Dengue in Brazil: Epidemiological situation and Contribution to a Research Agenda

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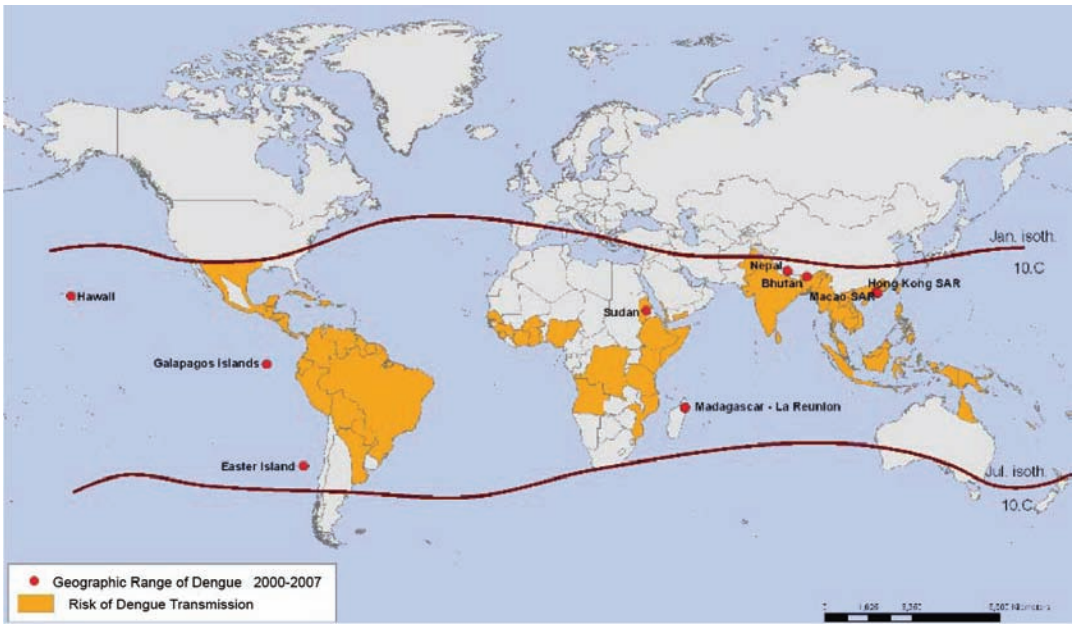
Introduction

The clinical and epidemiological characteristics peculiar to dengue in Brazil have aroused the interest of Brazilian and international public health agencies and researchers, because of the importance of identifying the factors that determine the distinct individual and collective expressions of these infections, to allow improved treatment and control. In terms of the number of cases, dengue is the world's second most important illness transmit by vector. (Dengue, 2007).

Dengue is distributed over a broad strip above and below the Equator, from 35º N to 35º S latitudes (Figure 1). Until the mid 1990s, Southeast Asia was the region most affected by dengue (Teixeira et al., 2008). Since then, the countries of Central and South America began to stand out and now have much more than half of the world's reported cases of this disease. In 1998 alone, Brazil registered more than 700 thousand cases (ibid).

In order to understand various factors related to the course of this disease, important differences found in the epidemiology of dengue between these two regions, have been identified, highlighted by the lower proportion of cases of dengue hemorrhagic fever (DHF) in the Americas given the high incidence of cases of DF (Halstead, 2006; Teixeira et al., 2005). Another difference between the regions concerns the age group of greatest risk. While in Southeast Asia dengue is predominantly a childhood disease, in Brazil, until 2006, the incidence of dengue fever, of dengue hemorrhagic fever and of even the inapparent infections from this agent were much higher in adults (Halstead, 2006; Siqueira-Jr. et al., 2005, Teixeira et al., 2005). However, in the epidemic that exploded in the summer of 2008in the municipality of Rio de Janeiro, Brazil's second largest urban center, there was a sharp rise of the disease among children younger than 15, both of DF as well as DHF (Barreto & Teixeira, 2008). Nevertheless, this shift in age had been occurring less visibly in the hospitalizations for DHF in 2007, for the country as a whole (Teixeira et al., 2008).



Source: http://gamapserver.who.int/mapLibrary/Files/Maps/World_DengueTransmission Extension 2007.png. Accessed: Oct. 10, 2008.
Figure 1 – Global region of risk for dengue.

The increase in the incidence of dengue has been a growing object of concern for society and particularly for healthcare authorities, due to the difficulties confronted in the control of the epidemics produced by this virus and by the need for expanding the installed capacity of health care service to attend to the individuals afflicted with serious cases, in particular DHF. A concrete and quite current example is the epidemic referred to in the municipality of Rio de Janeiro in 2008, which affected other cities of this state, where there were more than 240 thousand cases of DF (an incidence of 1,527/100 thousand residents), more than 11 thousand hospitalizations, 1,364 cases of DHF, 169 confirmed deaths and more than 150 other deaths under investigation. Nearly half of the cases of DHF took place among children younger than 15 and the risk of death was five times greater in children (Rio de Janeiro, 2008).

The purpose of this article is to present the situation and principal epidemiological characteristics of dengue in Brazil, the difficulties in its control and the challenges to the scientific research guided to complete the existing gaps in knowledge, which is essential for the development of control options.

The virus and its transmitters

The etiological agents of yellow fever and of dengue were the first microorganisms to be denominated as viruses in 1902 and 1907, respectively, and were described as filterable and submicroscopic agents. The isolation of the dengue virus only took place in the 1940s, by Kimura in 1943 and Hotta in

1944, with the strain being denominated by Mochizuki. Sabin and Schlesinger, in 1945, isolated the Hawaii strain and in the same year were the first to identify another virus in New Guinea. They observed that the strains had different antigenic characteristics and worked with the hypothesis that they were serotypes of the same virus. The first strains were denominated serotype 1 and that from New Guinea, serotype 2. In 1956, in the course of the hemorrhagic dengue epidemic in Southeast Asia, serotypes 3 & 4 were isolated (Martinez-Torres, 1990). Since then, the dengue complex is formed by four serotypes, currently designated: DENV-1, DENV-2, DENV-3 and DENV-4, which belong to the *Flaviviridae* family.

In the Americas, the *Aedes aegypti* is the only transmitter of this virus of epidemiological importance. This mosquito species originated in subSaharan Africa, where it domesticated and adapted to the urban environment, becoming anthropophylic, and its larvae were found in manmade deposits. This adaptive process has allowed its fast spatial diffusion utilizing a wide variety of transportation vehicles and its explosive growth in urban areas. The *Ae. Aegypti* was eradicated from the Mediterranean in the 1950s and from much of the Americas in the 1950s and 1960s. Nevertheless, there was reinfestation in most of the areas where it had been eradicated and today this vector is considered a "cosmotropical" species (Rodhain & Rosen, 1997). Its capacity for adaptation has been found to be expanding, because in 1987, it was found surviving in areas 1,200 meters above sea level (Herrera- Bastos et al., 1992). Contrary to what was previously believed, the *Ae. Aegypti* is capable of making multiple ingestions of blood during a single gonadotrophic cycle, which expands its ability to become infected and transmit the virus (Scott et al., 1993). In addition, in a single ovipositioning cycle the female places the eggs in various recipients, guaranteeing the survival and the dispersal of its offspring, which has been called ovipositioning leaps .

Another mosquito that has been found to have potential to transmit the dengue virus is *Ae. albopictus*. In the Americas, this mosquito has not been involved in its transmission, although the natural infection of this vector by the virus has been observed in specimens collected during an outbreak in the city of Reynosa, Mexico, in 1997 (Ibánez-Bernal et al., 1997). This species originated in the Asian jungles and until recently was restricted to that continent. In recent years, due to intense intercontinental maritime shipping of tires, the *Ae. albopictus* was disseminated to the Americas, and was initially detected in the United States in 1985. It was detected in Brazil in 1986, where it has been found in more than 1,000 municipalities. This vector is not domestic, as is the *Ae. Aegypti*. It prefers to deposit its eggs in tree hollows and has diurnal anthropophilic and zoophilic habits outside of homes. Its vectoral competence is being studied, given that its habits can establish a link between the cycle of the dengue virus in monkeys and in humans, in addition to having references to its responsibility for the transmission of epidemic outbreaks of

classic and hemorrhagic dengue in Asia (Metselaar et al., 1980; Ibánez-Bernal et al.,1997).

Conditional factors of viral circulation

There is a very complex inter-relation of the factors involved in the circulation of the four dengue virus serotypes. This generates confusion and uncertainties in various fields of knowledge, especially concerning the determinants of its clinical and epidemiological presentations, which are pleomorphic. Thus, grave epidemics have occurred, such as that in Southeast Asia, where the hemorrhagic forms have been frequent (Gubler, 1997;Halstead, 2006); the classic epidemics considered benign, such as that of 1979, in Cuba, caused by the DENV-1 serotype, were soon followed by another, in 1981, linked to serotype DENV-2, which was surprisingly grave, with thousands of hemorrhagic cases (Kouri et al., 1986). In contrast, the first epidemics in large urban centers were followed by others, in the same areas, provoked by the agents belonging to different serotypes (DENV1 and DENV2), with few reports of hemorrhagic dengue for more than 10 years (Teixeira et al., 2005).

The principal determinants of the clinical epidemiological expression of the infections caused by the dengue virus are systematized in Figure 2. To explain the phenomena involved in the production of these infections, in addition to the factors indicated, Teixeira et al. (1999) highlighted the importance of the form of social organization of the geographic spaces of the urban centers, the way of life of their populations and its reflections in the environment that provide the conditions for the proliferation of the vector of this agent (Kuno, 1995; Teixeira & Barreto, 1996; Costa & Teixeira, 1999).

Conditional factors for the occurrence of the hemorrhagic forms

The occurrence of the hemorrhagic forms of dengue, have in part been explained by the presence of antibodies due to sequential infections by different dengue serotypes. According to this theory, in the presence of antibodies against one serotype, after a second infection, the immunological response of the sensitized individual favors the replication of the new infectious sorotype. by the second infection (Antibody dependent enhancement-ADE) (Halstead, 1981, 2006). Although there is some clinical and epidemiological evidence (Bravo et al., 1987a) that corroborates this hypothesis, it has been observed that other factors can also be related to the clinical manifestations of the hemorrhagic forms of dengue, such as the virulence of the strains of the comorbidity agent, genetic, nutritional and others (Bravo et al., 1987a, 1987b; Guzman & Khouri, 2002; Blanton et al., 2008).

Dengue in the world

The evidence from the epidemics attributed to dengue reported before the period of the development of viral isolation techniques leave doubts if the

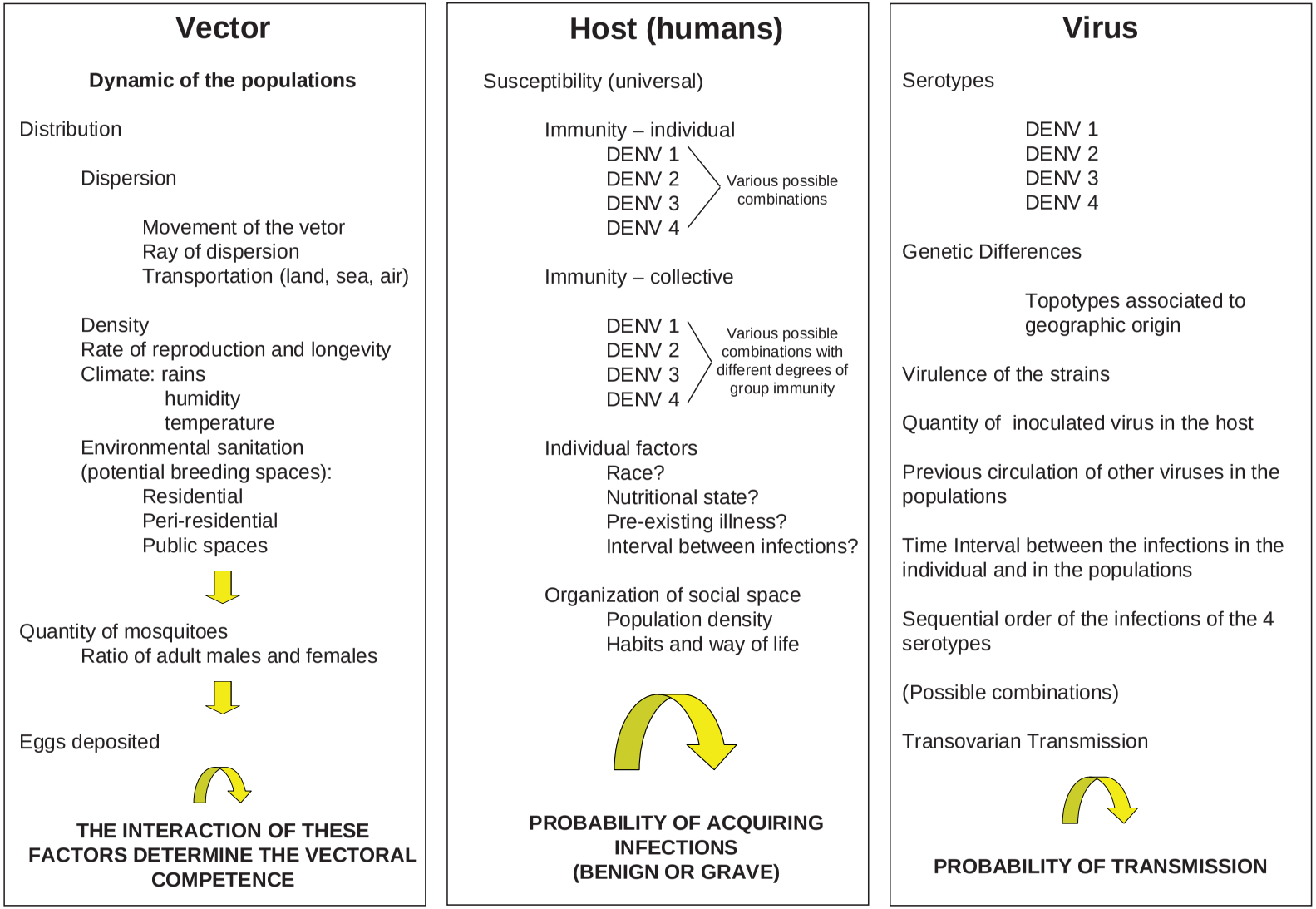


Figure 2 – Factors related to the vector, to human beings and to the virus that modulate the transmission and circulation of the dengue virus.

dengue virus was the etiological agent and if they were provoked by one or more serotypes of the same strain (Teixeira et al., 1999). Descriptions of the clinical situation of the epidemics compatible with this illness are reported in a Chinese encyclopedia dated from 610 d.C. Epidemic outbreaks of a highly feverish disease in the western French Indies, in 1635, and in Panama, in 1699, have been related to dengue, although without much consensus whether it was caused by this etiological agent or by the Chikungunya virus. It is believed that the best documented occurrences before the isolation of the agents are that of Philadelphia (1778) and the Island of Java, in Jakarta, and of Egypt, in 1779 (Martinez-Torres, 1990).

From the late 18th century until the first two decades of the 20th century, there were eight pandemics and or isolated outbreaks of dengue, which lasted from three to six years, which affected different parts of the world: the Americas, Africa, Asia, Europe and Australia (Howe, 1977). It appears that when the means of transport were slower than those today, the circulation of a single serotype persisted in a given area for some years, causing periodic epidemic outbreaks, possibly modulated by the reposition of the susceptible cohorts (Gubler, 1997).

For many centuries, dengue was considered a benign disease, but after World War II, it began to exhibit other characteristics, because the war caused the circulation of various serotypes in a single geographic region, which favored the occurrence of a grave hemorrhagic fever, which was later related to a serious form of dengue. The first outbreak of DHF was recorded in 1953 in the Philippines, and was confused at that time with yellow fever and with other hemorrhagic fevers. Only in 1958, with the epidemic in Bangkok, Thailand, was it confirmed that it was a hemorrhagic disease caused by the dengue virus, (Martinez-Torres, 1990).

After that, various Southeast Asia countries were hit by DHF epidemics, such as South Vietnam (1960), Singapore (1962), Malaysia (1963), Indonesia (1969) and Burma (currently Mynamar) (1970). In the 1980s and 1990s, the situation became more serious not only with the geographic expansion of the virus to India, Sri Lanka, the Maldives and eastern China, among other countries, but also by the rise in the magnitude of the epidemics, hyperendemic circulation among these events and records of thousands of cases and deaths from the hemorrhagic forms of the disease, predominantly in children (Gubler, 1997).

After twenty years without registration of the disease, in 1964, DENV-3 was found circulating in Tahiti, in the South Pacific, and it disseminated to other nearby islands. Another outbreak, with the same serotype as agent, revealed that this micro-organism continued to circulate on that island, in an endemic form, for five years. Then, DENV-2 was introduced in this region of the Pacific with outbreaks detected in various other islands and in 1975 DENV-1 was also isolated in this region. In Australia, reports of dengue have been made since 1800, with multiple epidemics occurring until 1955, after which there were no reports for quite some time. Then, in 1981, the virus reappeared in this country causing

epidemics in various cities where the four serotypes of the virus were isolated. The disease is not currently disseminated in Australia, because the viral circulation is restricted to the north of Queensland.[1]

Dengue in the Americas

Dengue occurred in the Americas in the 19th century, until the first decades of the 20th century, when there was an epidemiological silence. In 1963, the re-emergence of DENV1 and DENV2 was detected, associated to the occurrence of epidemics of classic dengue. In this decade, only four countries reported cases, rising to nine countries in 1979. Nevertheless, the large scale outbreak of dengue on the American continent took place in the 1980s, when 25 countries reported circulation of the virus in a rapidly growing trend. In 2002, the largest continental pandemic hit 69 American countries, with more than one million cases of DF reported. The dengue virus now circulates from the southern United States to Argentina, although it is most intense between the 35th north and south parallels. (WHO, 2008).

Dengue in Brazil

Since 1846, there have been reports of dengue epidemics in Brazil, particularly in the period from 1846 - 1853, in São Paulo and Rio de Janeiro. But the first reports in the scientific literature date to 1916 (Meira), in the city of São Paulo, and in Niterói in 1923 (Pedro, 1923). In 1928, a French ship with suspected cases arrived at Salvador, Bahia, but the virus did not circulate among the city's population (Soares, 1928).

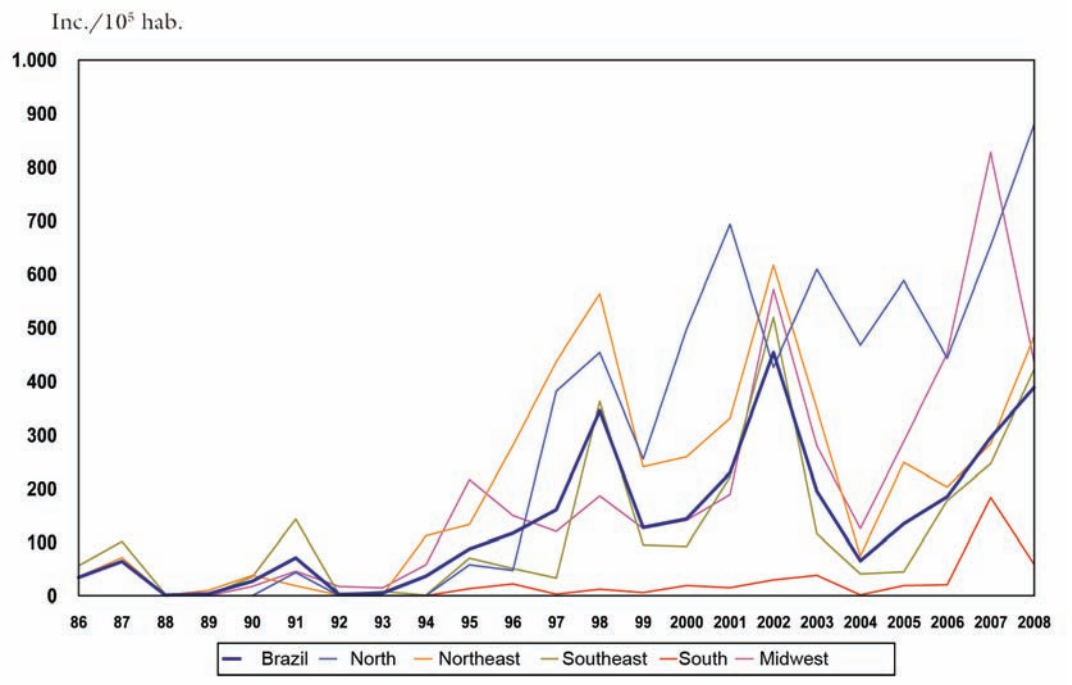
In 1953-1954, a serological investigation conducted in residents of the Brazilian Amazon found antibodies against the dengue virus, leading to the hypothesis that the virus had circulated in this region (Causey & Theiler, 1962). But the first evidence of a dengue epidemic in Brazil was in 1982 when DENV1 and DENV4 serotypes were isolated in Boa Vista, Rondonia. A serological study of this epidemic revealed that 11 thousand people were infected by the dengue virus in this episode (Osanai, 1984). It is possible that these serotypes were introduced by land from the Caribbean countries and from the north of South America, over the Venezuelan border. This epidemic quickly weakened and the virus did not extend to other regions because the *Ae. aegypti* was still not dispersed through Brazilian territory, and the combat of this vector in a few months practically eliminated it from the city of Boa Vista (Donalísio, 1995).

The DENV-1 serotype was reintroduced in Brazil in 1986, when it was isolated in Nova Iguaçu, a city in Rio de Janeiro State that is part of the country's second largest metropolitan region. Since then, dengue disseminated with surprising transmission strength to neighboring cities , including Niterói and Rio de Janeiro. In that first year of 1986 alone, more than 33,500 cases were reported, and in 1987 nearly 60 thousand, and the rates of incidence reached more than 276 and 490 per one hundred thousand residents, respectively in each

year. In 1986 it also reached Ceará and Alagoas with incidences of 411.2 and 138.1 per 100 hundred thousand residents respectively; and in 1987, spread to Pernambuco, where there were 31.2 cases per 100 hundred residents. São Paulo, Bahia and Minas Gerais States were hit by outbreaks in small cities (Teixeira et al., 1999).

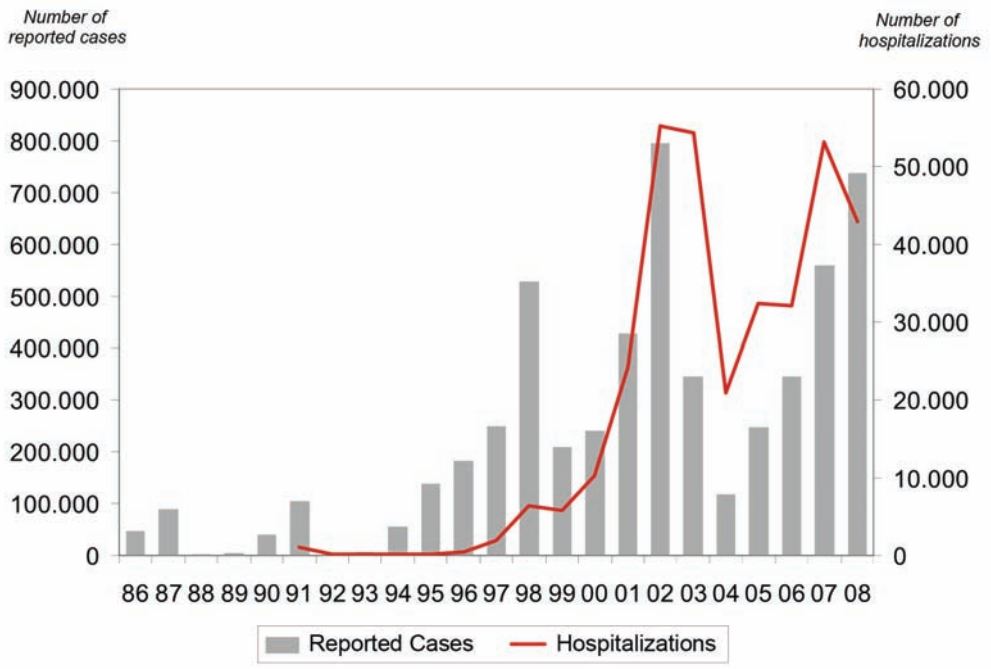
In 1986-1987 only DENV1 circulated, the epidemics were of DF, and then there was a two-year period characterized by low endemnicity of the disease. A resurgence of the disease, in proportions considered high at that time, began in 1990 (Figre 3), caused by an increase in the transmission of DENV-1 and introduction of DENV-2, also in Nova Iguaçu. The incidence in Rio de Janeiro reached 165.7 per 100 thousand residents, in that year and in 1991, 613.8 cases per 100 thousand residents. The entrance of DENV-2 brought the first diagnoses of DHF in the country when 462 cases and eight deaths were confirmed (Teixeira et al., 2005; Siqueira-Jr. Et al., 2005).

In the first years of the 1990's, dengue remained restricted to cities in Rio de Janeiro, Ceará, Alagoas and Pernambuco States, with few reports of cases from Mato Grosso and Mato Grosso do Sul (Teixeira et al., 1999). In the following years, the viral circulation (DENV-1 and DENV-2) quickly grew to other areas of Brazil, accompanying the expansion of its mosquito vector, the *Aedes aegypti*, and with simultaneous circulation of two serotypes (Figure 4).



Source: SVS/MS.
* Partial data for 2008.

Figure 3 – Annual incidence of dengue per region of the country. Brazil, 1986-2008.*

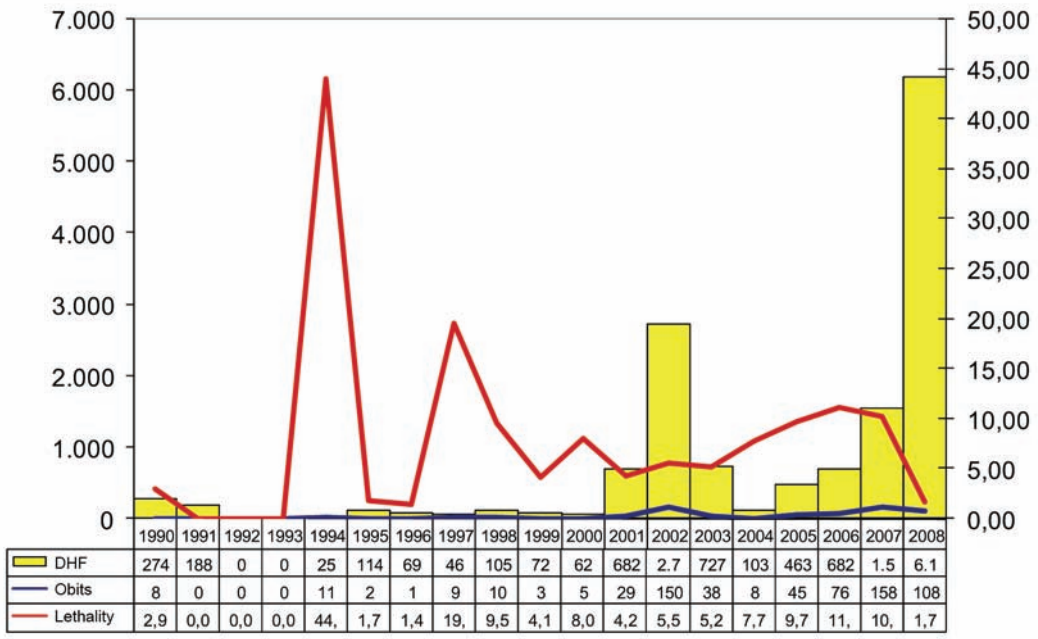


Source : SVS/MS.

* partial data for 2008.

Figure 4 – Reported cases of dengue and hospitalizations, Brazil and regions, 1986-2008.*

In January 2001, the introduction into the country of the DENV-3 serotype was confirmed, isolated from an individual living in Rio de Janeiro and who had become sick in the previous year (Nogueira et al., 2005). This serotype was responsible for the epidemic in 2002 in Brazil, when approximately 800 thousand cases were reported, or that is, nearly 80% of the cases on the American continent. After this year, there was a drop in the rate of reported cases, until 2005, when they began to grow again. (Figure 2) In 2008, preliminary data revealed that more than 700 thousand cases and more than 45 thousand hospitalizations for dengue were recorded by the Ministry of Health (Figure 4). The trend in hospitalizations recorded in the SIH-SUS system reflects the occurrence of grave cases, which, in general, accompany the incidence of the reported cases (Figure 5). Since 1988, there has been strong growth in hospitalizations for DHF (Teixeira et al., 2008). It should be considered that the rigid diagnostic criteria for confirmation of cases, established by the World Health Organization (WHO) and adopted by Brazil, could be underestimating the incidence of serious forms of the disease. From 1990, to June 2008, 8,885 cases of hemorrhagic DHF were included in the System of Epidemiological Inspection of which 995 (10.7%) occurred from 1990 and 2000. The rest (7,980 cases) occurred since 2001 and the first half of 2008, or that is, after the introduction of DENV-3. Among these cases, 661 deaths were observed, representing an average lethality of 7.4% (Figure 5). Another important factor related to DHF in Brazil is that until 2006, the cases predominated among people from 20- 40 years old, while in 2007, 53% of the cases occurred in those younger than 15 (Teixeira et al., 2008), a change that was maintained in the first half of 2008 (Barreto & Teixeira, 2008).



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
DHF	274	188	0	0	25	114	69	46	105	72	62	682	2.7	727	103	463	682	1.5	6.1
Obits	8	0	0	0	11	2	1	9	10	3	5	29	150	38	8	45	76	158	108
Lethality	2,9	0,0	0,0	0,0	44,	1,7	1,4	19,	9,5	4,1	8,0	4,2	5,5	5,2	7,7	9,7	11,	10,	1,7

Source: SVS/MS.

* Partial data for 2008.

Figure 5 – Confirmed cases, deaths and lethality rate of hemorrhagic dengue. Brazil, 1986-2008.*

Prevention and control

The lack of an effective and safe vaccine, the strength of the morbidity of the infection agent and the high vectoral competence of *Ae. aegypti*, a vector well adapted to densely populated urban environments, where the insufficient infrastructure and lifestyle of the population generate ideal habitats for this mosquito, make the prevention of dengue a formidable task nearly impossible to be achieved with the current means available. The objective of the current control measures is to eliminate this mosquito in its different phases; although in general, the effectiveness of these interventions has been very low, and they have not been able to contain the dissemination of the virus and epidemics continue in large and recently also in small urban centers (Dias, 2006). We also have to consider that, not only are the control actions poorly effective, they involve high costs and have unfavorable implications related to the environmental impact of insecticides.

In 1986, possibly because of the lack of funds, the American countries placed emphasis on the control of the mosquito population, instead of its eradication, despite a lack of solid scientific evidence that simply reducing the density of the *Ae. aegypti* would lead to control of the disease (Teixeira & Barreto, 1996). It was expected that lowering the vectoral infestation would reduce or even block transmission. However, data from a control progam in Singapore in 1991 show that the dengue virus has the ability to circulate even in

places with low vectoral density (Newton & Reiter, 1992), an observation that was later made in Brazil. (Teixeira et al., 2002).

The rapid expansion of the infestation of the dengue vector throughout the Brazilian territory since the second half of the 1980s (Figure 6), in addition to revealing that the control strategies adopted were ineffective, created epidemiological conditions for the appearance of dengue epidemics. This is combined with the fact that the transmission agent currently circulates in more than 70% of Brazilian territory (Dias, 2006). In 1996, a project was prepared with efforts on various fronts aimed at eradicating the vector. Associated to specific actions to combat the mosquito, the project included interventions in essential urban policies that would lead to remove the sustainability for the establishment, reproduction and expansion of the vector. In addition to the chemical combat of *Ae. aegypti*, strategies and goals were planned in the areas of environmental sanitation, education, information and broad social mobilization.

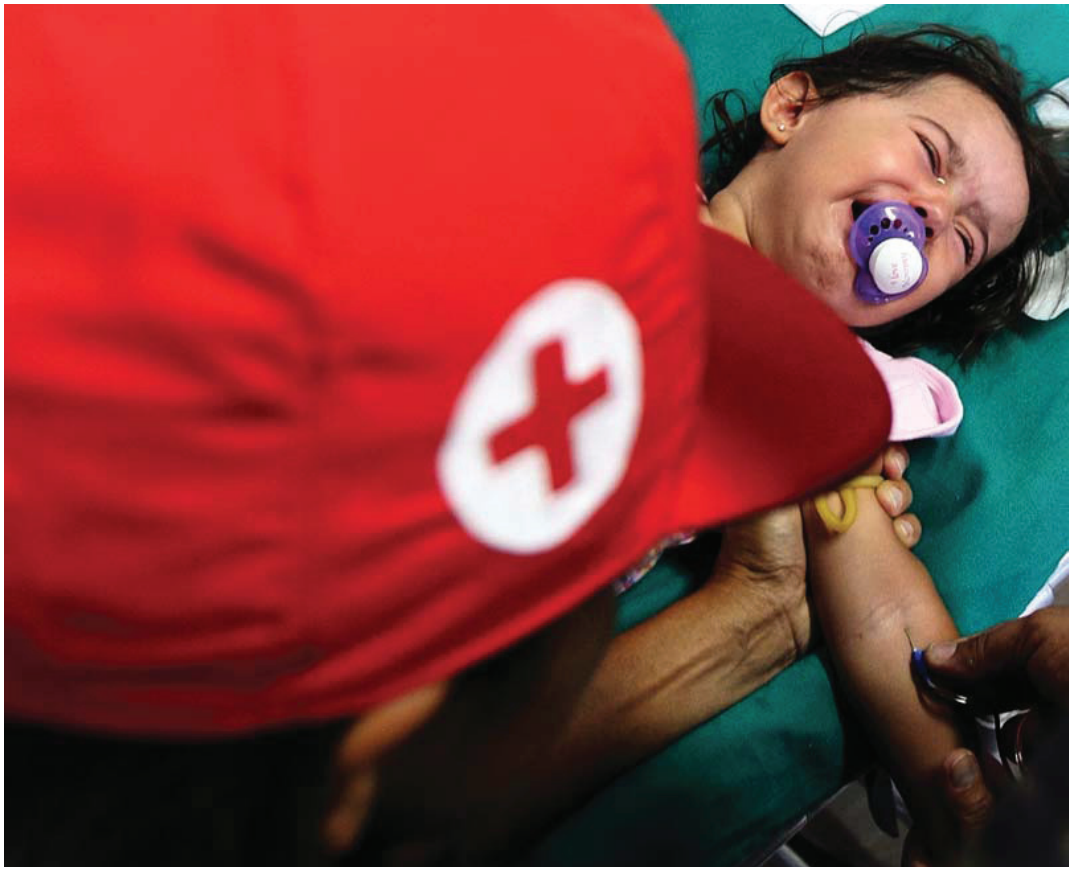
A technically solid project was sought that would be better capable of including broad social support, which required coordinated actions of various spheres of government and strong articulation with civil society. It was understood that its execution would have a positive impact on other health problems related to urban environmental conditions, such as infant mortality, diarrhea, leptospirosis, hepatitis A, cholera, and in turn, would substantially contribute to improvement of the quality of life in Brazil's urban centers (Teixeira & Barreto1996). Nevertheless, political, administrative and financial impediments prohibited its execution, and thus, it was not possible to verify if this proposal would bring the expected results.

In its place, a second project (Adjusted Plan for the Eradication of *Aedes aegypti* – PEAa) was implemented, which did not have the same principles of the previous plan - such as universal coverage in each territorial space, synchronicity and simultaneous actions . It also did not include funds to realize two of the three essential components (sanitation, education and social mobilization) of the previous project, and was reduced to direct combat of the vector. Thus, from 1997-2001, the execution of the PEAa consisted nearly exclusively in chemical combat of the vector, causing continued expansion of the area inhabited by the vector, and the maintenance of high levels of residential infestation, especially in the larger and more complex urban centers.

Given this situation, in 2002, the Ministry of Health emphasized a more efficient control strategy, which established the goal of reduction of rates of infestation of residence to levels lower than 1%, increasing the financial resources for the program and decentralizing its actions to the municipalities, through fund-to-fund pass-alongs. Despite these efforts, the dengue epidemics continued, DENV-3, introduced in 2001, disseminated to municipalities in 25 of Brazil's 26 federal districts in less than three years. In the first semester of 2008, the epidemic that hit Rio de Janeiro state caused panic, insecurity and political-

institutional disputes, particularly due to the gravity with which the disease hit children (International..., 2008; Barreto & Teixeira, 2008).

Photo Agência France Presse/Antonio Scorza – April 2, 2008



Doctor removes a blood sample from child suspected of dengue in Rio de Janeiro.

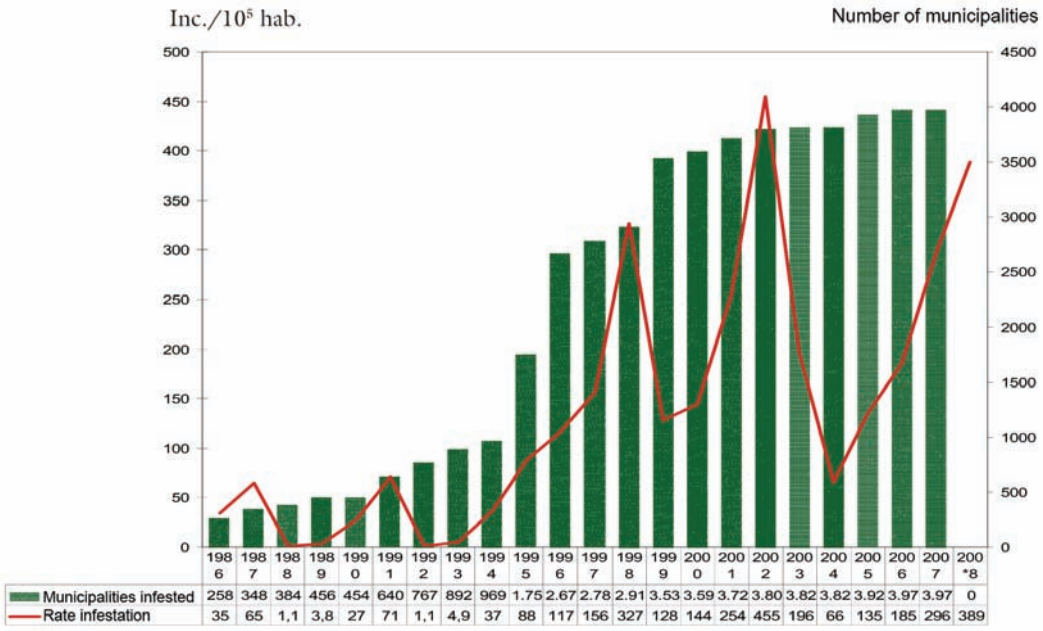
Contributions for the definition of a research agenda

The magnitude and the gravity of dengue in Brazil and in various other tropical countries and the difficulties confronted to control it indicate the urgent need for investments in research (Farrar et al., 2007), especially that aimed at reducing the lethality of this disease and for the development of new technologies aimed at the control of *Ae. aegypti*, seeking the reduction of the population of this vector to levels incompatible with the viral transmission.

Because of the gaps in knowledge and the difficulties in control indicated, a research agenda should be conducted that is focused on four broad lines of action:

a) Strengthening knowledge about the dynamic of infection and the improvement of antivectoral actions.

The actions for the elimination of the vectors have been aimed at the elimination of the larva of the existing breeders (using larvicides), to reduce potential breeding spaces where female mosquitoes can deposit eggs, and in a



	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	*8
Municipalities infested	258	348	384	456	454	640	767	892	969	1.75	2.67	2.78	2.91	3.53	3.59	3.72	3.80	3.82	3.82	3.92	3.97	3.97	0
Rate infestation	35	65	1,1	3,8	27	71	1,1	4,9	37	88	117	156	327	128	144	254	455	196	66	135	185	296	389

Source: SVS/MS.
* Partial data for 2008.
Figure 6 – Incidence of dengue and municipalities infested with Aedes aegypti. Brazil,

complementary form, at the use of insecticides to reduce winged forms of the vector, by detecting, in each space, the risk of increased transmission of the dengue virus (Brasil, 2002; Ooi et al., 2006). Activities for mobilizing the population are also undertaken through the mass media and multiple educational techniques used to disseminate information and conduct collective actions (community work projects, D Day, dengue prevention weeks, folders, posters, etc.) in order

to raise the awareness of individuals of the need to maintain residential and peri-residential environments free of potential breeding space for the vector. Nevertheless, recent studies have revealed that while these initiatives do raise the level of information about transmission of the disease, they generally do not permanently modify the habits and practices of individuals in order to maintain environments free of breeding spaces (Rangel-S, 2008). What has been found is that the antivectoral programs, even when undertaken in accord with that called for in scientific and technical documents issued by the WHO and other Brazilian and international organizations, are not achieving the expected results, and that the scientific and technical principles that guide these manuals do not have significant advances when compared with those that guided the campaigns to combat *Ae. aegypti* in the first half of the 20th century, which had as their object to eradicate urban yellow fever.

It has been observed that, after the introduction of one given serotype of dengue virus in a certain location, there is an epidemic explosion with high rates

of incidence and a large number of cases (Barreto et al., 2008). If it is possible to make reasonable predictions about the conditions that affect the unleashing of this process, perhaps more effective prevention strategies could be prepared and implemented. Nevertheless, despite the attempts made to develop models for forecasting occurrence of dengue epidemics, there are still no elements that allow a safe short term prognosis. The complexity of the dynamic of an infection that involves four serotypes, the peculiarities of the human immune response, the high vectoral competence of the *A. aegypti* and the environmental characteristics of the modern urban centers, require advances in the current level of knowledge that allow predictions based on scientific evidence. Efforts have been made using resources derived from the analysis of complex systems that include the possibility of capturing a series of elements that vary dynamically in a scenario as complex as an urban center. Nevertheless, despite efforts and attempts made until now, the models still have limitations (Santos et al., 2008).

b) Studies of the risk factors related to the occurrence of grave forms and their relations with the physiopathogeny of the disease.

The current literature only suggests some hypotheses about the causal mechanisms (for example, the hypothesis of sequential infections) and some individual risk factors that increase the chance of their occurrence (some chronic diseases, allergic diseases, white ethnicity, etc.). Nevertheless, the level of existing evidence still does not form a complete view of the problem much less help its prevention.

Thus important gaps remain in the knowledge of those factors that lead to the grave forms of dengue, particularly DHF. These gaps are related both to the physiopathogenic mechanisms (Halstead, 2007) and to the risk factors that impede the development of measures for prevention and management of these cases. Considering the uncertainties about these factors that determine the evolution of a case of DF into DHF, various hypotheses have been raised, linked to the virus, (Chen et al., 2008), to the individual (Nguyen et al., 2005) or to genetic factors (Blanton et al., 2008;Sakuntabhai et al., 2005). To the degree that there is an increasingly clear risk that future epidemics can be accompanied by growing numbers of DHF cases, the level of existing evidence still does not allow a complete understanding of the problem, indicating the pressing need for research in this direction.

c) Improvement in diagnosing dengue, and in the management and treatment of severe forms.

The suspect of hemorrhagic forms of the disease, in general, are only made between the fourth and sixth day from the beginning of clinical manifestations of classic dengue, when the denominated warning signs become manifest (abdominal pain, falling blood pressure, dizziness, bleeding, and others). There is still no specific and effective treatment against the virus, and in most cases, hospitalization of patients is not indicated in the first days of clinical manifestations of classic dengue. When these warning signs mentioned arise, most

patients are not in the health unit, creating a time lapse between the recognition of these danger signs, (by the afflicted individual or family members) and the initiation of crucial clinical care (rapid hydration), which can lead to the favorable conclusion of the illness. It is noted that some situations (grade IV DHF), can lead to death in a matter of hours. Thus, in terms of treatment, the identification of prognostic factors, such as the presence of comorbidities (Bravo et al., 1987a), biological characteristics such as skin color (Blanton et al., 2008), and others, need to be given priority in the research agendas, because they may contribute to improved triage protocols and clinical handling of dengue.

In spite of recent advances in laboratory tests for specific diagnosis of dengue (Mac ELISA, PCR RT, NS1 antigen, etc.), and the reduction of the time needed to obtain the results of the exams in serious infections (Kao et al., 2005), there are still difficulties in quickly and accurately determining if the individuals were previously infected by other serotypes (secondary infections). New possibilities in this direction should be explored, considering the importance of this knowledge for the understanding of the phyisiopathogeny of DHF, and so that population studies can identify with greater precision the real importance of sequential infections in the occurrence of DHF.

d) Development of vaccines.

Due to the complexity of the infections provoked by the four serotypes of the dengue virus, the development of a safe and effective vaccine for use in populations still must overcome many obstacles and clarify many of the uncertainties that are raised due to the gaps in scientific knowledge about the epidemiology and physiopathogeny of these infections. Although there are some candidate vaccines, for both the attenuated live virus as well as chimericals (Whitehead et al., 2007), which produce immunity for the four serotypes of the virus, serious problems persist related to safety. Doubts remain about the risk of the rise of grave forms of the disease as a consequence of the application of a vaccine in individuals who already have antibodies for one or more serotypes, or who in the future are exposed to infection from the wild virus (Dengue..., 2007; Halstead, 2007). The WHO has been seeking to lead a process that stimulates the advance of research into vaccines against dengue, through the formation of work groups. It is supporting interinstitutional programs and stimulating the provision of finance for research that can contribute to the safe realization of the necessary field studies, and for preparation of protocols and the promotion of meetings to disseminate the latest information and discuss the issues, among other initiatives (Farrar et al., 2007).

Note

1 Available at: <http://www.health.qld.gov.au/dengue/outbreak_update/previous.asp>. Access Oct. 2, 2008.

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ABSTRAT – The epidemiological situation of dengue in Brazil is presented, showing the introduction and spread of the vector and the different virus serotypes in Brazil. At the present time the Aedes aegypti, the vector, and 3 out of 4 existing virus serotypes (DENV-1, DENV-2 and DENV-3) are spread through virtually the entire national territory. The epidemiological picture has been characterized by recurrent epidemics, especially in large urban centers. A new characteristic in this scenario is the growth in the proportion of severe cases, particularly cases of dengue hemorrhagic fever. Existing control actions have been costly and ineffective. In order to meet the gaps in existing knowledge, some elements for a research agenda are presented. Finally, we must recognize that problems such as dengue have their roots in the explosive form urban populations in countries such as Brazil have grown and in the conditions and lifestyles under which these people live.

KEYWORDS: Dengue, Brazil, Epidemiological situation, research priority.

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