

## Dengue in Brazil in 2017: what happened?

Dear Editor

Brazil is a dengue-endemic country and over the years has been facing several outbreaks caused by different serotypes of the virus. More recently, between 2015 and 2016, the country reported an annual average of 1,586,155 probable cases<sup>1,2</sup>. However, in 2017, two or four years after the probable introduction of *Zika virus* (ZIKV)<sup>3,4</sup>, Brazil experienced a decrease in dengue fever to 252,054 cases, besides a reduction in the number of severe dengue and deaths<sup>2</sup>.

In 2017, the number of Zika cases also declined in Brazil in comparison to the previous year, about 92% reduction<sup>2</sup>. The decrease in Zika cases influenced by anti-ZIKV herd immunity has already been previously discussed<sup>5,6</sup>. However, regarding dengue disease, the causes of this decline are still not fully understood. Indeed, as shown below, the current data on herd immunity, cross-reactions between *Dengue virus* (DENV) and ZIKV, mosquito ecology, vector control measures and environmental factors are not sufficient to explain the dengue scenario in 2017.

First, the anti-dengue herd immunity does not seem to explain the decline in dengue cases in 2017. In Brazil, between 2009 and 2016, DENV-1 was the most prevalent serotype<sup>7</sup>. In the year 2015, for instance, the prevalence of DENV-1, DENV-2, DENV-3 and DENV-4 was 94.1, 0.7, 0.4 and 4.8%, respectively<sup>8</sup>. In the same way, in 2016 (up to epidemiological week 4), prevalences were 97.24, 0.69, 0.69 and 1.38% to DENV-1, DENV-2, DENV-3 and DENV-4, respectively<sup>8</sup>. In 2017, however, serotype 2 was the most prevalent (54.3%)<sup>7</sup>. This very low prevalence of DENV-2 in the years 2015 and 2016 reduces the possibility that dengue cases have fallen in 2017 due to the anti-DENV-2 herd immunity.

In another perspective, the studies on cross-reactivity between DENV and ZIKV also do not explain the fall in dengue cases in 2017. Regarding anti-ZIKV immunity in relation to DENV infections, to our knowledge, there are only two reports on the *in vivo* modulation of anti-ZIKV antibodies with respect to DENV infection: Stettler *et al.*<sup>9</sup> and George *et al.*<sup>10</sup> demonstrated the increase of DENV-2 infection by anti-ZIKV antibodies in mice and rhesus monkeys. Interestingly, DENV-2, as commented above, was the most prevalent serotype in 2017 in Brazil<sup>8</sup>. In this way, it would be expected that the herd immunity against ZIKV would increase, but not decrease the number of dengue cases in Brazil.

In Salvador, Brazil, Ribeiro *et al.*<sup>11</sup> suggested that the decrease in dengue cases between 2015 and 2017 would be the result of the cross-herd immunity to ZIKV. Although Ribeiro *et al.*<sup>11</sup> did not mention the circulating DENV serotypes in Salvador during the study, data from the Brazilian Ministry of Health demonstrated that the serotypes identified in Bahia in 2015 were DENV-1 (96.3%) and DENV-4 (3.7%)<sup>12</sup> (data for 2016 and 2017 were not found).

In addition to the immunological explanations, vector-related factors should also be considered. About this, the increase of confirmed cases of chikungunya between 2016 and 2017, from 151,318<sup>1</sup> to 151,966<sup>2</sup>, weakens the hypothesis of the fall of DENV infection in 2017 as a consequence of vector control measures or environmental factors. Since 2015, DENV, ZIKV and *Chikungunya virus* (CHIKV) circulate in Brazil and *Aedes aegypti* coinfection with these arboviruses could favor the transmission of a specific virus, reflecting the change in the epidemiological pattern. However, when the vector was coinfecting with two or three arboviruses (DENV-CHIKV and DENV-ZIKV) no advantages were observed for any of these viruses<sup>13-15</sup>.

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Therefore, despite the progress on cross-reactivity studies between flaviviruses and on the mosquito ecology, we believe that a more detailed analysis of the variables involved in the DENV-ZIKV interaction is required. We recognize that arboviruses outbreaks result from a complex interaction among several factors, such as environmental determinants, mosquito ecology, viral genetics, behavior and immunological background of the population<sup>5,6,16-19</sup>. However, it is important that the immunological studies are redesigned and carried out taking into account the multiple variables capable of influencing the cross-reaction between DENV and ZIKV: a) existence of different DENV serotypes, mainly DENV-4, which forms a group considerably distant from DENV-1, -2 and -3<sup>20</sup>; b) animal model for *in vivo* studies; c) naïve populations or with history of previous flaviviruses infections; d) coinfection or immunity to other flaviviruses (e.g. *Yellow fever virus* and *West Nile virus*); e) existence of antibodies against conserved or flavivirus-specific regions of the envelope protein; f) genetic diversity of individuals' immune responses; g) intrinsic factors related to the viruses, such as possible mutations, mainly in the gene sequence coding for the envelope. Finally, we argue that only by narrowing the gap between laboratory assays and natural infections it will be possible to make substantiated interpretations on the epidemiology of the areas with flaviviruses co-circulation.

## CONFLICT OF INTERESTS

The authors have no conflict of interest to disclose.

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