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COVID-19: concern about interrupting social isolation of healthcare workers and professionals. What should be done with the results of the available COVID-19 diagnostic tests?

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Abstract. – Management of SARS-CoV-2 requires safe decision-making to minimize contamination. Healthcare workers and professionals in confined areas are affected by the risk of the activity and the environment. Isolation of contaminated workers and healthcare professionals requires clinical and diagnostic criteria. On the other hand, interrupting the isolation of healthcare employees and professionals is critical because diagnostic tests do not support clinical decisions. In addition to defining the best test in view of its accuracy, it is necessary to consider aspects such as the stage of the disease or cure, the viral load and the individual's own immunity. Uncertainty about natural and herd immunity to the disease leads to the development of appropriate antivirals, diagnostic tests and vaccines.

Key Words:
Coronavirus infections, COVID-19, SARS-CoV-2, Social isolation, Interruption.

Introduction

Due to the rapid dissemination of the severe acute respiratory syndrome virus coronavirus 2 (SARS-CoV-2), we are facing a scenario of sustained community transmission of the coronavirus 2019 (COVID-19) disease worldwide. The SARS-CoV-2 pandemic has proved to be a challenge to science and public health policies.

COVID-19 is a respiratory disease caused by infection by the SARS-CoV-2 virus. This is a virus of the beta coronavirus family, characterized from the molecular perspective as a single-strand positive sense RNA virus. The genomic RNA has 30 Kb with four essential structural proteins[1]. The disease is characterized as a clinical syndrome with multiple presentations ranging from asymptomatic forms to severe manifestations. Common signs of infection include respiratory symptoms, fever, coughing and short breath. In severe cases, the infection can cause pneumonia, severe acute respiratory syndrome (SARS), metabolic acidosis, coagulation dysfunction, renal failure, neurological changes and death[1].

Although contagion is not limited to any specific population, the elderly, patients with chronic diseases and healthcare professionals are considered groups at risk for the disease. Pregnant women and newborns infected with SARS-CoV-2 may also develop severe pneumonia[1]. In Brazil, among the confirmed deaths from COVID-19, 70.0% were over 60 years of age, and 67% presented at least one risk factor. Cardiopathy was the main associated comorbidity followed by diabetes, renal disease, pneumopathy and neurological disease. In the obesity risk group, most of the patients were under the age of 60 years[2]. Due to the high mortality rate and lack of an ideal therapy, it is crucial to under-

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stand the biological characteristics of the virus and its possible pathogenesis, rendering the return to activities as safe as possible. Rapid diagnosis and effective treatment are also important interventions to manage infection control[3]. The lack of diagnostic tests and the emergency status led to an exceptionality of the release of tests by ANVISA, which leads to a worrying scenario, since there is no analysis of performance before putting it in the market. The tests available in the market are highly variable, differing in format, class of antibodies detected, target antigen and acceptable samples.

Transmission of the Disease and Monitoring the Isolation

The natural history of SARS-CoV-2 disease and the cycle of virus transmission were defined without including or explaining the exceptional cases reported in the literature[2-4]. Transmission of the new coronavirus (SARS-CoV-2) between human beings occurs through contact with contaminated respiratory tract secretions by respiratory droplets, saliva and conjunctiva[5] and the virus incubation period is approximately 3-14 days[1,6]. Research has shown that live SARS-CoV-2 was detected in the patients' feces, evidencing the subsistence of SARS-CoV-2 in the gastrointestinal tract, with probable recurrence and transmission of the virus by fecal-oral route[7]. The virus has a survival time on inanimate surfaces varying from 2 hours to 9 days[8].

Asymptomatic patients with COVID-19 may transmit SARS-CoV-2(1) during the incubation period. Since transmission begins during the pre-symptomatic phase, social isolation was a control measure promoted in order to minimize contact, until diagnostic methods were implemented[6].

Some essential activities occur in environments where there is a high risk of dissemination, due to the confinement, closeness and impossibility of adequate air exchanges. This group includes the professionals on the hospital front line, rest homes, and meatpacking firms that need to be constantly monitored to minimize dissemination. In this type of environment, the epidemiological outbreaks appear to represent a determining factor for the transmission of SARS-CoV-2 and the increased prevalence of cases. These are characterized by a greater than expected increase of the occurrence of cases of the disease and in one area, or among a specific group of people, and it was necessary to adopt timely and effective control and prevention measures. The traceability of occupational contacts is an alternative that requires testing.

The rationing of tests, at the beginning of the pandemic, led the CDC (Center for Disease Control and Prevention) of the USA to prioritize molecular testing for the symptomatic patients and health professionals[9]. On May 27, 2020, the World Health Organization (WHO) updated the criteria for diagnosis and discharge of healthcare professionals from isolation, balancing the risks and benefits on prioritizing the clinical aspects to the detriment of the diagnostic tests. It should be emphasized that, after this determination, there remained a minimum residual risk of transmission related to the activity of the healthcare professional and vulnerable group. In such situations, and in patients who were symptomatic for longer periods, a laboratory approach continued to be recommended.

On July 17, 2020 the CDC issued new guidelines based on evidence, in which it ruled out the use of tests to establish the interruption of isolation for SARS-CoV-2[10]. Retesting to confirm the cure was considered optional but encouraged when the conditions for this were present in symptomatic patients after 10 days since the confirmation of the virus by RT-PCR or of the onset of symptoms, and at least 3 days asymptomatic. In this clinical condition it is possible to interrupt isolation to return to work activities.

For health professionals previously diagnosed with COVID-19, who remain asymptomatic, a new RT-PCR test is not recommended during the period of 3 months after the beginning of the symptoms. The recent decision of the CDC to not require retesting is not exclusively related to rationing of the diagnostic tests but rather to the absence of scientific evidence regarding their benefit at this stage.

The WHO, CDC and Brazilian Ministry of Health have plans to monitor transmission and, in this scenario, define the diagnosis to help guide public health actions and control measures, since it allows monitoring the trends and efficacy of the strategies and interventions of the State, during the pandemic[1,11].

Factors that Have an Impact on Post-Infection Immunity

Immunity is the result of an infection process that develops the unspecific innate response, by involving macrophages, neutrophils and dendritic cells to delay the progress of the virus, followed

by an adaptive response in which the body produces antibodies that are specifically connected to the virus. There is also cell immunity in which the T cells recognize and eliminate other infected cells[12]. An adaptive immunity established for a virus that is intimately related may reduce susceptibility or improve the prognosis of the disease. The antibody levels appear to diminish faster than the T cells, similarly to what occurred in SARS, where the T cells with a specific memory were detected up to 11 years after infection, while the specific antibodies fell below the limit of detection within 2 to 3 years. Studies demonstrated that patients who recovered from SARS-CoV1 can develop cross immunity against SARS-CoV-2, nevertheless, multi-specific T cell immunity was also observed in individuals who had not had contact with SARS[4,13]. Regardless, it is possible to define that the specific T cells produced for viral infections by beta coronavirus are long-lasting[13].

WHO continues to review evidence of the antibody response to infection by SARS-CoV-2[14]. The possibility that the infection itself, symptomatic or not, may immunize those who have been exposed is still being discussed, since milder clinical manifestations were observed, that resolved before seroconversion[15]. The results of a small study with nine patients who had COVID-19, found that the greater clinical severity produced higher antibody titers. However, the presence of higher antibody titers was not correlated to clinical improvement. In this study, it became evident that the viral load typically reaches its peak at the beginning of the disease and then diminishes as the antibodies develop. Subsequently, the antibody titers increase in the following 2 to 3 weeks (Figure 1).

Some patients present a high viral load even after the infection period commonly reported in most cases of SARS-CoV-2 and, in those cases, there is a suspicion of reinfection or of a false positive result of RT-PCR. The persistent detection of viral RNA many days after recovery from COVID-19 at concentrations close to the limit of detection of available tests[16] probably does not represent a significant clinical or public health risk, especially in the absence of symptoms. Another probable cause of false positivity in RT-PCR may be the persistent spilling of viral RNA, and not necessarily a reinfection. Furthermore, there are several factors such as

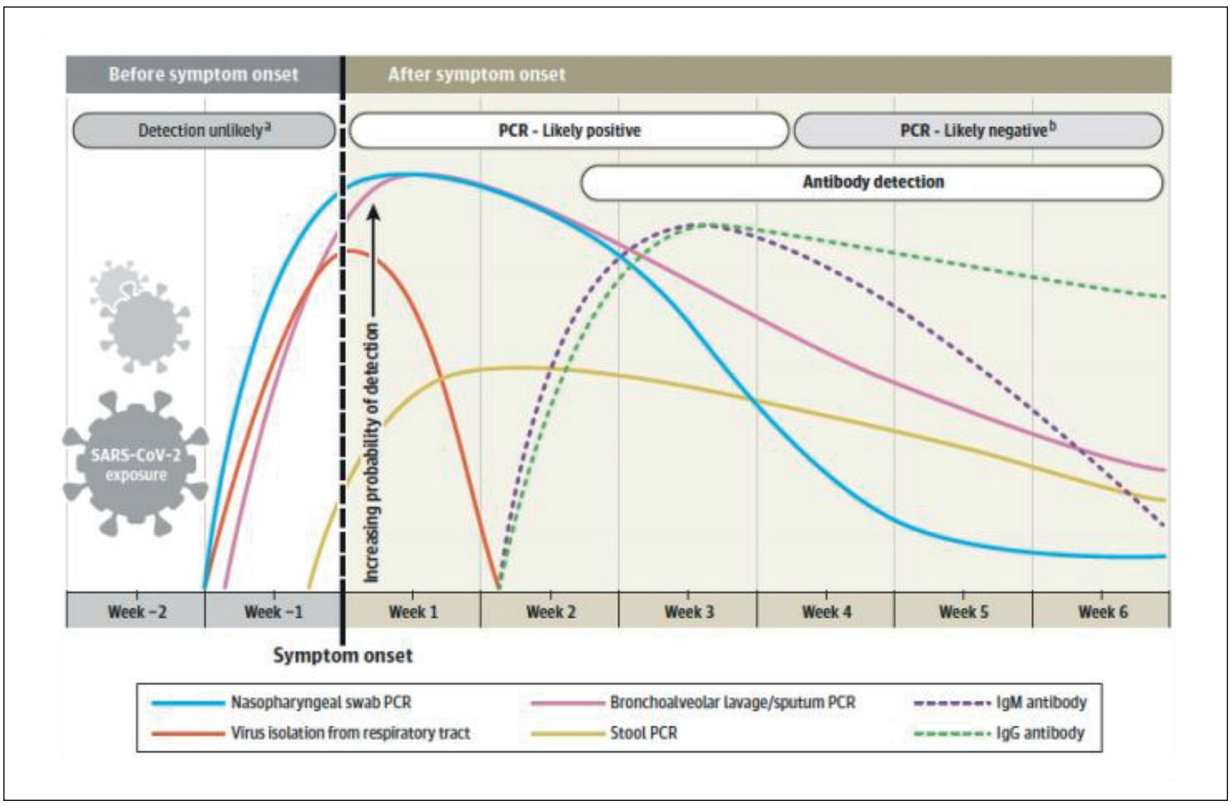

Figure 1. Estimated variation over time in diagnostic test for detection of SARS-CoV-2 infection[19].

inadequate collection of the sample, type of biological sample, time elapsed between collection and the beginning of the symptoms, and fluctuation of the viral load that may influence the test result. Reinfection, however, is not ruled out and the first case was confirmed in a young patient from Hong Kong, 4.5 months after the first episode. Genetic sequencing of the virus showed contamination by different strains and reinfection was asymptomatic, detected in a social monitoring test. People infected with related endemic beta human coronaviruses appear to become susceptible again about 90 days after the infection begins[17].

Uncertainties about immunity are also due to the great number of mutations in the virus genome and to the compromised immunity in patients with low levels of neutralizing antibodies[15]. It is not yet known to what extent these changes interfere in the immunological memory. There is a hypothesis that the propagation of the virus exhausts the susceptible since, considering the current evidence of antibody duration, the concept of "herd immunity" is not applicable, because exposure to the virus does not protect the group that is at risk.

The durability of the neutralizing antibodies (NAbs, mainly IgG) against SARS-CoV-2 is still uncertain, but studies indicate that the levels of IgG and neutralizing antibodies in a high proportion of individuals who recover from SARS-CoV-2 infection begin to diminish within 2 to 3 months after infection[18].

Diagnostic Methods

SARS-CoV-2 is diagnosed by clinical evaluation of the symptoms, confirmed by the diagnostic tests that have different methods to be recommended, depending on the phase of the disease. Outstanding among the tests are the molecular assays, that detect the virus in real time, and the immunological ones based on the antibody response produced by the body in response to SARS-CoV-2. Both must be validated before they are used, since false results may have a broad impact on how the patient is treated and also on public health. The FDA supplied recommendations about the minimum tests that should be performed to ensure the analytic and clinical validity of the diagnostic tests. However, the demand required extraordinary rules in the regulating agencies of many countries, preventing an adequate technical analysis, before they are given an emergency permission for sale[20-22]. Since these are products for professional use, and the practice of the laboratories that utilize them is to apply internal controls to validate an analytic system, the risks involved in utilizing the diagnostic products are minimized[23]. The manufacturers and importers are responsible for making available on the market products that conform strictly with the information approved in the registration. When deviation of quality is observed in the products, the healthcare services/professionals must notify ANVISA in order for the appropriate measures to be taken.

Molecular Assays

The detection of the virus by RT-PCR in real time (polymerase chain reaction with reverse transcription) is still the laboratory test of choice for the diagnosis of symptomatic patients in the acute phase. The detection of the viral RNA analyzed while processing the sample occurs in cycles called *threshold cycle* (Ct). The value of the detection cycle increases gradually until the viral RNA becomes non-detectable by the method. The availability of equipment and inputs for the tests is still limited and normally it is technology that requires specialized laboratories which take relatively long to execute. Some technologies based on rapid molecular tests are in the stage of launching and licensing and are not yet available on the Brazilian market.

FDA recommends the determination of the Limit of Detection (LoD), clinical evaluation, inclusivity and cross reaction to validate these tests. It is recommended that the LoD be defined as the lowest concentration at which 19/20 samples have a positive result in a triplicate analysis. For clinical evaluation, the FDA defines the acceptance criteria as 95% concordance at 1×-2× LoDand 100% concordance at all the other concentrations and negative samples, and a minimum of 30 positive reactive and 30 non-reactive species are tested. For the inclusivity test, the laboratories must document the results of an analysis *in silico* indicating the percentage of correspondences of identity with the publicly available SARS-CoV-2 sequences that can be detected by the proposed molecular assay. The FDA foresees that 100% of the published sequences of SARS-CoV-2 are detectable with the selected primers and probes. For the cross reactivity test *in silico*, the FDA defines as acceptable a homology greater than 80%[22]. The PCR test depends on the pre-analytical phase and requires a good technique for the collection

of material[24] from the naso and oropharynx and/or lower respiratory tract, its conservation and transport until the time of analysis. Studies have demonstrated variability of the viral recovery based on naso or oropharyngeal swab samples[25,26].

In convalescent patients, there is a tendency toward a lower recovery of viral RNA from the material collected. In asymptomatic patients the RT-PCR has a relatively low predictive value, demonstrating that the negative result does not exclude the infection. The detection of RNA for periods longer than 3 months after the disease begins, represents viral residue and infers low infection power. Studies did not find any evidence that people who have clinically recovered, with the persistence of viral RNA have transmitted SARS-CoV-2 to other people[9,17,25]. A few studies show that there is no identification of viable virus, i.e., viral replication from viral cultures cultured from samples of RT-PCRs for SARS-CoV-2 detected in Ct above 34[17,27].

Tests utilizing diagnostic method to detect nucleic acids using the gene editing technology, with the SHERLOCK (Specific High-Sensitivity Enzymatic Reporter Unlocking) technique which can consistently detect sequences that are the target of SARS-CoV-2 were developed using comparative studies with RT-qPCR which proved to be precise, without the need for elaborate instrumentation and the time of detection reduced to half that of RT-qPCR[28].

Serological Tests to Determine Antibodies

There are serological tests that use blood, serum or plasma samples and a methodology called immunochromatography (generation of color from a reaction between the antigen and the antibody) to detect antibodies produced by the patient's body itself in response to infection by the new coronavirus, called IgM and IgG. Since the body requires some time to produce these antibodies (immunological window) after contagion, immunochromatography is indicated for tests from 10 days after the beginning of the symptoms. The immunochromatography tests are all called rapid tests.

Tests were also approved to detect antibodies using other methodologies, such as ELISA – which is based on an enzymatic reaction; chemiluminescent immuno assay (CLIA) – which makes the antigen-antibody reaction visible through a chemical reaction; and immunofluorescence – in which the result is read based on the fluorescence formed in the reaction of the antigen with the antibody.

Some of them are based on the detection of total antibodies, and others identify IgM and IgG separately, few detect IgA. Independently of the characteristics of the appearance of antibodies in the individual, the power of detection of these antibodies using laboratory techniques depends on a number of properties of the assay, which are translated into the characteristics of performance of the test, such as, for instance, analytic sensibility (limit of detection) and the analytic specificity (less interference by other substances or antigens).

The FDA recommends that these tests be validated by studies regarding cross reactivity/analytic specificity; class specificity and study of clinical concordance.

Cross reactions may represent a bias, and in the case of COVID-19 there is an intrinsic relationship due to the possibility that cell immunity may develop by prior infection through another coronavirus (SARS-CoV-1, MERS)[13]. In this sense it appears to be important to relate the families of viruses used in the cross-reactivity tests panel. The study of clinical concordance aims to establish the performance characteristics (for instance sensibility; PPA, specificity/PPA/NPA) of the test. The FDA recommends that clinical precision be established in human samples of patients with confirmed COVID-19 infection. Thus, there is a clear need to add the clinical evaluation, with an analysis of the more prevalent symptoms in the picture of COVID-19 as a predictive factor to establish the diagnosis, influencing the positive predictive value of the test.

Serological Tests by Antigen Detection

The FDA defines the SARS-CoV-2 antigen detection tests as those that detect SARS-CoV-2 antigens directly from clinical samples. The FDA recommends that the following validation studies be conducted for SARS-CoV-2 antigen tests: limit of detection/analytic sensibility; cross reactivity/analytic specificity; microbial interference and study of clinical concordance. For devices that require multiple clinical matrices, the most challenging matrix must be used in the validation studies. Considering the rapid tests, the blood matrix is the most challenging.

The antigen detection tests can use ELISA methods, immunochromatography and immunofluorescence among others.

Methods

Although the methods can utilize the same matrices, they have some particularities that interfere in virus detection.

ELISA Method – Qualitative Determination

The kits that utilize the ELISA methodology, in blood (serum or plasma) samples, enable a sensitive and specific detection of the IgA, IgM and IgG antibodies by using the recombinant structural protein S1 of SARS-CoV-2 as an antigen. Tests with AgA antibody detection allow a sensitive detection in the initial phase of the disease, since IgA antibodies are detected in high titers in respiratory infection diseases and are described as markers in the diagnosis of acute infection. Some tests present sensibilities of 100% and specificity of 92.5% for IgA after ten days since the onset of the symptoms. The presence of IgM indicates an acute infection. For IgG the accuracy of the tests varies according to the period of onset of the symptoms, but usually they declare a sensibility of 80% and a specificity of 98.5% after ten days since the onset of the symptoms.

This technique requires careful preparation, since one must not utilize lipemic, icteric or highly hemolyzed samples. Such samples could present false results. It is also not recommended to inactivate the samples with heat, since this may make the molecule which is the target of the reaction deteriorate. The technique requires prior stabilization of all reagents and samples at room temperature by incubation at an adequate time and temperature.

A negative result does not exclude the presence of the virus. Other methods and techniques must be performed to confirm the result. Every ELISA technique can present falsely reactive results. Control samples and/or internal controls must be routinely used. The positive results must be clinically confirmed.

Immunofluorescence

Immunofluorescence (FIA) utilizes the sandwich immunodetection method, i.e., the fluorescent conjugates in the detection buffers are bound to the antibodies present in the sample, forming antigen-antibody complexes and migrate to the nitrocellulose matrix, where they are captured by other human anti-IgG and anti-IgM antibodies immobilized in the test strip. The more antibodies in the sample, the more antigen-antibody complexes are formed, generating a stronger intensity of the fluorescence signal in the detecting antigen.

The test may present false-negative result. Non-responsivity of the antigen to the antibodies is more common when the epitope is masked by an unknown component, so as to not be detected or captured by the antibodies. The instability or degradation of the antigen over time and/or temperature may lead to false-negative results, since the antigen becomes unrecognizable to the antibodies.

Immunochromatography

The system consists of a membrane in which human anti-IgG and anti-IgM antibodies were immobilized in the IgG test region and in the IgM test region, respectively. In executing the assay, the sample is placed to react with the conjugate that contains particles of colloidal gold bound to the recombinant antigens of COVID-19. The conjugate complexifies with the anti-COVID-19 antibodies present in the sample. After adding the buffer, the antibody-conjugate complex migrates chromatographically through the membrane and finds the test region in which the human anti-IgG and anti-IgM antibodies are immobilized forming a colored line. The presence of this line indicates a positive result and its absence indicates a negative result, as long as the control line, utilized as a control for the procedure, appears in the assay.

For SARS-CoV-2, what the studies have found so far is that the antibodies of classes IgA and IgM are detected, on average, beginning on the 7th day after the onset of the symptoms, followed by the elevation of the IgG levels. This means that in the acute phase the test has a low negative predictive value, i.e., a negative result does not exclude the disease nor the possibility of infecting other individuals. On the other hand, a positive result has a high predictive value.

The immunological response depends on individual factors, both of the host and of the characteristics of the antigen utilized, which means that the onset of antibodies may occur earlier or later, depending on the individual. The imprecise immunodiagnostic tests may falsely categorize people and suffer the interference of past SARS-CoV-2 infections and those caused by the known set of six human coronaviruses[4,13].

Precision Data Regarding the Registered Tests

The imprecision of the diagnostic tests sold in Brazil[29] together with the presence of other

manifestations caused by the known set of six human coronaviruses, typical of the southern hemisphere during the winter months, represent biases of interpretation. With the release of rapid tests in pharmacies, it is recommended to be very careful when interpreting them, especially regarding the decision regarding healthcare professionals returning to work, or immunocompromised essential services. The application of molecular methods together with repeated immunodiagnostic tests appears to be the best alternative for safety in the diagnosis of essential professionals when returning to work.

Information on accuracy and cross reactivity of 59 tests registered at ANVISA was verified[30]. The immunochromatography tests to mark IgM/IgG represented 61% (n=36) while RT-PCR only 25.4% (n=15). Cross reactivity was not performed or informed by 32% of the tests (n=19). Most of the tests, 54% (n = 32) did not present cross reactivity with the panel tested. Some presented cross reactivity with positive samples for antibody SARS-CoV, influenza, rhinovirus and respiratory syncytial virus. The ranges of accuracy, in the way they are informed, result in the lack of a clear understanding of what the tests indicate, or, possibly even more important, of what they do not indicate. Few explain the adequate temporality regarding the course of the disease or the onset of symptoms, for the appropriate choice of test.

Sensibility, Specificity and Predictive Value of a test

Test accuracy depends on establishing a relation to know whether a disease is or not present, when compared to the gold standard of diagnosis of a pathology. According to the study by Lisboa et al[31], 2020, Table I, the accuracy of the diagnostic test by antibody detection varies according to the testing methodology used. The predictive value is the probability of the disease in relation to the data of test results. This depends on their sensibility, their specificity and also on the prevalence of the disease among the population. We emphasize that the data on the prevalence of COVID-19, in Brazil and worldwide, do not reflect the real scenario, since cases are sub notified to the epidemiological surveillance agencies, mainly due to lack of access to performing the tests. This limits even further the analysis of the accuracy of the different methodologies employed. Thus, the lower the prevalence of the disease in the population, with tests that are not very significant or with imprecise sensibilities and specificities, the more difficult will be the evaluation of the predictive value of the test[31].

Table I. Comparative of the diagnostic accuracy of three serological testing methods for COVID-19.

COVID-19*	True positive	False negative
Positive		
ELISA	84%	16%
LFIA	66%	34%
CLIA	98%	2%
Negative		
ELISA	98%	2%
LFIA	97%	3%
CLIA	98%	2%

Legend: *Estimate prevalence of the 10%; ELISA = Ezyme-linked immunosorbent assay; LFIA = Lateral flow immunoassay; CLIA = Chemoluminiscent immunoassay. Source: Adapted from Lisboa, 2020.

Final Considerations

There is no standardization in the presentation of the test validation data. The variability of tests to determine the performance characteristics provided by the manufacturers for validation, or the absence of data, especially when they are rapid tests, are a matter of concern and in general do not show the characteristics of the population tested. Information on cross reactivity is a bias of interpretation, and is not given due importance, since the patients who have recovered from SARS-CoV-1 may develop cross immunity against SARS-CoV-2. Many tests present a number of samples that is too small and inadequate for test reliability. The importance of analytic verification of the tests should be emphasized, before using any laboratory method. Besides, it will be necessary to define correctly the quality of the sample, the professional's skill, the type of sample (secretion, capillary blood, serum) and the availability of the tests, based on the possibility of interpretation together with the clinical and epidemiological condition[2].

A recent systematic review (Lisboa et al[31], 2020) of the accuracy of diagnostic tests pointed out several limitations of their use in clinical practice, such as variability of sensibility and specificity in different diagnostic methodologies employed, lack of studies utilizing diagnostic tests that distinguish between the scenario where they are used (ambulatorial *vs.* hospitalized patient), and also the absence of stratification of the

patients according to the level of severity of the disease and the time of evolution since the beginning of the symptoms[31]. Further, the reduction of antibodies beginning 2 to 3 months after infection does not support the adoption of the rapid test as a factor of interruption of isolation, but may screen occupational contacts. The sensibility of many tests available was evaluated mainly in hospitalized patients, and therefore it is not clear whether the tests are able to detect lower levels of antibodies, where COVID-19 presents as milder and asymptomatic.

The design, execution and reporting of studies on the precision of the COVID-19 tests require considerable improvements. The studies must report data on the sensibility disaggregated by time since the onset of the symptoms. It is essential to establish the initial date of the symptoms presented by the patient in order to be able to establish the type of diagnostic test to be employed, and when it should be applied. Knowledge on viral transmission can be improved, contributing to the analysis of the determining criteria in contamination, contributing to diminishing the need to maintain social isolation[10]. The diagnosis must be applied by professionals with the capacity to analyze the clinical history of the patient, understanding their immunological window.

The importance of high-quality clinical studies to evaluate the diagnostic precision of serological tests for COVID-19 was confirmed, since the evidence does not support the utilization of serological tests as concluded by the CDC[17] which does not recommend utilizing tests for the purpose of interrupting the isolation of healthcare professionals.

We only managed to obtain data from a small proportion of available tests, and it is necessary to carry out an action to ensure that all results of test evaluation will be available in the public domain to avoid selective reports.

The positive cases of COVID-19 should be notified to contribute epidemiological studies, since the EPICOVID study revealed that in Rio Grande do Sul, Brazil, for every case notified, there are approximately 12 that have not been notified (EPICOVID19, 2020, First phase). The subnotification is also reported by the WHO (statement on April 27, 1920), and therefore testing is important. Furthermore, COVID-19 prevalence tests are essential to help evaluate the accuracy of the tests utilized, since they directly influence the predictive value of the test, especially in populations with a low prevalence of the disease[31].

Conclusions

There is a worldwide effort, rarely seen before in the history of science, to develop a cure or vaccine for SARS-CoV-2. Even so, it can be said that SARS-CoV-2 has characteristics that are not yet well known, and a very intriguing behavior of the virus, and also the immune response of the individuals. Knowledge of the natural history of COVID-19, the date of onset of the symptoms, the most prevalent symptoms and the prevalence of the disease itself, as well as the possibility of reinfection are fundamental to understand the transmission of SARS-CoV-2 in the different populations. The correct diagnosis is a strategic part of the planning actions to control the pandemic and therefore it is necessary to be extremely careful in choosing and applying the tests, especially in critical environments that involve a risk of transmission to vulnerable groups or epidemiological outbreaks. Applying molecular methods together with repeated immunodiagnostic tests appears to be the best alternative for a secure diagnosis of immunocompromised healthcare professionals, or who develop symptoms for more than 20 days[14,17].

Certainly, in the near future, new, more assertive diagnostic methods will become available, supplying greater certainty and accuracy. At this time, information is the best alternative besides preventive measures. This is a field that is rapidly evolving and is very important in public health.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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