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Short Communication

Evaluation of serological cross-reactivity between yellow fever and other flaviviruses

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ABSTRACT

Objectives: This study was performed to determine whether neutralizing antibodies against yellow fever virus (YFV) generated by YFV vaccine could interfere in the specificity of dengue virus (DENV) and Zika virus (ZIKV) IgG ELISA tests.
Methods: Seventy-nine pairs of serum samples (pre- and post-vaccination), collected during the years 1997–1998 from children with no history of yellow fever disease who had been vaccinated against YFV, were tested. The seroconversion post-vaccination was evaluated through plaque reduction neutralization test (PRNT), and four different commercial ELISA kits were used for the detection of DENV and ZIKV IgG antibodies.
Results: A cross-reactivity rate of 3.9% with DENV IgG antibodies was found only with the Dengue Virus IgG Dx Select kit (Focus Diagnostics).
Conclusions: As several countries have local transmission of multiple arboviruses, the absence of cross-reactivity or minimum cross-reactivity of YFV neutralizing antibodies with DENV and ZIKV antigens is a relevant finding, since the interpretation of sero-epidemiological investigations would be seriously impacted in many regions where YFV vaccination is mandatory.

Introduction

In recent years, Brazil has experienced several epidemics caused by arboviruses, such as dengue virus (DENV serotypes 1–4), Zika virus (ZIKV), chikungunya virus (CHIKV), and yellow fever virus (YFV). In the past 2 years, the largest epidemic of sylvatic yellow fever in decades occurred in areas that were not considered at risk (Faria et al., 2018). As part of the response to this recent outbreak, federal and state authorities conducted mass vaccination campaigns against YFV, and the vaccination is now recommended and offered in 19 Brazilian states (Saúde, 2018b). Preliminary results from the mass yellow fever vaccination campaign have indicated that 8.8 million persons in São Paulo, 6.9 million persons in Rio de Janeiro, and 1.8 million persons in Bahia have been vaccinated (Saúde, 2018a).

As may occur with other flaviviruses, it is possible that the antibodies produced against YFV may cross-react with antibodies against other viruses from the same genus, such as DENV or ZIKV, which are responsible for many outbreaks and are distributed across the country. In settings where routine or mass immunization against YFV is conducted, cross-reactions between yellow fever vaccine-induced antibodies and DENV and ZIKV ELISA IgG tests might significantly impact the results of sero-epidemiological surveys.

The aim of this study was to determine whether neutralizing antibodies against YFV generated by the yellow fever vaccine could interfere in the specificity of DENV and ZIKV IgG ELISA tests.

Methods

Serum samples

Archived serum samples containing vaccine-induced neutralizing antibodies against YFV were selected from a panel of serum samples maintained at the Laboratory of Virology of the Instituto de Medicina Tropical, USP, for arboviral serological studies. These samples were collected during a previous study (Stefano et al., 1999), from 9-month-old children vaccinated against yellow fever with

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1000 $TCID_{50}$ of the 17DD vaccine strain (Bio-Manguinhos, RJ, Brazil). Two blood samples were collected from each child, one before yellow fever vaccination and the other 6 weeks after vaccination. Antibodies against YFV were confirmed by plaque reduction neutralization test (PRNT) and the geometric mean titer (GMT) for yellow fever antibodies in children responsive to the vaccine was 4.45 ± 0.60 (Stefano et al., 1999). For this study, 79 pairs of samples that fulfilled the following criteria were selected: children with no history of yellow fever disease or previous yellow fever vaccination; availability of pre- and post-vaccination samples; negativity for yellow fever PRNT antibodies in the pre-vaccination sample and seroconversion in the post-vaccination sample.

Determination of antibodies against dengue and Zika viruses

Three commercial ELISA kits were used to detect DENV IgG antibodies in post-vaccination samples: Dengue Virus IgG Dx Select (Focus Diagnostics, Cypress, CA, USA), Anti-Dengue Virus ELISA (IgG) (Euroimmun, Lübeck, Germany), and Dengue IgG Indirect ELISA Panbio (Abbott, Brazil). Anti-ZIKV antibodies were assessed in post-vaccination samples using the commercial kit Anti-Zika Virus ELISA IgG (Euroimmun, Lübeck, Germany), according to the manufacturer's instructions. For samples that tested positive with any kit, the corresponding pre-vaccination serum was also tested.

Results

The 79 post-yellow fever vaccination samples were first tested with all three DENV kits. None of them was positive by anti-DENV IgG Euroimmun or Panbio ELISA kit. However, five samples were positive by Dengue Virus IgG Dx Select (Focus Diagnostics). The corresponding pre-vaccination serum samples for these five samples were then tested with all DENV ELISA kits. Two of the five were positive only with the Focus Diagnostics kit and were excluded from the analysis. Thus there was cross-reactivity of 3.9% (3/77) for this particular commercial kit.

The post-yellow fever vaccination samples were also submitted to the anti-ZIKV ELISA IgG kit and none of them was positive. Therefore, no pre-vaccination sample was tested.

Discussion

When the serum samples included in the present study were collected (1997–1998), DENV was not as widespread as today and ZIKV had not been introduced into the country, making this an ideal cohort to evaluate cross-reaction between YFV and these flaviviruses. However, assuming the possibility that some children could have been exposed to DENV before the yellow fever vaccination, samples for which the pre-vaccination (in addition to the post-vaccination sample) was also positive for either anti-DENV or anti-ZIKV antibodies were tested and excluded.

All kits describe their limitations due to the risk of cross-reaction when used on samples seropositive for other flaviviruses. However, in the present study, cross-reaction of YFV neutralizing antibodies was absent with the commercial ZIKV IgG ELISA test and with the Euroimmun and Panbio DENV IgG ELISA test kits. Only the Dengue Virus IgG Dx Select kit (Focus Diagnostics) showed a cross-reaction, with cross-reactivity for 3.9% of samples.

In conclusion, the absence of cross-reactivity or minimum cross-reactivity with neutralizing antibodies to YFV is a relevant finding, considering that the vaccine is part of the official vaccination schedule in many regions of Brazil and in other Latin American countries and also because the immunization recommendation is being expanded due to the epidemic situation. Critically, the interpretation of sero-epidemiological investigations would be impacted if cross-reaction of the yellow fever vaccine antibodies with DENV and/or ZIKV assays was significant.

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Ethics statement

All procedures were performed according to the terms agreed by the Institutional Review Board of the Hospital das Clínicas, University of São Paulo Medical School (CAPPesq – Research Projects Ethics Committee – 2.001.818).

Conflict of interest

No conflict of interest to declare by any of the authors.

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