DOI: 10.1590/1413-81232020259.17812020

Challenges and proposals for scaling up COVID-19 testing and diagnosis in Brazil

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Abstract *The Brazilian context of social inequalities and barriers in accessing health services may deteriorate the situation of the COVID-19 pandemic, which already affects all Brazilian federative states, with the growing curve of increasing confirmed cases and deaths. National governments and scientific field agents have been looking for evidence for the best practices of prevention and control of transmission, and care of infection and disease, including diagnosis, treatment, and health care measures. The large-scale testing strategy, aimed at early diagnosis, quarantine of the mild cases identified, as well as those of the contacts, and adequate care of severe cases, has been revised and indicated as one of the efficient pandemic control measures in several countries in the world. This paper aims to discuss the challenges of COVID-19 testing and diagnosis in Brazil.*
Key words *COVID-19, Testing, Diagnosis, Epidemiological surveillance, Brazil*

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Introduction

Coronaviruses are part of a family of viruses that cause respiratory infections in humans and are the second leading cause of the common cold and, until the last decades, rarely caused more severe diseases. There are seven known human coronaviruses (HCoVs), including SARS-COV (which causes Severe Acute Respiratory Syndrome-SARS), MERS-COV (Middle East Respiratory Syndrome), and SARS-CoV-2.

On December 31, 2019, the World Health Organization (WHO) office in China received notifications of cases of pneumonia of unknown cause among workers at a seafood market in Wuhan, China. In March 2020, WHO characterized this disease as a pandemic, called "Coronavirus Disease 2019" (COVID-19)[1,2]. The etiologic agent of this disease is Coronavirus subtype 2, or SARS-CoV-2[2]. Since then, national governments and scientific field agents have sought scientific evidence for the best practices for prevention and control of transmission and care for infection and disease, including diagnostic testing, treatment, and health care. As of May 31, 2020, 5,934,936 cases of COVID-19 and 367,166 associated deaths have been confirmed worldwide, which corresponds to a fatality rate of 6.2%[3]. The WHO has declared this pandemic as a "public health emergency of international concern".

SARS-CoV-2 rapidly spread to various parts of the world, indicating a high transmissibility rate[4,5]. There are not yet enough studies relating its high rate of transmission to socioeconomic issues, but notably, locations with a low human development index (HDI) and high socioeconomic inequality are likely to have a high risk of virus spread and reports of higher incidence and fatality rates due to COVID-19, since these communities may struggle to follow and cope with social distancing[6]. Another critical factor is that these locations have a high demographic density with people living in houses with few rooms, which hinders social distancing, considered a risk factor for the transmission of respiratory diseases[7]. Moreover, people living in these environments already suffer from a more significant burden of other acute infectious diseases or chronic non-communicable diseases (NCDs), potential COVID-19 severity factors, such as HIV infection and tuberculosis[8], hypertension, and diabetes[9,10] and obesity[11]. No less critical to the deteriorating situation in these communities is the difficulty of quick access to health services and quality information that enable self-care[6].

Brazil has one of the highest rates of social inequality, with a Gini index of 53.9[12], ranking as the second poorest income distribution in the world[13], and showing profound regional inequalities. About 40% of the Brazilian population is in an informal work situation[14], without access to labor rights, which can hamper adherence to social distancing measures i because of the need to circulate on the streets to retain their jobs, and, consequently, to secure income. Furthermore, Brazil experiences an incomplete epidemiological transition, when compared to European countries. For example, Brazil has high rates of incidence and prevalence of infectious diseases and, at the same time, of NCDs[15]. In this context, COVID-19 outbreak officially reached Brazil on February 26th, and the first COVID-19-related death was notified on March 17th in São Paulo state. As of May 31, 2020, the country had accumulated 514,849 COVID-19 cases and 29,314 related deaths - fatality rate of of 5.7%. The regions with the highest proportion of cases are the Southeast, with 36.4%, (187,240), and the Northeast, with 34.8% (179,401)[16]. Compared to the influenza A (H1N1) pdm09 pandemic when a total of 53,797 cases were recorded in the 2009-2010 period, with a fatality rate of 3.9% in 2009[17], the COVID-19 pandemic already exceeded the numbers in Brazil.

A significant increase in the incidence rate of SARS was recorded in the first months of 2020 in Brazil, the most severe manifestation of COVID-19, especially among people over 60 years of age, when compared with the incidence data from the previous ten years[18,19]. However, it has been speculated that this higher incidence is due to the underreported cases in Brazil[20]. A study recorded high inequality in the underreporting rates of COVID-19 with states in the north and northeast regions[21] leading the first seven places. Studies report that countries that are not testing their populations do not have a reliable estimate of the infection incidence rate[22,23]. In this sense, this paper aims to discuss the challenges of testing and diagnosing COVID-19 in Brazil.

Challenges for the diagnosis of COVID-19

The diagnosis of COVID-19 is a challenge worldwide. Some of the reasons for this are: 1) the biological material to be used, for example, nasal or oropharynx swab, plasma, serum or whole blood; 2) the definition of the biological marker to be detected; 3) the type of methodology employed (virological methods, molecular

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biology, and immunoassays); 4) the ideal time of the infection for sample collection and the ideal type of sample; and 5) the accuracy of the available diagnostic tests.

Moreover, the pandemic declared by the WHO has hampered the acquisition of supplies for greater availability of molecular tests for the detection of viral RNA, since this has become a global need. Brazil depends on imports of many equipment/supplies, due to the limited number of local companies[24,25].

However, the laboratory methods may be precise and fast, we should consider that the diagnosis of COVID-19 requires an adequate collection of the patient samples at the right moment of the infection to increase the likelihood of detecting the investigated biomarker[26]. The confirmatory test is the detection of the genetic material of the virus, such as viral RNA, by real-time PCR (RT-qPCR), which can be detected in stool, urine, and blood samples, albeit with less sensitivity and specificity than in respiratory samples[26]. An exception is the SARS-CoV-2 RNA, which is continuously detected in the stool up to two weeks after the onset of symptoms[27]. Thus, the combined oral/nasal swab RT-qPCR is considered as a gold standard test for SARS-CoV- 2 so far. However, there are some limiting aspects of this test, such as: 1) test positivity usually occurs within the first 4 to 8 days after the onset of symptoms, usually becoming negative after about 14 days[28,29]; 2) It is a test of high technical complexity, which requires an infrastructure with an adequate level of biosafety to perform it. It is relatively expensive, costing between R$ 150.00 to R$ 350.00 (currently around US$ 30 and US$ 70, respectively) per sample, with significant variations among supplying establishments[26,30].

Some studies have shown the importance of assays based on blood antibody detection for the diagnosis of COVID-19 in asymptomatic and symptomatic individuals, besides the production of data on the humoral immune response for the development of vaccines or treatment[28]. They are called Enzyme-Linked Immunosorbent Assay (ELISA) and allow detecting specific antibodies. Moreover, their edge lies in the speed of results and detection of relatively low cost, but they may show low sensitivity[26]. The average detection time of IgM and IgA antibodies for SARS-CoV-2 infection is five days (IQR=3-6 days), while IgG can be detected in less than 14 days (IQR=10-18 days) after the onset of symptoms, with a positivity rate of 85.4%, 92.7% and 77.9%, respectively[31]. On the other hand, an essential disadvantage of methods based on antibody detection is the possibility of cross-reactions with other viruses, especially those of the same family, which cause colds and other respiratory diseases[32].

Considering the potential and limitations of the main diagnostic methods used, it is essential to note that the advantages of tests based on immunoassays are: 1) the shorter time to perform and obtain the results (rapid tests range from 15 to 30 minutes; ELISA, from 1 to 2 hours); 2) rapid tests (immunochromatography) can be performed in field research, from a drop of blood collected from the digital pulp; 3) ELISA, while of medium complexity, can be performed by automation with results obtained in a maximum of 2 to 3 hours; 3) since it is an acute infection, the test based on the detection of viral RNA is likely not to be positive after 10 to 14 days, whereas the IgG class antibodies may be detected, in principle, throughout life. Furthermore, IgG titers may be measured to investigate recent serological conversion[31]. While information regarding cut-off points for days of sensitivity and specificity of RT-qPCR and immunological tests are still under investigation, some studies point to that the more at the onset of symptoms, the higher the likelihood of positive RT-qPCR, and the more distant from the onset of symptoms, the higher the likelihood of positive IgM and IgG. Tests with methodological principles of molecular biology and immunology are essential at different times of the infection, and the simultaneous application has been shown with more exceptional diagnostic and prognostic proficiency[33]. Thus, detecting the production of antibodies, especially IgM, which are produced quickly after infection, can be a tool combined with RT-qPCR to improve sensitivity and diagnostic accuracy[31].

Testing for COVID-19: evidence, strategies, challenges

The transmission of the coronavirus can occur through droplets of saliva, sneeze, cough or phlegm, which can be passed on by touching or shaking hands, objects or surfaces contaminated by the infected person[5,34], and the early diagnosis of new cases of COVID-19 through testing is crucial to stop the virus spread[35] through social distancing and quarantine strategies.

Confirming COVID-19 cases is a challenge, as there is usually a mismatch between the onset of symptoms and the precise laboratory diagnosis[36]. Furthermore, about 80% of COVID-19 cases are asymptomatic or oligosymptomatic[37] and often go undiagnosed. In China, at the onset of the outbreak in Wuhan, it is estimated that non registered infections were the source of infection for 79% of recorded cases[34].

Studies with infectious diseases such as tuberculosis[38] and African viral hemorrhagic fever[39], besides COVID-19[40], highlight how the delayed diagnosis and treatment of infected individuals are decisive for the speed of the spread of infections in epidemic contexts. In several countries, one of the most effective measures for detecting and preventing new COVID-19 cases was the large-scale testing of the population[41-43], already recommended by the WHO[1], and the indication of quarantine for 14 days for the identified cases, and their direct contacts after the onset of symptoms[44].

Some countries in Asia and Oceania have shown control of the pandemic by combining strategies with extensive testing. For example, in China, important measures for the control of COVID-19, were: early detection of cases through testing, isolation of cases and screening of all contacts, and quality clinical care for those infected[40]. In Singapore, epidemiological surveillance included testing all suspected cases and contact persons. Thus, this strategy contributed to the early detection of approximately half (53%) of the COVID-19 cases and was also an effective strategy for the progressive reduction of the appearance of indigenous cases of the disease right at the onset of the epidemic[41]. The example of Singapore and Hong Kong indicates the importance of expanding testing, the surveillance system with selective control of travelers, and financing measures for state funding for treatment, planning, articulation, and management of health services[45]. New Zealand has managed to control the pandemic in its territory and eliminate community transmission[46], by adopting, among other strategies (such as lockdown, border control, health education promotion, among others), large-scale testing of the population for screening and rapid detection of cases and contacts, and implementation of quarantine[47]. In Australia, the testing actions associated with the organization of the health system combined with telehealth actions resulted in a low fatality rate, with 7,185 confirmed cases and 103 deaths, equivalent to fatality rate of 1.4% on May 31, 2020[3,48].

In Europe, we observed some countries that experienced a collapse of the hospital care network, such as Italy, which implemented extensive testing, including for asymptomatic people, only after the dramatic situation of lack of intensive care beds[49]. Spain adopted a testing protocol only for people with symptoms of the acute respiratory syndrome and symptomatic health professionals, and also exceeded the installed capacity of the number of intensive care beds[50]. The United Kingdom also adopted late measures to tackle the pandemic and testing[51], but recently adopted a surveillance protocol that involves people with influenza-like symptoms, and the collection of serological samples from all age groups, with regular data monitoring[52]. On the other hand, Germany is one of the continent's exceptions, showing a rapid and coordinated response to the pandemic, associated with decentralized testing, including young people and cases with mild symptoms from the start of the pandemic[53].

Two countries are highlighted in the Americas. First, the United States of America, the largest country in North America, which showed a late and uncoordinated national response to testing and social isolation[50], which may have led it to rank first in the number of confirmed COVID-19 cases (1,716,078) and deaths (101,567) as of May 31, 2020[54]. Then Brazil, the largest country in Latin America, which registers an increasing trend of confirmed cases and deaths, with an uncoordinated response from national government[55] and with limited testing of the population[21]. On the other hand, the importance of the National Health System (SUS) with universal access[56], with a broad National Health Surveillance System (SNVS), which favors the adoption of quick responses by many regional and local governments.

Thus, while not exhausting the literature on the countries' testing response, the importance of testing strategies[42] associated with the organization of the health system in addressing the pandemic is emphasized, as the number of confirmed cases allows monitoring of progression disease[57], which can prevent the collapse of the hospital care network, based on the articulation between different health care levels. Moreover, although we are still unable to isolate the effect of the testing strategy on disease incidence rates, international experiences show the importance of these efforts coordinated with health systems in controlling the COVID-19 pandemic.

Epidemiological surveillance

The process of investigation, notification, and monitoring of COVID-19 cases by the SNVS of the Brazilian SUS is fundamental in response to COVID-19, as it operates throughout the Brazilian territory in an articulated and hierarchical

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way, through the Strategic Health Surveillance Information and Response Centers (CIEVS), from the municipal and state health secretaries[58]. Besides routine activities, the SNVS is triggered in the event of situations of Public Health Emergencies of National Importance, such as the COVID-19 pandemic[44]. In these cases, the service network must be organized to respond quickly with the urgent use of measures to prevent, control, and contain risks, damage, and harm to public health[59].

Decentralized testing is a fundamental strategy for increasing the detection of new cases, linking to adequate care and epidemiological surveillance, but it faces some challenges such as socioeconomic inequalities and the distribution of equipment/supplies and infrastructure available for diagnosis. In this sense, some initiatives aimed at expanding testing have been adopted by the National Health Surveillance Agency (ANVISA), such as the approval of rapid tests (RT) in pharmacies[60], and new diagnostic tests for the detection of antibodies for SARS-CoV-2[61,62]. Furthermore, a national epidemiological and laboratory surveillance strategy for COVID-19 was launched on May 6, 2020 to test about 22% of the Brazilian population[63].

However, the testing strategy should consider the accuracy of the tests for antibody detection, since the sensitivity and specificity of the tests approved in Brazil vary between kits from different manufacturers[64]. Few validation studies have been published[65]. For example, among the tests approved in Brazil, sensitivity is found in low to moderate levels, which may result in the difficulty in detecting infected individuals, especially in tests for the detection of anti-SARS-CoV-2 antibodies of the IgM class in the initial phase of infection[65]. Moreover, the positive predictive value may vary with the prevalence of infection in the population, with higher values in populations with a prevalence equal to or greater than 10%[66]. It is also important to note that many of the tests available are still in the process of technical improvement. Besides, there are few studies related to the dynamics of biomarkers in the humoral immune response.

Thus, information and communication on the limiting aspects of these tests and the interpretation of the tests by the professionals who will apply the RT and other tests are essential, so that there is no low perception of the risk of transmission by the population, due, for example, to false-negative results, as it could enhance social interaction and increase transmission. Moreover, we should consider that testing must be linked to the recording and monitoring of the SNVS, and the assistance of trained health professionals for clinical-individual care in case management, and guidance on the limitations of sensitivity and specificity of the tests. It is also necessary to ensure the testing of Brazilian citizens from local income communities who cannot pay for tests, as well as the secrecy and confidentiality of individual results.

The Brazilian and international response to the HIV/AIDS epidemic showed that testing decentralization is fundamental to increase the early diagnosis of the infection, and the rapid link to care, also through the application of RT for screening by trained lay people[67-69]. In this way, primary health care (PHC), which is the preferred gateway to the SUS, can play an essential role in expanding testing, as it is present in the remote Brazilian locations[70], with teams of community workers accessing communities[71], and health professionals trained in the application of other RTs (HIV, syphilis and viral hepatitis)[72]. Thus, PHC can become the central locus for decentralized and democratized RT to identify COVID-19 cases in the Brazilian territory, with an active search of cases and contacts, with the link of users to quarantine strategies, and the provision of primary care to those infected with mild symptoms and the articulation with other points in the health care network.

In this sense, the testing response for COVID-19 can be coordinated by SNVS on two fronts: 1) *individual*: with access to the test through the supplementary health network (private services: hospitals, clinics or pharmacies), with notification of cases and monitoring by local epidemiological surveillance, and clinical care with appropriate guidance; and 2) *community*: with priority access through PHC (without the elimination of access via other levels of care), with due notification of cases, organized and monitored through local epidemiological surveillance. Furthermore, the active search should be adopted as a starting point for the investigation of all contacts of confirmed COVID-19 cases, using the RT-qPCR test with an oral/nasal swab sample collected within seven days after the onset of symptoms or immunological test (rapid test by immunochromatography or serology by ELISA) seven days after the onset of symptoms. For asymptomatic patients, the collection can be based on the number of days reported after contact with the infected person: <7 days (RT-qPCR) and ≥ 7 days (immunological). Cases confirmed with a positive result should be tested and recommended to be quarantined for 14 days, according to the Ministry of Health protocol (Figure 1)[44].

Conclusions

The expansion of the COVID-19 testing and diagnosis is a challenge to Brazilian society and the SUS. While we have faced a process of chronic de-financing and constant threats to the public health system for years, we have decentralized management and epidemiological surveillance mechanisms capable of responding appropriately to the challenge. Moreover, we have a network of laboratories, universities, and public research institutes in all states of the country, which can organize a diagnostic service network, under the coordination of the SNVS, to expand COVID-19 testing. Therefore, it is necessary to eliminate bureaucratic barriers for the accreditation of laboratories in universities and research institutes for diagnosis, expand financing for training and hiring staff, invest in research studies on serological diagnosis, epidemiology, vaccine development and treatment, and have a political-scientific articulation for decision-making based on local and global scientific evidence.

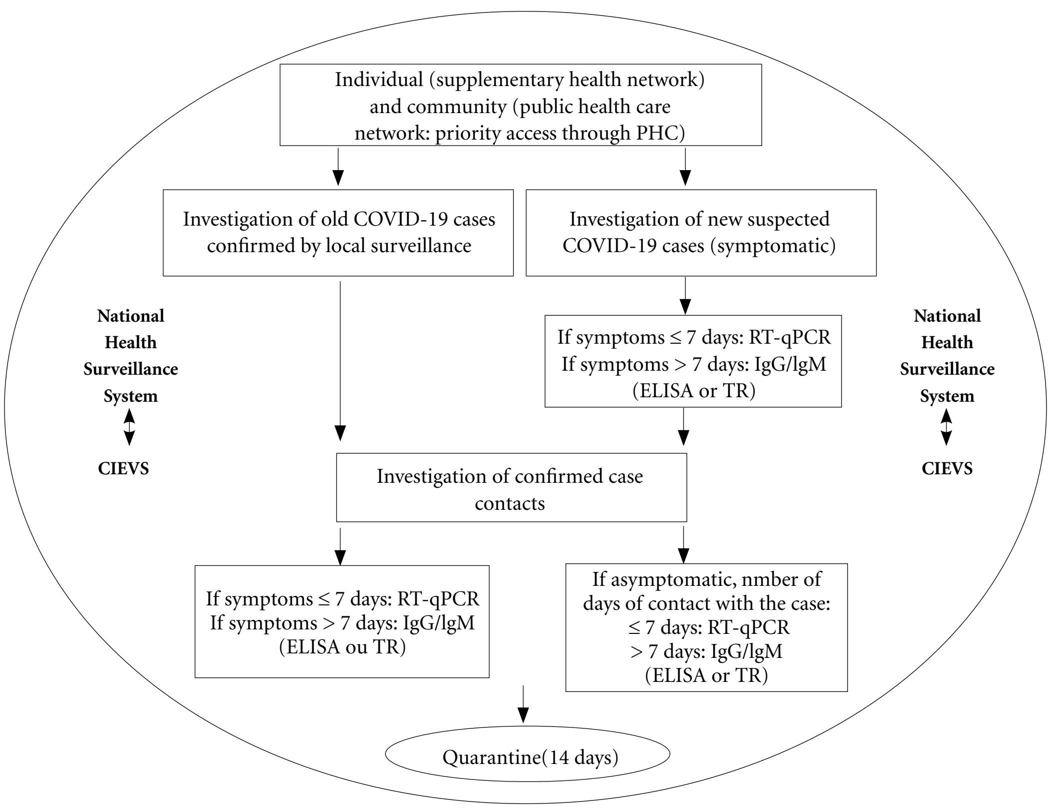

Figure 1. Integrated testing response for suspected and contact cases.

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Collaborations

L Magno: design of the paper, literature review, writing, and final review of the paper. TA Rossi, CC Santos, LM Marques, GB Campos, M Pereira and NMBL Prado: Writing, literature review, and final review of the paper. FW Mendonça-Lima: Writing, literature review, critical review of the manuscript, and final review of the paper. I Dourado: Writing, literature review, critical review of the manuscript, and final approval of the paper.

Acknowledgments

We are grateful to the Brazilian Health Reform Movement for helping to found and build the National Health System (SUS), which is a source of inspiration for all of us Brazilian health workers. We also thank the Brazilian public universities for having trained us and for being our workspace.

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Article submitted 01/06/2020
Approved 01/06/2020
Final version submitted 03/06/2020