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Diagnostic performance of antigen testing for severe acute respiratory syndrome coronavirus 2



To the Editor:

We read the brief report by Villaverde et al¹ in which the authors posit a low diagnostic performance of antigen testing for severe acute respiratory syndrome coronavirus 2 in children. We agree that reverse transcriptase polymerase chain reaction (RT-PCR) testing is the diagnostic gold standard and that it would be desirable to perform timely RT-PCR testing in every suspect case, which unfortunately is not realistic. After a detailed consideration of their article, we want to offer the following remarks.

When validating a diagnostic tool a proper definition of the gold standard is required.² The authors claimed that testing targeted E and RdRp genes,¹ but no description of the RT-PCR kit or kits that were used were presented, nor were the definitions of “positive RT-PCR test” specified in terms of the required number of replicated genes and the cycle threshold cut-off values. Because in a pandemic setting even a low viral load in a symptomatic patient should prompt a coronavirus disease 2019 (COVID-19) diagnosis,³ the quantitative aspect of this issue seems to be minor in contrast to the reproducibility issues.

In addition, the study is stated to be retrospective,¹ so it is unclear why (and how many) patients were asked consent for paired sampling, and when the sample size was estimated. If patients truly were enrolled retrospectively, selection criteria and whether paired sampling was standard of care in the participating centers should be clarified. Simply put, a diagnostic test validation study should not have a retrospective design.²

Lastly, we want to remark that 98 out of every 100 negative-testing patients in the study were not infected by severe acute respiratory syndrome coronavirus 2,¹ which should be reassuring for clinicians in their everyday emergency department practice.

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Reply



To the Editor:

We welcome the opportunity to explain our findings further. First, we want to clarify that we included 6 expert microbiologists from the centers involved in the study. All co-authors played a fundamental role in the design and methodology of the study, as well as in the interpretation of the results. We want to especially highlight the input of microbiologists concerning these critical issues in our research.

Reverse transcriptase polymerase chain reaction (RT-PCR) positivity criteria are determined by the identification of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) E and RdRp genes.¹ However, there is currently no clear consensus on which cycle threshold marks the positivity of the RT-PCR test.² The pandemic situation entails a shortage of microbiological diagnostic resources, which has not allowed Spanish microbiology laboratories to use a single RT-PCR technique. Furthermore, RNA extraction equipment also varies between laboratories. For all of these reasons, it would not be accurate to set a singular criterion for the required number of replicated genes and the cut-off values of cycle threshold. Regarding the reproducibility between laboratories, although the use of different techniques is a potential source of variability, all RT-PCR techniques used in the laboratories involved in this study are validated and accredited by the European Union.³ All subjects included were symptomatic (inclusion criteria) and have been reported qualitatively, therefore, in our opinion, the results are comparable.

At the time of the design of our study, we calculated the sample size choosing a prevalence of SARS-CoV-2 infection of 5% and an expected sensitivity of the antigen test of 90%. We collected data from the paired samples taken at participating hospitals after verbal consent and followed the Panbio Coronavirus Disease 2019 Ag Rapid Test Device (Abbott Rapid Diagnostic Jena GmbH) manufacturer's instructions and the implementation protocols of the sites.^{4,5} As we describe in our report, patients with inclusion criteria were children age 0-16 years with symptoms compatible with SARS-CoV-2 infection within 5 days of attendance at an emergency department of 1 of 7 centers involved.

We agree that the validation of a diagnostic technique should be carried out with prospectively collected data. As mentioned in our discussion, this pilot study has allowed the working group (EPICO-AEP) to initiate a prospective validation study on the diagnostic accuracy of the Panbio