

## Dengue and dengue hemorrhagic fever epidemics in Brazil: what research is needed based on trends, surveillance, and control experiences?

Dengue e febre hemorrágica do dengue no Brasil: que tipo de pesquisas a sua tendência, vigilância e experiências de controle indicam ser necessárias?

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### Abstract

*Dengue epidemics account annually for several million cases and deaths worldwide. The high endemic level of dengue fever and its hemorrhagic form correlates to extensive domiciliary infestation by Aedes aegypti and multiple viral serotype human infection. This study analyzed serial case reports registered in Brazil since 1981, describing incidence evolutionary patterns and spatial distribution. Epidemic waves followed the introduction of every serotype (DEN 1 to 3), and reduction in susceptible individuals possibly accounted for decreasing case frequency. An incremental expansion of affected areas and increasing occurrence of dengue fever and its hemorrhagic form with high case fatality were noted in recent years. In contrast, efforts based solely on chemical vector control have been insufficient. Moreover, some evidence demonstrates that educational measures do not permanently modify population habits. Thus, as long as a vaccine is not available, further dengue control depends on potential results from basic interdisciplinary research and intervention evaluation studies, integrating environmental changes, community participation and education, epidemiological and virological surveillance, and strategic technological innovations aimed to stop transmission.*

*Dengue; Dengue Hemorrhagic Fever; Incidence*

### Introduction

Dengue is currently the human arbovirus disease of greatest epidemiological magnitude and widest geographic range, affecting 56 countries. Its high endemic level and a well-known potential for explosive epidemics defy surveillance and control strategies, in addition to challenging current knowledge on the disease's prevention. International estimates indicate 50 million infected individuals per year, and reported cases of dengue hemorrhagic fever reach nearly 500,000, with at least 12,000 deaths <sup>1</sup>. Moreover, the increasing incidence of dengue hemorrhagic fever and simultaneous circulation of more than one viral serotype <sup>2</sup> are sufficient to include dengue among the most serious current public health problems involving transmissible diseases.

While the accumulated information on pathophysiology and treatment of severe forms of dengue have decreased the case-fatality rate, recurrent epidemics and isolated severe cases in endemic situations require an active epidemiological surveillance system <sup>3</sup>. Equally important, a structured network of healthcare services, capable of providing prompt and adequate clinical management in affected areas, can reduce mortality, such that appropriate control actions should be planned and executed.

According to the Brazilian data, three dengue virus serotypes have been isolated (DEN-1,

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DEN-2, and DEN-3), and the introduction of DEN-4 is imminent, due to intense air and maritime transportation between Brazil and countries in both the Americas and other affected continents. Furthermore, despite government efforts to promote surveillance, control, and adequate treatment, the epidemiological prospects can be considered negative, due partly to the country's complex urban environment, facilitating proliferation of the disease's main vector, *Aedes aegypti*, and persistently high infestation levels<sup>4</sup>. It is thus crucial to understand dengue transmission dynamics by examining the relative influence of factors in the disease's temporal and spatial distribution, helping identify research needs to offer solutions to halt the current epidemic pattern and reduce the endemic level.

### Spatial-temporal evolution of dengue epidemics

The first report of a dengue epidemic with viral isolation was in 1981, in Boa Vista, Roraima, a State in the North of Brazil where serotypes DEN-1 and DEN-4 were isolated<sup>5</sup>. However, widespread dissemination of DEN-1 only began after its first occurrence in Rio de Janeiro, Southeast Brazil, in 1986, when some urban areas in the Northeast were also affected. Incidence rates of 268.2 per 100,000 inhabitants (46,309 cases) in the city of Rio de Janeiro and 34.5 in the country as a whole were recorded. This was followed by the introduction of DEN-2 in 1990 in Rio de Janeiro, producing an epidemic that mainly affected that State and others in the Southeast (incidence rate of 143.2 in 1991). Previously, *A. aegypti* had been detected in only 640 municipalities (11.6%) and States in Central-West Brazil (Mato Grosso and Mato Grosso do Sul), with a few cases of dengue. The two epidemic waves presented a clearly similar pattern during the period from 1986 to 1991 (Figure 1). The rates decreased in the second semester of each year due to seasonal variation, with a two-year supervening inter-epidemic period displaying lower incidence.

The year 1998 witnessed a dengue pandemic, and an exponential increase in the number of cases recorded since 1994 reached a peak during that year, when countrywide incidence reached the highest level for the 1990s (326.6/100,000 inhabitants, or over 500,000 recorded cases). A major territorial expansion of viral circulation characterized this period. Case reports came from 155 municipalities (or counties) in 1994 and from 638 the following year,

reaching some 2,675 municipalities in 1998. In 1998, both the highest incidence (564.1) and the largest number of case reports (258,441) were observed in the Northeast (Figure 2). By the end of the 1994-98 period, viruses DEN-1 and DEN-2 circulated in some 49.0% of the country's 5,507 municipalities, and the vector was detected in over 50.0% (2,910), comprising the third major epidemic wave. No autochthonous cases were reported in the South, an area where climate could be a factor hindering vector proliferation.

In 1999 there was an important decline in incidence, possibly due to the reduction in the number of previously affected individuals susceptible to circulating serotypes in large urban areas, and to some extent also due to the control measures adopted (Figure 1). Nevertheless, dengue spread to other areas of the country, especially the North, which showed the highest incidence rate in subsequent years (408.1 per 100,000 inhabitants in 2001) However, since the North has areas of low population density and mostly small towns, the spread to that region accompanied an apparent decline in the national incidence curve. Of all the epidemic waves, the third differed from the preceding two by a continuous and progressive increase in attack rates, a process that lasted five years, reaching nearly five times the highest previously observed level. The subsequent reduction in incidence was also less marked, settling at an inter-epidemic incidence rate much higher than those observed between the two previous epidemic peaks.

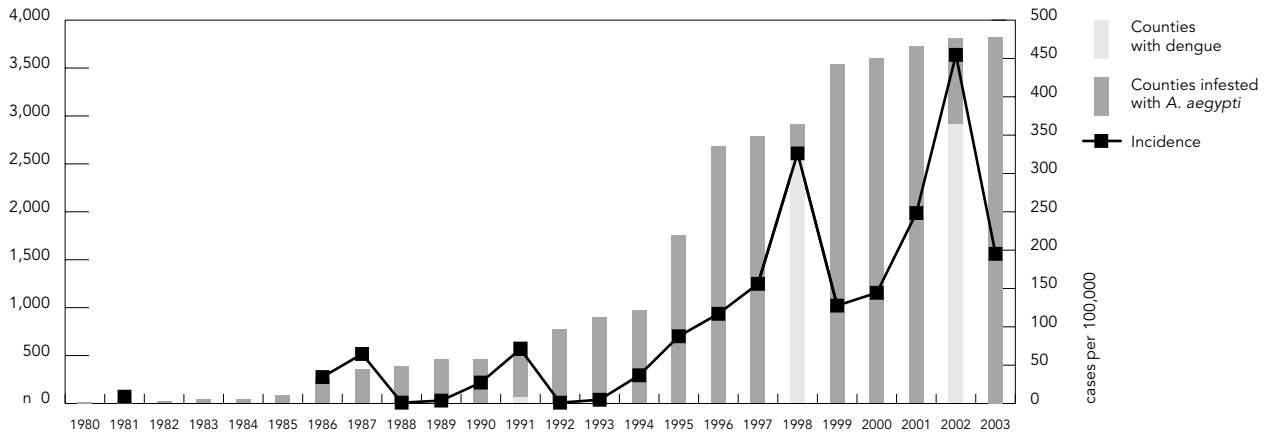
Isolation of DEN-3 occurred for the first time in Brazil in December 2000, also in Rio de Janeiro, producing another large-scale epidemic in that city, where incidence rates in the two subsequent years reached 470.1 and 1,735.2 cases per 100,000 inhabitants, constituting the fourth major epidemic, beginning in January 2001 and lasting two years like the previous epidemics (Figure 1).

Unlike the others, the DEN-3 epidemic expanded more rapidly, affecting numerous small towns and the previously dengue-free States of the South. Only two-and-a-half years after it was first detected, DEN-3 had been isolated in 22 of Brazil's 27 States and in over 2,900 municipalities (counties).

The over-15-year-old population was the most heavily affected<sup>6</sup>, a pattern also observed in areas where dengue virus was recently detected. The reason for such age frequency remains unexplained, although changes in the age profile of cases has recently been observed, possibly due to a gradual reduction in the num-

Figure 1

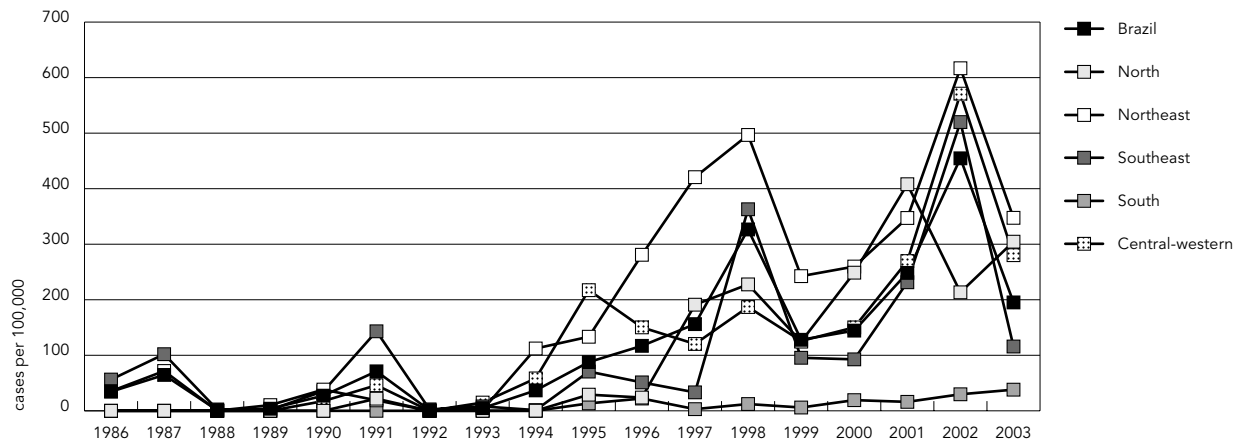
Annual distribution of dengue incidence rates per 100,000 inhabitants, number of *A. aegypti* infested municipalities and those with dengue cases. Brazil, 1980/2003.



Source: Ministry of Health, Brazil.

Figure 2

Distribution of annual dengue incidence rates per 100,000 inhabitants, by region. Brazil, 1986/2003.



Source: Ministry of Health, Brazil.

ber of older susceptible individuals and to the accumulation of children exposed to the virus, a fact already demonstrated <sup>7</sup>.

### Dengue hemorrhagic fever

Until 2000 Brazil had recorded relatively few cases of dengue hemorrhagic fever, given the thousands of reported cases of classical dengue <sup>6</sup>. This is similar to findings in Peru <sup>8</sup> but different from other countries in the Americas <sup>9,10,11</sup> and Southeast Asia. The first detected cases of dengue hemorrhagic fever in Rio de Janeiro followed the isolation of DEN-2 in 1990. Until 1991, over 50.0% (462) of all dengue hemorrhagic fever cases were diagnosed in that area, and during the following years the relatively small number of cases detected per year was only exceeded by a maximum of 112 recorded in Fortaleza, Ceará State, in Northeast Brazil, in 1995. However, considering the wide circulation of two viral serotypes, an explanation is still needed for the apparent divergence between the large number of cases of classical dengue and the limited number of confirmed cases of dengue hemorrhagic fever (937, or 0.05% of all reported dengue cases). In fact, seroprevalence surveys <sup>12,13,14,15,16</sup> showed that millions of individuals had already been infected by both circulating serotypes at that time, leading to a higher expected frequency of dengue hemorrhagic fever than actually reported. At least three complementary hypotheses have been considered: low virulence of the DEN-2 strain circulating in the Americas <sup>8</sup>; diagnostic difficulties related to deficiencies in the Brazilian healthcare system; and the rigorous nature of the WHO case-confirmation criteria adopted in Brazil.

An important increase in dengue hemorrhagic fever incidence accompanied the introduction of DEN-3 (Figure 3), changing the overall clinical expression of the disease during the fourth epidemic. Failure to reach an early diagnosis and adequate treatment accounted for rather high dengue hemorrhagic fever case-fatality in Brazil, generally greater than 5.5%, whereas in some Southeast Asian countries, such as Thailand <sup>17</sup>, case-fatality has been reported as less than 1.0%.

### Dengue prevention and control

The lack of an effective vaccine, the infectious agent's morbidity force, and the predominance of the high vector competence of *A. aegypti*, a

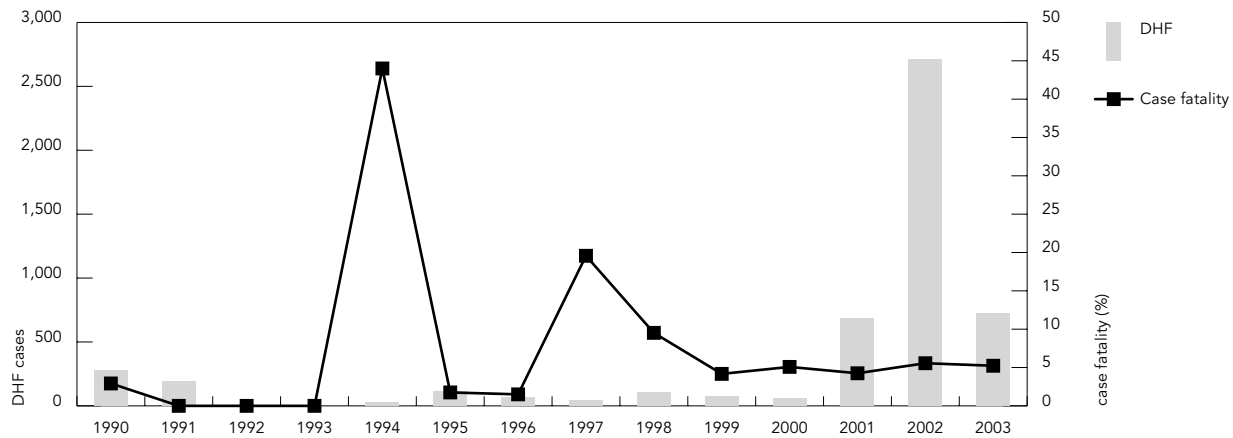
persistent vector in crowded urban areas, are three factors that make prevention of the four dengue serotypes' circulation a formidable task. Control measures aim solely at the elimination of the disease's main vector <sup>4</sup>, a mosquito well-adapted to different environmental conditions and to the so-called modern lifestyle of many different countries, especially conditions in developing countries that help maintain domiciliary vector breeding sites.

Past efforts to eliminate yellow fever from Brazil's urban areas kept the country free of *A. aegypti* <sup>18</sup> until the mosquito's reintroduction in 1976. Unfortunately, this did not motivate the reactivation of the national entomological surveillance system. The result was that cities became progressively infested as described above, despite the alerts issued by the scientific community to government officials <sup>19</sup>, who were already aware of the risk posed by widespread vector infestation <sup>20</sup>. In 1986, possibly due to lack of funds to combat the vector in the Americas, among other factors, policy changed from eradication to simply controlling the mosquito population <sup>18</sup>, despite the lack of sound scientific evidence to support such a decision. In fact, the literature included only one observation of an apparent interruption of yellow fever transmission in Senegal <sup>21</sup>, in areas where *A. aegypti* infestation rates fell to 1.0%. According to an erroneous interpretation of these findings by analogy to dengue transmission dynamics, low dwelling infestation would control transmission, as opposed to research results based on a Singapore epidemic <sup>22</sup>, known since 1991, showing that the dengue virus was able to circulate even when rates dropped close to 1.0%. In fact, since the 1980s the official control policies in Brazil have not achieved very effective results, for several reasons <sup>23,24</sup>.

The rapid expansion of dengue vector infestation throughout Brazilian territory during the latter 1980s and thereafter (Figure 1) demonstrates that the control strategy adopted did not succeed, and that the epidemiological conditions for the onset of dengue epidemics thus became firmly established. Efforts to combat the mosquito continued, including an attempt in 1996 to establish the goal of complete vector eradication. A project was thus proposed, including well-structured eradication stages (planning, attack, consolidation, and maintenance) and decentralized actions according to the guidelines of the Unified National Health System (SUS). Besides the chemical attack on *A. aegypti*, the project was essentially based on sanitation, education, information, and extensive social mobilization, in an attempt to trans-

Figure 3

Temporal distribution of confirmed cases of dengue hemorrhagic fever (DHF) and associated case fatality, Brazil, 1990/2003.



Source: Ministry of Health, Brazil.

form it into a program backed by society as a whole. It is possible that if fully executed it would have brought a wide range of social benefits, and similarly, it could have had a positive impact on the incidence of health problems related to environmental deficiencies such as infant mortality, diarrhea, leptospirosis, hepatitis A, cholera, and certainly dengue itself<sup>19</sup>. Several political, administrative, and financial difficulties hindered the project's full implementation and impeded its expected benefits. An alternative second project (Adjusted Plan for the Eradication of *Aedes aegypti* – aPEA) was implemented instead, which did not include the same principles described above, such as universal coverage and continuity in all regions, and failed to provide resources to accomplish the basic components of the previous project. Thus, during 1997-2001 the implementation of the aPEA consisted solely of chemical vector control, leading to a further expansion of the affected area and the maintenance of high domiciliary infestation rates, especially in larger and more complex urban areas.

In 2002, the Ministry of Health (MoH) thus adopted the control strategy, establishing the goal of reducing domiciliary infestation rates to below 1.0%, increasing the program's financial resources and decentralizing action to the county level. In addition, centralized follow-up and evaluation mechanisms were located in the MoH headquarters<sup>25</sup>. One year after the

program's implementation, infestation rates appeared to be decreasing in some areas, and there was a considerable reduction in dengue incidence.

## Discussion

Where the dengue virus has emerged or re-emerged, infections have changed the population morbidity profile, and in some countries the transmissible disease mortality patterns. Future perspectives suggest a worsening of the current situation, with major consequences for the world's disease profile in the coming decades<sup>4</sup>. In Brazil the dengue endemic level has already altered morbidity indicators, and the magnitude of its incidence in the past years has surpassed that of all other diseases of mandatory notification. Moreover, despite all efforts, analysis of available secondary data and serological surveys<sup>13,14,15,16</sup> indicate the limited effectiveness of the vector control measures. However, failure to control dengue is a worldwide phenomenon, occurring even in places where vector control programs were considered successful until recently, as in Singapore<sup>26</sup>.

Current biological, ecological, and social circumstances are very different from those of the 1950s, when *A. aegypti* was eradicated from the Americas. In contrast, the present state of knowledge is considered insufficient to deal

with the dengue situation. These difficulties and limitations are reflected in the Brazilian government's action and decision-making process, with strategies since 1976 that have had little if any consistency or continuity. Furthermore, actions have often been based on technically erroneous concepts. This is the case of control measures exclusively based on chemical vector control, neglecting important factors that modulate virus transmission dynamics, especially those related to social determinants of spatial occupation, lifestyle, and living conditions<sup>26,27,28</sup>. As implemented, the programs have been weak, with limited impact on health education, social communications, or community participation. Investments in sanitation have also been insufficient in light of the needs in large cities. The questionable results obtained by vector control programs have led to discussion about their possible abandonment, since paradoxically, the short-term reduction of mosquito density does not prevent the outbreak of explosive epidemics<sup>22,26</sup>. It is thus appropriate to consider not supporting a program that requires large amounts of resources to achieve a sustained effective control. This is a controversial subject, because it involves ethical issues due to the lack of other preventive measures.

If a firmly established decision favors the continuation of vector control, the program must include permanent mobilization of society, allocation of sufficient human resources, availability of long-term budget and financial funds, and actions that minimize the adverse effects of environmental contamination by insecticides. All these requirements should be closely related to the desired epidemiological impact, aimed at continuous, contiguous, and universal action in all regions. The magnitude and severity of dengue in Brazil and the difficulties in controlling the disease indicate the need for research, especially directed towards developing new vector control technologies, which in turn determine the reduction of the vector population to levels incompatible with viral transmission.

#### **Occurrence patterns and control difficulties: research needs**

Despite attempts develop models for predicting dengue epidemics, there are still no tools allowing a secure short-term prognosis. The complexity of infection dynamics involving four serotypes, the peculiarities of the human immune response, the high vector competence of *A. aegypti*, and environmental characteristics

of urban areas require advances in the current level of knowledge in order to allow predictions firmly based on scientific data and improvements in the disease's prevention.

It has been shown that shortly after a recent introduction and circulation of a virus serotype, an epidemic outbreak occurs. In addition, a repetitive pattern of dengue epidemics and evolution of case waves, in which a period of low incidence has followed a two-year peak, indicates that a reduction in incidence was due more probably to the decrease in the number of susceptible individuals than to control measures. Although vector control was presumably more consistent for the severe 2002 epidemic and the heavy rainfall in Southeast Brazilian cities during the first semester of 2003 may have contributed to decreasing mosquito density, the high attack rates in the previous year could be related to a rapid reduction in the susceptible population. The apparently different patterns observed in 1994 and 1998 actually reflect the progression of DEN-1 and DEN-2 into urban populations previously free of the disease. In fact, a closer look at dengue occurrence by municipalities generally reveals biennial epidemics that presented a reduction in incidence, regardless of whether control interventions were implemented.

An important tool in dengue epidemiological surveillance is to monitor viral circulation, identifying the genetic characteristics of the distinct serotypes, which in turn has been demonstrated to be an important factor for determining the magnitude and severity of epidemics. Investments should aim to strengthen the technical and operational capability of health services and laboratories, notably those responsible for research to expand knowledge in the area.

Key examples of this pattern have been recorded in Salvador, Bahia State, in the Northeast region (1995-1996) and Vitória, Espírito Santo, in the Southeast (1997-1998). Upon entering the Brazilian territory, DEN-3 encountered high vector infestation levels in most cities. This may explain the pace and intensity of this serotype's dissemination, favoring the occurrence of the largest and most severe dengue epidemic recorded in the country. The recurrent epidemic pattern may have resulted from intense viral circulation in a previously non-immunized population for a given dengue serotype in places with high vector density. Therefore, the country is still exposed to further epidemics due to the DEN-4 serotype at a moment in which dengue caused by the other three serotypes has become endemic.

Given the enormous challenge of controlling dengue infection, the World Health Organization has prioritized the development of a specific vaccine<sup>1,29</sup>. Efforts have been made in several countries for over a decade, and candidate virus-attenuated and genetic-variant based vaccines are already being tested<sup>30,31</sup>. However, the complexity of human immune response to four different serotypes has limited the progress with a secure and effective immunogen to allow for a population-wide immunization trial.

Thus, vector control programs will continue to be the sole option for long-term control of the disease, although the evolution of dengue in Brazil and other countries has demonstrated the limited effectiveness of this strategy, in addition to the major public health expense, especially for developing countries. In fact, high dengue serological incidence (56.0%) was observed in Salvador, even in areas where vector control interventions were being carried out and the level of domiciliary vector infestation was below 3.0%, indicating that control of viral circulation will be achieved only when the infestation rate falls close to zero<sup>16</sup>. These findings agree with data gathered in other contexts<sup>22,26</sup>. Currently, such interventions are concerned mainly with the elimination of the mosquito's larval stage and complementarily its winged form. However, *A. aegypti* eggs submitted to adverse hatching conditions remain viable in the environment for over one hundred days. This resistance and the mosquito's great ability to adapt to the urban environment significantly hinder efforts to reduce and maintain the vector population at the extremely low levels required. In addition, operational strategies for larval control and entomological assessment require a large number of trained personnel, systematic domiciliary visits including inspection of all rooms in the household, and the use of larvicides that cause environmental contamination. Entomological indicators applied by such programs, usually based on larval surveys, may also not be the most appropriate for dengue epidemiological surveillance<sup>32</sup>.

In attempting to expand the knowledge on dengue control, two approaches should be prioritized. The first is the search for new community participation strategies to reduce the number of potential *A. aegypti* breeding sites. There is evidence that education and communication strategies currently used in vector control programs are efficient to motivate the assimilation of knowledge, but generally do not permanently modify habits and practices that tend to maintain breeding sites<sup>22</sup>. The other is financing interdisciplinary projects with researchers from anthropology, education, geography, and epidemiology to consider issues like social organization of space, specificities of public versus private spaces, culture, education, and continuous participation by the population.

More research is needed on the development of new methods for eliminating vector eggs and winged forms, as well as more sensitive entomological risk indicators. This will require comprehensive research including different areas of biology, entomology, virology, chemical ecology, and epidemiology. Besides the impact evaluation of control strategies in relation to viral circulation in human populations, the research should pay special attention to environmental issues. The traditional epidemiological surveillance model, based on passive case reporting, may also not be sensitive enough to detect the results of vector control measures. When local surveillance is active, launching control measures after an increase in incidence does not generally block epidemics, due to the disparity between the agent's transmission force and the low effectiveness of available vector control methods.

While waiting for an effective and safe vaccine, better perspectives for dengue control will only be found if applicable results are obtained from research based on the three pillars mentioned above: improvement in health education, new models and methods for epidemiological and virological surveillance, and strategic technologies for interrupting transmission based on direct, specific vector control.

## Resumo

*As epidemias de dengue são responsáveis por milhões de casos e óbitos no mundo, anualmente. O alto nível endêmico desta doença está relacionado à elevada infestação domiciliar pelo Aedes aegypti e infecções humanas pelos diferentes sorotipos do agente. Este estudo analisa os casos registrados no Brasil, descrevendo os padrões da evolução da incidência e sua distribuição espacial. Observou-se que as curvas epidêmicas delineadas após a introdução de cada sorotipo do vírus, e a redução da população de susceptíveis, possivelmente, foram responsáveis pelo declínio das epidemias. Expansão das áreas afetadas e aumento de casos de febre hemorrágica do dengue com alta letalidade foram observados em anos recentes. Esforços baseados apenas no combate vetorial químico têm sido insuficientes para impedir a circulação viral. Evidências demonstram que ações de educação não modificam permanentemente hábitos da população. Enquanto não se dispuser de vacina efetiva para a sua prevenção, o controle dependerá de potenciais resultados de pesquisas interdisciplinares e de mudanças ambientais que dificultem a reprodução do vetor, educação e participação comunitária, vigilância epidemiológica e virológica, e inovações tecnológicas estratégicas com o objetivo de interromper a transmissão.*

*Dengue; Febre Hemorrágica do Dengue; Incidência*

## Contributors

All the authors participated in the article's conceptualization. M. G. Teixeira and M. C. N. Costa wrote the first draft, which was reviewed and received original contributions from the other two authors (M. L. Barreto and E. Mota). All four authors reviewed and approved the final format.

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