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EDITORIAL

Behind the curtain of a weak diagnosis of acute SARS-CoV-2 infection in children*

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After the declaration of the pandemic in March 2020, we are still facing a persistent COVID 19 crisis worldwide.[1] As the virus continues to spread globally and common symptoms overlap with those of other acute respiratory infections, the need for adequate actions based on robust diagnostic tests that support active surveillance systems seems yet to be key.[2,3] Huge scientific advances have been made in COVID-19 diagnosis, and several high-performance technologies have been developed in recent years.[2–4] Consequently, it is essential to select cost-effective diagnostic methods for monitoring in a different type of action settings, especially in ambulatory care backgrounds, where case management, isolation, contact tracing and quarantine are relevant to prevent viral transmission in the community.[3]

Originally developed for being used in a pregnancy test, lateral flow immunoassay (LFI), or "point of care testing" has been essential for in vitro diagnostics for a long time now.[5] Typically, they involved antibodies coupled to a nitrocellulose membrane as a line on an immuno-chromatographic strip.[5] Lateral flow devices for COVID 19 asymptomatic mass testing are proving controversial, and in a similar way, its uses seem to be questionable too in symptomatic patients.[6,7] In the study accomplished by Scotta et al., the authors investigated the accuracy of a SARS-CoV-2 antibody LFI test in symptomatic children and adolescents compared to a real-time polymerase chain reaction (RT-PCR), as a reference test, in acute care settings.[7] To achieve this goal, the authors designed a prospective multicenter observational study, from May to November 2020, where enrolled pediatric patients (> 2 months and < 18 years) that were admitted at emergency rooms (ERs) or visited outpatient clinics with a suspected diagnosis of COVID 19 within 14 days of onset of symptoms.[7] The authors analyzed data from 175 enrolled patients, of whom 51 (29.14%) were positive for SARS CoV-2 by RT-PCR and 36 (20.57%) by LFI. [7] To evaluate the antibody LFI test performance, authors assessed the sensitivity, specificity, positive predictive value, and negative predictive value. They found that the LFI had a sensitivity of 70.6% and a specificity of 96.8% measured after 7 days of the onset of symptoms compared with RT-PCR.[7] The performance of LFI did not improve statistically between 7 and 13 and after 14 days of symptoms onset and did not present significant differences between ages (< 2 or > 2 years old).[7] Furthermore, the authors found even a lower performance of the LFI in comparison with the commercial description.[7]

Several explanations can be postulated on the low precision of LFI in acute SARS-CoV-2 infection in children. First, not all infected patients with SARS CoV-2 elicited IgG antibodies against the virus.[8,9] In fact, more than half of the children infected with SARS CoV-2 cannot elicit detectable antibodies in the acute phase of infection.[10] Second, the antibodies response seems to be higher in a convalescent period in comparison with the acute phase of infection in both children and adults.[10,11] Sera kinetics from infected subjects showed that antibodies response is associated with time after symptoms onset.[11] Third, children have lower levels of Spike and Nucleocapsid antibodies than adults.[12] This could explain why Scotta et al. showed less performance than attributed by the manufacturer.[7] The antibody lateral flow test explored in the study (Wondfo Biotech Co., Guangzhou, China) evaluates the presence of antibodies against the Spike protein of SARS CoV 2, which may be lower in children and adolescents enrolled in the study.[7,12] Lastly, severe COVID-19 correlates with higher antibody levels in infected patients.[11,13]

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Scotta et al. showed in this journal and others authors explored elsewhere that lateral flow tests based on antibodies measurement may not be the best approach for early diagnose of SARS CoV-2 acute infection in children.[6,7] From this perspective, the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control recommend that these methods should not be used to establish acute SARS-CoV-2 infection.[14,15] Diagnostic methods based on virologic testing should be done to detect viral infection.[16] However, we understand that early, quick, and affordable acute COVID 19 detection is key for the management of triage, isolation, quarantine, and follow-up of patients and their contacts, mainly in health facilities of low-settings countries. In this way, antigen test represents an alternative to antibody tests, RT-PCR, or other nucleic acid amplification tests (NAATs).[17] However, a correct interpretation of each test result is essential for case management. Finally, the "gold standard" for acute SARS-CoV-2 infection remains laboratory-based RT-PCR and NAATs.[18] Thus, LFI for antibody detection test or antigen-based test results should be confirmed with a laboratory-based NAAT, especially if the result of the antigen test is inconsistent with the clinical context.[17]

Facing the persistence of viral circulation in a context of low vaccine coverage in the developing world and in the emergence of new viral variants, it is essential to clearly establish the correct use of diagnostic tests for acute SARS CoV2 infection. Each diagnostic test should be applied for the correct purpose, and its indication must be weighed against well-designed cost-effectiveness studies. Then, each country will have to decide which are the best affordable and possible strategies that can be applied for diagnosis and then design clear and consistent decision algorithms.

Conflicts of interest

The author declares no conflicts of interest.

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