

The burden of dengue: Jundiaí, Brazil – January 2010

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SUMMARY

Objective: To study the antibody prevalence against dengue in the municipality of Jundiaí, São Paulo, Brazil, due to the low number of official confirmed autochthonous cases. **Methods:** A serological study on dengue infection was conducted during January 2010 and previous reports on dengue and entomological surveillance during that period were reviewed. **Results:** A prevalence of 7.8% IgG positive (68:876) was found. Furthermore, based on the detection of IgM antibodies in five samples, it was observed that the incidence of dengue in the city at the time of the survey contrasts with the absence of notifications by local health authorities over the same period of time. **Conclusion:** These results highlight the discrepancies between the actual and the detected number of dengue infections, possibly due to significant numbers of asymptomatic infections aggravated by difficulties with dengue clinical diagnosis.

Keywords: Dengue; epidemiology; serology.

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INTRODUCTION

Dengue fever (DF) is caused by any of the four closely related flaviruses transmitted by *Aedes aegypti* mosquitoes (serotypes 1 through 4)¹. Accordingly, the geographic distribution of *Aedes* mosquitoes globally matches the area of dengue transmission². Currently, the dengue virus (DENV) is the most common arbovirus causing a neglected human disease around the world. Furthermore, the number of cases has increased dramatically during the past three decades in the Americas³. Currently, there is no available dengue vaccine or antiviral therapy; therefore, dengue prevention is based almost entirely on vector control⁴.

The Pan American Health Organization (PAHO) reports that Brazil comprised approximately 46% of the reported cases in 2009 (528,883) and 60.65% of the cases in 2010 (1,004,392)⁵. Moreover, the State of São Paulo was among those that had the most reported cases, according to the 2010 dengue epidemiological report from the Brazilian Ministry of Health⁶. During that year, the State of São Paulo accumulated 188,593 cases, a sharp increase (2,096%) compared to 8,996 cases reported in 2009 (Centro de Vigilância Epidemiológica Alexandre Vranjac – CVE)⁷. Despite efforts to contain the disease, dengue keeps growing in most states of Brazil where the vector thrives.

In 2010, the municipality of Jundiaí, in the state of São Paulo, had an estimated population of 369,710⁸. Dengue cases have been documented since 2004 by the municipal health authorities, and there was a peak of 51 autochthonous cases in 2008. Interestingly, in 2009 only four autochthonous cases were reported.

The low number of confirmed autochthonous cases in Jundiaí suggests that there were cases that went undetected, either by difficulties with the diagnosis or because they were asymptomatic (in which case patients do not show up for testing), or as a result of broad herd immunity in the human population that does not allow for the onset of epidemics with many symptomatic cases. To address this issue, a serological survey following a random sampling was conducted during January 2010 (when virus activity is expected to occur in the Southern Hemisphere) and also reviewed previous technical reports on dengue and entomological surveillance from both the state of São Paulo and the city of Jundiaí.

POPULATION AND METHODS

Jundiaí is a well-developed city located in the eastern part of the State of São Paulo at 23° 11' 11" S and 46° 53' 03" W, at an elevation of 762 m above sea level, occupying a land area of 431.97 km² within at the Atlantic rainforest biome. According to the state of São Paulo's Metropolitan Planning Company (Empresa Paulista de Planejamento Metropolitano – Emplasa), Jundiaí is composed of an agglomeration of municipalities (Cabramatta, Limpo Paulista, Itupeva, Jarinu,

Jundiaí, Louveira, and Várzea Paulista) totaling 800,000 inhabitants, located between the important urban-industrial centers of São Paulo and Campinas, with about 18 million people within a radius of 80 km. Most of the dislocations that occur every day are directed towards the agglomeration itself, with the second destination being the metropolitan area of São Paulo. It is noteworthy that, in health grounds, all municipalities in the conurbation have a heavy transit flow with Jundiaí. Most treatments outside the municipality of residence that require hospitalizations occur in health facilities of Jundiaí in the following proportions: Várzea Paulista (91.7%), Jarinu (90.9%), Itupeva (86.8%), Limpo Paulista (86.2%), and Cabramatta (75.6%).

The approach to this dengue serological survey was to check the immunological status of the population of Novo Horizonte and São Camilo, which where the neighborhoods that reported most dengue cases during the 2008 outbreak (37 cases in Novo Horizonte and six cases in São Camilo). The sample size was calculated assuming a prevalence of 0.25% and the estimated population size of the municipality, which means that a dengue prevalence ~ 250 times higher than what can be inferred from technical reports issued by the health authorities in Jundiaí (~ 0.01%) was considered. Therefore, partitioned according to the estimated population size of each neighborhood, the experimental design entailed approximately 340 samples from São Camilo and 560 samples from Novo Horizonte, for a total expected sample size of 900. Households for sample collection were randomly selected from address records provided by the municipality. Health technicians randomly selected one resident per household, from which a single blood sample of 5 mL was collected. The ethical institutional review boards of Instituto de Ciências Biomédicas (ICB) - Universidade de São Paulo (USP) and Faculdade de Medicina de Jundiaí (FMJ) reviewed and approved the study. All participants volunteered to provide blood samples and age information for this study, after receiving a detailed explanation of the study and signing an informed consent.

The serological survey was carried out using the dengue IgG and IgM enzyme-linked immunosorbent assay (ELISA) (Bioeasy), following suppliers' recommendations. Data on entomological surveillance during 2009 were retrieved from the Superintendency of Endemic Diseases Control (Superintendência de Controle de Endemias – SUCEN). DENV technical reports were obtained from the CVE or provided by the health authorities of the municipality. A total of 886 samples were collected from January 11 to 25, 2010 (299 samples from São Camilo and 587 from Novo Horizonte). By comparing the sampling age distribution with that of the State of São Paulo⁹, it was found that both age structures were not significantly different ($\chi^2 = 0.0046$, d.f. = 7, $p = 1.0$), meaning that the sampling from Jundiaí could be considered a random sampling of the state population.

RESULTS AND DISCUSSION

ELISA was carried out for 876 serum samples, since ten samples from Novo Horizonte were not included due to technical problems. The 83 samples that were initially positive for IgG, were re-tested immediately after the first trial resulting in 68 confirmed positives (68:876) (Table 1). Subsequently, a serological test for dengue IgM antibodies was performed using the 68 IgG positive samples, resulting in five IgM seropositives (5:68). Remarkably, a 7.8% seropositivity for IgG in the two neighborhoods under study was found. Assuming that the sample reflects to some extent the local population, one could extrapolate a cumulative number of approximately 28,690 possible seropositive cases in Jundiaí. In contrast, the local authorities in Jundiaí reported a cumulative number of 98 autochthonous cases from 2004 to 2008. Likewise, a serological survey carried out in the region of the US-Mexican border revealed, for two cities, that the prevalence of the antibody against dengue was of 39% to 50%, a percentage 20 times higher than the cumulative number of cases from 1980 to 2007¹⁰. Discrepancies between reported dengue disease cases and actual level of transmission may arise due to silent transmission given the high asymptomatic infection rate¹¹. Another explanation foresees a scenario of re-introductions of viremic patients or vectors, which do not ignite large outbreaks. For example, five imported dengue cases were reported in Jundiaí during 2009, and the daily population commutes towards Jundiaí, indicating a strong interaction between the municipalities of the conurbation. In any case, it can be argued that proper verification of the actual number of infected people is paramount in localities with reduced number of notified cases, especially in countries such as Brazil where suspected dengue cases are among the diseases of compulsory notification. This notification does not require the confirmation of diagnosis, and all suspected cases do not have to be reported to and further investigated by the public health agencies. Notably, it has been shown that insufficient political commitment, inadequate financial resources, and increased urbanization have contributed to the dramatic increase in dengue cases in the Americas and, consequently, the epidemic control will largely be financially dictated, whereby budgetary allocations should match the size of the problem^{3,12}. Furthermore, an analysis combining available information on

reported cases, levels of underreporting, and cost per case, showed that Brazil is the country with highest economic impact of dengue, and that roughly 60% of these costs are due to productivity losses (indirect costs), which affect households, employers, and government¹³, highlighting a need for improved surveillance.

Given the disagreement between officially reported cases and the estimated and predicted seroprevalence, available statewide data on the yearly number of notified dengue cases and the yearly-averaged mosquito infestation indexes for Jundiaí and other 124 municipalities from 2009 was further analyzed. Previous studies^{14,15} were able to predict dengue transmission based on the Breteau Index (BI). The control of vector-borne diseases, intermediate hosts, and entomological surveillance performed by the SUCEN in the State of São Paulo is based on the BI and on a larval index (PI, which indicates the number of containers positive for larvae per 100 houses). Therefore, both BI and PI were contrasted with reported cases. Although the infestation indexes and number of cases showed seasonal increase in summer months, a simple linear regression did not show any significant correlation between the number of total dengue cases to either the annual averaged BI ($r^2 = 0.003$) or PI ($r^2 = 0.003$). In any case, it is important to highlight that yearly-averaged infestation indexes for Jundiaí (IP = 0.93, IB = 0.94) were similar to those measured for nearby cities that registered higher numbers of cases, such as Campinas (IP = 0.99, IB = 1.08, with 168 autochthonous and 22 imported cases). These data, in agreement with the present serology data, suggests that the real number of infections in Jundiaí (and maybe elsewhere) may be considerably higher than the detected by the health authorities. The numbers of dengue cases (autochthonous and imported) reported by the CVE, which varied quite significantly across the State, were also considered. As an example, in the 42 cities within the administrative area XVII (where Jundiaí belongs), the number of both types of cases had a strongly right-skewed distribution (skewness coefficient ≈ 4.7) with a median of zero cases for both imported (range = 22) and autochthonous (range = 168) cases, with mean values of 9.3 ± 4.3 , and 1.7 ± 0.6 respectively. Other than low numbers, these results evidenced a significant variation on the actual figures at nearby cities, which means that there is a great locality-specific fluctuation in reported cases for

Table 1 – Serological results for IgG and IgM antibodies during January 2010 in two neighborhoods of Jundiaí, São Paulo, Brazil

ELISA	São Camilo		Novo Horizonte		Total	
	Tested	Positive	Tested	Positive	Tested	Positive
IgG	299	20 (6.7%*)	577	48 (8.3%)	876	68 (7.8%)
IgM	20	1 (5%)	48	4 (8.3%)	68	5 (7.3%)

*Percentages of positives from the number of samples tested, respectively; ELISA, enzyme-linked immunosorbent assay.

neighboring cities with similar demographic and ecological characteristics to sustain dengue transmission.

However, from the present data alone, it cannot be concluded that dengue cases must have occurred and were underreported in Jundiaí, because the 68 seropositive individuals were not interviewed for a history of dengue-like illness in the past five to ten years. Consequently, it cannot be asserted that there is a sub-notification of cases. As an additional caveat, it is worth considering that the IgG negative samples were not tested for IgM. Therefore, a proper distinction between primary or secondary infections was not possible. Nevertheless, IgM antibodies are usually detected during the first three months post-infections. Additionally the present findings may also imply five recent infection events, which had to have occurred between November 2009 and January 2010 and could be significant for a sustained silent transmission of dengue.

Remarkably, the appropriate method to estimate sub-notification would be by reviewing medical records of acute febrile illnesses at the primary care facilities and identifying those patients with clinical symptoms compatible with acute dengue fever, then addressing why dengue was considered. Moreover, in- and out-patient records from Jundiaí hospitals were not analyzed for febrile syndromes observed during 2009-2010. Nevertheless, perhaps some dengue cases were diagnosed as influenza following the H1N1 flu pandemic. Given that dengue infection with any of the dengue serotypes may be asymptomatic in the majority of cases or may result in a wide spectrum of clinical symptoms, ranging from a flu-like fever to an incapacitating high fever, many dengue cases go undiagnosed. In addition, passive surveillance has been shown to significantly underestimate infection rates and is a factor constraining the control of dengue in the Americas¹².

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