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Letter to the Editor

Possible drawbacks of relying only on molecular testing for diagnosing SARS-CoV-2 infections



We read with interest the article of Smith and colleagues,¹ who concluded that it should be widely communicated to the public that molecular assays are superior to lateral flow tests (LFT) in symptomatic people with suspected severe acute respiratory coronavirus 2 (SARS-CoV-2) infection. Although widespread diagnostic testing remains a major cornerstone in strategies aimed at limiting or preventing the transmission of SARS-CoV-2 in the community, we are willing to highlight some limitations in preventive policies exclusively based on a molecular approach.

The first limitation is the current availability of molecular tests, which remains rather limited around the world. According to updated data from a survey by the American Association of Clinical Chemistry (AACC), the vast majority of clinical laboratories, which responded all around the world (i.e., nearly 80%) are still facing hard challenges in providing routine SARS-CoV-2 testing or increasing their testing capacity (most difficulties were attributed to recruiting staff and obtaining supplies).² Therefore, widespread sole use of molecular testing cannot be considered a feasible or effective solution, at least not presently, since these types of assays will not be accessible by many patients worldwide, neither they will permit the generation of timely test results, thus leaving several laboratories plagued by a dramatic backlog of samples to be processed.² Providing rapid results is especially important given the emergence of new SARS-CoV-2 variants of concern (e.g., delta or lambda) that are associated with higher and longer periods of infectivity compared to the prototype strain that originally emerged in Wuhan in 2019,³ which requires the adoption of tests with the capability of rapid viral detection, especially in subjects with higher viral load.

The diagnostic performance of LFTs and laboratory-based SARS-CoV-2 antigen immunoassays is a second aspect that must be considered. Although we would all agree that molecular testing is still characterized by higher diagnostic sensitivity for detecting SARS-CoV-2 mRNA, it seems important to reaffirm that a positive test does not always translate into real infectiveness. Several lines of evidence attest that subjects with a positive molecular test but low viral load (e.g., above 30–32 cycle thresholds) detected 1–2 weeks after the onset of symptoms have a very low, virtually meaningless risk of being infective and capable of transmitting the virus, as reflected by the negativity of viral cultures.⁴ The positivity with molecular tests in these subjects may hence be attributable to residually low viral load, which is unlikely to be sufficient for infecting other people, or to the shedding of non-viable SARS-CoV-2 genetic material present within or outside the host cells, which is not associated by any infective potency.

Replacing genetic testing with antigen immunoassays in symptomatic subjects seems the best strategy for rapid and widespread

screening and/or diagnosis of SARS-CoV-2 infections. A meta-analysis has recently concluded that the pooled diagnostic sensitivity of SARS-CoV-2 antigen testing in subjects with onset <7 days of typical symptoms of coronavirus disease 2019 (COVID-19) is as high as 84% compared to molecular tests,⁵ thus underpinning that these tests represent a trustable means for large population screening, especially during sudden emergence of large local outbreaks.

In conclusion, we do not agree with the concept that the use of LFTs and laboratory-based SARS-CoV-2 antigen immunoassays should be discouraged to the public, but we rather proffer that the use of (rapid) antigen tests shall be incorporated into validated algorithms aimed at filling the still important gaps that testing programs experience when relying only on SARS-CoV-2 molecular testing, especially when demand is high.

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