Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Perspective

Algorithms for testing COVID-19 focused on use of RT-PCR and high-affinity serological testing: A consensus statement from a panel of Latin American experts

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ABSTRACT

The COVID-19 pandemic has caused an unprecedented public health, social, and economic crisis. Improving understanding on available tests for detecting COVID-19 is critical for effective management of the pandemic. We proposed that a multidisciplinary expert panel can establish recommendations on ideal use of diagnostic tools, with a focus on RT-PCR and serological high-affinity antibodies (both IgM and IgG) tests for the Latin America region.

Study design: A collaborative multidisciplinary panel of 5 recognized experts in Latin America (an infectious disease specialist, three pathologists, and an immunologist) was convened and supported by Roche Diagnostics to develop standard guidelines and an evidence-based document of best practices on the use of diagnostic tools for COVID-19.

Results: The authors reached consensus on the applicability of diagnostic tools to provide testing algorithms for the use of RT-PCR and serological high-affinity antibodies (both IgM and IgG) tests in three settings: 1) For asymptomatic subjects exposed to a SARS-CoV-2 infected person; 2) For epidemiological purposes and; 3) For symptomatic subjects.

Conclusion: The serological high-affinity SARS-CoV-2 antibodies (both IgM and IgG) tests play a key role in COVID-19 diagnosis. These tests can be applied for suspected false-negative RT-PCR results and for individual determination of response. The use of these tests can also contribute greatly to public health strategies, such as population screening and supporting vaccination planning. Serological status for high-affinity antibodies (both IgM and IgG) should be performed ideally 21 days after potential infectious contact, given that the majority of exposed individuals will have seroconverted.

Introduction

In December 2019, atypical pneumonia cases caused by a new coronavirus were identified in Wuhan, a city of Hubei Province in China (Zhu et al., 2020). Within days, the virus had spread, resulting in an epidemic throughout China (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). An increasing number of cases were reported in countries around the world in the ensuing weeks (WHO, 2020b). In February 2020, the World Health Organization (WHO) named the disease as COVID-19, which stands for "coronavirus disease 2019" (WHO, 2020c). The virus that causes COVID-19 was then named as Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) (Coronaviridae Study Group of the International Committee on Taxonomy of

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Viruses, 2020). COVID-19 has since been declared a global pandemic (Cucinotta and Vanelli, 2020), with 15,301,530 cases worldwide and 625,005 deaths globally. In the Americas, the numbers are also staggering: 11,667,196 confirmed cases with 419,995 deaths (as of August 17th, 2020) (PAHO, 2020).

The initial stage involves an incubation period when SARS-CoV-2 multiplies and establishes itself mainly in the respiratory system. During the second stage, localized inflammation can occur in the lungs. The third (and most severe) stage of the disease can cause the syndrome of extrapulmonary systemic hyperinflammation (Siddiqi and Mehra, 2020).

RT-PCR is a test for diagnosing COVID-19, based on nasopharyngeal swab samples or other upper respiratory tract samples (Wang et al., 2020b). In symptomatic individuals, viral RNA can be detectable early on day one of symptoms and culminate within the first week of symptom onset. By week three, positivity of the test for detecting viral RNA starts to decline (Sethuraman et al., 2020). A downside of this sample collection approach involves false-negative results, largely due to inappropriate timing of sample collection relative to illness onset and poor sampling technique, especially for nasopharyngeal swabs. Given that the design for the RT-PCR test is based on the genome sequence of SARS-CoV-2, its specificity is almost 100%, with few false-positive results (Sethuraman et al., 2020).

Another diagnostic tool for detecting SARS-CoV-2 infection is serological testing which evaluates the host immune response (Loeffelholz and Tang, 2020). It is essential for patients with mild to moderate illness who may present two weeks after illness onset. Serological diagnosis is also becoming an important tool to help understand the extent of COVID-19 in the community (Sethuraman et al., 2020).

Antibodies start to increase from the second week of symptom onset, constituting the earliest and most sensitive serological marker, with IgM and IgG levels peaking in the second and third weeks of illness. Subsequently, IgM decreases by week 5, while IgG remains high beyond 7 weeks (Sethuraman et al., 2020).

These findings together with the plethora of available testing methodologies (CDC, 2020b; Loeffelholz and Tang, 2020), evolving knowledge on the behavior of the virus, and the complexity of the human immune response, have led to the need for guidance on how to use and appropriately interpret results of the available tests.

As the pandemic progresses, it has become clear that the primary transmission pathway is through respiratory aerosols (Bahl et al., 2020) as well as through direct contact of eyes, nose, or mouth with contaminated surfaces (Ong et al., 2020). The virus has also been detected in nonrespiratory samples such as stools, urine, blood, ocular secretions, and semen (Wang et al., 2020b). The risk of transmission of SARS-CoV-2 from an infected person to another appears to vary and depends on the type and duration of exposure, use of preventive measures, and other individual factors (Rosenberg et al., 2020).

Latin America is a large and heterogeneous territory, including well-developed and poor areas with limited resources, in which the pandemic rapidly spreads. The aim of this paper is to provide Latin American clinicians with guidance on the use of RT-PCR and serological high-affinity antibodies (both IgM and IgG) tests.

Methods

Five recognized experts in Latin America joined an online expert panel and worked collaboratively on an online application (Within3®) from June 12th to 24th, 2020, supported by Roche Diagnostics. Panel members had either clinical or scientific experience in infectious disease or immunology and serological tests. Adopting standard guideline development processes (Linstone and Turoff, 2015), a literature review was performed on serological diagnosis and panelists shared the articles on COVID-19 listed in Chart 1 .

1. Callow et al. 1990;	16. Long et al. 2020;
2. Linstone HA and Turoff M 2015;	17. Lou et al. 2020;
3. Altmann et al. 2020;	18. Muench et al. 2020;
4. Bahl et al. 2020;	19. Ong et al. 2020;
5. Bermingham et al. 2020;	20. PAHO 2020;
6. Brasil 2020;	21. Perkmann et al. 2020;
7. CDC 2020a, 2020b, 2020c;	22. Rosenberg et al. 2020;
8. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020;	23. Sethuraman et al. 2020;
9. Cucinotta and Vanelli 2020;	24. Shen et al. 2020;
10. Dramé et al. 2020;	25. Siddiqi and Mehra 2020;
11. Guan et al. 2020;	26. Tang et al. 2020;
12. Hase et al. 2020;	27. To et al. 2020;
13. Lau et al. 2020;	28. Wang et al. 2020a, 2020b;
14. Liu et al. 2020a, 2020b;	29. WHO 2020a, 2020b, 2020c;
15. Loeffelholz and Tang 2020;	30. Yong et al. 2020;
	31. Zhao et al. 2020;
	32. Zhu et al. 2020).

Chart 1. Articles selected by panelists for discussion during expert pane.

The search was performed on Medline only, from January 2020 until the start date of the expert panel in June 2020.

All MESH Terms related to "COVID19" and "COVID19 testing" were used as main descriptor terms by using the Boolean connector "OR" to include all their supplementary concept terms; plus "AND" to connect both. These are shown in Chart 2 .

The purpose of the expert panel was to develop a test algorithm for the three situations proposed in the paper, not including antigen or antibody rapid testing, and no search for rapid testing was conducted.

On the basis of the papers retrieved, an infectious disease specialist prepared nine questions (Chart 3) and drafts of algorithms testing for SARS-CoV-2, focusing on the use of RT-PCR and serology testing in different settings. Panelists had the opportunity to suggest modifications to these algorithms and were required to propose evidence-based best practices for the RT-PCR and serological diagnosis of COVID-19.

These preliminary efforts served as the basis for discussion and to establish the guidelines. The panelists had the opportunity to make further reviews and remarks using the online platform in reaching the consensus for the guidelines presented.

Results

Algorithms emerged in a consensus of the panelists on serologic testing for COVID-19 in Latin America in three different settings:

1. **Asymptomatic individual exposed to Sars-CoV-2 infected patients – Algorithm 1**.

For asymptomatic individuals who had contact with a confirmed case of COVID-19 (Algorithm 1), RT-PCR should be performed preferably after 5 days of contact, while a serology test can be performed to detect mature antibodies against SARS-CoV-2, high-affinity antibodies (both IgM and IgG), ideally 21 days after contact.

Accordingly, because of the lower sensitivity of antibody tests in detecting infection during earlier phases (To et al., 2020), the panelists proposed adoption of a minimum cut-off period after potential infectious contact for performing serological evaluation of asymptomatic individuals (Figure 1) (Dramé et al., 2020; Zhao et al., 2020).

2. **Epidemiological purposes – Algorithm 2**.

Serological testing also has utility for epidemiological purposes such as virus exposure screening, especially of high-risk populations (police and military personnel, food market suppliers, traffic agents, medical personnel), planning public health strategies and actions for seronegative asymptomatic populations, and planning vaccine distribution through population sampling. In these situations, the use of mature antibodies serological tests can help understand those who are sensitized to SARS-CoV-2. For those, PCR testing should be considered in the case of a new set of symptoms. In such cases, social distancing and other precautionary measures according to local health authority decisions should be taken. For nonsensitized individuals, performing daily activities using personal protection equipment (PPE) should be considered as well as regular retesting with PCR and serological tests (Figure 2).

3. **Symptomatic individuals – Algorithm 3**.

For symptomatic individuals, the gold standard is the RT-PCR test performed predominantly on nasopharynx and/or oropharyngeal swab samples. If patients present with a negative PCR test, retesting for PCR (same and/or other body site) should be considered, as well as performing a respiratory virus panel. In all symptomatic people, a serology test to measure high-affinity antibodies (both IgM and IgG) could be performed at least 14 days after PCR test or 21 days after symptom onset (Figure 3).

The rationale for this timeframe relies on a study that reported the proportion of patients with positive virus-specific IgG reached 100% approximately 17 to 19 days after the onset of symptoms (Long et al., 2020).

COVID19	COVID19 testing
2019 novel coronavirus disease 2019 novel coronavirus infection 2019-nCoV disease 2019-nCoV infection COVID-19 pandemic COVID-19 virus disease COVID-19 virus infection COVID19 SARS-CoV-2 infection coronavirus disease 2019 coronavirus disease-19	2019 novel coronavirus testing 2019-nCoV RT-PCR diagnostic panel 2019-nCoV disease testing 2019-nCoV infection testing 2019-nCoV testing 2019-novel coronavirus real-time reverse transcriptase diagnostic panel COVID-19 antibody testing COVID-19 blood antibody testing COVID-19 nucleic acid testing COVID-19 serological testing COVID-19 testing COVID-19 virus testing COVID19 antibody testing COVID19 nucleic acid testing COVID19 serological testing COVID19 testing COVID19 virus testing SARS-CoV-2 infection antibody testing SARS-CoV-2 infection nucleic acid testing SARS-CoV-2 infection serological testing SARS-CoV-2 testing SARS2 testing Serology Testing for COVID-19 coronavirus disease 2019 testing coronavirus disease-19 testing severe acute respiratory syndrome coronavirus 2 testing

Chart 2. All MESH Terms related to "COVID19" and "COVID19 testing" used as main descriptor.

1. If an asymptomatic person has had continuous contact (i.e. living in the same house) with someone diagnosed with COVID-19 (by the PCR test) for the preceding 14 days or longer, which test would you recommend to the asymptomatic person? And why?
According to our experts, it is often difficult to establish the exact time moment of infection for people who have hadith close contact with a SARS-CoV-2 infected subject. RT-PCR-SARS-CoV- 2 of the upper nasopharynx remains the method of choice for diagnosingis of COVID-19 in patients within the 5- day -period after contact with the index case. However, for more than 21 days in contact, was recommended to asymptomatic contact person perform a serological test for mature anti- SARS-CoV-2 Ig G. Some of the specialists highlighted the importance of test cut-off in the interpretation of these results (recommendations of re-test in 2 weeks´ time for those negative with antibodies levels close to cut- off limits values). Some experts also stressed the need to use antibodies against specific viral antigens (anti-S and anti-N).

2. Considering the previous scenario, if the contact person has done the PCR test within the last 14 days, which test would you consider for the asymptomatic person? And why?
For this situation, it was almost unanimous among experts that the most suitable diagnostic method would be the RT-PCR-SARS-CoV-2. Specialists considered these contact persons to be more likely to spread the virus and should therefore be identified as asymptomatically infected, allowing dissemination control since social distancing measures can be applied.

3. In the event a person has only had a clinical diagnosis of COVID-19 (not confirmed by PCR test), for less than 2 weeks, which test would you recommend for follow-up? If any?
The majority of experts suggested performing RT-PCR-SARS-CoV-2 in the situation above. According to the panel, a period of less than 14 days can negatively impact antibody detection in blood samples. They recommended the use of RT-PCR via nasopharyngeal swabs and, if testing negative with high clinical suspicion (as suggested by radiological images from CT scans), a second RT-PCR test should be applied. Social distancing measures must be followed until infection can be ruled out.

4. Considering the previous scenario, if an asymptomatic person has had close contact with the clinically diagnosed patient, which test would you recommend for the person, if any?
Panelists recommended adopting temporal analysis to determine which methodology would best apply. Use of a cut-off of 21 days after contact was deemed reasonable for use of antibodies Ig G and Ig M (anti-N and anti-S) only. Asymptomatic persons who have had close contact with a clinically diagnosed patient less than 14 days prior, should undergo a RT-PCR-SARS-CoV-2 test. For individuals who have had contact 14-21 days earlier, both diagnostic methods could be of value.

5. In the case of front-line healthcare professionals (HCP), which test would you recommend for screening? And which actions would you recommend in response to the results of this screening test?
In this specific situation specialists recommended splitting HCP into 2 categories: asymptomatic and symptomatic. For the first group, RT-PCR-SARS-CoV-2 test should be used to guarantee timely social distancing measures. For the second group, serological tests for detecting IgG and IgM levels would help to identify those professionals who are sensitized to SARS-CoV-2. Nevertheless, as neutralizing activities of detected IgG antibodies when a previously sensitized subject becomes symptomatic have yet to be determined, distancing measures and RT-PCR are imperative.

6. **Is there any other situation where you would consider the use of a mature antibodies serology test for screening an asymptomatic population?**
Use of these test may be considered in the following situations: 1) determination of immunity status of asymptomatic subjects before of a high risk of exposure to high-risk areas, 2) seroprevalence studies in specific groups or population to help health authorities plan intervention measures such as vaccination; 3) generate data on SARS-CoV-2 transmission dynamics and allow interventions to reduce transmission of the disease.

7. **What is the role of the mature antibodies serology test in COVID-19 diagnosis for PCR-negative symptomatic patients?**
According to the panelists, the serological test is of value, especially in cases where a symptomatic subject with RT-PCR tests negative. In this situation, paired serum samples may support diagnosis of COVID-19.

8. **What is the role of the mature antibodies serology test for COVID-19 diagnosis where there is no access to the PCR test?**
Its role is limited. Serology testing for COVID-19 is useful for determining sensitization to SARS-CoV-2 after infection, but not for defining acute infection.

9. **How frequently would you suggest repeating the serological test (mature antibodies), if testing negative, for an asymptomatic person with a history of contact with an infected patient? And for an individual without a history of contact with an infected person (for the epidemiological purposes of a company for example)?**
-For the first scenario, experts suggested repeat serological study 7-15 days after the previous negative exam.

- For the second scenario, this approach seems to be of no value and experts did not recommend this except for epidemiological studies to determine virus dynamics in specific populations.

Chart 3. Narrative summaries of clinical questions addressed by panel to formulate recommendations for algorithms .

4. **Special situations – no algorithm proposed**.

Some clinical conditions were not discussed in this expert panel, such as patients with or without symptoms that have long-term SARS-CoV-2 RNA detection in nasopharyngeal swabs, developing weak or no clinical signs, and undetectable antibodies in serum 15–20 days after manifesting clinical symptoms, and the rare clinical condition of patients suspected to have SARS-CoV-2 reinfection.

A decrease in IgG antibodies in patients with SARS-CoV-2 has been documented. A recent study showed a drop of 26.5% in detectable IgG antibodies over 3 months by using lateral flow assay. In the population aged 75+ years, the drop was 39%. These data suggest that the possibility of decreasing population immunity over time could increase the risk of reinfection (Ward et al., 2020). Currently the importance of antibody decline for reinfection by SARS-CoV-2 is not yet answered and further longitudinal studies are needed. SARS-CoV-2 vaccine studies will also support the clarification of this issue.

Lastly, the participants explained the rationale for their recommendations until a final consensus was reached (Figure 4).

Discussion

RT-PCR for SARS-CoV-2, based on samples obtained preferably from the upper nasopharynx (Loeffelholz and Tang, 2020) remains the gold standard for the diagnosis of the acute phase of COVID-19 (Loeffelholz and Tang, 2020; Wang et al., 2020b). However, there are some drawbacks of this technique, namely its variability in accuracy depending on the specimen (Wang et al., 2020a), hazards in collecting samples (Shen et al., 2020), and sensitivity concerns (Hase et al., 2020; Shen et al., 2020). For instance, negative tests in patients with SARS-CoV-2 lower respiratory tract infection and

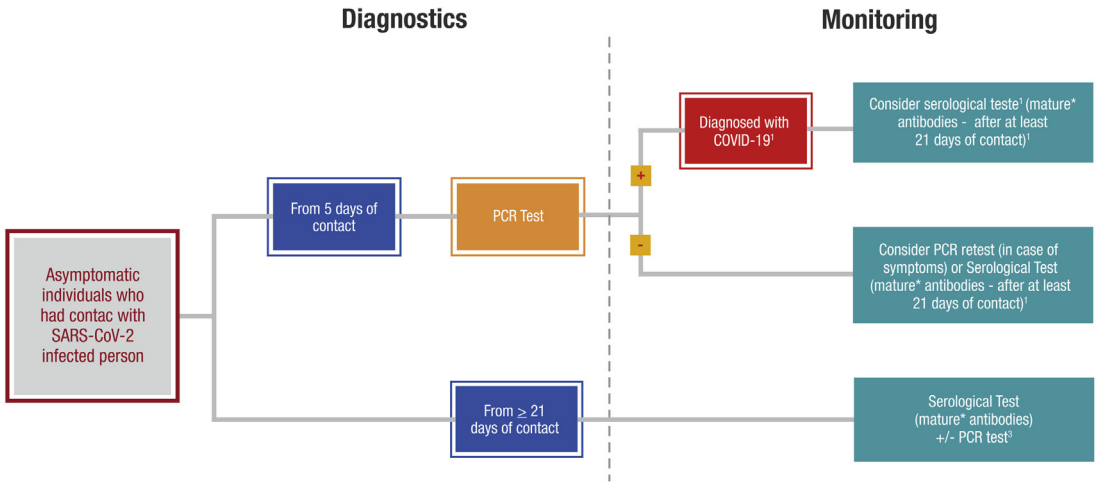

Figure 1. Asymptomatic individual exposed to Sars-Cov-2 infected patients — Algorithm 1.

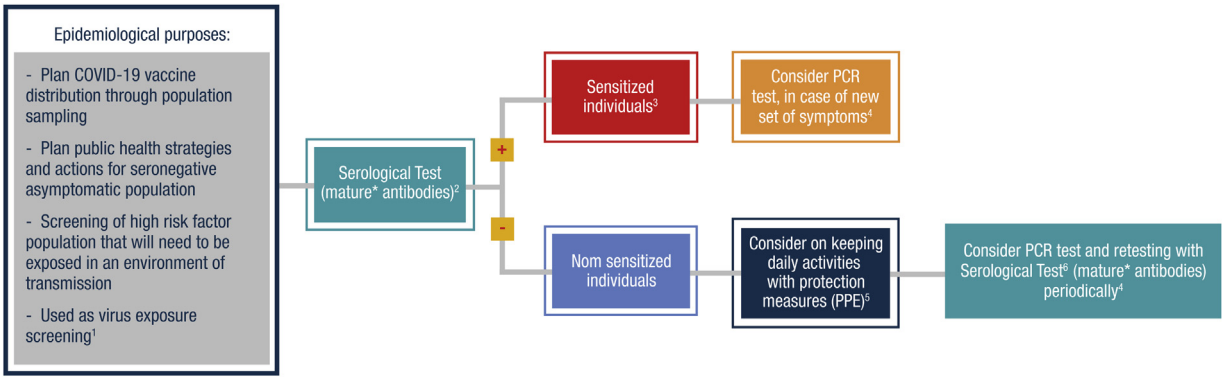

Figure 2. Epidemiological purposes — Algorithm 2.

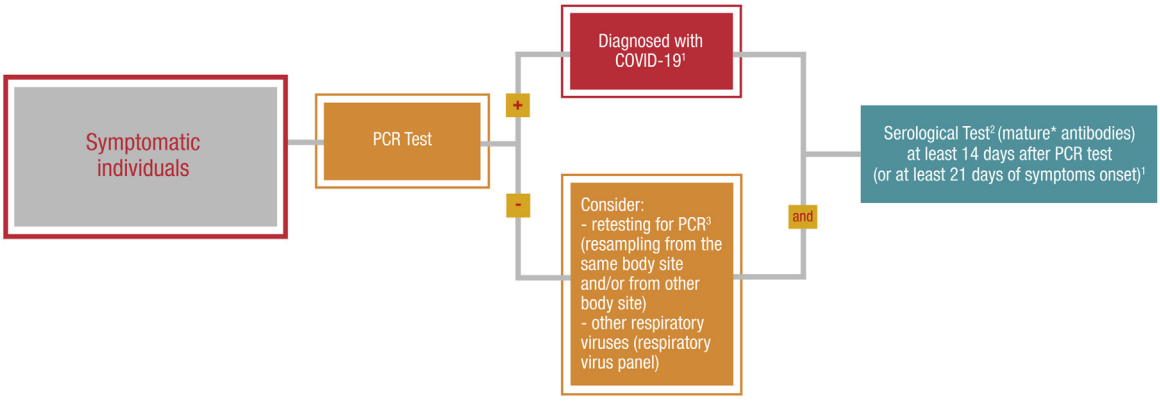

Figure 3. Symptomatic individuals — Algorithm 3.

minimum upper respiratory symptoms are not uncommon (Hase et al., 2020; Liu et al., 2020a). Given the limitations of the RT-PCR, in the context of urgent need for accurate detection of infected subjects and their subsequent isolation as a pivotal step for effective prevention of the spread of the SARS-CoV-2 virus (Guan et al., 2020), serological testing plays an essential role in differential diagnostic and epidemiological settings (CDC, 2020b; Lou et al., 2020; Yong et al., 2020).

Nevertheless, relying solely on IgM serological detection for the diagnosis of acute disease is not a suitable strategy, particularly for the early acute phase. In one study (Loeffelholz and Tang, 2020), all 39 patients had both IgM and IgG after 5-7 days of symptom onset. In another Chinese study of 285 patients, three seroconversion patterns were observed: synchronous seroconversion of both IgM and IgG, IgM seroconversion earlier than IgG (expected pattern), and IgM seroconversion after IgG. The proportion of patients with virus-specific IgM peaked at 94.1% in approximately 20–22 days, whereas for IgG, 100% reached a peak 17–19 days after symptom onset (Long et al., 2020). However, antibody responses against SARS-CoV-2 are not fully understood (Callow et al., 1990), and the

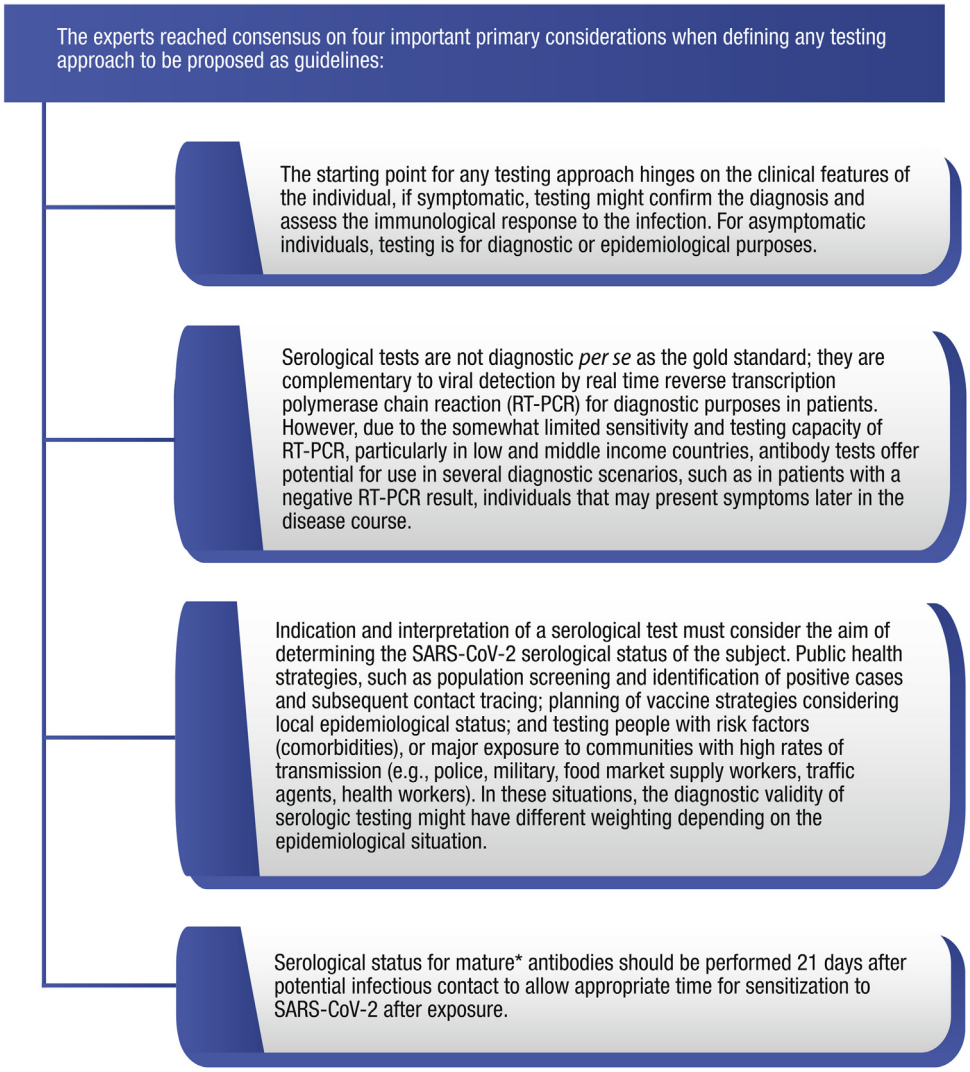

Figure 4. Important primary considerations when defining any testing approach.

neutralizing activities of detected IgG antibodies have yet to be determined (Lou et al., 2020).

According to the North American Centers for Disease Control (CDC-USA), the results of serological tests should not be used as a single diagnostic test for an acute infection, excluding, or diagnosing SARS-CoV-2 infections (CDC, 2020b). Moreover, the US Food and Drug Administration (FDA) recommends use of serological tests to detect SARS-CoV-2 antibodies by health professionals, as this may help identify individuals exposed to or who have recovered from COVID-19 infection (CDC, 2020a). In Latin America, the Brazilian Ministry of Health recommends the use of laboratory tests, RT-PCR until the eighth day of symptom onset and immunological, which detects the presence of antibodies in samples collected from the eighth day of symptom onset in patients presenting with a flu-like syndrome or Severe Acute Respiratory Syndrome (SARS) (Brasil, 2020). Despite the increased knowledge on the utility of serological tests, a recent survey by the Royal College of Physicians highlighted misinterpretation issues, where 40% of respondents considered patients to have "cleared COVID-19" in cases with active symptoms and IgM–IgG + serologies (Bermingham et al., 2020).

Serological testing for SARS-CoV-2 high-specificity antibodies can also be used as an additional diagnostic tool for suspected false-negative RT-PCR results (Perkmann et al., 2020) or for individual determination of antibody levels to trace who has been infected in the past (Perkmann et al., 2020; Yong et al., 2020). In some situations, the use of serological testing may also be applied to determine the immunity status of asymptomatic subjects with an epidemiological history of a high risk of exposure to people with COVID-19 (Lou et al., 2020). In such settings, serologic testing at appropriate intervals following contact with infected subjects might result in relatively fewer false-positive results (Liu et al., 2020b).

Serological testing also plays a pivotal role in population-based seroepidemiological studies. It provides essential data about SARS-CoV-2 transmission dynamics and allows interventions to reduce transmission of the disease. Moreover, this testing can be used to assess seroprevalence overall or in specific groups, thereby helping to estimate core characteristics of the pandemic and to plan intervention measures such as vaccination of populations (Altmann et al., 2020; Tang et al., 2020; Yong et al., 2020).

The World Health Organization (WHO) states that seroepidemiological investigation can help understand and provide robust estimates of clinical, epidemiological, and virological characteristics of COVID- 19 (WHO, 2020a).

In Latin America, given the high prevalence of SARS-CoV-2 infection, a serological test can be used to determine the level of exposure and identify people who may be sensitized. The latter

tests should ideally provide high specificity, with a small confidence interval, detection of high-affinity antibodies and no cross-reactivity with other coronaviruses (Lau et al., 2020; Muench et al., 2020).

Finally, the CDC Interim Guidelines for COVID-19 Antibody Testing (CDC, 2020b) recommend the use of serological assays in some other scenarios: (a) as a method to support the diagnosis of acute COVID-19 illness for persons who present late onset, for whom serologic testing is offered in addition to RT-PCR; (b) as a method to support establishing a diagnosis when patients present with late complications of COVID-19 illness; and (c) as a method to reduce false-positive results in high prevalence settings.

Limitations

Although based on well-established consensus formation techniques and drawing on panelist'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 (different features and pace of the COVID-19 pandemic in each country of Latin America).

Implications

This expert panel consensus can help clinicians to apply testing for SARS-CoV-2 on an individual level. Moreover, the guidance can also support decision-making stakeholders when acting on public health measures such as seroprevalence studies and business reopening. Lastly, the consensus can support payers from both private and public settings with a more straightforward tool for evaluating the use of a specific test (or sequence of tests).

Conclusion

In conclusion, serological testing and studies are of great importance for public health strategies, such as population screening, and will prove pivotal to support planning of vaccination strategies. Serological status for high-affinity antibodies (both IgM and IgG) should be determined 21 days after potential infectious contact to allow appropriate time for sensitization to SARS-CoV-2 following exposure.

Conflict of interests

Antonio Condino-Neto: no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Pablo E. Bonvehi: My only conflict of interest statement on this issue is that I was convened to participate in this white paper by Roche. Juan Carlos Gómez de la Torre: Speaker for Sanofi - Vaccines, Speaker for MSD - Vaccines, Speaker for Cepheid - Molecular diagnostics in infectious diseases. Klever Vinicio Sáenz-Flor: I do not have any financial interests or personal relationships which may be considered as potential competing interests. Carlos Eduardo Ferreira: I participate as a speaker of company events: Ortho Clinical Diagnostics, Roche Diagnostics, Siemens Healthineers, Snibe and Abbott Diagnostics. I participated as a member of the Advisory Board: Roche Diagnostics. Associative Activity: President of the Brazilian Society of Clinical Pathology / Laboratory Medicine (SBPC / ML) - Biennium 2020-2021

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Not applicable.

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