

Letter to the editor: Specificity of Zika virus ELISA: interference with malaria

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To the editor: We read the study by Huzly et al. [1] with interest and agree on the high specificity of the Euroimmun Zika virus (ZIKV) ELISA (Euroimmun, Lübeck, Germany).

We evaluated the specificity of this test on convalescent samples of 10 PCR-confirmed dengue patients (n=3 DENV-1, n=4 DENV-2, n=2 DENV-3 and n=1 DENV-4) with high IgM antibody ratios and a positive (n=9) or negative (n=1) result for IgG antibodies. We also tested the assay on 10 samples with high titres of neutralising antibodies against yellow fever virus and on five samples positive for rheumatoid factor. Except for one borderline result (ratio between 0.8 and 1.1) of ZIKV IgM in the convalescent sample from a patient infected with DENV-1 after a stay in Thailand, all results for ZIKV IgM and IgG were negative.

However, when we tested samples from malaria patients with a current infection (thick smear and PCR-positive) with *Plasmodium falciparum* (n=12), *P. falciparum/P. ovale* (n=1), *P. vivax* (n=3), *P. ovale* (n=5) or *P. malariae* (n=5), or a recently treated *P. falciparum* infection (microscopy-negative, PCR-positive) (n=8), 14 of these 34 samples tested positive or borderline for ZIKV IgM, IgG or both. Positive or borderline results for both ZIKV IgM and IgG were registered in two of 13 samples from patients with a current infection with *P. falciparum* (including the patient with the mixed *P. falciparum/P. ovale* infection) and in one of eight samples from patients with a recently treated *P. falciparum* infection. Nine samples tested positive or borderline for ZIKV IgM only: four from patients with a current *P. falciparum*, two each from patients with a *P. vivax* and recently treated *P. falciparum* infection, and one from a patient with a *P. malariae* infection. Finally, one of 13 samples from patients with a current *P. falciparum* infection and one of five samples from patients with a *P. ovale* infection tested positive for ZIKV IgG only.

Virus neutralisation tests could not demonstrate a ZIKV infection in 11 of the 14 samples with positive or borderline results. Notably, we confirmed a recent ZIKV infection in one patient with a recently treated *P. falciparum* infection who had travelled in several African countries in the first half of 2015 and most recently in Cameroon (ZIKV IgM and IgG ratios in the ELISA were 2.61 and 7.50 respectively). The results from two patients with *P. ovale* (ZikV IgG ratio: 1.84) and *P. vivax* (ZIKV IgM ratio: 0.87) infection were not conclusive. The samples from patients with a current or recently treated *P. falciparum* infection with false positive ZIKV ELISA results showed ratios between 1.10 and 6.93 for ZIKV IgM and between 0.92 and 7.02 for IgG. One sample from a patient with a *P. vivax* infection tested borderline for ZIKV IgM. The ELISA ratio for ZIKV IgM in the sample from the patient with a *P. malariae* infection was 1.10.

False positive results were not correlated with parasite densities.

Plasmodium is known for its ability to trigger polyclonal B-cell activation resulting in the production of antibodies that are not microorganism-specific [2], possibly leading to false positive results in serological assays. Samples from malaria patients should therefore be included in panels used to evaluate the specificity of assays, particularly those detecting antibodies against tropical diseases.

Although the risk for malaria in South and Central America is limited and false positive results in the ZIKV ELISA due to *Plasmodium* infections may not pose a large problem in that part of the world, species distribution modelling has shown environmental suitability for ZIKV in a large part of tropical and sub-tropical regions including Africa where malaria is endemic [3]. According to the information available for our patient with a confirmed infection, active transmission of ZIKV may occur in Africa. We therefore believe that users

of the ZIKV ELISA should be aware of the possible interference.

Conflict of interest

None declared.

Authors' contributions

KM conceived the study, KM, DVDB and MVE analysed the data, JM and KA performed and analysed neutralisation tests, MVE and DVDB wrote the manuscript.

References

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