Hyperendemicity in Urban Centers of Brazil

Detection of Four Dengue Serotypes Suggests Rise in Hyperendemicity in Urban Centers of Brazil

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Dengue fever is the most common infectious disease transmitted by a mosquito and a major economic and disease burden in endemic countries. The reported number of dengue cases in 2013 evidences the disease’s disturbing impact on human health in Brazil: 950,193 clinical cases, 3,749 with severe manifestations, and 201 deaths (data up to July 13, 2013 by the Pan American Health Organization); any of the four serotypes was the etiologic agent in these outbreaks. The first autochthonous cases of dengue in the southern hemisphere were reported in Venezuela in 1982 in a focal epidemic in the northwest of the country, we determined whether one serotype or multiple ones caused the 2013 epidemic in some critical localities in the state of São Paulo. In collaboration with our public health authorities, we collected acute-phase sera from suspected dengue patients from the cities of Guarujá (located in the coastal region with 290,752 inhabitants and 2,035 inhabitants/km²) and Jundiaí (located in the mountain range with 370,126 inhabitants and 856 inhabitants/km²) from December 20, 2012 to May 2013 (summer months). Jundiaí in the west and Guarujá in the east (seaside) are adjacent to, and tightly interconnected with, the densely populated municipality

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of São Paulo. We expected that this approach would inform on the cocirculation of viruses in the entire metropolitan area. Viral RNA was extracted from sera of 24 positive samples selected at random (20 from Guaruja and the only four samples that tested positive from Jundiaí), and we amplified and sequenced the capsid/premembrane junction that was proposed by Lanciotti et al. [10] for typing DENV. All sequences determined in this study were deposited in GenBank (427 bp; accession KF286626-KF286649). To help in classifying our sequences, a small time-stamped dataset comprising 35 sequences that were representative of both serotypes and genotypes was retrieved from GenBank and aligned with our sequences. A phylogenetic tree (Figure 1) was built using a Bayesian approach, and our evolutionary estimates matched those of Twiddy et al. [11], which validated our analysis. Sequences from both cities belonged to different serotypes. Remarkably, samples from Guaruja clustered within the four serotypes, while samples from Jundiaí grouped with either DENV-1 or DENV-4. We will argue that these findings corroborate a change in epidemiological pattern accompanying a rise in Brazilian urban hyperendemicity that constitutes a greater challenge for surveillance and control. Crucially, the presence of two serotypes in the same outbreak may be considered as an important warning for high levels of transmission, since Jundiaí has no significant historic record of epidemics.

Our DENV-1 samples grouped within genotype V, and our DENV-4 samples grouped within genotype II, as they did for strains from those serotypes reported elsewhere in Brazil. Besides, our tree showed closely related viral lineages in both municipalities, which implied viral movement across the metropolitan area. Moreover, DENV-1 samples from Jundiaí fell within divergent clades, suggesting that
there are two different lineages in the city. We consider these results important, since multiple viral lineages cocirculating in densely populated places acted as major dengue transmission hubs as noted in Raghwani et al. [12]. On the other hand, DENV-3 samples grouped with genotype V. DENV-3 genotype III has been the most prevalent genotype in the country, but genotypes I and V have also been associated with Brazilian outbreaks [13]. In this respect, our findings raise the intriguing question of whether our DENV-3 samples represent in situ evolution and dissemination from Brazilian regions, or if they are due to a novel introduction from Asia. Most significantly, we consider these results important, since there are two different lineages in the city. Recurring dengue epidemics in that country resulted in the establishment of hyperendemic areas, typically in large, densely populated cities, where most DENV serotypes circulate in a sustained fashion [15]. Roughly two years after the report on the presence of DENV-4 in Manaus (Amazon), we now find the four serotypes cocirculating in the south of the country in the outskirts of the municipality of São Paulo. Therefore, a continued advocacy of long-term prevention and control is imperative. Our concern is that if we ignore the urban hyperendemicity, children will be at greater risk for severe disease [5].

**Ethics Statement**

Both the Human Research Ethics Committee from the Biomedical Sciences Institute of University of São Paulo and the Research Ethics Committee from the Faculty of Medicine of Junedi approved the study; a written informed consent was obtained from all patients.

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