

Dengue viruses in Brazil, 1986–2006

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Suggested citation

Nogueira RMR, Araujo JMG, Schatzmayr HG. Dengue viruses in Brazil, 1986–2006. *Rev Panam Salud Publica*. 2007;22(5):358–63.

ABSTRACT

A total of 4 243 049 dengue cases have been reported in Brazil between 1981 and 2006, including 5 817 cases of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) and a total of 338 fatal cases. Although all Brazilian regions have been affected, the Northeast and Southeast regions have registered the highest number of notifications. DENV-1 and DENV-4 were isolated for the first time in the Amazon region of Brazil in 1981 and 1982. The disease became a nationwide public health problem following outbreaks of DENV-1 and DENV-2 in the state of Rio de Janeiro in 1986 and 1990, respectively. The introduction of DENV-3 in 2000, also in the state of Rio de Janeiro, led to a severe epidemic with 288 245 reported dengue cases, including 91 deaths. Virus strains that were typed during the 2002 epidemic show that DENV-3 has displaced other dengue virus serotypes and entered new areas, a finding that warrants closer evaluation.

Unusual clinical symptoms, including central nervous system involvement, have been observed in dengue patients in at least three regions of the country.

Key words

Dengue, dengue/epidemiology, dengue virus/classification, diagnosis, genome, Brazil.

The high level of dengue virus activity on the American continent and the reinfestation of Brazil by the *Aedes aegypti* vector in 1977 contributed to the reintroduction of the dengue viruses (DENV) into Brazil in the 1980s (1, 2). Since that time, more than 60% of the reported cases of dengue in the Region of the Americas have occurred in Brazil (Figure 1). In this article, we describe the introduction of dengue viruses in Brazil, the virus strains, and

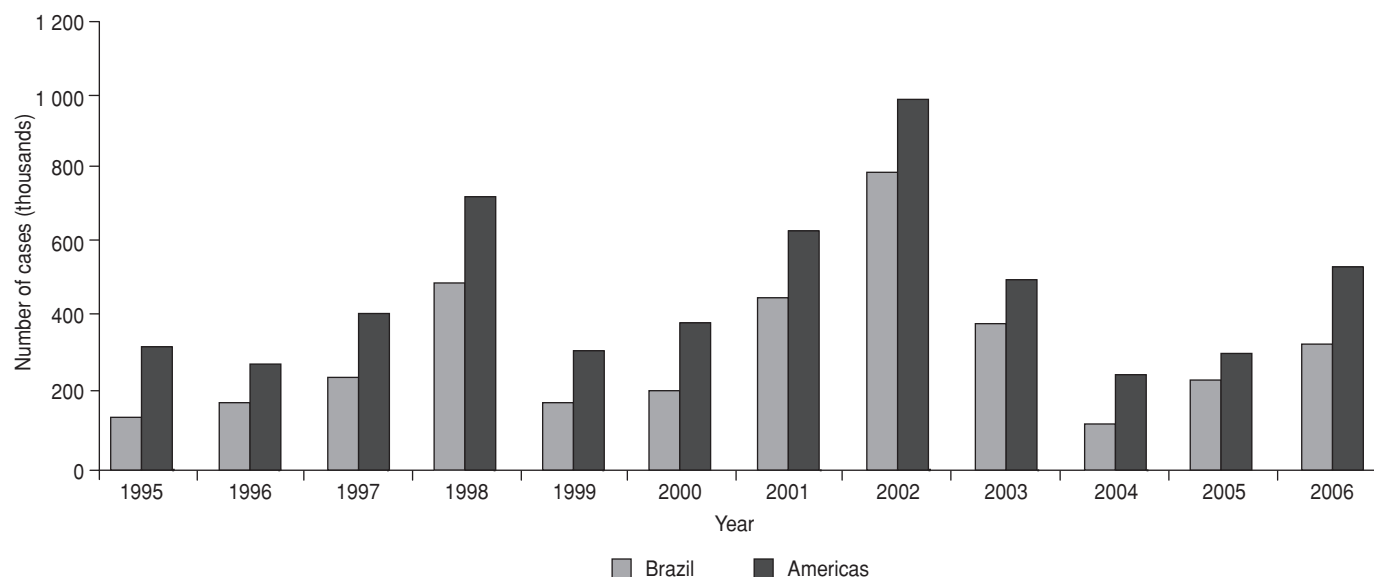
spread of the disease to different regions of the country.

A dengue outbreak caused by the DENV-1 and DENV-4 viruses (1981–1982) occurred in the city of Boa Vista, in the state of Roraima, in the Amazon region close to the Venezuelan border (3). This outbreak was contained by local vector control measures and no dengue activity was reported for the next four years in Brazil. It was only after 1986, with the DENV-1 virus introduction into the state of Rio de Janeiro (4), that dengue infections became a nationwide public health problem. Difficulties implementing effective vector control programs in large

urban communities resulted in the rapid spread of the virus and explosive virgin soil epidemics in several states. The situation was aggravated in 1990 by the introduction of DENV-2 virus, also into the state of Rio de Janeiro (5). With its subsequent spread to other regions of the country, there were more severe clinical presentations and the first fatal cases due to secondary infections.

Absent from the Americas for almost 15 years, DENV-3 was reintroduced in 1994 (6), reaching Brazil by 2000 where it caused a widespread and severe dengue epidemic in the summer of 2001–2002 (7–9).

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FIGURE 1. Reported dengue cases in Brazil and the Region of the Americas, 1995–2006

Note: Figures were compiled from information provided by the Ministry of Health, Brazil (available at <http://portal.saude.gov.br/portal/arquivos/pdf>) and the PAHO Health Surveillance and Disease Management Web site (available at: <http://www.paho.org/english/ad/dpc/cd/dengue.htm>).

The three dengue virus serotypes spread successively throughout the country and by the end of 2006, 25 of the 27 Brazilian states had reported dengue epidemics. A total of 4 243 049 reported cases in the last 20 years in Brazil were caused by DENV-1, DENV-2, and DENV-3 circulation (10).

Dengue in the State of Rio de Janeiro

The state of Rio de Janeiro was the site of the introduction and dissemination of DENV-3, a new serotype in the country, as well as DENV-1 and DENV-2, making it obvious that this area is important for dengue epidemiology in Brazil. As an important tourist center with high levels of *Ae. aegypti* infestation, the area merits close attention in terms of entry of dengue viruses into Brazil.

Dengue infection was first confirmed in the state of Rio de Janeiro by the Flavivirus Laboratory at the Oswaldo Cruz Institute in April 1986. The DENV-1 virus was isolated from patients presenting with exanthematic

disease during an explosive epidemic in the municipality of Nova Iguaçu (4). This municipality belongs to the Greater Metropolitan Area of the state, which includes the capital Rio de Janeiro and 20 other municipalities, and has a population of over 11 million out of the state's 14.7 million total. Nova Iguaçu is located about 25 km from downtown Rio de Janeiro, with a large population that commutes daily to surrounding areas. This heavy circulation of people facilitated the rapid spread of dengue virus to susceptible populations, causing an epidemic of approximately 92 000 cases reported during the 1986–1987 period (11). The infections were clinically characterized as classic dengue fever. The only fatality reported as a result of this episode was that of a young patient.

From Rio de Janeiro, the virus spread rapidly along the coast to different states, all previously infested with the vector. Epidemics in these areas presented similar characteristics to that of Rio de Janeiro: only DENV-1 was involved and no severe cases of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) were reported.

By April 1990, an active surveillance program established by the municipality of Niterói in the Rio de Janeiro Greater Metropolitan Area allowed for early identification of DENV-2 during a period of high DENV-1 virus activity, exactly four years after the first DENV-1 strain isolations. The epidemic in 1990–1991 presented two waves and a significantly higher proportion of patients with thrombocytopenia and clinical presentations requiring hospitalization were seen in the period when DENV-2 was predominant (5).

Both the DENV-1 and DENV-2 viruses were isolated during an epidemic recognized in 1995–1996, with a total of 51 465 reported cases of dengue fever. In January 1998 a new epidemic occurred in the Paraíba river valley, in the western part of the state of Rio de Janeiro and quickly spread to other municipalities, including an important tourist area on the northern coast (11). DENV-2 spread from Rio de Janeiro to different parts of the country, showing more severe clinical presentations in comparison with the previous DENV-1 outbreaks.

Because of the epidemiological importance of the state of Rio de Janeiro, a virological surveillance program was mounted in the city of Nova Iguaçu over the years, including during periods between epidemics. This made it possible to isolate a strain of the DENV-3 virus in 2000 from a case of classic dengue fever as well as from the vector *Ae. aegypti* collected in the field (7, 8, 12).

DENV-3 virus introduction increased the number of reported cases to 69 269 in 2001 and during the summer of 2002, DENV-3 caused the most severe epidemic so far observed in the state of Rio de Janeiro (8, 9). The number of cases in 2001–2002 exceeded the epidemic of 1990–1991, when about 100 000 cases with 462 DHF/DSS cases and 8 deaths were reported. In the DENV-3 epidemic in the summer of 2002, a total of 288 245 cases were reported, with 1 831 cases of DHF/DSS and 91 deaths, corresponding to 1 735 reported cases per 100 000 inhabitants (9). The highest notification of cases was in the Greater Metropolitan Area of the state.

Laboratory studies carried out in 2000/2001 on 1 478 reported dengue cases confirmed a 54.5% infection rate by serology and/or virus isolation and polymerase chain reaction (RT-PCR) (8). Three DENV-1, one DENV-2, and 320 DENV-3 strains were detected, revealing that DENV-3 represented 98.7% of the circulating viruses during the 2002 epidemic in the state of Rio de Janeiro. Forty fatal cases were confirmed for DENV-3 by our institution and at least two different laboratory methodologies were used on 20 of these cases. DENV-3 was the only serotype detected in these fatal cases and virtually all of them were primary infections by DENV-3 (9).

Dengue viruses in other Brazilian states

The southeastern and northeastern regions of Brazil have been the most affected by dengue infections, with epidemics occurring almost yearly. In the southeastern region, besides Rio

de Janeiro, the states of Minas Gerais and Espírito Santo have reported epidemics in both the state capitals and inland municipalities. In the state of São Paulo, dengue virus activity was mainly observed in inland municipalities, with some severe epidemics and sporadic activity in coastal locations.

The northeastern region, an important tourist area comprising seven states along the coast, has suffered successive dengue epidemics and was responsible for the highest number of dengue notifications during the late 1990s. In 1994, the state of Ceará reported an epidemic with 47 889 cases, including 25 cases of DHF and 12 deaths. An increase in DHF was observed in 2003, when 23 796 dengue cases were reported, including 291 DHF cases and 20 deaths. This scenario was also observed in 2005 with 22 817 cases reported, including 195 DHF cases and 20 deaths (13–16).

The midwestern region, which includes the Federal District and the nation's capital Brasília, confirmed DENV-1 circulation in 1990. In 1995 DENV-2 was isolated and one case of dual infection was reported (17).

Dengue epidemics caused by DENV-2 occurred in the state of Tocantins in 1991 (18) and in the state of Pará in 1995 (19), both in Brazil's northern region. The state of Roraima confirmed dengue activity in 1996, 14 years after the first outbreak occurred in that area. In 1998, the state of Amazonas reported a dengue epidemic with 23 910 cases. In 2001, all the states in the Amazonas region had epidemics of different magnitudes (10), including Acre and Amapá, confirming the expansion of *Ae. aegypti* in the Amazon basin.

In the southern region, the state of Paraná is the only one that has reported dengue since 1995. No autochthonous cases were reported in 2006 in the states of Santa Catarina or Rio Grande do Sul (10).

It should be emphasized that, according to available epidemiological data, dengue infections in the country are found in all age groups in the period studied, with no predominance in children.

Genetic characterization of dengue viruses

The co-circulation of DENV-1 and DENV-2 in Brazil began in 1990 with the subsequent appearance of DHF/DSS and fatal cases (Figure 2). This occurred initially in Rio de Janeiro and later in other states (5, 20–22). An increase in the number of more severe cases in Brazil, similar to other countries of the Americas, coincided with the introduction of the DENV-2 Southeast Asian genotype into the continent (23).

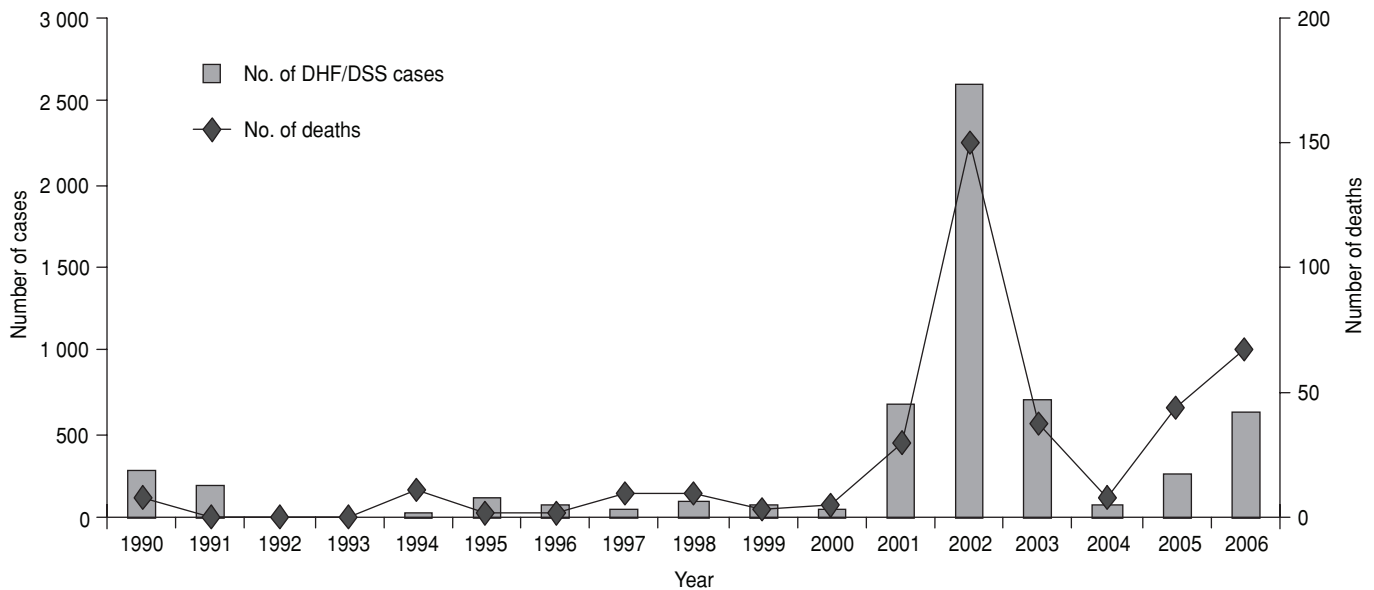
Analysis by genome sequencing performed on DENV-1 and DENV-2 isolated in Brazil identified genotypes from the Americas and Southeast Asia of DENV-1 and DENV-2, respectively (24–26). The complete nucleotide sequence analysis in our laboratory of one Brazilian DENV-2 isolated in 1998 confirmed that the Southeast Asian genotype III is circulating in Brazil (27).

The DENV-3 genotype introduced into the continent has been associated with major DHF/DSS epidemics in Sri Lanka and India and with DHF/DSS cases and deaths in Mexico and Central American countries (28, 29). DENV-3 strains isolated in Rio de Janeiro in 2000, 2001, 2002, and 2003 have been sequenced by our group and in one strain the complete genome was detailed (GenBank accession no. AY679147), confirming that this strain corresponds to genotype III of the Indian subcontinent (30–32).

The data on dengue strain typing after introduction of DENV-3 show that this genotype dislodged other serotypes when first introduced into the area, showing its high infection capacity in both humans and vectors. These data however, need more careful evaluation and comparison with epidemiological data from other countries in the Region of the Americas.

Clinical symptoms

Besides the usual symptoms of dengue observed in the cases of DHF/DSS, unusual manifestations involving the central nervous system were

FIGURE 2: Number of DHF/DSS cases and deaths resulting from dengue infections reported in Brazil, 1990–2006

Source: Ministry of Health, Brazil, <http://portal.saude.gov.br/portal/arquivos/pdf>

reported during the 1986–1987 epidemic in Rio de Janeiro and later in different states, including one case in which the dengue antigen was detected in neuronal cells by immunohistochemistry (33–36). Neurological manifestations in 41 patients were reported in the state of Pernambuco between March and July 1997 and February and May 2002. The brain was involved in 5 of 7 of these cases in 1997 and 20 of 34 cases in 2002; the spinal cord was involved in 2 of 34 cases in 2002; peripheral nerves were involved in 2 of 7 cases in 1997 and 12 of 34 cases in 2002. Cerebral hemorrhage and acute disseminated encephalomyelitis were also diagnosed (16, 37).

In the state of Rondonia, acute encephalomyelitis was observed in 51 patients presenting signs and symptoms of dengue from November 2004 to March 2005. Anti-dengue IgM antibodies were detected in sera, and one patient, in whom the RT-PCR test detected DENV-3, presented IgM in cerebrospinal fluid (38, 39).

Dengue cases with high levels of serum aminotransferases have also been observed. Yellow fever infections

were occasionally suspected but not confirmed by epidemiologic investigations and laboratory results.

During the DENV-3 epidemic in Rio de Janeiro in 2002, viral RNA was detected in the cerebrospinal fluid, liver, brain, lung, spleen, and kidneys of fatal cases by RT-PCR (9).

CONCLUSIONS

Dengue virus activity in Brazil during the past 20 years is demonstrated by the high number of reported cases and states involved in epidemics. The co-circulation of three dengue serotypes is responsible for the increased occurrence of severe forms of the disease, such as DHF/DSS.

The presence of *Ae. aegypti* in about 80% of the country and the difficulties of implementing successful vector control are well-known in Brazil and in many other countries in the region. Barriers to adequate vector control include poor urban planning, demographic pressure, and the shortage of vector surveillance and personnel able to cover huge geographic areas.

While vector control continues to be difficult, progress has been made in notification of dengue outbreaks in Brazil. A network of laboratories that are capable of diagnosing dengue infections has been established in all states of Brazil, under the supervision of Reference Laboratories at the regional level.

Considering the widespread presence of the disease vector and the lack of a vaccine to prevent dengue infections, constant improvement in the rapid identification and correct clinical management of dengue cases by health services is crucial in order to reduce the impact of the disease and the number of fatal cases.

Acknowledgments. The authors would like to thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (grant No. 501564/03-9) and Fundação de Amparo a Pesquisa Científica e Tecnológica (grant No. E-26/152.490/2002) for their financial support of this work. We are also grateful to the Brazilian Ministry of Health and the Rio de Janeiro State Health Secretariat for providing epidemiological data.

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Manuscript received on 28 June 2006. Revised version accepted for publication on 12 July 2007.

**Virus del dengue en Brasil,
1986–2006****RESUMEN**

En Brasil se han notificado 4 243 049 casos de dengue entre 1981 y 2006, de ellos 5 817 casos de dengue hemorrágico/síndrome de choque por dengue (DH/SCD) y un total de 338 casos mortales. A pesar de que la enfermedad ha afectado a todas las regiones brasileñas, el mayor número de casos se ha notificado en las regiones nororiental y suoriental. Los virus del dengue (DENV) 1 y 4 se aislaron por primera vez en la región amazónica de Brasil en 1981 y 1982. La enfermedad se convirtió en un problema nacional de salud pública después de los brotes de DENV-1 y DENV-2 en el Estado de Río de Janeiro en 1986 y 1990, respectivamente. La introducción del DENV-3 en 2000, también en el Estado de Río de Janeiro, llevó a una grave epidemia con 288 245 casos notificados de dengue y 91 muertes. Las cepas del virus identificadas durante la epidemia de 2002 demostraron que el DENV-3 ha desplazado a los otros serotipos y se ha expandido a nuevas zonas, algo que merece una evaluación más profunda. En los pacientes con dengue de al menos tres regiones del país se han observado síntomas clínicos atípicos, entre ellos alteraciones del sistema nervioso central.

Palabras clave

Dengue, dengue/epidemiología, virus del dengue, diagnóstico, genoma viral, Brasil.
