

Can Zika virus antibodies cross-protect against dengue virus?

Guilherme Ribeiro and colleagues (February, 2018)¹ report a major downward trend in dengue virus infection cases after the recent Zika virus outbreak in the Americas. They used epidemiological data collected between 2009 and 2017 in Salvador, Brazil, to suggest that the decline in dengue virus infection cases observed since 2015 could be the result of cross-protective immunity to dengue virus induced by Zika virus infection.

As part of the National Reference Centre for Arboviruses, we do neutralisation assays for a variety of arboviruses, including Zika and dengue viruses.² Between 2016 and 2017, we examined 382 human serum samples (from 323 patients) for Zika virus neutralising antibodies. A subset of 55 serum samples (from 44 patients) were examined for in-vitro neutralising potential against both Zika virus and dengue virus serotypes 1–4. Samples with low Zika virus neutralisation titres (unlikely to be Zika) and high dengue virus neutralisation titres (likely to be dengue) were removed from the subset before further analysis. In a serum sample with pre-existing dengue virus neutralising antibodies, measuring the specific contribution of Zika virus antibodies to the neutralisation of dengue virus is difficult (if not impossible). Therefore, we limited our analysis to dengue virus-naïve patients with a documented Zika virus infection (confirmed by PCR or virus neutralisation; n=21) and investigated dengue virus neutralisation potential in vitro. Only one of 21 Zika virus serum samples showed a weak cross-neutralisation titre (the neutralisation titre that inhibited 90% of viral infection [NT₉₀] was 86) against dengue virus serotype 2, and two additional

serum samples showed NT₅₀≥50. This finding is in line with earlier reports that showed the absence of Zika virus neutralisation among primary dengue virus infections and low-frequency cross-neutralisation in repeat dengue virus infections,^{3,4} suggesting that independent neutralising antibody populations against these two viruses are raised. This picture is more complex in a population with pre-existing flavivirus immunity resulting from previous exposures to flaviviruses other than Zika or vaccination, as is the case in Latin America, and the attribution of immunity against Zika virus to dengue infection in such a population can only be determined when pre-Zika infection archived serum samples are available. Of note, the epidemiological data presented by Ribeiro and colleagues¹ already showed a downward trend in dengue virus infection cases in 2012 and 2013, before the Zika virus epidemic occurred. The further decline in dengue virus infections in 2016 and 2017 could merely result from existing immunity against dengue virus in the population of Salvador, and not necessarily from Zika virus antibodies that cross-protect against subsequent dengue virus infections.

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*Kevin K Ariën, Johan Michiels,
Nikki Foqué, Leo Heyndrickx,
Marjan Van Esbroeck
karien@itg.be

Virology Unit, Department of Biomedical Sciences (KKA, JM, LH), and National Reference Centre for Arboviruses, Department of Clinical Sciences (KKA, JM, NF, LH, MVE), Institute of Tropical Medicine, B-2000 Antwerp, Belgium; and Department of Biomedical Sciences, University of Antwerp, Wilrijk, Belgium (KKA)

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- 4 Swanstrom JA, Plante JA, Plante KS, et al. Dengue virus envelope dimer epitope monoclonal antibodies isolated from dengue patients are protective against Zika virus. *MBio* 2016; **7**: e01123–16.

