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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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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Highlights

- The algorithm is divided into three parts according to time after first contact.
- rRT-PCR is recommended as the primary test in the initial 14 days.
- Antigen detection tests may be used as an alternative.
- Antibody detection assays are recommended 14 days after infection or close contact.
- Testing for other respiratory diseases should also be considered.

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 regarding the best use of diagnostic tests during the pandemic. There is a need for a simplified guideline, considering the region's health resources' low availability, international guidelines, medical literature, and local expertise.

Methods - Nine experts from Latin American countries developed a simplified algorithm for COVID-19 diagnosis, using a modified Delphi method. Twenty-four questions related to diagnostic settings were proposed, followed by discussion of the literature and experts' experience.

Results - The algorithm considers three timeframes (≤7 days, 8-13 days, and ≥ 14 days) and discusses diagnostic options for each one. SARS-CoV-2 rRT-PCR is the test of choice from day 1 to day 14 after symptom onset or close contact, although antigen testing may be used in particular situations, from days 5 to 7. Antibody assays may be used for confirmation, mainly after day 14. If the 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 day 13.

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

Keywords: SARS-CoV-2; COVID-19; diagnosis; Latin America; algorithm

Introduction

In May 2020, the Pan American Health Organization (PAHO) declared the region an epicenter of the disease(Pan American Organization, 2020), and in November 2020, cumulative COVID-19
cases in Latin America accounted for around 24% of all cases and 33% of all deaths globally. (World Health Organization, n.d.)

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 recommendations. Latin America is a region with great socio-economic contrasts (World Bank Development Indicators DataBank, n.d.), as well as health resources, and, like in developed countries (Pablos-Méndez et al., 2020), COVID-19 tests and trained personnel are not exempt from the supply chain or 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). Nine experts from Latin American countries iteratively answered 24 online questions about diagnostic methods and their application in specific cases for two weeks. The questions were written by an external microbiologist infectious disease specialist with high expertise in the area and reviewed by a multidisciplinary panel. The experts also met to review the proposed algorithm in two online meetings during this period.

The consensus level was determined for every 24 initial 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 three parts according to time after first contact or time after symptoms onset (Fig. 1).

The rRT-PCR is recommended as the primary test in the initial 14 days of symptoms or close contact. Early sample collection from the upper respiratory tract minimizes the probability of negative rRT-PCR test 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 (within the 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.

The rRT-PCR is the diagnostic test of choice between 8 to 13 days after initiation of symptoms. If results are negative, rRT-PCR may be repeated. In some cases, antibody assays may be used during this period, but considerations should be taken when the results are negative (false negative tests are still common in this period), or IgM is positive, and IgG is not, raising the possibility of a false positive test (J. Deeks et al., 2020).

Fourteen days of symptoms onset or close contact, antibody detection assays are recommended as the initial test for detecting SAR-CoV-2 infection in immunocompetent hosts. In most cases, antibody assays are used to trace contacts or for other epidemiological reasons (Jayamohan et al., 2020) but may be used for individual diagnosis in specific circumstances.

**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. 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 also identified six 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.

These six steps should all be considered when selecting an in vitro diagnostic test for routine use.

Viral detection according to the clinical course

The detection of virus particles, (Mallett et al., 2020) (Ravi et al., 2020) or its corresponding immunological response, (Siam et al., 2020) varies with post-infection time (Fig. 2). 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. (J. J. Deeks et al., 2020) All showed low sensitivity during the first week (30.1%, 95% CI 21.4 to 40.7), which increased in the second week (72.2%, 95% CI 63.5 to 79.5), and peaked in the third (91.4% (95% CI 87.0 to 94.4)
and fourth weeks (96.0% (95% CI 90.6 to 98.3). Specificity was not evaluated according to time but was generally high (IgM 99.1% (97.5 to 99.8) and IgG 98.6% (96.7 to 99.5)).

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

Real-time polymerase chain reaction (rRT-PCR) is the gold-standard molecular technique for detecting SARS-CoV-2 viral RNA in all recommended samples. It targets the following sequences that code for structural viral proteins: spike (S), membrane (M), envelope (E), nucleocapsid (N), and RNA-dependent RNA polymerase (RdRP). Both S and N proteins are highly immunogenic. (Ravi et al., 2020) The S proteins seem to be the major target of neutralizing antibodies for correlated coronaviruses. (Berry et al., 2010) High infectivity of SARS-CoV-2 has compelled the CDC 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 between 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 one of the most commonly used specimen types for diagnosing COVID-19 active infection (Lai and Lam, 2020). In September 2020, the WHO published a guideline not recommending saliva as the only specimen type for routine clinical diagnostics because of the wide variation in collection methods. (World Health Organization, 2020a)

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

Pooling PCR samples increases testing efficiency, given that only a limited number of tests are available, particularly in areas with low prevalence and few health resources (CDC, 2020b). The idea is to pool samples from several individuals and test the combined sample 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 FDA initially proposed (CDC, 2020b) that 5 was the maximum number of samples to be pooled for rRT-PCR, but other studies (CDC, 2020b) (Food and Drug Administration USA, 2020) (Hanel and Thurner, 2020) (Deckert et al., 2020) found that the ideal number of pooled samples depends on the disease's prevalence in the tested population. One potential constraint of pool testing is that the false-negative rate may increase owing to dilution of positive samples, and therefore, high-sensitivity rRT-PCR tests are adequate to minimize this limitation (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 highly on its specificity, sensitivity, and the prevalence of the disease in the target population (Lorentzen et al., 2020) (Table 1). False-negative results may also 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 the initial results are negative and the clinical characteristics are very suggestive (Lai and Lam, 2020) (Lorentzen et al., 2020).

*Antigen detection assay*

Another COVID-19 detection method involves the direct detection of SARS-CoV-2 virus particles using immunoassays (Ji et al., 2020). SARS-CoV-2 nucleocapsid protein may be detected in
nasopharyngeal swabs and urine samples of COVID-19 patients within three days of onset of fever (Diao et al., 2020).

A Cochrane systematic review (Dinnes et al., 2020a) found that sensitivity varied considerably across studies (from 0% to 94%): the average sensitivity was 56.2% (95% CI 29.5 to 79.8%), and average specificity was 99.5% (95% CI 98.1% to 99.9%; based on eight evaluations in five studies on 943 samples). Data for individual antigen tests were limited, with no more than two studies for any test. There were nos studies in asymptomatic persons (Dinnes et al., 2020a).

For asymptomatic individuals, a non-peer-reviewed study (Alemany et al., 2020) showed that for a pre-test probability of 5%, the negative predictive value (NPV) was 99·6% (95% CI 99·5 – 99·7), and the positive predictive value (PPV) was 81·5% (95% CI 65·0 – 93·2). At this pre-test probability, the estimated number of false-negative and false-positive values 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 (Alemany et al., 2020).

In comparison with rRT-PCR, rapid antigen detection tests tend to have a lower sensitivity, and owing to the increased risk of false-negative results; some authors consider such tests only as an adjunct to rRT-PCR tests (Siam et al., 2020). Alternatively, antigen detection tests have the advantage of being simple to perform and can play a role in the settings where accessibility to rRT-PCR tests is limited, particularly on symptomatic patients with a high viral load and within the first 5–7 days from symptom onset (Lai and Lam, 2020). The viral load is directly related to the sensitivity of the test (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, three types of seroconversion were observed: synchronous seroconversion of IgG and IgM (nine patients), IgM seroconversion earlier than that of IgG (seven patients), and IgM seroconversion later than that of IgG (ten patients). A study (Guo et al., 2020) profiling the early SARS-CoV-2 humoral response found that IgM median time for detection was five days after symptom onset, and IgG was detected at a median of 14 days after symptom onset.

For SARS-CoV-2, IgG and IgM produced against the S and N proteins are of particular diagnostic interest. A 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 to measure patient antibodies include rapid diagnostic tests (RDTs), enzyme-linked immunoassays (ELISAs), chemiluminescent immunoassays (CLIA), or neutralization assays (Ravi et al., 2020), performed only at specialized laboratories. Another review found that some differences were noted by test technology, CLIA methods appearing more sensitive (97.5%, 95% CI 94.0 to 99.0) than ELISA (90.7%, 95% CI 83.3 to 95.0) or CGIA-based lateral flow assays (90.7%, 95% CI 82.7 to 95.2) for IgG/IgM, (there are also differences for IgG but no differences for IgM). There was little clear evidence of differences in specificity between technology types (J. Deeks et al., 2020).

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 the early phase (up to 28 days) immunogenicity profile of approved vaccines is established, the long-term immunogenicity data is unknown at this time (Sui et al., 2021). To evaluate the evidence of a previous infection in an individual with a history of COVID-19 vaccination, an antibody test specifically evaluating IgM/IgG to the nucleocapsid protein should be used (CDC, 2020c), if available.

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

Other Tests

**CRISPR Technology**

CRISPR gene-editing tool has been utilized to construct an accurate, faster, and simple-to-use SARS-CoV-2 detection test. DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTR) assay is 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 minutes (Broughton et al., 2020).

**LAMP**

LAMP is a method of isothermal DNA replication that utilizes six DNA oligos that hybridize with eight different regions of a target molecule in an accelerated format. Reverse transcriptase can
be included to improve sensitivity within the reaction when detecting an RNA target (RT-LAMP), such as the 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 SAR-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, 2020a) (CDC, 2020d). However, as the number of patients presenting with COVID-19 symptoms increases, there has been a shortage of diagnostic resources, like swabs, polymerase chain reaction (PCR) reagents, RNA isolation kits, and growing demand for rapid, onsite diagnostics (Ravi et al., 2020). Point-of-care (POC) tests, including rapid antigen detection tests, are also recommended as an initial test by the Center for Disease Control (CDC, USA) (CDC, 2020e), particularly in the early days of symptoms or in cases of close contacts in a high risk congregated setting. 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 a lower sensitivity (CDC, 2020e). The choice of which test should be used depends on the test’s availability and trained personnel, along with the above factors.
Types and results of immunological tests

Antibody tests available for laboratory use include enzyme-linked immunosorbent assay (ELISA) methods, more advanced chemiluminescence immunoassays (CLIA), and laboratory-independent, point-of-care lateral flow assays for rapid detection of antibodies (CGIA), among others (Deeks et al., 2020).

CLIA methods appear more sensitive (97.5%, 95% CI 94.0 to 99.0) than ELISA (90.7%, 95% CI 83.3 to 95.0) or CGIA-based lateral flow assays (90.7%, 95% CI 82.7 to 95.2) for IgG/IgM (Deeks et al., 2020). 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).

Negative rRT-PCR or Antigen detection tests and need for quarantine

In the case the individual was only in close contact and never developed symptoms, he/she should complete 14 days of isolation. No tests are necessary, except for particular cases, like hospitalized patients or other epidemiological reasons (World Health Organization, 2020b).

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 showed that the pooled sensitivity of CT was 86.2% (95% CI: 71.9 to 93.8) (13 studies, 2346 participants), and specificity was 18.1% (95% CI: 3.71 to 55.8) (Salameh et al., 2020). In patients with negative rRT-PCR tests, Ai et al. (Ai et al., 2020) suggested that a combination of exposure history, clinical symptoms, typical CT imaging features, and Chest CT dynamic changes should be used to identify COVID-19.
SARS-CoV-2 genotyping

Genotyping tests, the most common being 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 the COVID-19 outbreak (Yin, 2020). There are no current guidelines recommending 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 always a cause for uncertainty among physicians, health professionals, and public health authorities. Our methodology involving 24 questions answered by Latin American experts resulted in a simplified algorithm involving symptomatic people or close contacts in 3 windows of time (≤7 days, 8-13 days, and ≥14 days).

Even considering the high disparities in health care access within the region, we regarded rRT-PCR tests as the standard diagnostic tests for SARS-CoV-2 infection, from the onset of symptoms until 13 days afterward. This recommendation is consistent with all main published guidelines (Pan American Health Organization, 2020) (World Health Organization, 2020a) (World Health Organization: Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases, n.d.). Sample pooling should be used in low-resource and low prevalence (<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 (5-7 days after onset of symptoms) in symptomatic patients (World Health Organization (último), 2020). We considered it a good alternative in those situations, particularly when rRT-PCR tests are not readily available. Antigen detection tests also appear as 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 SAR-CoV-2 infection according to WHO and PAHO guidelines (Pan American Health Organization, 2020) (World Health Organization, 2020a). However, we suggest that they can be used after 14 days of symptom onset or 21 days after close contact for tracing close contact cases or in exceptional situations when an individual diagnosis is necessary (or before that period, from the eight-day onward) 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 other conditions such as malaria, dengue, typhoid, influenza, and other respiratory diseases should also be considered (Chi et al., 2020) (United Nations. 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, taking into account published international guidelines and the region’s health access inequalities.

**Limitations**

Although based on well-established consensus formation techniques and drawing on panelists’ 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 (different features and pace of the COVID-19 pandemics 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 establish the best ways for diagnosing COVID-19 in vaccinated individuals. It is probable that these recommendations may be modified once long-term data is presented.

**Implications**

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

**Declaration of interests**
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of Interest Statements

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

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

Dr. Bonhevi 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 & Dohme Chile, ViiV Healthcare.

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

Funding Source

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Ethical Approval

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

References


Figure captions

Figure 1. A proposal for an alternative simplified diagnostic algorithm for SARS-CoV-2 suspected asymptomatic patients and close contacts (asymptomatic individuals)

Footnote

*a Ideal 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).

*b Consider 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 Dziedzic, 2020). Repeat determination with other methods, like high-affinity antibody assays (total immunoglobulins or IgG).

*c Consider 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).

*d Consider 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).

*e Consider antibody tests if other results are negative.

*f Consider day 14 of symptoms or day 21 of close contact.

Ig, immunoglobulin; PCR, polymerase chain reaction; rRT-PCR, real-time reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RSV, Respiratory Syncytial Virus

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. (Sethuraman et al., 2020))

Footnote

*a 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; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
Figure 1. A simplified alternative diagnostic algorithm for SARS-CoV-2 suspected symptomatic patients and confirmed close contacts (asymptomatic)

*Ideal use only in high-prevalence (>5–10%) scenarios with symptomatic patients or selected settings (e.g., emergency rooms, elderly residences, healthcare personnel, and 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 RT-PCR test (Virginia Department of Health, 2020).

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*Consider antibody tests if other results are negative.

*Consider Day 14 of symptoms or Day 21 of close contact. Ig, immunoglobulin; PCR, polymerase chain reaction; rRT-PCR, real-time reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RSV, Respiratory Syncytial Virus

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; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 1. Correlation between pre-test probability and test results*

<table>
<thead>
<tr>
<th>Pre-test probability*</th>
<th>Negative Predictive Value (NPV)*</th>
<th>Positive Predictive Value (PPV)*</th>
<th>Increased likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>False Positives (FP) True Negatives (TN)</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>True Positives (TP) False Negatives (FN)</td>
</tr>
</tbody>
</table>
a. Pre-test probability is correlated with the prevalence of the disease and clinical presentation.

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

c. PPV is the probability of a patient with the disease having a positive result (True Positive).
Table 2. Comparison of diagnostic options for SARS-CoV-2 detection*

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Specimen Sample</th>
<th>Test</th>
<th>Time (min)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Cross-reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAAT*</td>
<td>Nasopharyngeal swab, sputum, bronchoalveolar lavage fluid</td>
<td>RT-PCR</td>
<td>240</td>
<td>71-98</td>
<td>95</td>
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<td>Antigen Detection</td>
<td>Nasopharyngeal swab</td>
<td>-</td>
<td>15-30</td>
<td>62-92</td>
<td>100</td>
<td>Yes</td>
</tr>
<tr>
<td>Immune Assay</td>
<td>Blood</td>
<td>-</td>
<td>15-30</td>
<td>92-100</td>
<td>93-100</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Modified from Siam et al. (Siam et al., 2020)

*Nucleic Acid Amplification Test

b Hellou et al. (Hellou et al., 2020)