Pan American Health Organization

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TECHNICAL NOTE: Clarification on the possible cross reactivity in serological tests for IgM-measles and IgM-Zika virus

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Considering the occurrence of measles outbreaks in areas where the circulation of arboviruses has been documented or suspected, specifically those that are part of the differential diagnosis of febrile rash syndrome, the use and adequate interpretation of laboratory tests is critical to support the confirmation or discard of cases.

While molecular techniques based on the detection and amplification of viral genetic material can confirm the etiology of an infection, serological diagnosis (detection of antibodies by ELISA or immunochromatography) usually requires a more careful interpretation of the results.

The serological diagnosis of an acute infection is made by detecting IgM type antibodies or identifying a significant increase in IgG antibody titers (seroconversion) in paired serum samples, one sample having been obtained during the acute phase of the disease, and the other sample during the convalescent phase. IgG seroconversion confirms recent infection, however, considering that it is not always feasible to obtain paired serum samples, serological confirmation of acute infection is usually made by detecting IgM antibodies. Serological tests for the detection of IgM can sometimes generate false positive results, which can occur due to (i) the presence of antibodies that cross-react, (ii) the presence of substances that can interfere with the technique, or (iii) the limitations inherent to the test used.

False-positive results due to cross-reactions have been documented between measles IgM antibodies and human parvovirus (B19), rubella and herpesvirus 6. **However, no cross-reactivity has been described between species of the *Flaviviridae* family (Zika, dengue, etc.) with those of the *Paramyxoviridae* family (measles).**

With regard to factors that can interfere with the technique, the most common is the rheumatoid factor, a group of autoantibodies (antibodies that react against the body's own proteins) that are usually present in patients with rheumatoid arthritis. Similar interference has also been described with other infections such as leprosy, infective endocarditis, tuberculosis, trypanosomiasis, infectious mononucleosis, cytomegalovirus, influenza A, and hepatitis A.

Finally, the technical limitations of the available serological tests are also factors in determining the diagnosis. Thus, false-positive results may be expected for any laboratory test with less than 100% specificity (i.e., the ability of a test to correctly identify patients who do not have the infection). Taking into account that most of the commercial ELISA's for measles have specificities ranging from 94-98%, false positive results are possible and therefore careful interpretations are required in light of the clinical findings and the epidemiological context. Likewise, the positive predictive value of an assay (i.e., the frequency with which a positive result corresponds to a true positive) varies according to the prevalence of the disease. In situations where the prevalence of the disease is low, the positive predictive value of the assay is correspondingly low, and a higher proportion of false positive results would expected.

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