Analysis of COVID-19 diagnostic test implementation in Brazil: strategies in place at the beginning of the pandemic

Análise da implementação do teste diagnóstico da COVID-19 no Brasil: estratégias em vigor no início da pandemia

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ABSTRACT
The World Health Organization considers the mass testing one of the main tools for controlling the COVID-19 pandemic. The aim of this study was to evaluate the strategies adopted by the Brazilian Federal Government to promote population testing and access to in vitro diagnostic products for COVID-19 within the Unified Health System. Thus, we analyzed the information collected in databases from ANVISA (Brazilian Health Regulatory Agency), the Ministry of Health and Our World in Data on regulatory flexibility for in vitro diagnostic products for COVID-19, the impacts of acquisition and distribution for tests and the pandemic indicators, respectively. Around 65% of the tests registered at ANVISA were from China, while only 17% were Brazilian tests. Of the 441 registered tests, 67.8% were rapid antibody tests. Brazil only carried out 20 million of the 46 million tests planned for 2020 by the Diagnosis to Care Program. The reduced mass testing and the use mainly of rapid tests for antibodies detection may contribute to the underreporting of the disease and to Brazil's position among the countries that test the least and with a high number of cases and deaths presented in the early years of the COVID-19 pandemic.

Keywords: COVID-19; Diagnostic; Public health; SARS-CoV-2; Point-of-care

RESUMO

Palavras-chave: COVID-19; Diagnóstico; Saúde pública; SARS-CoV-2; Ponto de atendimento
INTRODUCTION

The COVID-19, disease caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a global pandemic responsible for one of the most significant public health challenges of the 21st century (RAMOS-CASALS; BRITO- ZERÓN; MARIETTE, 2021). At the end of the first year of pandemic (2020), the number of confirmed cases worldwide was already over 84.3 million, while Brazil had about 7.7 million cases and 195.8 thousand confirmed deaths, occupying the position of second country with the highest number of deaths in the period (GCDL, 2022a).

Since the beginning of the COVID-19 pandemic, the World Health Organization (WHO) has recommended the mass testing as main strategy to controlling the spread of the new coronavirus, especially since there were still no approved vaccines against the disease (OMS, 2020b). Consequently, several regulatory agencies have adopted a posture of flexibility in their rules considering different critical items in the emergency moment, including applications for registration of in vitro diagnostic kits (Bolislis et al., 2021; Klein et al., 2022). Thus, WHO’s recommendation was efficiently adopted in different countries, such as the Republic of Korea, Germany, among others (DEKA; KALITA, 2020; LEE; LEE, 2020).

Between the years 2020 and 2021, Brazilian strategies to contain the advance of the pandemic were composed of a mix of political and economic interests, logistics problems, and ideological disputes, causing the country to be characterized by regional inequalities in the allocation of resources for the health system (Bigoni et al., 2022; Hallal & Victora, 2021). One of the most remarkable problems was the process of vaccine acquisition. Differently from the United States and the United Kingdom, which prioritized and guaranteed the acquisition of vaccines as soon as possible, even those still in development, Brazil initially delayed and restricted the purchase of immunizations to a few suppliers, such as Oxford/AstraZeneca, Sinovac and Pfizer/BioNTech (BRASIL, 2023; CNBC, 2020; National Audit Office,, 2020; U.S Department of Defense., 2020). Therefore, the mass vaccination started later, only on January 17, 2021, and was characterized by slowness, dose escalation, and heterogeneity in the acquisition and application of immunizations around the country (Brasil, 2020).

The Brazilian government also established measures to promote the testing of the population, coordinated by the Health Surveillance Secretariat (SVS), of the Ministry of Health (MoH), which decreed the "Programa Diagnosticar para Cuidar" (Diagnosis to Care Program) (BRASIL. Anvisa, 2020c). Within this perspective, few studies have been
conducted in order to evaluate the actions taken in the country at the beginning of the pandemic when it comes to mass testing of the population for COVID-19, which can be a useful tool to analyze the lessons learned when it comes to combating new health crises. Hence, this study aimed to evaluate the strategies adopted by the Brazilian federal government to promote population testing and access to in vitro diagnostic products for COVID-19 within the scope of the Unified Health System (“Sistema Único de Saúde” - SUS) at the first year of the COVID-19 pandemic in the country, in 2020, and compare them to other organizations/institutions elsewhere in the world. The analyses of these strategies linked to the two institutions were considered because they represent an important indication of the policies to confront COVID-19 in Brazil in the first year of the pandemic.

MATERIALS AND METHODS

A brief scheme of the methodology employed is shown in Figure 1, which was based mainly on the analysis of official documents and online database research.

Figure 1. Overview of the methodology applied in the work, highlighting which databases were used. Created with BioRender.com (accessed on January 23, 2023).

Regulatory flexibility and in vitro diagnostic products for COVID-19 registered in ANVISA

The analysis of regulatory flexibilities of in vitro diagnostic products for COVID-19 was based on the Resolution of the Collegiate Board of ANVISA, RDC 348/2020
This resolution allowed the registration of products without performance studies and data restriction for one year. The data of in vitro diagnostic kits for COVID-19 registered at ANVISA were collected between May 18, 2020, when the first kit records were published in Brazil, and December 9, 2020, totaling an approximate period of 51 weeks or 205 days. Data research and collection was performed on the ANVISA website, in the "Fila Completa de Produtos de Diagnóstico in vitro para COVID-19". As in Brazil, the same product can be registered by different distributor companies, the analyses performed in this work were based on the product manufacturer instead on the registration holder (BRASIL. Anvisa, 2020a). Furthermore, a survey of the products included in the WHO Emergency Use Listing Procedure for in vitro diagnostics was also conducted to compare the WHO’s recommendations, intended mainly to advise regulatory agencies, and the records granted by ANVISA (WHO, 2020a).

In vitro diagnostic tests for COVID-19 under the “Programa Diagnosticar para Cuidar” (Diagnosis to Care Program)

The research related to the "Programa Diagnosticar para Cuidar" (Diagnosis to Care Program) was performed on the website of the Brazilian Ministry of Health (MoH), which is dedicated to sharing information about the COVID-19 pandemic and includes data on the disease, clinical protocols, information on research and development, among others (Brazil. Ministério da Saúde, 2020b). In this context, the following path was employed to collect the data: i) Ministério da Saúde; ii) Localiza-SUS: Coronavírus (COVID-19); iii) Painel de Leitos e Insumos Gastos com COVID-19; iv) Painel de Testes. On January 22, 2020, was founded the Public Health Emergency Operations Center for the Novel Coronavirus (COE-nCoV), which is coordinated by the Health Surveillance Department (SVS) of MH. Epidemiological Bulletins are being published weekly, widely used in this work to collect data on epidemiological surveillance, purchases, distribution, and testing by SUS. Data were analyzed based on information collected in Bulletins 01 to 40, the latter referring to epidemiological week nº 49 (November 29, 2020, to December 05, 2020).

In addition, the top five countries that carried out the highest total number of COVID-19 tests (United States, India, China, Russia, and the United Kingdom) were selected for a comparative analysis with Brazil. To this end, data were collected about the number of tests performed, the number of cases and deaths, the positivity rate, and the
methods chosen for testing (until May 12, 2020), in the Our World in Data database, which MoH has used to present international data in COE-nCoV Bulletins. The database did not present data of Brazil from September onwards. Therefore, data from Brazil were extracted from Bulletin COE-nCoV no. 40. Thus, the number of PCR tests performed, the number of serological tests, and the positivity rates were from tests performed in the SUS. The total number of cases registered in Brazil does not make it clear whether these data refer to tests carried out in the public and private network, nor the types of tests used to provide those results, as highlighted on the Our World in Data website (GCDL, 2020b). In addition to reports indicating underreporting of cases, there are also reports of delays in the transfer of notifications, which are factors that can generate distortions in the Brazilian data analyzed.

RESULTS AND DISCUSSION

In Brazil, the enactment of normative acts (laws, decrees, ordinances, and resolutions) related to COVID-19 began in February 2020, when the MoH deflagrated the status of a public health emergency of national importance (Ordinance no. 188, February 3, 2020) (Figure 2). From this, the MoH was given the responsibility of coordinating health system responses, while ANVISA, an arm of the MoH, became actively engaged in regulatory oversight, ensuring the safety and efficacy of COVID-19-related products and providing guidance to protect public health (Bigoni et al., 2022). Therefore, the MoH and ANVISA have different roles and this has been reflected in the actions of each within the context of the COVID-19 pandemic in Brazil, including access to in vitro diagnostic products. The WHO has played a crucial role in setting global health policies, guidelines, and recommendations. It collaborates with member states to develop and promote international health regulations, monitor disease outbreaks, conduct research, and provide guidance on various health-related issues, which may have implications for the actions of ANVISA and the MoH (KUZNETSOVA, 2020). Thus, we considered in this manuscript the comparison between the WHO recommendations and the two Brazilian authorities.
COVID-19 in vitro diagnostic products registered in ANVISA: regulatory aspects

Regulatory flexibilities adopted by ANVISA

The pandemic caused by SARS-CoV-2 has boosted the development of innovation projects worldwide aiming to produce supplies and kits for diagnosis employing in vitro techniques (Lai et al., 2021). To this end, regulatory agencies in many countries, such as the US Food and Drug Administration (FDA) and ANVISA, have adopted measures that have allowed for greater flexibility in the registration processes, which include issues associated with the analytical performance of tests (LAUREANO; RIBOLDI, 2020; RAVI et al., 2020). Therefore, ANVISA published the RDC 348/2020 in March 2020 (Figure 2), which defines the extraordinary and temporary criteria and procedures for handling petitions for the registration of medicines, biological products,
and in vitro diagnostic products and post-registration change of medicines and biological products due to the international public health emergency resulting from the new Coronavirus. As shown in Figure 3, the main difference between Brazilian and WHO regulatory flexibilities for in vitro diagnostic products is on the quality management system and registration validity period.

**Figure 3.** Main points addressed by ANVISA and WHO for in vitro diagnostic products for COVID-19. Legend: PHE: Public Health Emergency; asterisk (*): mandatory documentation only for imported products. Created with BioRender.com (accessed on March 14, 2023).

<table>
<thead>
<tr>
<th>ANVISA</th>
<th>WHO - EUL Regulatory review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Registration petition</strong></td>
<td><strong>Information on manufacturer's quality management system</strong></td>
</tr>
<tr>
<td>✓ Proof of payment of the Taxa de Fiscalização de Vigilância Sanitária (Health Surveillance Inspection Fee)</td>
<td>✓ Specific manufacturing documents</td>
</tr>
<tr>
<td>✓ Completed electronic application form</td>
<td></td>
</tr>
<tr>
<td>✓ Product Dossier</td>
<td></td>
</tr>
<tr>
<td>✓ Consent sterilization or apostille declaration, issued by the legal manufacturer*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Product Dossier</strong></th>
<th><strong>Product information</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Product description</td>
<td>✓ Design</td>
</tr>
<tr>
<td>✓ Performance study</td>
<td>✓ Manufacturing information</td>
</tr>
<tr>
<td>✓ Clinical performance</td>
<td>✓ Product performance specification</td>
</tr>
<tr>
<td>✓ Instructions for use</td>
<td>✓ Associated validation and verification studies</td>
</tr>
<tr>
<td>✓ Information on quality control</td>
<td>✓ Clinical or diagnostic sensitivity and specificity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Registration validity period</strong></th>
<th><strong>EUA's that have been issued by WHO or FDA for VIDs during a PHE are authorizations but not approvals. These authorizations are only in effect for as long as the PHE lasts.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ One year for products without stability information evaluated in a period longer than 6 (six) months.</td>
<td></td>
</tr>
<tr>
<td>✓ Ten years for products accompanied by stability information evaluated in a period longer than 6 (six) months.</td>
<td></td>
</tr>
</tbody>
</table>

Regarding the documentation required for registration of in vitro diagnostic products, the RDC 348/2020 advises following the instructions provided by RDC 36/2015 (BRASIL. Anvisa, 2015). Similarly, WHO already possessed a procedure for assessing and listing candidates for in vitro diagnostics, therapeutics, and vaccines for use primarily during public health emergencies, such as Emergency Use Assessment and Listing (EUAL) during Ebola Virus Disease outbreak in West Africa (USAID, 2021). During the COVID-19 outbreak, EUAL was replaced by Emergency Use Listing, a process based on an essential set of available quality, safety, and performance data of in vitro diagnostics candidates (OMS, 2020b). Similarly to US government and to WHO, ANVISA, in collaboration with the National Institute for Quality Control in Health of Fundação Oswaldo Cruz (FIOCRUZ), created a monitoring program for rapid tests in order to
conduct the necessary validations and verify the veracity of the information declared in the registration process (BRASIL. Anvisa, 2020d).

**Types of COVID-19 in vitro diagnostic products registered in ANVISA**

We found three types of COVID-19 in vitro diagnostic products registered in ANVISA during the analyzed period, those that: (1) act by molecular detection of the genetic material, in this case, viral RNA, through the RT-PCR assay; (2) or serological tests, through the detection of antibodies, mainly immunoglobulin IgM, IgA, and IgG; and yet (3) through detection of viral antigens. In order to facilitate reading, we categorize serological and antigen tests as immunological tests. Among the immunological tests are the Enzyme-Linked Immunosorbent Assay (ELISA), the chemiluminescence immunoassay (CLIA), and the so-called “rapid tests”, which is the term whether it has been used for immunochromatographic tests and lateral flow tests. These last two tests are performed using manual and easy-to-use devices (which can be antibodies or antigens), giving results in up to 30 minutes and without the need to use complex equipment and laboratory structure, also known as point-of-care tests (XU et al., 2020).

Figure 4 shows the records granted by ANVISA for specific diagnostic products for COVID-19 published from March 2020. Until December 9, 2020, 441 tests were approved, of which 83% were immunological tests and 17% were molecular tests (Figure 4a). Until then, 116 registrations had been rejected, and 105 needed to clarify some technical points (technical requirements) for the regulatory agency. This scenario shows that the flexibilities promoted by ANVISA made registration possible, even considering that most of these products did not pass the usual validations (Brazil. Ministério da Saúde, 2020b). Regarding the methodology employed by the tests, approximately 73% were related to immunochromatographic, while 16.3% were related to RT-PCR. While CLIA and ELISA tests represented 5.7% and 3.6%, respectively, only one record (0.2%) was found for the reverse transcriptase-loop mediated isothermal amplification (RT-LAMP) molecular assay, this being a test registered by the North American company Abbott; together, these tests represented 10.4% (“Others”) of the evaluated tests (Figure 4b).

Subsequently, we analyzed the main manufacturing countries of COVID-19 in vitro tests registered in ANVISA. According to Figure 4c, Chinese immunological test manufacturers account for 65% of deferred registrations, domestic manufacturers account for 14%, South Koreans 8%, and North Americans 6% (“Others”). Other countries also
appear in this list, with an unrepresentative amount of registrations. Regarding RT-PCR tests, we observed 71 tests registered in ANVISA, of which 37% had Chinese origin, 22% were South Korean. North American tests (13%), as well as the tests registered by national manufacturers (10%) and other countries, such as Germany, the United Kingdom, and Italy, also appear on the list, but with an insignificant amount of registrations and correspond to approximately 41% (“Others”) (Figure 4d). Despite the leading role of Chinese registrations in ANVISA, Brazil was the second country regarding the number of immunological COVID-19 diagnostics tests registrations. The reduced participation of the national industry in the production of diagnostic tests results from several factors, such as the external dependence on acquiring essential inputs, which China mainly produces.

**Figure 4.** Characteristics of diagnostic tests for COVID-19 registered in ANVISA between May 18 and December 9, 2020: (a) percentage between total serological and molecular tests and (b) records of diagnostic tests by methodology. Legend: Others: RT-LAMP; CLIA, ELISA tests. (c) records of immunological tests, by country. Legend: “Others”: South Korea, USA, Canada, Germany, Switzerland, Japan, United Kingdom, Italy, Finland, France, Israel, Portugal. (d) RT-PCR records, by country. Legend: “Others”: Brazil, USA, Germany, United Kingdom, Italy, Finland, Spain, Luxembourg, Turkey.
Further, we found twenty-five national companies that have registered in vitro diagnostic products for COVID-19 in ANVISA, of which Quibasa (n = 9), Eco Diagnóstica (n = 8) and Advagen Biotech (n = 6) possessed the highest number of registered products (Figure 5). Besides, FIOCRUZ obtained five approved registrations and, through one of its laboratories, Biomanguinhos, presented ten approved tests: four RT-PCR and six immunological tests, surpassing Advagen Biotech in many approved tests (nine). In addition, Butantan and Bahiafarma, two other public laboratories, also presented registrations, but only as distributors of tests manufactured by South Korean companies (BRAZIL. MINISTÉRIO DA SAÚDE, 2020b).

**Figure 5.** Number of registrations in ANVISA for in vitro diagnostic tests for COVID-19 (between May 18 and December 9, 2020) by Brazilian companies. LMG Lasers: LMG Lasers Comércio, Importação e Exportação; Mobius Life Science: Mobius Life Science Indústria e Comércio de Produtos para Laboratório.

Brazilian versus WHO strategies

As of February 2020, manufacturers of in vitro diagnostic products were encouraged by the WHO to submit an “Expression of Interest” for evaluation of products
to be included in the Emergency Use Listing Procedure. The procedure was developed to expedite availability and to support purchasing agencies and member states of the organization, starting from a minimum analysis of available information on safety and efficacy (WHO, 2020b). Although the list includes three types of tests (molecular tests, serological tests for antibody de-tection and rapid tests for antigen detection), only rapid tests (point-of-care) based on antigen detection and molecular tests were approved (Table 1).

Table 1. World Health Organization (WHO) Emergency List for recommended in vitro diagnostic products for COVID-19 during the study period (WHO, 2020).

<table>
<thead>
<tr>
<th>Date</th>
<th>Product Name</th>
<th>Product Code</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 02, 2020</td>
<td>PANBIO COVID-19 Ag Rapid Test Device (NASOPHARYNGEAL)</td>
<td>41FK10</td>
<td>Abbott Rapid Diagnostics Jena GmbH</td>
</tr>
<tr>
<td>September 22, 2020</td>
<td>STANDARD Q COVID-19 Ag Test</td>
<td>09COV30D</td>
<td>SD Biosensor, Inc</td>
</tr>
<tr>
<td>September 15, 2020</td>
<td>SARS-CoV-2 Nucleic acid detection kit based on Real-Time PCR Platform</td>
<td>PGA4102P1 (liquid) / PGA4102P2 (lyophilized form)</td>
<td>Tellgen Corporation</td>
</tr>
<tr>
<td>September 02, 2020</td>
<td>Novel Coronavirus (2019-nCoV) RT-PCR Detection Kit (commercial name: Fosun 2019-nCoV qPCR)</td>
<td>PCSYHF</td>
<td>Shanghai Fosun Long March Medical Science Co., Ltd</td>
</tr>
<tr>
<td>August 28, 2020</td>
<td>SARS-CoV-2 Virus Detection Diagnostic Kit (RT-qPCR Method)</td>
<td>XC25073</td>
<td>Ningbo Health Gene Technologies Co., Ltd</td>
</tr>
<tr>
<td>August 14, 2020</td>
<td>TaqPath COVID19 CEIVD RTPCR Kit</td>
<td>A48067</td>
<td>Thermo Fisher Scientific</td>
</tr>
<tr>
<td>August 14, 2020</td>
<td>Wantai SARS-CoV-2 RT-PCR</td>
<td>WS-1248</td>
<td>Beijing Wantai Biological Pharmacy Enterprise Co., Ltd</td>
</tr>
<tr>
<td>July 09, 2020</td>
<td>COVID-19 Coronavirus Real Time PCR Kit</td>
<td>JC10223-1NW-50T</td>
<td>Jiangsu Bioperfectus Technologies Co., Ltd</td>
</tr>
<tr>
<td>July 06, 2020</td>
<td>Simplexa COVID-19 Direct and Simplexa COVID-19 Positive control Pack</td>
<td></td>
<td>DiaSorin</td>
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<tr>
<td>July 23, 2020</td>
<td>Xpert Xpress SARS-CoV-2</td>
<td>XPRSARS-COV2-10</td>
<td>Cepheid AB</td>
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<td>June 11, 2020</td>
<td>Novel Coronavirus 2019-nCoV Nucleic Acid Detection Kit (Real Time PCR)</td>
<td>GZ-D2RM25</td>
<td>Shanghai GeneoDx Biotechnology Co., Ltd</td>
</tr>
<tr>
<td>June 08, 2020</td>
<td>Diagnostic kit for SARS-CoV-2 Nucleic acid (Real-time PCR)</td>
<td>KH-G-M-574-48</td>
<td>Shanghai Kehua Bio-engineering Co., Ltd</td>
</tr>
<tr>
<td>May 22, 2020</td>
<td>Novel Coronavirus (SARS-CoV-2) Real Time Multiplex RT-PCR Kit</td>
<td>RR-0485-02</td>
<td>Shanghai ZJ Bio-Tech Co., Ltd</td>
</tr>
<tr>
<td>May 21, 2020</td>
<td>FTD SARS-CoV-2 (FTD-114-32)</td>
<td>11416300</td>
<td>Fast Track Diagnostics Luxembourg S.à r.l</td>
</tr>
<tr>
<td>Date</td>
<td>Company</td>
<td>Test Description</td>
<td>Catalog Numbers</td>
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</tr>
<tr>
<td>May 19, 2020</td>
<td>Beijing Applied Biological Technologies Co. Ltd. (XABT)</td>
<td>Multiple Real-Time PCR Kit for Detection of 2019-nCoV</td>
<td>CT8233-48T</td>
</tr>
<tr>
<td>May 14, 2020</td>
<td>DaAn Gene Co., Ltd. Of Sun Yat-sen University</td>
<td>Detection Kit for 2019 Novel Coronavirus (2019-nCoV) RNA (PCRFluorescence Probing)</td>
<td>DA0930, DA0931 and DA0932</td>
</tr>
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<td>May 7, 2020</td>
<td>PerkinElmer Inc.</td>
<td>Real-time fluorescent RT-PCR kit for detecting 2019-nCoV</td>
<td>MFG030011 and SY580</td>
</tr>
<tr>
<td>April 24, 2020</td>
<td>PerkinElmer Inc.</td>
<td>PerkinElmer SARS-CoV-2 Real-time RT-PCR Assay</td>
<td>MFG030011 and SY580</td>
</tr>
<tr>
<td>April 09, 2020</td>
<td>Abbott Molecular Inc.</td>
<td>Abbott Realtime SARS-CoV-2</td>
<td>09N77-090 and 09N77-080</td>
</tr>
<tr>
<td>April 03, 2020</td>
<td>Roche Molecular Systems, Inc.</td>
<td>cobas SARS-CoV-2 Qualitative assay for use on the cobas 6800/8800 Systems</td>
<td>09175431190 and 09175440190</td>
</tr>
</tbody>
</table>

On the other hand, Brazil adopted measures from a different perspective from the WHO deliberations and authorized the entry of rapid antibody detection tests in the country. The percentage of deferred records for rapid tests found (73%, n=323) was higher than the total deferred records for all other types of tests (26%, n=118) (Figure 6a). Among the registrations granted for rapid tests, 92.5% (n=299) were based on the detection of antibodies, while only 7.5% (n=24) registrations were granted for products for the detection of antigens (Figure 6b). China was the leading manufacturer of COVID-19 rapid antibody and antigen detection tests (Figures 6c e 6d). Thus, this high number of rapid test records may be due to the ease of development and manufacturing process of this product, in addition to the ease of recording even without specific validation processes (Rogers et al., 2020).

The distribution and use of rapid tests were widely adopted by states and municipalities in Brazil, due to advantages related to the shorter analysis time and the practicality in the sample collection in the test execution steps, which would allow a wide testing of the population. However, rapid tests employing antibodies detection methodology showed serious disadvantages due to low sensitivity compared to serological techniques (e.g., ELISA test) or molecular techniques (e.g., RT-PCR test). Such factors can lead to a misdiagnosis of COVID-19, implying inaccurate epidemiological determinations and hindering the implementation of effective strategic measures. For this reason, the WHO guidance is to use tests employing molecular methods and rapid antigen tests, with RT-PCR being the gold standard (OMS, 2020a; WHO, 2020b). Consequently, ANVISA has indicated the use of rapid serological tests (IgM/IgG) only for monitoring the population already exposed to the virus since RT-PCR
Tests are the only methodology considered to confirm the diagnosis in Brazil (Brasil. Ministério da Saúde, 2020c).

Figure 6. Rapid antibody detection tests and rapid antigen detection tests registered in ANVISA between May 18 and December 9, 2020: (a) number of tests registered by methodology; (b) types of rapid tests (c) countries of origin of rapid tests for antibody detection and (d) countries of origin of rapid tests for antigen detection. Legend: “Others”: Canada, Germany, Switzerland, Japan, United Kingdom, Italy, Finland, France, Israel, Portugal.

Tests adopted within the scope of the “Programa Diagnosticar para Cuidar”: MoH strategy

The “Programa Diagnosticar para Cuidar” (Diagnosis to Care Program) was created in May 2020 by the MoH to manage diagnostic actions, which is still part of the national strategy for epidemiological and labor-atory surveillance for COVID-19 (Figure 2). Initially, the program set the goal of performing 46 million tests in 2020 configuring testing for approximately 22% of the Brazilian population. From a stra-tegic point of view, the program is composed of two strands: “Confirma COVID-19”, which has used RT-PCR (molecular biology) tests to confirm COVID-19 diagnosis, and “Testa Brasil,”
which aims to use rapid tests (immunochromatographic) for detection of antibodies, in order to assess the virus progression in the country.

**Testing framework implementation**

Even using the existing national infrastructure, expanding the supply of RT-PCR tests in the public health network was necessary. Thus, states and municipalities were allowed to use the equipment that made up the National Network of Laboratories for HIV viral load and viral hepatitis B and C, as well as the machines that made up the Rapid Molecular Tuberculosis Test Network to carry out automated RT-PCR tests COVID-19 diagnostic. In addition, the capacity to offer exams was expanded through partnerships between the MoH with 28 LACENs (Central Laboratories) and 49 partner institutions around the country (Brazil. Ministério da Saúde, 2020b).

However, the mentioned testing structure was not enough to supply the testing demand and only severe cases of COVID-19 disease were being tested by care network (Marson & Ortega, 2020). Brazil faced many difficulties in providing the necessary inputs to operationalize an effective mass testing program at the beginning of COVID-19 pandemic due to the low capacity to supply products from the national industry and the initial difficulty in acquiring inputs from the United States and China (Brasil. Ministério da Saúde, 2020d). The initial MoH’s proposal for tests acquisition pre-dicted a total of 41.2 million of tests, mainly RT-qPCR tests and rapid tests for antibody detection (Table 2). However, this goal was not met, since rapid tests were all acquired via donation (Brasil. Ministério da Saúde, 2020d). In June 2020, despite the announcement by the MoH about the inclusion of a serological test employing ELISA or CLIA methods in the “Testa Brasil” program (Folha, 2020), until December 20, 2020, the MoH declared the acquisition and distribution under the "Programa Diagnosticar para Cuidar" (Diagnosis to Care Program) only of RT-PCR tests and rapid tests for antibody detection. In all, 20,420,097 tests were distributed, of which 8,811,425 were composed for rapid tests and 11,478,624 for RT-PCR tests, representing about 43% and 56% of the total tests acquired, respectively (BRASIL. MINISTÉRIO DA SAÚDE, 2020e).

Although Brazil possesses legal provisions, such as the “Lei da Inovação” (Law 10.973/2004), the “Marco Regulatório da Inovação” (Law 13.243/2016) and the regulatory Decree (Decree 9.283/2018) (Brasil. Presidência da República, 2016), which
indicates the use of the purchasing power of strategic products to promote innovation in
the country, the panorama suggests that the MoH pulverized the purchasing process and
did not use a centralized public purchasing strategy that would allow bargaining in the
prices and increase in the number of tests offered by the federal government (Gadelha &
da Costa Braga, 2016). Thus, unlike that made for vaccines, the State's purchasing power
to induce innovation and technology transfer to national institutions, aiming at developing
kits and strategic inputs needs, was not observed for COVID-19 diagnostic products
(Gadelha et al., 2012).

Table 2. Initial proposal for COVID-19 tests acquisition by the Ministry of Health (BRAZIL.
MINISTÉRIO DA SAÚDE, 2020).

<table>
<thead>
<tr>
<th>Acquisition Source</th>
<th>Form of Acquisition</th>
<th>Number of Test</th>
<th>Type of Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIOCRUZ - Bio-Manguinhos/IBMP</td>
<td>Supply</td>
<td>3 million</td>
<td>RT-qPCR</td>
</tr>
<tr>
<td>Private Companies</td>
<td>Acquisition</td>
<td>10 million</td>
<td>RT-qPCR</td>
</tr>
<tr>
<td>Pan American Health Organization (PAHO)</td>
<td>Acquisition</td>
<td>10 million</td>
<td>RT-qPCR</td>
</tr>
<tr>
<td>Petrobrás</td>
<td>Donation</td>
<td>0.6 million</td>
<td>RT-qPCR</td>
</tr>
<tr>
<td>Cepheid Enterprise</td>
<td>Acquisition</td>
<td>0.6 million</td>
<td>Rapid Tests for Antibody Detection</td>
</tr>
<tr>
<td>Vale do Rio Doce</td>
<td>Donation</td>
<td>5 million</td>
<td>Rapid Tests for Antibody Detection</td>
</tr>
<tr>
<td>Public Call</td>
<td>-</td>
<td>12 million</td>
<td>Rapid Tests for Antibody Detection</td>
</tr>
</tbody>
</table>

Testing data

Analyzing the Brazilian test capacity in 2020 was found that 11 million rapid
antibody tests, 6 million RT-PCR tests, 1.2 million rapid antigen tests, and approximately
0.7 million ELISA/CLIA tests were per-formed by SUS (Table 3). Notably, the results
presented for the rapid antigen tests and ELISA/CLIA tests were obtained through the
number of purchases operated individually by states, municipalities, or partner
institutions, not being part of the Federal Government's strategy adopted within the scope
of "Programa Diagnostico para Cuidar" (Diagnosis to Care Program). According to
Table 3, the number of rapid tests per-formed is greater than the sum of tests performed
using other methodologies. Therefore, due to its low sensi-tivity, the federal government's
strategy for using this type of methodology becomes questionable.
Table 3. Number of tests performed by SUS according methodology of COVID-19 diagnosis and positivity rate until December 5, 2020 (Brasil. Ministério da Saúde, 2020d).

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Amount Performed</th>
<th>Positive Results</th>
<th>Positivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT-PCR</td>
<td>6,662,639</td>
<td>2,011,585</td>
<td>30,46</td>
</tr>
<tr>
<td>Rapid Tests for Antibody Detection</td>
<td>11,409,144</td>
<td>3,048,695</td>
<td>25,70</td>
</tr>
<tr>
<td>Rapid Antigen Tests</td>
<td>1,243,336</td>
<td>446,664</td>
<td>35,90</td>
</tr>
<tr>
<td>ELISA or CLIA</td>
<td>192,855</td>
<td>79,984</td>
<td>41,50</td>
</tr>
<tr>
<td>Total</td>
<td>19,507,974</td>
<td>5,586,928</td>
<td></td>
</tr>
</tbody>
</table>

In 2020, Brazil ranked 94th among the countries that performed the most diagnostic tests per million inhabitants, (30,000 tests/ million inhabitants). Regarding the total number of diagnostic tests performed, the United States appears in the first place, followed by India, China, Russia, the United Kingdom, and Germany, while Brazil occupies only the 33th position in the ranking (GCDL, 2020b). Currently, the country remains one of the least testing countries in the world. According to Global Change Data Lab (GCDL), the last Brazilian testing data update was on March 11, 2022, when the country had an accumulated 330.91 tests (per thousand inhabitants), while Denmark and the United States performed a total of 10,827.52 and 7,018.23 tests per thousand inhabitants, respectively (GCDL, 2022a).

Brazil has a higher positivity rate than the other countries studied in 2020 (Table 4). According to the WHO (WHO, 2020b), a positivity rate of less than 5% indicates that the surveillance carried out for suspected cases is comprehensive, which can be observed in the cases of the United Kingdom and Russia, with the United States and India, have rates just above the limit established by the organization. The analysis of the positivity is related to the effectiveness of the testing measures implemented, as well as to the spread of the virus (GCDL, 2020b). Also, according to Table 4, it is possible to observe that the positivity rate in Brazil is 30.46% when analyzing only the results of the RT-PCR tests and 28.80% when analyzing the results of the RT-PCR tests plus the rapid antibody tests, which demonstrates a non-comprehensive surveillance action. In addition, the lack of an efficient mass testing program generated a substantial underreporting of cases and deaths due to COVID-19, since Brazil had the lowest number of tests performed (6.66 tests/per million people), while presented the second highest number of confirmed deaths in the same period (176,628) (Table 4). A survey conducted by the School of Medicine of Federal University of Minas Gerais (UFMG) showed that the number of deaths due to COVID-19 in Brazil in 2020 is underestimated by at least 18% (Franç et al., 2022).
Furthermore, it is clear that the Brazilian strategy of offering rapid tests for antibody detection on a large scale to enable broader testing, did not allow the country to monitor the number of tests carried out among the countries that test the most in the world. The Brazilian Federal Government could have invested in increasing the offer of rapid antigen tests. Studies have already shown that compared to RT-PCR tests, its sensitivity has ranged from 0 to 94%, and the observed specificity has been greater than 83-96% (Brazil. Ministério da Saúde, 2020f; Krüttgen et al., 2020). In addition, because it is a quick and inexpensive test, it can fill specific gaps left by RT-PCR tests and allows rapid clinical management of patients, especially those with high viral load (WHO, 2020a).

**Table 4.** Tests performed, positivity rate, confirmed cases, confirmed deaths and official methods employed to confirm COVID-19 disease among the countries that carry out the most tests and Brazil.

<table>
<thead>
<tr>
<th>Country</th>
<th>Performed Tests (Millions) *</th>
<th>Positivity Rate (%)</th>
<th>Confirmed Cases (Millions)</th>
<th>Confirmed Deaths (Thousands)</th>
<th>Official Methods Employed for Case Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>207.25 **</td>
<td>7.10</td>
<td>14.66</td>
<td>281.465</td>
<td>RT-PCR Test + RT Antigen</td>
</tr>
<tr>
<td>China</td>
<td>160.00</td>
<td>Not Found</td>
<td>93.467</td>
<td>4.746</td>
<td>Not Found</td>
</tr>
<tr>
<td>India</td>
<td>145.89</td>
<td>6.60</td>
<td>9.64</td>
<td>140.182</td>
<td>RT-PCR Test + RT Antigen</td>
</tr>
<tr>
<td>Russia</td>
<td>79.32</td>
<td>3.00</td>
<td>2.41</td>
<td>42.228</td>
<td>RT-PCR Test</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>42.79</td>
<td>4.00</td>
<td>171</td>
<td>61.111</td>
<td>RT-PCR Test + RT Antigen</td>
</tr>
<tr>
<td>Brazil (Rt-Pcr)</td>
<td>6.66</td>
<td>30.46</td>
<td>6.58</td>
<td>176.628</td>
<td>RT-PCR Test</td>
</tr>
<tr>
<td>Brazil (Rt-Pcr + Rapid Test)</td>
<td>18.07</td>
<td>28.80</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Data from tests performed and Brazil’s positivity rate were collected in the Bulletin COE 40 of the Ministry of Health, considering that the GCDL data for the country only considered the numbers counted up to September 2020 (Brazil. Ministério da Saúde, 2020b).

** The official source for the country does not make explicit the type of methodology being considered in this data (Brazil. Ministério da Saúde, 2020b; GCDL, 2020b).

The European Commission started to recommend using rapid antigen tests for contact tracing. Furthermore, this test was widely used by European countries and the United States, with the purpose of epidemiological monitoring or as a reference for diagnosis in hospitals and emergency rooms (Guglielmi, 2020). Also, countries with economic reality similar to Brazil, such as Cambodia, Colombia, Ecuador, and India, recommended the use of rapid antigen test for confirmation of new cases, following the trend of European countries and the United States (GCDL, 2020b). The low testing capacity observed in the country must be related, in short, to an inadequate strategy...
adopted by the federal government. Indeed, in December 2020, the Brazilian media published in-formation about the existence of 6.86 million RT-PCR kits, which were about to lose the expiration date, stored in the MoH warehouse in the city of Guarulhos - São Paulo (Globo, 2020). This number total corresponds to more than the total number of tests carried out in the country so far (Table 3) (Vargas, 2020). Thus, we demonstrate that logistics action, planning, and management of the test acquisition and distribution process could have been better implemented, and the lack of local production and access to raw materials was not the main problem in Brazil.

CONCLUSIONS

The flexibilities adopted by ANVISA and the epidemiological strategy adopted by the MoH led to the registration, approval, and wide use of rapid tests for antibody detection. Nonetheless, the approval of registrations of foreign tests, not approved by regulatory agencies in their respective countries and not recom-mended by WHO, as well as the permanence of these tests in the national market, generated discussion and concern about the effectiveness and possible consequences for epidemiological surveillance and, thus, COVID-19 disease control. Besides, prioritizing the use of RT-PCR tests and rapid antigen tests, as well as developing and disseminating protocols with testing recommendations (e.g., type of tests used according to sample type and day of cycle of infection), the country could have better controlled viral dissemination and carried out better and faster clinical management of infected people, preventing deaths due to the aggravations of the disease.

Consequently, despite the regulatory flexibilities adopted, the creation of national programs aimed at performing mass testing, such as the "Programa Diagnose para Cuidar" (Diagnosis to Care Program), and the mobilization of several public laboratories to implement molecular diagnosis via RT-PCR (gold standard), Brazil remains one of the countries that perform testing the least and that have the highest number of con-firmed cases and deaths. This scenario suggests that the strategy adopted by the Brazilian federal government to promote the testing of the population faced many serious issues, ranging from problems of logistics actions, planning, and management of test acquisition and distribution processes, especially the choice of using an-tibody tests. Thus, the results obtained through this study become relevant because they are, among other factors, possible lessons learned.
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WHO. Regulation and Prequalification.

WHO. Public health criteria to adjust public health and social measures in the context of COVID-19.