

## Can Zika virus antibodies cross-protect against dengue virus?

### Authors' reply

We welcome the comments by Kevin Ariën and colleagues on our recent Correspondence, in which we presented epidemiological data showing a large decline in detected dengue virus infection cases in Salvador, Brazil, following the 2015 Zika virus outbreak.<sup>1</sup> Our aim was to raise the hypothesis that massive population exposure to Zika virus might have an inhibitory role in dengue virus transmission and symptomatic infections, and to open a new avenue for discussion, experimental studies, and epidemiological data analyses from other groups. We appreciate that Ariën and colleagues did neutralisation assays to investigate the biological basis of our hypothesis.

After examining 21 clinical samples of dengue virus-naïve patients with Zika virus infection confirmed by RT-PCR or neutralisation assays, they found that one sample (5%) showed weak cross-neutralisation against dengue virus serotype 2, and argued that Zika virus infections are unlikely to cross-protect against dengue. However, the majority of the Salvador and Latin American population are not dengue virus-naïve, and have been infected by dengue virus before the Zika virus outbreak. Following Zika virus infections, the antibodies produced in dengue virus-immune people against the Zika virus non-structural 1 protein (NS1) cross-react extensively against dengue virus NS1, whereas in dengue virus-naïve individuals less cross-reaction occurs.<sup>2</sup>

A potential cross-protection elicited by Zika virus is also supported by studies showing that envelope-specific antibodies produced during Zika virus infection cross-react with the envelope protein of all four dengue virus serotypes, regardless of previous dengue virus infection.<sup>2</sup> More

importantly, Zika virus infections in dengue virus-immune individuals boost cross-reactive memory B cells, resulting in broader flavivirus neutralisation capacity and eliciting cross-neutralising immunity against Zika virus and dengue virus.<sup>3</sup> This cross-protection could be sufficient for herd immunity. Yet, cross-protective immunity might not be long lasting (and might differ by dengue virus serotypes), because cross-neutralising antibodies usually do not persist for more than 12–18 months.

Dengue virus transmission is cyclical as a function of the circulation of different serotypes, proportion of susceptible individuals, and severity of *Aedes (Stegomyia)* spp infestation. Our hypothesis was supported by the strength and consistency of the analyses done on two distinct datasets, coupled with the persistent high detection rate of chikungunya virus following the Zika virus outbreak, indicating that conditions unrelated to human immunity are conducive for dengue virus transmission. In other parts of Brazil, where the effect of the Zika virus outbreak was reduced and occurred later than in Salvador, a substantial decline in the number of reported dengue virus infection cases did not occur until 2017.<sup>4</sup>

Given the potential implications for vaccine development and assessment, immunopathogenesis studies, and surveillance, we welcome additional experimental and epidemiological investigations to elucidate the putative role of Zika virus infection in the inhibition of dengue virus transmission.

We declare no competing interests.

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- 2 Stettler K, Beltramello M, Espinosa DA, et al. Specificity, cross-reactivity, and function of antibodies elicited by Zika virus infection. *Science* 2016; **353**: 823–86.
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- 4 BRASIL. Monitoramento dos casos de dengue, febre de chikungunya e febre pelo vírus Zika até a Semana Epidemiológica 3, 2018. *Boletim Epidemiológico* 2018; **49**: 1–13.