THE CHALLENGE OF ZIKA VIRUS DIAGNOSIS AFTER ACUTE INFECTION - ANTI-ZIKA VIRUS NS1 ANTIBODY ELISAS EXHIBIT POOR ACCURACY IN BRAZILIAN PATIENTS

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Accurate Zika virus (ZIKV) diagnostics are fundamental for an appropriate public health response to the current outbreak and to guide management of at-risk patients such as pregnant women. A false positive ZIKV diagnosis may trigger catastrophic consequences, such as abortion. The World Health Organisation (WHO) recommends serological testing for patients presenting seven or more days after symptom onset. However, serological ZIKV diagnosis is complicated by cross-reactivity with other flaviviruses such as dengue and yellow fever viruses, which are highly prevalent in South and Central America.

The WHO has emphasised the urgent need for field validation of available ZIKV serology tests. The Euroimmun IgG and IgM ZIKV NS1 ELISAs (Euroimmun, Lübeck, Germany) diagnostic tests widely used across South America, use recombinant ZIKV NS1 antigen, expressing mostly specific ZIKV epitopes, to reduce cross-reactive immune responses.

We determined assay sensitivity and specificity for the IgM and IgG assay among the Brazilian population, who have been exposed to all four serotypes of dengue over the last 30 years.Samples were sent for routine diagnostics to the reference Flavivirus laboratory at the Institute Oswaldo Cruz, Rio de Janeiro. Sensitivity was measured using paired sera collected in 2015-2016 from ZIKV PCR positive cases (n=57). Specificity was assessed using sera from subjects positive for dengue (serotypes 1-4 [n=89]), yellow fever infection (n=10) or vaccination (n=9); collected in or before 2013. ZIKV is estimated to have arrived in Rio in January 2015.

Overall IgG sensitivity and specificity was 0.72 (81/112) and 0.66 (70/106). Overall IgM sensitivity and specificity was 0.24 (26/109) and 1.00 (102/102).

The Euroimmun ZIKV ELISAs showed low accuracy among the Brazilian patients. The low IgG specificity is likely to reflect the repeated and long-term exposition to dengue and/or yellow fever in Brazil. The low IgM sensitivity probably indicates that these patients had experienced a previous primary infection with another flavivirus. Supporting this concept, our ZIKV IgM negative patients exhibited high IgG levels more typical of secondary flavivirus response.

Our findings highlight the necessity for more accurate serological ZIKV diagnostics. The low IgM, but high IgG levels, observed among the acute ZIKV-infected Brazilian patients, reinforce concerns that development of specific serological tests, in populations with chronic heterologous flavivirus exposure, is challenging. Accurate serological tests are essential for managing patients that present following acute infection, especially in pregnant women or those with neurological complications.