Dengue: clinical forms and risk groups in a high incidence city in the Southeastern region of Brazil

Dengue: formas clínicas e grupos de risco em município de alta incidência do sudeste do Brasil

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ABSTRACT

Introduction: The article describes the epidemiologic profile of dengue cases in Vitória, the capital of Espírito Santo, Brazil, from 2000 to 2009, aimed at identifying risk groups regarding the incidence and severity of the disease. Methods: Confirmed cases of dengue among city residents during ten years were classified as dengue fever, dengue hemorrhagic fever, dengue shock syndrome and dengue with complications, and analyzed according to sex, age, race-color and education. Results: The proportion of dengue cases was highest among women aged 20 to 29 years-old and similar between whites and blacks. A gradual decrease occurred in the percentage of dengue cases in the population aged 15 years-old or more, in the historical series of 10 years, and a growing increase in individuals less than 15 years-old, showing statistical significance. The fatality rate ranged from zero to 0.3% for all forms of dengue and from 0.2% to 18.2% for severe forms. Conclusions: The profile of those affected by the disease in the municipality is similar to those affected in Brazil. The increasing number of cases in individuals under 15 years-old corroborates the results of recent studies in other Brazilian municipalities.

Keywords: Dengue fever. Dengue hemorrhagic fever. Risk factors.

INTRODUCTION

Dengue is an acute infectious disease, whose etiologic agent is a flavivirus that has four known serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. The dengue virus is transmitted to humans through the bite of mosquitoes of the genus Aedes, subgenus Stegomyia, and Aedes aegypti is its only vector in Brazil. The disease is currently considered the most important arbovirus in the world in terms of morbidity, mortality and economic implications. In the 21st century, Brazil has become the country with the highest number of dengue cases in the world, with over three million in the period of 2000 to 2007, and currently records the circulation of all four serotypes viruses. The incidence of severe forms has increased in the last few decades and the mortality of the disease is still above acceptable levels. Up to the present, no effective vaccine exists against the disease and infection control is currently restricted to combating the vector.

Infection by any of the four serotypes leads to a similar clinical presentation, which can range from mild forms, such as dengue fever (DF) or classic dengue, to serious and even fatal forms. The main severe form of dengue is dengue hemorrhagic fever (DHF), characterized by bleeding tendency, thrombocytopenia and plasmatic effusion, which can progress to circulatory failure, characterizing dengue shock syndrome (DSS), and death. The immunity conferred by the infection is permanent for the serotype that caused it (homologous immunity), but temporary and partial for the other three serotypes (heterologous). Many studies have attempted to identify risk factors associated with the development of severe dengue forms. Undoubtedly, the main risk factor identified is the presence of a second infection. Other factors associated with the development of DHF are: female sex, white race, age under 15 years-old, previous chronic diseases and the virulence of the viral strain.

In 1995, dengue was introduced to the State of Espírito Santo, located in the Southeastern region of...
Brazil, and to its capital, Vitória14. In the majority of the subsequent years, notification of the disease in the municipality has not failed to occur, reaching incidence rates considered high (above 300 cases/100,000 inhabitants), even so, its epidemiology has never been described. Analysis of the distribution of dengue among residents of Vitória could indicate possible risk factors for the presentation of several clinical forms of the disease and thus indicates more effective strategies for handling the same. This article specifically describes the epidemiological profile of dengue cases and severe dengue in the City of Vitória from 2000 to 2009.

METHODS

Delineation study

This work describes an ecological time series study, in which the frequency of the disease is compared among different groups for the same period, or in the same population at different points in time. In this type of study, the variables are attributes present in the population studied, which are quantified in order to characterize risks to a specific damage15,16.

Description of the study area

Vitória, the capital of Espírito Santo, is a coastal city 93.38 sq km in extent, consisting of Vitória Island and 34 smaller islands and a mainland portion. The municipality is part of the Greater Vitória Metropolitan Region, which concentrates 46% of the state population. The population census of the capital in 2000 was 282,606 inhabitants and the estimated population for the year 2009 was 320,156 inhabitants. The municipality has 79 districts, eight administrative regions and six healthcare regions. Its climate is tropical humid, with temperatures ranging on average between 24.4°C and 34.4°C. It produces 27.2% of the Gross Domestic Product, 29.6% of the consumption potential and 28.6% of the workforce employed in the state. In 2000, it had a human development index (HDI) of 0.856, an adult literacy rate of 95.5%, 99.5% of households with water supply, 89.8% with treated sewage and 99.6% with garbage collection17.

Data collection

Data collection was performed in the Information System for Notifiable Diseases (SINAN), accessed through the Municipal Health Department of Vitória. The population data used was obtained from the Brazilian Institute of Geography and Statistics (IBGE), based on the 2000 Census. The statistical analysis was performed using SPSS software version 17.0.

Study population

The SINAN is where suspected notified dengue cases are registered and following an epidemiological investigation, are terminated as a confirmed case, discarded, inconclusive and ignored. In epidemic years, the suspected cases are confirmed by laboratory criteria and epidemiological links, while in years with no epidemic, only laboratory criteria are used. Confirmed cases are further classified as: classic dengue (CD), dengue hemorrhagic fever (DHF), dengue with complications (DWC) and dengue shock syndrome (DSS)18,19. The study population consisted of all confirmed cases of dengue in residents of the City of Vitória from January 1st 2000 to December 31st 2009.

Variables studied

Confirmed case of dengue: is any suspected case that is confirmed by clinical-epidemiological or laboratory criteria18. In Vitória, laboratory confirmation is mostly achieved by serology (IgM ELISA) or, more rarely, by viral isolation.

Dengue hemorrhagic fever: a confirmed case of dengue that presents fever, bleeding tendency, thrombocytopenia < 100,000/mm³ and plasmatic effusion, which may be verified by an increase in the hematocrits, ascites, pleural effusion or hypoproteinemia19,20.

Dengue with complications: a confirmed case that does not fit the criteria for DHF and when the classification of dengue fever is unsatisfactory, given the potential risk. In this situation the presence of one of the following items characterizes the case: neurological alterations; cardiac dysfunction; liver failure; thrombocytopenia equal to or less than 50,000/mm³; gastrointestinal bleeding; serous effusions; total leukocyte equal to or less than 1,000/mm³; death19.

Severe forms of dengue: all cases of DHF, DWC and DSS.

The group variables studied were sex, race-color, age and education. The categories of race and education present on the Dengue Notification Form were used.

Data analysis

For the data comparative analysis, rates, proportions and ratios were used. The denominator used to calculate incidence rates was the total population and stratified by sex, age and race, obtained from the IBGE Census 2000. The statistical analysis was performed using SPSS software version 17.0.

Ethical considerations

This study was approved by the Research Ethics Committee of the Federal University of Espírito Santo, under protocol no. 202/09, in line with resolution 196 of the National Research Ethics Committee (CONEP) and permission was obtained from the Municipal Health Secretariat of Vitória to use the SINAN database. Although this is a study that uses secondary data, the confidentiality of the identification data of the individuals was guaranteed.

RESULTS

The first notifications of dengue cases in the City of Vitória occurred in 1995. The municipality has suffered four principal outbreaks, which reached their peak in 1998, 2000, 2003 and 2009, probably caused by the introduction of sequential dengue virus serotypes DENV-2 (1995), DENV-1 (1996), DENV-3 (2003) and the reintroduction of DENV-2 in 2008 (Table 1). Considering notified dengue cases, observation showed that since 1995, the City of Vitória has experienced high rates of dengue incidence. Only in the years 1999 and 2004 were incidence rates of less than 300 cases/100,000 inhabitants reported. In order to identify the groups most affected by dengue in Vitória, our group decided to work only with confirmed cases. The study period was from 2000 to 2009, since no data is available regarding the final classification of cases from 1995 to 1999. Annual variations in the percentage of confirmed cases are due to differences in the criteria for the confirmation of cases in epidemic and non-epidemic years recommended by the Brazilian Ministry of Health.

The distribution of confirmed dengue cases and severe dengue according to age group is presented in Table 2. The most affected age group was 20 to 29 year-olds, with progressive reduction in case numbers towards the extremes of age. The proportion of severe cases was also higher in this age group, but the incidence rate was higher among those 50 to 59 years-old. A gradual decrease in the percentage of dengue cases occurred in the population aged 15 years
or over, in the historical series of 10 years, while a steady increase in individuals under 15 years-old was observed (Figure 1). The simple linear regression model detected statistical significance in the growth trends in individuals under 15 years-old and decrease in individuals aged 15 years-old or over ($R^2 = 0.521$, $p = 0.018$).

The proportion of dengue cases was higher among women (57.7%) throughout the period. The male/female ratio was 1:1.36. Among the clinical severe forms, the sex ratio for DHF was 1:1.27 and 1:1.36 for DWC.

The proportion of dengue cases was similar among whites (36.8%) and African descents, when combining the black (8.3%) and brown (29.3%) self-declared racial-skin color denominations. The proportions of ignored race and others (Asian and Indigenous) were 23.6% and 2.03% respectively. Among the severe forms, the highest proportion was verified in the category ignored (54.6%), which complicates further analysis.

It was not possible to analyze the education data for dengue and severe dengue cases, due to the level of completion of the SINAN database for this variable, i.e., the percentage of completion of the field education was 69.1% and 62.1%, respectively, considered low.

The total number of DWC cases was eight times that of DHF (Table 3). In the period studied, the proportion of DWC ranged from 0.5% (2007) to 26.8% (2001) of the total dengue cases and for DHF, from zero (2004) to 2.6% (2008). The fatality rate for dengue, including all forms, ranged from zero to 0.3%. For DHF/DSS, the rate was high in 2003, 2006, 2008 and 2009 and null in other years (Table 3). For DWC, the fatality rate was 0.23% in 2000, 1.3% in 2008, 1.4% in 2009 and absent in the remaining years. The incidence rate of severe dengue clinical forms decreased from the epidemic of 2000 (DENV-1 and 2) to the 2003 (DENV-3) and increased again in 2009 (DENV-2). The epidemic in 2000 had the highest incidence of severe forms (Figure 2). From 2000 to 2009, 15 dengue deaths...
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was confirmed in Vitória. Of this total, six deaths were attributed to DWC, four to DHF, three to classical dengue and two to DSS. The deaths occurred in individuals aged 26 to 93 years-old, eight of them (53.3%) occurred in individuals over 60 years-old. There have been 10 deaths (66.6%) recorded among women. The incompleteness of the data was very high for race and education.

### DISCUSSION

When introduced in unaffected cities with high vector density, the dengue virus has the ability to produce explosive epidemics. Since each serotype only produces permanent immunity for itself, the introduction of a new serotype causes a new epidemic, which usually only ends when the susceptible individuals are depleted. On the other hand, the reintroduction of the same serotype in the same location will determine the infection of individuals who were not infected in the first epidemic, for example, those born when that serotype was no longer in circulation. Thus, the persistence of dengue in human populations only occurs in urban areas that maintain high levels of vector infestation and large numbers of susceptible individuals.

The circulation of the several serotypes is an important event for the observation of the clinical severity of the infection during periods of epidemic. The characteristics of the sequence of introduction and cocirculation of specific serotypes have been implicated in the increase in cases of DHF/DWC. According to Halstead, the most important epidemiological observation regarding dengue is that cases of severe dengue regularly occur in places two or more serotypes are simultaneously or sequentially epidemic. In these places, DHF/DSS mainly occur in two groups: individuals aged 1 year-old or over who are infected by two or more different serotypes with intervals of 1 to 20 years and individuals less than 1 year-old who passively acquired maternal antibodies and are infected with dengue virus for the first time. Another theory assumes that the dengue virus is mutating and could take different phenotypic expressions depending on the gene content of the strain, which can influence the increase in replication and viremia, the severity of the disease and its epidemic potential. Although most studies associate the incidence of DHF with secondary infection by DENV-2 serotype, sequential infections with the other three serotypes were also virulent.

The judicious observation of the behavior of dengue in several urban areas can provide the understanding necessary for its adequate control. As such, studies like this one, despite the limitations of its descriptive nature and the use of preexisting data, permit the formulation of hypotheses that will be tested by analytical studies.

In the period studied, dengue presented high incidence in the City of Vitória, a situation shared by other Brazilian cities that can be largely explained by the great capacity of spatial diffusion of the virus and its tendency for outbreaks in areas favorable to vector proliferation. The proximity of neighboring municipalities that make up the metropolitan region of Vitória, the importance of the capital as an economic hub of the state and the use of its roads by the intermunicipal transport system may have favored the spread of the disease due to the circulation of individuals in full viremia.

Seroprevalence studies in the Brazilian population have shown varied percentages of positivity for dengue virus, according to the research site: Mossoró (97.8%), Salvador (67%), Niterói (66%), Macapá (48.4%), Rio de Janeiro (44.5%), Fortaleza (44%), São Luís (41.4%), Goiânia (29.5%), Belo Horizonte (23.3%) and Ribeirão Preto (5.4%). In general, the number of notified cases is lower than would be expected from the percentages of seroprevalence. This could be related to the large number of asymptomatic cases (an estimated 5 to 15 cases for each symptomatic case), to the undifferentiated febrile form and to undernotification. Although no seroepidemiological survey has been conducted in Vitória, the circulation of serotypes 1, 2 and 3, the number of individuals already infected by the dengue virus should be well above the number of registered cases.

In Vitória, the largest proportion of dengue cases, 25.6%, occurred in individuals aged 20 to 29 years-old and 44.1% in those aged 20 to 39 years-old. In Brazil, approximately 50% of the cases occurred in those aged 20 to 39 years-old from 1998 to 2003, featuring a high incidence in the adult population, unlike in Southeast Asia, where dengue has been circulating for over 50 years and more frequently affects children. In Brazil, this may be due to the fact that this age group comprises the majority of the economically active population, which circulates more frequently both inside and outside the city, and thus subject to exposure to a greater number of foci of the mosquito vector.

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### TABLE 3 - Proportion and mortality of severe dengue forms, Vitória, State of Espírito Santo, Brazil, 2000-2009.

<table>
<thead>
<tr>
<th>Years</th>
<th>Dengue N</th>
<th>DHF/DSS* P(%)</th>
<th>DWC P (%)</th>
<th>Total 19,843</th>
<th>DHF DSS* DWC</th>
<th>N</th>
<th>P (%)</th>
<th>D</th>
<th>FR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>1,652</td>
<td>11 0.7</td>
<td>0 0.0</td>
<td>442 26.8 1 0.2</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2001</td>
<td>357</td>
<td>4 1.1</td>
<td>0 0.0</td>
<td>3 0.8 0 0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>4,258</td>
<td>11 0.3</td>
<td>0 0.0</td>
<td>54 1.3 0 0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>6,140</td>
<td>2 0.03</td>
<td>11 0.2</td>
<td>283 4.6 0 0.0</td>
<td></td>
<td></td>
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<tr>
<td>2004</td>
<td>324</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>37 11.4 0 0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>228</td>
<td>1 0.4</td>
<td>0 0.0</td>
<td>7 3.1 0 0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2006</td>
<td>704</td>
<td>3 0.4</td>
<td>1 33.3</td>
<td>8 1.1 0 0.0</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>218</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>1 0.5 0 0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>985</td>
<td>2 0.2</td>
<td>26 2.6</td>
<td>79 8.0 1 1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>4,977</td>
<td>78 1.6</td>
<td>2 2.6</td>
<td>279 5.6 4 1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19,843</td>
<td>145 0.7</td>
<td>6 14.1</td>
<td>1,193 6.0 6 0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

DHF: dengue hemorrhagic fever; DSS: dengue shock syndrome; DWC: dengue with complications; N: number of cases; P: proportion of cases in relation to the total dengue cases; D: deaths; FR: fatality rate. * there was a case of DSS in 2006 and another in 2009.

Source: Information System for Notifiable Diseases (SINAN), Municipal Health Secretariat of the City of Vitória 2010.
However, analyzing the historical series in the City of Vitória from 2000 to 2009 (Figure 1), there is a trend of growing increase in the percentage of cases in individuals less than 15 years-old, with statistical significance. This trend was also observed in cities of Northeastern Brazil, from 2007 onward. In the epidemic of 2008 in Rio de Janeiro, 50% of dengue cases and 86% of deaths occurred in this age group. These data are worrying, since studies have shown that children show up to 40-fold greater risk than adults of developing the severe forms of the disease when they acquire a second dengue virus infection. Diagnostic confusion is more frequent due to the myriad of exanthematic and febrile diseases in children, of nonspecific evolution; moreover, semiological difficulties in disease characterization and atypical manifestations with unusual symptoms, corroborate the diagnostic difficulties.

The incidence of dengue among boys and girls has been shown to be similar in countries where dengue is endemic. Sex does not seem to be a risk factor for hospitalization for DHF, but the DSS has been observed more frequently among girls than boys and mortality is higher among females. In Cuba, the ratio of cases among men and women was different in the three epidemics: in 1981 it was 1:5.4; in 1997 it was 1:1, and in 2001-2002 it was 2.0:1. Analyzing the notified dengue cases in Brazil from 1981 to 2002, Siqueira et al determined a male/female sex ratio of 1.1:1. In Vitória, dengue has affected more women, both in its classic form and in severe forms. Two possible hypotheses exist that could explain this data: the fact that women access health services more than men and thus dengue is more frequently notified among them; and women spend more time inside the residence, the preferred habitat of *Aedes aegypti*, and are therefore more exposed to the disease.

In populations of equal size, the attack rate for DHF and DSS is 18 times higher in Southeast Asia than in the Americas. In Africa, although dengue virus infection exists, clinical manifestation of the disease is rare, and the severe forms are almost nonexistent. These observations suggest the possibility that the clinical presentation of dengue is controlled by certain genetic and racial factors of the host. During the epidemics in Cuba in 1981, 1997 and 2001-2002, the hospitalization rate among blacks was significantly lower than whites, despite the same rate of infection in both races. In Haiti, a country with a predominance of the black race, where all four serotypes of the dengue virus co-circulate, the occurrence of DHF/DSS in children was expected, but was not observed. Halstead suggests that the absence of major epidemics of DHF/DSS in Brazil may be related to the high prevalence of dengue-resistant genes in the Brazilian African descent population. A case-control study in Salvador, Bahia, using genetic markers of African ancestry, showed an inverse association between African ancestry and the occurrence of DHF.

In Vitória, dengue incidence was similar in whites and African descents. In order to analyze this data, first, it is necessary to take into account that the classification of the population of Vitória according to race/color, using the IBGE data, is an individual self-declared characteristic, which, in Brazil, for cultural reasons, does not always correspond to the phenotype of the individual. Secondly, the race-color classification of dengue cases is declared by the notifying healthcare professional, i.e., it is also subject to bias, since an individual’s phenotype is characterized only by skin color, which is not always sufficient to predict an individual’s genetic ancestry. A study conducted in Queixadinha, MG, where individuals were rated by trained observers, taking into account not only color, but other phenotypic characteristics, determined an African Ancestry Index of 32% in whites, 44% in browns, and 51% in blacks. Another study in the City of São Paulo, identified an average of 25% of African ancestry in whites and 65% in blacks. For Pena, the high miscegenation rate of the Brazilian population makes the physical appearance characteristics poor indicators of the genetic structure of a particular individual and the color of any particular individual has a very weak correlation with the degree of African ancestry.

In Brazil, the proportion of DHF cases has gradually increased, ranging from 0.06% of cases in the 1990s to 0.2% from 2000 to 2007. In Vitória, the proportion of DHF cases ranged from zero to 1.1% from 2000 to 2007 and presented an increase in 2008 and 2009 (Table 3). The proportion of DWC was greater than that of DHF for all years, except 2001. This can be explained, in part, by the difficulties in completing the classification criteria in DHF recommended by the WHO (World Health Organization) and Ministry of Health, which depend on additional tests, often not realized in time, and by atypical forms of the disease. The classification of clinical forms of dengue recommended by the WHO three decades ago - DF, DHF and DSS - has been criticized in many studies, for being too rigid and leaving out a large percentage of cases. In order to resolve this problem, the Ministry of Health included the classification of DWC in 2002, and the WHO itself has proposed a new classification of dengue in two forms: dengue and severe dengue. The fatality rate of DHF in Brazil ranged from 1.45% to 44% from 1994 to 2002, with an average of 10.49% per year. In 2002, the Ministry of Health proposed the goal of reducing mortality by DHF to less than 1%. In Vitória, no mortality by DHF was observed in 6 of the 10 years studied; however, in 2003 and 2006, mortality was high (Table 3). For DWC, the mortality rate was lower and presented a small increase in 2008 and 2009. The highest incidence of severe dengue in the epidemic years of 2000 and 2009, a period when DENV-2 circulated in Vitória, confirms the observation that most epidemics of DHF are associated with sequential infection by this serotype.

A study of deaths by dengue in Brazil, from 2000 to 2005, indicated male sex, age over 50 years-old, race/color black or brown, low education, rural residence, non epidemic period and difficulty accessing healthcare services as risk factors for death. In Vitória, the number of deaths was small, making comparisons difficult, but the occurrence of 60% of deaths in adults over 50 years-old confirms the trend of the Brazilian study and can be explained by the greater frequency of comorbidities in the elderly, which are risk factors for the severe forms.

Given the above results, it can be concluded that the changes in the age pattern in the disease incidence observed in the historical series of 10 years in Vitória, with a growing increase in the number of cases in individuals under 15 years-old, may represent a new trend in the distribution of cases in the population of the municipality and a higher risk for the development of severe dengue forms, reinforcing the need for a more intense surveillance in the coming years. In addition to continuing to combat the mosquito vector in an attempt to reduce the dengue incidence, the municipality must organize its support network in order to recognize and treat dengue cases in individuals less than 15 years of age. The proportion of severe forms and their fatality should also be monitored to detect trends and plan actions.
CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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