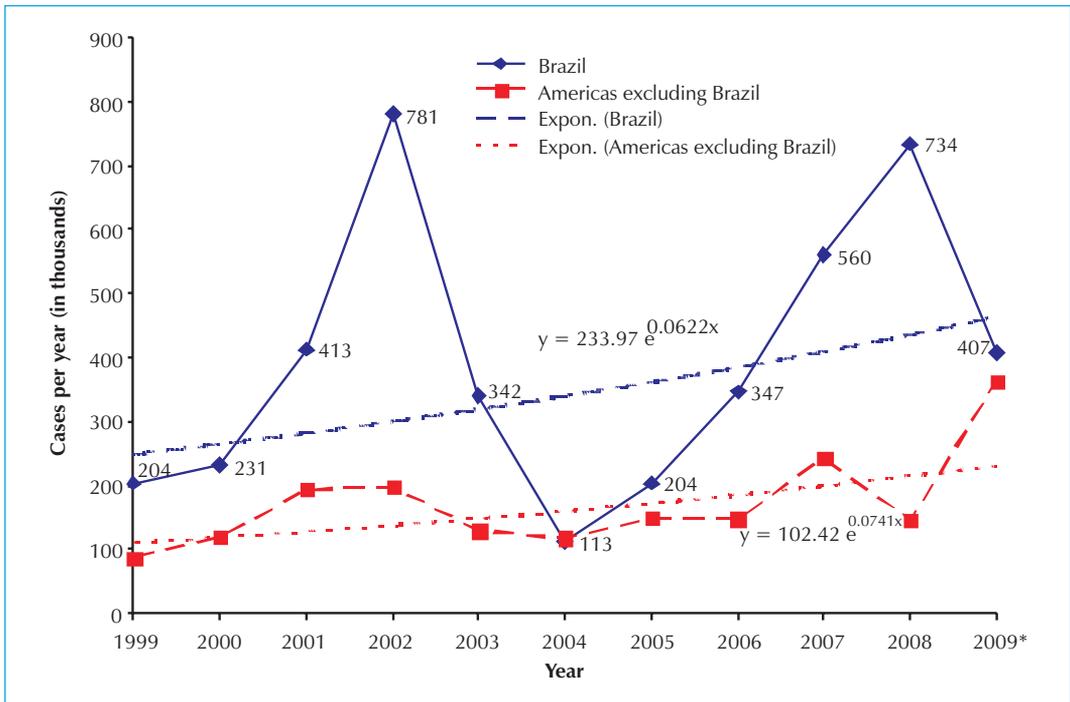


[Source: Brazilian state public health laboratories (LACEN) and www.santiagosiqueira.pro.br]

Distinct dengue virus serotypes and genotypes have been observed in molecular epidemiology studies, spreading from Rio de Janeiro toward the Northeast and Midwest in large outbreaks. Dengue viruses have also spread from Brazil to neighbouring countries such as Paraguay and Argentina. Two introductions of DENV-3 into the country were also observed, in Rio de Janeiro and in the North, both probably from the Caribbean.^[5] In 2008 DENV-2 genotype I resurfaced in Rio de Janeiro leading to a huge outbreak with hundreds of DHF/DSS cases.^[6]

About five million dengue cases were reported in Brazil from 1985 to 2008.^[7] Figure 2 shows that the number of cases has fluctuated seven-fold from 113 000 to 781 000 cases per year over the period 1999 through 2009. In the years 2002 and 2008, the annual number of reported dengue cases exceeded

Figure 2: Dengue (including DHF) cases in Brazil and elsewhere in the Americas



Source: Pan American Health Organization/World Health Organization
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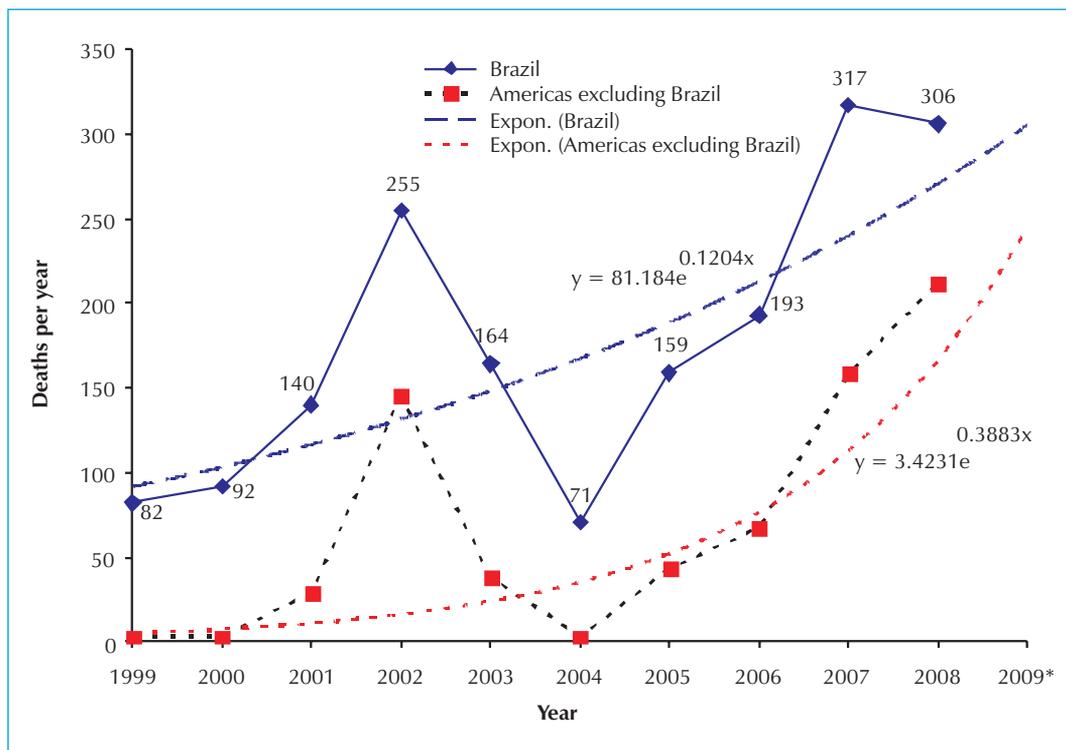
700 000,^[8] and the reported numbers have shown a general upward trend: an exponential curve fitted to these data shows a compound rate of growth of 6.2% per year. Similar data for nine countries in the Americas (Argentina, Columbia, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Peru and Venezuela) with complete data over the same years show an even more rapid upward trend (7.4% per year), but the peak values in Brazil have been much higher than those in the peak years for the other countries in the region. In 2009, however, the cases did not peak in Brazil as they did for other countries in the region, such as Argentina, which saw more cases in one year (25 000) than in the previous 10 years combined.

The number of deaths from dengue in Brazil shows a similar upward trend (Figure 3). Exponential curves show average annual increases of 12% for Brazil and 38.8% for the other nine countries in the Americas. The figure for the highest year in Brazil (317 in 2007) is four times that for the lowest year (71 in 2004).

Dengue diagnosis

Diagnosis of dengue in Brazil has been made mostly by enzyme immunoassays detecting IgM-specific antibodies. Considering the increased number of dengue secondary infections it is possible that many patients

Figure 3: Dengue deaths in Brazil and elsewhere in the Americas



Source: Pan American Health Organization/World Health Organization



presenting anamnestic responses, with low anti-dengue IgM serum levels, have been undiagnosed. In addition, virus isolation has been performed in only a small number of samples and diagnosis by reverse transcription followed by real-time polymerase chain reaction (RT-PCR) has been sporadic.

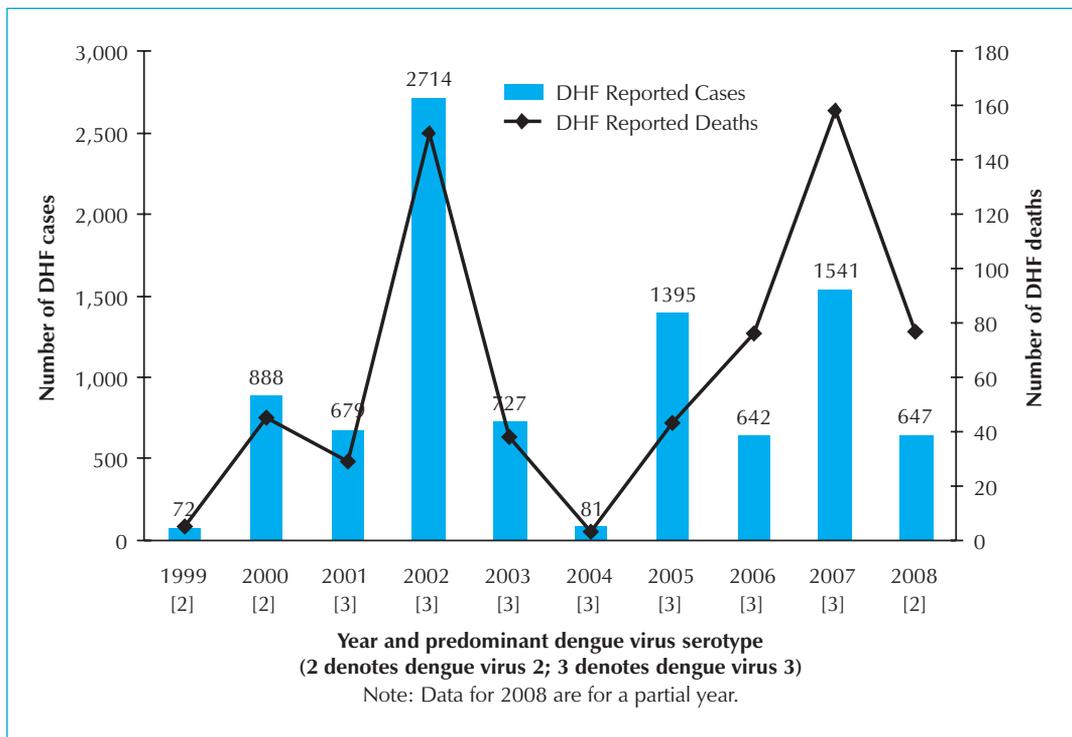
To improve dengue diagnosis, Brazilian authorities could consider more widespread adoption of at least two routine diagnostic methods. Ideally, these methods should be simple, sensitive and able to diagnose dengue at the onset of symptoms. Examples are dengue virus NS1 protein detection by enzyme immunoassay, RT-PCR allowing virus types and genotypes to be determined, or RT-PCR allowing determination of the dengue

virus load in the blood.^[9] Other useful methods are serological tests for detection of anti-dengue IgG antibodies allowing differentiation between primary and secondary dengue infections.

Dengue secondary infections and DHF/DSS

The hyper-endemic dengue situation in Brazil has led to many secondary infections. In addition, the presence of DENV-3 genotype III and DENV-2 genotype I, both virulent, resulted in an increasing number of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) cases. During 1999–2000 DHF/DSS outbreaks were caused by DENV-2,

Figure 4: DHF/DSS cases and deaths reported in Brazil, 1999–2008



Source: FVS, Brazilian Ministry of Health



from 2001 to 2007 by DENV-3, and in 2008, again, by DENV-2. About 10 000 DHF/DSS cases with 1000 deaths have been reported in these last 10 years.^[6] However, it is possible that a large number of DHF/DSS cases remain unreported. Figure 4 presents information on the number of dengue, DHF/DSS and fatal dengue cases, as well as the viral types predominant in each year from 1999 to 2008. Years with a high number of dengue cases also tend to experience a larger number of dengue deaths.

In the last seven years, the average age of DHF/DSS patients has been decreasing. In large cities of the North such as Manaus, the disease is already predominant in children, and this trend has also been seen in the Northeast and in Rio de Janeiro.^[6] Therefore, DHF/DSS in Brazil is gradually becoming a children's disease, as it is in Asia,^[10] although with a smaller number of patients.

Dengue management and control

The management of dengue patients, and especially DHF/DSS cases, has been a challenge in Brazil. The surveillance data show that case-fatality rates from DHF have reached as high as 20 per cent. The programme for dengue control aims at lowering *Aedes aegypti* infestation to under 5% of houses,^[11] but the periodic outbreaks show the challenges in realizing this goal.

Other arboviruses

A final challenge in managing dengue cases in Brazil is that many patients with acute febrile illness diagnosed as having dengue fever are, probably, infected by other arboviruses. The nature of these infections remains unknown in

most cases since the public health authorities focus on dengue diagnosis. Flaviviruses such as Saint Louis encephalitis were found to be causing an outbreak which included meningoencephalitis cases in São José do Rio Preto County, in rural Southeastern Brazil, in 2006 and 2007.^[12]

Despite the availability of an efficient vaccine, sylvatic yellow fever remains a worrisome problem in Brazil. Epizootics of sylvatic yellow fever were reported in the South, Southeast and Midwest regions in 2008–2009, and first observed to be causing a high mortality in sylvatic monkeys followed by the appearance of human disease: more than 100 individuals have been assaulted by yellow fever in the last two years.^[13] Likewise, cacipacore, another flavivirus, has been reported to be causing acute febrile illness in the West^[14] (Batista W., personal communication 2009). Oropouche orthobunyavirus has caused outbreaks in Manaus, a large city and capital of Amazon state (Mourão M.P., personal communication 2009) as well as in Pará^[15] and Acre^[16] states, during 2006, 2007 and 2008. Mayaro alphavirus is also producing dozens of acute febrile illness cases in the North of Brazil (Mourão M.P., personal communication 2009).

Conclusions

In conclusion, the burden of dengue in Brazil has increased during the decade 1999–2009. On average, the number of dengue cases and numbers of deaths have grown by 6.2% and 12% per year, respectively. These facts suggest that dengue is becoming more frequent and more severe. These trends parallel increases throughout the Americas. In both Brazil and other countries, the number of both dengue cases and deaths vary enormously on a year-to-year basis.



The efforts to control *Aedes aegypti* face many challenges, and the four dengue serotypes continue to cause large and successive outbreaks, characterizing a hyper-endemic situation in Brazil and more widely in the Americas. With a disproportionate increase in the number of children affected, dengue is becoming a children's disease in Brazil.

Furthermore, other arboviruses such as yellow fever, Saint Louis encephalitis, cacipacore, oropouche and mayaro are also causing outbreaks and sporadic human

cases in the country. These infections are commonly confused with dengue and remain undiagnosed. This should be of concern to public health authorities, and should stimulate the use of arbovirus diagnostic methods in national and state public health laboratories.

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