Usefulness and limitations of implementing rapid tests for the diagnosis of COVID-19 in Latin America

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Dear Editor

Currently, the diagnosis of COVID-19 is made through the identification of the SARS-CoV-2 virus by the RT-PCR technique [1]. The most accepted protocol, the one from the Charité Virology Institute, Germany, was recommended by the World Health Organization [WHO]. Experiences in countries such as South Korea have shown that large-scale diagnostic capacity is key to controlling this pandemic. However, the protocol for these tests still complicated and expensive, being primarily suited to robust, centralized diagnostic laboratories, which would be limited in regions such as Latin America. For these reasons, performing molecular assays for the diagnosis of suspected cases of COVID-19 has been a challenge in many Latin American countries, as well as low and middle-income countries undergoing sustained community transmission. A cost-effective rapid diagnostic device that could be used by the healthcare system without the need for a well-established molecular laboratory - not requiring specialized human resources management, is crucial for diagnosis [2]. Even now, there are multiple settings where decision is still very complex. For example, which tests can be used for pre-surgical elective patients? Serological tests are limited and out of interpretation for single use. Then, combined approaches, such as serological, plus molecular tests joint with screening surveys, isolation, and strict education before an elective surgery, would be an approach [3].

An initiative towards the creation of rapid tests for COVID-19 was taken by China at the early stages of the outbreak [nowadays declared a pandemic], by developing a rapid test for combined IgG-IgM SARS-CoV-2 antibodies using immunological approaches. These tests require less than 15 minutes to generate results and determine a recent SARS-CoV-2 infection. To carry out these tests, 397 blood samples from patients infected with SARS-CoV-2 were analyzed, of which 352 were positive, resulting in a sensitivity of 88.66%; 128 patients with respiratory infections other than those caused by SARS-CoV-2 were also analyzed, of which 12 were positive, generating a specificity of 90.63%. Considering that SARS-CoV-2 belongs to the same large virus family of the previously known MERS and SARS coronavirus, rapid tests presumed that IgM and IgG antibodies production could be detected in

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the patient's blood within 3-to-6 days and after eight days, respectively. Approximately 22.0% of the patients who were confirmed positive by RT-PCR showed a negative result in rapid immunological assays [4].

A recent Chinese study outlined the temporal kinetics of the antibody response to SARS-CoV-2 in infected patients. The authors showed that IgM and IgA antibodies production against SARS-CoV-2 start from the first day after the onset of the symptoms. However, they observed that each patient has different kinetics for the development of antibodies. Therefore, the meantime of appearance of the antibodies is affected by factors such as the day of sample collection and when the onset of symptoms occurred in each patient. They also showed that RT-PCR sensitivity within the first three days after symptom onset was higher than 90%, decreasing to less than 50% after 14 days. Therefore, the positive detection rate increases significantly for each patient when an immunoassay test is combined with RT-PCR, reaching a diagnostic sensitivity of 98.6% [5].

Serological test outcomes depend on the time of the onset of symptoms, increasing the risk of viral transmission. The antibody response can take several days or weeks to be reliably detectable. Herein, negative results would not exclude an ongoing SARS-CoV-2 infection, particularly among those with the recent exposure of the virus. Moreover, another potential issue in these tests is the cross-reactivity with non-SARS-CoV-2 proteins, generating false-positive results that may be due to past infections. Thus, serological tests seem to be more relevant when patients undergo late complications of the disease, time when RT-PCR can show a false negative result due to the elimination of the virus over time. Its use will be valuable in epidemiological studies, vaccine studies, or for risk assessment in health workers [6]. Therefore, rapid serological tests are substantially limited compared to the RT-PCR approach, and, therefore, should not be used for individual risk assessment or decision-making on public health measures [7].

Regarding the use of rapid tests, in early April 2020, the US Food and Drug Administration [FDA] authorized Cellex INC to market a rapid antibody test for COVID-19 [Rapid Test IgG/IgM CelS qSARS-CoV-2], being the first antibody-related test-launched during the pandemic [https://www.fda.gov/media/136622/download]. During pre-market trials, 128 samples were positively confirmed through RT-PCR, 120 were positive for IgG, IgM, or both, and 250 confirmed negatives, 239 were negative in the rapid test. Thus, compared to the RT-PCR results, the tests achieved 93.8% (IC 95%: 88.06-97.26%) of true positive findings and 96.4% (IC 95%: 92.26-97.78%) of true negatives, according to the insert (https: //www.fda.gov/media/136625/download). Currently, there is an extensive list of rapid tests approved by National Regulatory Authorities belonging to the International Forum of Medical Device Regulators (IMDRF), these include the United States FDA, Australian TGA, Singapore HSA, ANVISA from Brazil, HEALTH CANADA from Canada, PMDA from Japan, MFDS from South Korea and authorities from the European Community. This list (updated until April 14) comprises a total of 32 kits manufactured mostly in countries such as China, the United States, and Brazil. On the other hand, the WHO recommends the implementation of the SARS-CoV-2 molecular detection protocol by RT-PCR due to the series of limitations of the use of IgM and IgG antibody detection tests previously indicated in this document [8].

In conclusion, according to the scientific evidence available so far, it is essential to emphasize that tests based on the detection of antigens or antibodies [rapid tests], would help us significantly to improve the demand for COVID-19 diagnosis facing by many countries. Nevertheless, the kinetics of IgG or IgM antibodies production against the SARS-CoV-2 virus is still unknown, being hard to determine the appropriate period to perform rapid tests. Therefore, we reinforce the usefulness of RT-PCR diagnostic tests as a standard approach in the diagnosis. Rapid tests must have their performance evaluated in clinical practice by specialized people to be used in the COVID-19 diagnosis, avoiding inadequate false-negative information.

Funding
None

Conflicts of interest
All authors report no potential conflicts, except AJRM. AJRM is a COVID-19 consultant for Abbott Laboratories de Colombia S.A.

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