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A simplified alternative diagnostic algorithm for SARS-CoV-2 suspected symptomatic patients and confirmed close contacts (asymptomatic): A consensus of Latin American experts

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ABSTRACT

Introduction: Latin America accounts for one-quarter of global COVID-19 cases and one-third of deaths. Inequalities in the region lead to barriers to the best use of diagnostic tests during the pandemic. There is a need for simplified guidelines that consider the region's limited health resources, international guidelines, medical literature, and local expertise.

Methods: Using a modified Delphi method, 9 experts from Latin American countries developed a simplified algorithm for COVID-19 diagnosis on the basis of their answers to 24 questions related to diagnostic settings, and discussion of the literature and their experiences.

Results: The algorithm considers 3 timeframes (≤ 7 days, 8–13 days, and ≥ 14 days) and presents diagnostic options for each. SARS-CoV-2 real-time reverse transcription-polymerase chain reaction is the test of choice from day 1 to 14 after symptom onset or close contact, although antigen testing may be used in specific circumstances, from day 5 to 7. Antibody assays may be used for confirmation, usually after day 14; however, if clinical suspicion is very high, but other tests are negative, these assays may be used as an adjunct to decision-making from day 8 to 13.

Conclusion: The proposed algorithm aims to support COVID-19 diagnosis decision-making in Latin America.

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Introduction

In May 2020, the Pan American Health Organization (PAHO) declared Latin America an epicenter of COVID-19 (Pan American Organization, 2020). In November 2020, cumulative cases in the

region accounted for approximately 24% of cases and 33% of deaths globally (World Health Organization, 2020c).

Although PAHO (Pan American Health Organization, 2020) and other organizations (2020), (2019-nCoV Working Group. Communicable Diseases Network Australia, 2020; CDC, 2020a) have released laboratory guidance for diagnosing COVID-19 cases, few have considered the availability of tests when making their recommendations. Latin America is a region with great contrasts in socio-economic status and health resources (World Bank Development Indicators DataBank, 2020) and, as in developed countries

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(Pablos-Méndez et al., 2020), the availability of COVID-19 tests and trained personnel are subject to supply chain and personnel pressures.

A panel of Latin American experts gathered to discuss the best use of diagnostic methods in the region and propose a simplified algorithm alternative.

Methods

A modified Delphi method was used to prepare an algorithm using the iAdvise platform (Within3, OH, USA). Over 2 weeks, a panel of 9 experts from Latin American countries iteratively answered 24 online questions about diagnostic methods and their application in specific cases. The questions were written by an external microbiologist infectious disease specialist with high-level expertise in the area and reviewed by a multidisciplinary panel. The experts also met twice during this period to review the proposed algorithm.

The consensus level was determined on each of the 24 questions using a simple yes/no count. Further discussion was necessary to reach a consensus for questions with a low level of agreement (less than 7/9 matched responses). Recommendations were only made if the consensus level was above this threshold.

Consensus results

The proposed algorithm is divided into 3 parts according to time after close contact or time after symptoms onset

(Figure 1, ≤ 7 days, 8-13 days and ≥ 14 days from close contact or symptoms).

The expert panel recommended real-time reverse transcription-polymerase chain reaction (rRT-PCR) as the primary test in the initial 14 days from symptoms onset or close contact. Early sample collection from the upper respiratory tract minimizes the probability of negative rRT-PCR results (Mallett et al., 2020). If negative, rRT-PCR may be repeated in a different sample at the discretion of the physician. Antigen detection tests are most likely to perform well in patients with high viral loads, pre-symptomatic (1–3 days before symptom onset) and early symptomatic phases of the illness (first 5–7 days of illness) (World Health Organization (último), 2020). These tests may be used as an alternative in high prevalence settings or exceptional cases when rRT-PCR tests are unavailable.

rRT-PCR is the diagnostic test of choice 8–13 days after symptoms onset. If results are negative, rRT-PCR may be repeated. In some cases, antibody assays may be used during this period; however, consideration should be taken when the results are negative (false negative tests are common in this period), or when immunoglobulin(Ig)M is positive, and IgG is not, raising the possibility of a false positive test (Deeks et al., 2020a).

Antibody detection assays are recommended 14 days after symptoms onset or close contact for initial testing in immunocompetent hosts. In most cases, antibody assays are used to trace contacts or for other epidemiological reasons (Jayamohan et al., 2020); however, they may be used for individual diagnosis in specific circumstances.

A proposal for an alternative simplified diagnostic algorithm for SARS-CoV-2 suspected symptomatic patients and confirmed close contact (asymptomatic) v3

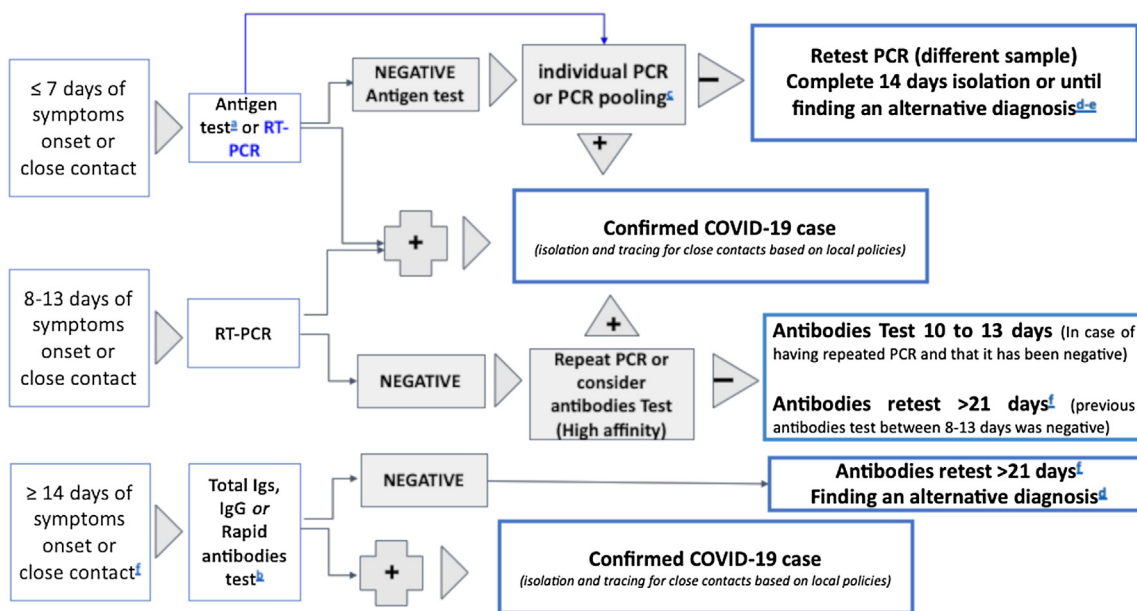


Figure 1. A proposal for an alternative simplified diagnostic algorithm for SARS-CoV-2 suspected asymptomatic patients and close contacts (asymptomatic individuals).
^aIdeal use only in high prevalence (>5–10%) scenarios with symptomatic patients or selected settings (Emergency Rooms, elderly residences, health care personnel, surgical urgencies). The best timeframe for collection in asymptomatic individuals is 5–7 days after the close contact. Providers conducting testing on asymptomatic populations must be aware of the potential for a presumed false-positive result with an antigen test that will necessitate confirmation with a subsequent PCR test (Virginia Department of Health, 2020).

^bConsider the interpretation of the result as “Confirmed exposure to SARS-CoV-2”, and in the case of IgM positivity only, consider as a probable false positive (Kubina and Dziejdzic, 2020). Repeat determination with other methods, like high-affinity antibody assays (total immunoglobulins or IgG).

^cConsider PCR pooling for population screening with low pre-test probability (<10%) to ensure assay cost-effectiveness or in negative antigen patients. If the pooling result is positive, individual rRT-PCR must be performed for each pooled sample, so the maximum number of samples to be included in a pool is 10 (CDC, 2020b).

^dConsider multiplex PCR, including influenza A/B or respiratory panel with influenza, VSR, and other viral/bacterial/fungal pathogens (Kim et al., 2020; Zhu et al., 2020). The presence of other respiratory virus does not rule out co-infection by SARS-CoV-2, therefore this possibility should not be neglected (and should be thoroughly investigated if the clinical- epidemiological context suggests it).

^eConsider antibody tests if other results are negative.

^fConsider day 14 of symptoms onset or day 21 of close contact.

Ig, immunoglobulin; PCR, polymerase chain reaction; rRT-PCR, real-time reverse transcription PCR; RSV, Respiratory Syncytial Virus.

Discussion

Available diagnostic methods

Criteria for choosing a test in resource-constrained settings

The World Health Organization (WHO) has published the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free, and Deliverable to end-users) criteria that may be used as a benchmark for identifying the most appropriate diagnostic tests for resource-constrained settings (Kosack et al., 2017). However, these criteria are non-specific and need to be adapted to each diagnostic need, and not all test methods can be simplified to match the ASSURED criteria.

The WHO authors identified 6 steps that must be addressed when selecting an in vitro diagnostic test: (a) define the test's purpose; (b) review the market and check each product's specification; (c) review the test's regulatory approval; (d) obtain data on the diagnostic accuracy of the test under ideal conditions (i.e., in laboratory-based evaluations); (e) obtain data on the diagnostic accuracy of the test in clinical practice; and (f) monitor the test's performance in routine use.

Viral detection according to the clinical course

The detection of virus particles or the corresponding immunological response varies with time since infection (Figure 2) (Siam et al., 2020; Mallett et al., 2020; Ravi et al., 2020). A systematic review concluded that collecting samples early in the course of the disease minimizes the risk of false-negative results (Mallett et al., 2020).

Another systematic review of immunological response studies summarized assay results for IgG, IgM, IgA, total antibodies, and IgG/IgM since the onset of symptoms (Deeks et al., 2020b). All showed low sensitivity during the first week (30.1%, 95% CI 21.4–40.7), which increased in the second week (72.2%, 95% CI 63.5–79.5), and peaked in the third (91.4%, 95% CI 87.0–94.4) and fourth weeks (96.0%, 95% CI 90.6–98.3). Specificity was not evaluated over time but was generally high, IgM 99.1% (range 97.5%–99.8%) and IgG 98.6% (range 96.7%–99.5%).

Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR)

rRT-PCR is the gold-standard molecular technique for detecting SARS-CoV-2 viral RNA in all recommended samples. It targets the

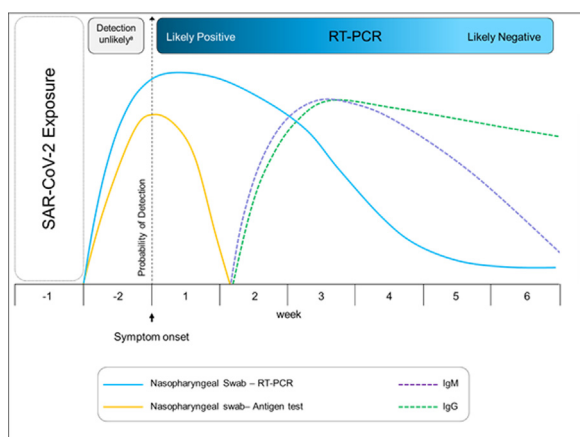


Figure 2. Estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset (modified from Sethuraman et al. (2020)).

*Detection only occurs if patients are followed up proactively from the time of exposure.

Ig, immunoglobulin; PCR, polymerase chain reaction; RT-PCR; real-time reverse transcription PCR.

following sequences that code for structural viral proteins: spike (S), membrane, envelope, nucleocapsid (N), and RNA-dependent RNA polymerase. Both S and N proteins are highly immunogenic (Ravi et al., 2020). The S proteins seem to be the primary target of neutralizing antibodies for correlated coronaviruses (Berry et al., 2010). The high infectivity of SARS-CoV-2 has compelled the US Centers for Disease Control to publish rRT-PCR primers and probes together with all relevant literature for public access (Khalaf et al., 2020). The positive rate of rRT-PCR detection is dependent on the sample type, with differences among bronchoalveolar lavage fluid (93%), fiber bronchoscope brush biopsy (46%), sputum (72%), nasal swabs (63%), pharyngeal swabs (32%), feces (29%), and blood (1%) (Wang et al., 2020). Combining nasopharyngeal and oropharyngeal swabs is now the most commonly used sample type for diagnosing COVID-19 active infection (Lai and Lam, 2020). In September 2020, the WHO published a guideline recommending that saliva should not be the only sample type used for routine clinical diagnostics because of the wide variation in collection methods (World Health Organization, 2020a).

The virus can be detected at least 48 h before the onset of symptoms (pre-symptomatic cases) and 12–14 days (at least 6–7 days) after, in samples from the upper respiratory tract (nasopharyngeal and oropharyngeal swabs) and for a median of 20 days in samples from the lower respiratory tract including sputum, tracheal aspirate and bronchoalveolar lavage (Pan American Health Organization, 2020; Mallett et al., 2020; Lippi et al., 2020; He et al., 2020).

Pooling PCR samples increases testing efficiency, especially where few tests are available, particularly in areas with low prevalence and scarce health resources (CDC, 2020b). Samples from several individuals are pooled, and the combined sample is tested with a single test. If the test is negative, all subjects are negative. If the test is positive, all individuals must be tested again to find the infected ones (CDC, 2020b). The US Food and Drug Administration initially proposed (CDC, 2020b) that 5 was the maximum number of samples to be pooled for rRT-PCR; however, other studies found that the ideal number of pooled samples depends on the disease prevalence in the tested population (CDC, 2020b; Food and Drug Administration USA, 2020; Hanel and Thurner, 2020; Deckert et al., 2020). One constraint of pool testing is that the false-negative rate may increase owing to the dilution of positive samples; however, this limitation can be minimized by using high-sensitivity rRT-PCR tests (Cherif et al., 2020). In general, the larger the pool of specimens, the higher the likelihood of generating false-negative results (CDC, 2020b).

As with all diagnostic tests, the rRT-PCR predictive value depends on its specificity and sensitivity, and the disease prevalence in the target population (Lorentzen et al., 2020) (Table 1). False-negative results may result from technical issues, from sampling to amplification, including thermal inactivation (Lippi et al., 2020). A confirmatory test (e.g., repeated rRT-PCR) may be warranted if initial results are negative and the clinical characteristics are very suggestive of infection (Lai and Lam, 2020; Lorentzen et al., 2020).

Antigen detection assay

SARS-CoV-2 virus particles can be directly detected using immunoassays (Ji et al., 2020). SARS-CoV-2 N protein may be detected in nasopharyngeal swabs and urine samples of COVID-19 patients within 3 days of onset of fever (Diao et al., 2020).

A Cochrane systematic review (Dinnes et al., 2020a) of 8 antigen detection test evaluations (5 studies, 943 samples) found that sensitivity varied considerably (0%–94%). Average sensitivity was 56.2% (95% CI 29.5–79.8) and specificity 99.5% (95% CI 98.1–99.0). Data for individual antigen tests were limited, with no more than 2

Table 1
Correlation between pre-test probability and test results^a.

Pre-test probability ^b	Negative predictive value (NPV) ^c	Positive predictive value (PPV) ^d	Increased likelihood
Low	High	Low	False positives (FP) True negatives (TN)
High	Low	High	True positives (TP) False negatives (FN)

^a Modified from CDC information for laboratories about coronavirus (COVID-19) (CDC, 2020e).

^b Pre-test probability is correlated with the prevalence of the disease and clinical presentation.

^c NPV is the probability of a patient without the disease having a negative result (True negative).

^d PPV is the probability of a patient with the disease having a positive result (True positive).

studies for any test. There were no studies in asymptomatic persons (Dinnes et al., 2020a).

For asymptomatic individuals, a non-peer-reviewed study (Alemany et al., 2020) found that for a pre-test probability of 5%, the negative predictive value was 99.6% (95% CI 99.5–99.7), and the positive predictive value was 81.5% (95% CI 65.0–93.2). At this pre-test probability, the estimated number of false-negatives and false-positives per thousand tests were 4 (95% CI 3–5) and 12 (95% CI 4–27), respectively. The authors stressed the need for confirmatory testing of positive tests with nucleic acid amplification techniques in these circumstances (Table 2).

In comparison with rRT-PCR (Table 2), rapid antigen detection tests tend to have lower sensitivity, and, owing to the increased risk of false-negative results, some authors consider such tests only as an adjunct to rRT-PCR (Siam et al., 2020). However, antigen detection tests have the advantage of being simple to perform, and they can play a role in settings with limited access to rRT-PCR, particularly for symptomatic patients with a high viral load and within the first 5–7 days from symptoms onset (Lai and Lam, 2020). The viral load is directly related to the test's sensitivity (Dinnes et al., 2020b).

Antibody assays

Serological tests are essential because they provide information on patients who have been infected and already recovered and asymptomatic patients who were never diagnosed (Ravi et al., 2020). In a study (Long et al., 2020) that followed the immunological response in COVID-19 patients, 3 types of seroconversion were observed: synchronous seroconversion of IgG and IgM (9 patients), IgM seroconversion earlier than that of IgG (7 patients), and IgM seroconversion later than that of IgG (10 patients). A study (Guo et al., 2020) profiling the early SARS-CoV-2 humoral response found that IgM median time for detection was 5 days after symptoms onset, and IgG was detected at a median of 14 days after symptoms onset.

For SARS-CoV-2, IgG and IgM produced against the S and N proteins are of particular diagnostic interest. One study indicates that the S protein tends to cause a more significant immune response than the N protein, eliciting neutralizing antibodies (Amanat et al., 2020). However, other studies argue that the N

protein is more immunogenic, as it is expressed abundantly during active infection (Ravi et al., 2020).

Some examples of serological tests performed at specialized laboratories to measure patient antibodies are rapid diagnostic tests, enzyme-linked immunoassay (ELISA), chemiluminescent immunoassay (CLIA), and neutralization assay (Ravi et al., 2020). One review found differences in sensitivity by test technology. CLIA was more sensitive (97.5%, 95% CI 94.0–99.0) than ELISA (90.7%, 95% CI 83.3–95.0) or colloidal gold immunoassay-based lateral flow assays for IgG/IgM (90.7%, 95% CI 82.7–95.2) (there were also differences for IgG but not IgM). There was limited evidence of specificity differences among technology types (Deeks et al., 2020a).

Vaccination status should be considered in the interpretation of antibody assays, and caution should be exercised because the natural immune response differs from the vaccine immune response. Vaccine efficacy may vary according to age, geography, dosing schedule, and variant type (He et al., 2021). Neutralizing antibodies are the most common correlates of vaccine efficacy, and their titer is highly associated with the protective effect and its duration (He et al., 2021). In patients previously infected with SARS-CoV-2, IgM and IgG antibody titers decreased significantly over 6.2 months while increasing neutralizing breadth and potency (Gaebler et al., 2021). Although in the early phase (up to 28 days) immunogenicity profile of approved vaccines is established, the long-term immunogenicity data are unknown at this time (Sui et al., 2021). In an individual with a history of COVID-19 vaccination, an antibody test specifically evaluating IgM/IgG to the N protein should be used to evaluate the evidence of previous infection (CDC, 2020c).

Other essential considerations for antibody testing include the test timing, previous infection, immune status of the individual, and cross-reactions, which can alter test results (Siam et al., 2020).

Other tests

CRISPR technology

The CRISPR gene-editing tool has been used to construct an accurate, fast and simple-to-use SARS-CoV-2 detection test. DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTR) assay is

Table 2
Comparison of diagnostic options for SARS-CoV-2 detection^a.

Type of test	Specimen sample	Test	Time (mm)	Sensitivity (%)	Specificity (%)	Cross-reactivity
NAAT ^b	Nasopharyngeal swab, sputum, bronchoalveolar lavage fluid	RT-PCR	240	71–98	95	No
		CRISPR	40	97	100	No
		LAMP ^c	30–60	75–90	93–99	No
Antigen detection	Nasopharyngeal swab	–	15–30	62–92	100	Yes
Immune assay	Blood	–	15–30	92–100	93–100	Yes

^a Modified from Siam et al. (2020).

^b Nucleic acid amplification test.

^c Hellou et al. (2020).

based on CRISPR–Cas12, and it can distinguish SARS–CoV-2 with no cross-reactivity for related coronavirus strains using N gene gRNA within 40 min (Broughton et al., 2020).

Loop-mediated isothermal amplification (LAMP)

Loop-mediated isothermal amplification (LAMP) is a method of isothermal DNA replication that uses 6 DNA oligos that hybridize with 8 different regions of a target molecule in an accelerated format. Reverse transcriptase can improve sensitivity within the reaction when detecting an RNA target (RT-LAMP), such as SARS-CoV-2 RNA (Rabe and Cepko, 2020).

Special considerations

Choice of rRT-PCR vs antigen test

rRT-PCR is the initial recommended test for diagnosing SARS-CoV-2 in symptomatic patients in all international guidelines (Pan American Health Organization, 2020; 2019- nCoV Working Group. Communicable Diseases Network Australia, 2020; World Health Organization, 2020; CDC, 2020d). However, as the number of patients presenting with COVID-19 symptoms increases, there has been a shortage of diagnostic resources, like swabs, PCR reagents, RNA isolation kits, and growing demand for rapid, on-site diagnostics (Ravi et al., 2020).

Point-of-care tests, including rapid antigen detection tests, are also recommended as an initial test by the CDC, particularly in the early days of symptoms or in cases of close contacts in a high-risk congregated setting (CDC, 2020e). Infection prevalence at the time of testing and the clinical context impact pre-test probability (CDC, 2020e) (Table 1) and should be taken into account before and after test results. Testing of asymptomatic contact cases may be considered after 5–7 days of contact, even if the antigen detection tests are not explicitly authorized for this use. Asymptomatic cases have been demonstrated to have viral loads similar to symptomatic cases. A negative antigen detection test should not remove a close contact individual from quarantine requirements (World Health Organization (último), 2020).

Compared with rRT-PCR, antigen detection tests are cheaper, have a similar specificity, and usually deliver results faster, but have lower sensitivity (CDC, 2020e). The choice of test should depend on availability of the test and trained personnel, along with the above factors.

Types and results of immunological tests

Antibody tests available for laboratory use include ELISA, advanced CLIA, and laboratory-independent CGIA (Deeks et al., 2020a). See details above. Tests that detect antibodies with a high affinity for the SARS-CoV-2 virus are more likely to indicate neutralizing antibodies (Jayamohan et al., 2020).

The need for quarantine

The need for quarantine has been revised recently and depends on vaccination status and test positivity. See (CDC, 2022)

Image studies

Chest computed tomography (CT) is considered the primary imaging diagnostic modality for examining patients with COVID-19 (Güneyli et al., 2020). A Cochrane review of radiologic tests (13 studies, 2346 participants) showed that the pooled sensitivity of CT for the diagnosis of COVID-19 was 86.2% (95% CI 71.9–93.8) and specificity was 18.1% (95% CI 3.71–55.8) (Salameh et al., 2020). Ai et al. suggested that in patients with negative rRT-PCR tests, a combination of exposure history, clinical symptoms, and typical CT imaging features and dynamic changes should be used to identify COVID-19 (Ai et al., 2020).

SARS-CoV-2 genotyping

Genotyping tests, most commonly amplicon-based methods, are central to the epidemiology work of tracking SARS-CoV-2 transmission and evolution, although technical issues may affect their accuracy (Kubik et al., 2021). Rapid detection of different genotypes is important for an effective response to COVID-19 outbreaks (Yin, 2020). No current guidelines recommend viral genotyping for the diagnosis of SARS-CoV-2 infected individuals, and it is our understanding that such tests should only be performed in an epidemiology setting or in the exceptional case of investigating reinfection (Tomassini et al., 2021).

Conclusions

COVID-19 diagnosis is a cause for uncertainty among physicians, health professionals and public health authorities in Latin America. Our methodology, involving 24 questions answered by Latin American experts, resulted in a simplified algorithm for testing involving symptomatic people or close contacts in 3 windows of time (≤ 7 days, 8–13 days, and ≥ 14 days).

Despite the disparities in health care access within the region, we regarded rRT-PCR as the standard diagnostic test for SARS-CoV-2 infection, from the onset of symptoms to 13 days post. This recommendation is consistent with all of the key published guidelines (Pan American Health Organization, 2020; World Health Organization, 2020b; 2020). Sample pooling should be used in low-resource and low prevalence of the disease ($<30\%$) settings (CDC, 2020b; Hanel and Thurner, 2020).

We also recommend tests for antigen detection from upper respiratory tract samples as a simple point-of-care diagnostic test in high prevalence settings, during a short time after onset of symptoms (5–7 days) (World Health Organization (último), 2020). We considered it a good alternative in these situations, particularly where rRT-PCR is not readily available. Antigen detection tests are also a reasonable option in the CDC guidelines for SARS-CoV-2 detection (CDC, 2020f).

Immunological assays are not ideal for the diagnosis in the early days of SARS-CoV-2 infection according to the WHO and PAHO guidelines (Pan American Health Organization, 2020; World Health Organization, 2020a). However, we suggest that they can be used 14 days since symptoms onset, or 21 days since close contact, for tracing close contact cases or in exceptional situations when an individual diagnosis is necessary (or before that period, from 8 days since symptoms onset) or when clinical suspicion is very high, but other diagnostic tests are negative.

Depending on local epidemiology and clinical symptoms, for all suspect COVID-19 patients, diagnostic testing for conditions such as malaria, dengue, typhoid, influenza, and other respiratory diseases should also be considered (Chi et al., 2020; United Nations and Department of Healthcare Management and Occupational Safety and Health, 2020).

In summary, the proposed simplified algorithm aims to support medical decision-making in Latin America, considering published international guidelines and the region's health access inequalities.

Limitations

Although based on well-established consensus formation techniques and drawing on the panel's expertise, these recommendations do not constitute a statement from the institutions or associations to which these professionals are affiliated. The main limitations of this expert panel consensus are selection bias, observer bias, confirmation bias, publication bias, and cohort effects (i.e., the different features and pace of the COVID-19 pandemic in each country of Latin America).

These recommendations were developed before vaccination was widely available and understanding the long-term immunogenicity profile of each vaccine platform is paramount to establishing the best way to diagnose COVID-19 in vaccinated individuals. These recommendations will probably be modified once long-term data are presented.

Implications

The proposed algorithm may support COVID-19 diagnosis decision-making in Latin America, considering published international guidelines and the region's health access inequalities.

Conflict of interest statements

Dr. Marcano received honoraria as a Roche Diagnostics Latam External Advisor and participated in Advisory Boards sponsored by Novartis Pharma and Pfizer.

Dr. Condino worked as a consultant for Roche, Takeda, CSL Behring, Octapharma, Sanofi Genzyme, GSK, Astra Zeneca, and Novartis.

Dr. Bonvehi has received honoraria as a speaker from Productos Roche SAQel Argentina and is the PI in two clinical trials of vaccines for COVID-19 sponsored by Laboratorio Elea and Janssen.

Dr. Cucho received honoraria from Roche Diagnostics LATAM and Mindray.

Dr. Perez acted as a consultant for Roche Chile and Sanofi Pasteur Chile. He also received research support from Merck, Sharp and Dohme Chile, Viiv Healthcare.

Dr. Saenz-Flor acted as a speaker for Roche Diagnostics in Ecuador and Peru.

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Ethical approval

As a consensus guide for practitioners, without human or animal involvement, there was no request for ethical approval.

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