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Post-market monitoring of rapid tests for detecting COVID-19 antigens in combating the pandemic

Monitoramento pós-mercado dos testes rápidos para detecção de antígenos da COVID-19 no enfrentamento à pandemia

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ABSTRACT

Introduction: Since the identification of atypical pneumonia of unknown etiology in Wuhan, China, in December 2019, called COVID-19, the disease caused by SARS-CoV-2 requires scientists and governments to take urgent and decisive measures for monitoring and control. **Objective:** To present the results of post-market monitoring of COVID-19 rapid antigen detection tests (AgTR) regarding clinical or diagnostic sensitivity and specificity. **Method:** Analysis of AgTR performance results were made available on the electronic panel of Microsoft® Power BI platform on the Brazilian National Health Surveillance Agency (Anvisa) portal from 04/06/2020 to 12/28/2021. **Results:** 504 results relating to performance analysis were identified: 366 (72.6%) rapid tests (RT), 56 (11.0%) chemiluminescence tests, 31 (6.15%) molecular tests, 22 (4.4%) immunoenzymatic assays, and 29 (5.7%) auxiliary products for the diagnosis of COVID-19. Of the 366 RT results, 304 (83.1%) were RT for antibody detection (AcTR) and 62 (16.9%) were AgTR. Of the 62 AgTR monitored, 49 (79.1%) presented compliant results and 13 (20.9%) did not. The 62 AgTR results corresponded to 50 lots from 42 manufacturers. **Conclusions:** Monitoring post-market products in compliance with RDC No. 379/2020 enabled the analysis and monitoring of COVID-19 tests. The analyses carried out (guidance and fiscal) in accordance with current legislation (Law No. 6360/1976, Law No. 6437/1977) guaranteed the transparency of the process and reinforced the precepts of health surveillance regarding resolving or preventing health risks. Non-compliant products were not sold, thus guaranteeing the safety and effectiveness of the tests available in the country.

KEYWORDS: COVID-19; SARS-CoV-2; Test for SARS-CoV-2 Antigen; Post-market Monitoring

RESUMO

Introdução: Desde a identificação da pneumonia atípica de etiologia desconhecida em Wuhan, na China em dezembro de 2019, denominada de COVID-19, a doença causada pelo SARS-CoV-2 exige de cientistas e governos medidas urgentes e decisivas para o monitoramento e o controle. **Objetivo:** Apresentar os resultados do monitoramento pós-mercado dos testes rápidos (TR) para detecção de antígenos (AgTR) da COVID-19, quanto à sensibilidade e especificidade clínica ou diagnóstica. **Método:** Análise dos resultados de desempenho dos AgTR disponibilizados no painel eletrônico da plataforma Microsoft® Power BI no portal da Agência Nacional de Vigilância Sanitária (Anvisa) no período de 6 de abril de 2020 a 28 de dezembro de 2021. **Resultados:** Foram identificados 504 resultados referentes à análise de desempenho sendo: 366 (72,6%) TR, 56 (11,0%) ensaios de quimioluminescência, 31 (6,15%) testes moleculares, 22 (4,4%) ensaios imunoenzimáticos e 29 (5,7%) produtos auxiliares ao diagnóstico da COVID-19. Dos 366 resultados de TR, 304 (83,1%) foram para detecção de anticorpos (AcTR) e 62 (16,9%), AgTR. Do total de 62 AgTR monitorados, 49 (79,1%) apresentaram resultados conformes e 13 (20,9%) não conformes. Os 62 resultados de AgTR corresponderam a 50 lotes de 42 fabricantes. **Conclusões:** O monitoramento de

produtos pós-mercado em cumprimento à RDC nº 379/2020 possibilitou a análise e o acompanhamento dos testes para o diagnóstico da COVID-19. As análises realizadas (orientação e fiscal) segundo a legislação vigente (Lei nº 6.360/1976, Lei nº 6.437/1977) garantiram a transparência do processo e reforçaram os preceitos da vigilância sanitária no que diz respeito a dirimir ou prevenir riscos à saúde. Os produtos não conformes não foram comercializados, garantindo, assim, a segurança e a eficácia dos testes disponibilizados no país.

PALAVRAS-CHAVE: COVID-19; SARS-CoV-2; Teste para Antígeno do SARS-CoV-2; Monitoramento Pós-mercado

INTRODUCTION

On December 31, 2019, China observed an atypical pneumonia not identified etiologically in workers at a food market in Wuhan, capital of Hubei province[1]. Referred to as novel coronavirus "2019-nCoV" by the World Health Organization (WHO), the virus was later named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) by the International Committee on Taxonomy of Viruses (ICTV) due to its similarity to SARS-CoV[2,3].

SARS-CoV-2 is an enveloped virus with single-stranded RNA and positive polarity. The virus is made up of the (N) nucleocapsid, (M) membrane, (E) envelope, (S) spike, and several accessory proteins. The N protein is associated with the genetic material inside the virus, while the (S), (E), and (M) proteins are structural and are associated with the virus membrane[4,5].

COVID-19 is a highly transmissible disease among humans, with the capacity to infect efficiently and sustainably. With the occurrence of more than 118,000 cases distributed in more than 110 countries and territories around the world, the WHO declared COVID-19 a pandemic on March 11, 2020[6,7].

COVID-19 diagnostic tests have become an essential tool for tracking the spread of the disease. The main methodologies used to diagnose COVID-19 are the molecular test for detecting nucleic acids (RT-qPCR - reverse transcriptase quantitative polymerase chain reaction), considered the gold standard, rapid immunochromatographic tests (RT) for detecting antigens (AgTR) and for detecting anti-SARS-CoV-2 antibodies (AcTR) (IgA, IgM and IgG), enzyme linked immunosorbent assays (ELISA), and chemiluminescence immunoassays (CLIA). The applicability of each methodology varies at different stages of SARS-CoV-2 infection[4,8].

RTs for AgTR are widely used to diagnose viral diseases, including COVID-19, and are typically qualitative (positive or negative), as they determine the presence of the antigen with results obtained between 5 and 30 min after execution. Given their better performance in the early stages of infection, in the acute phase, when viral replication is greatest, AgTR should be prioritized in symptomatic COVID-19 patients within 10 days of the onset of symptoms (preferably five to seven days from the onset of symptoms)[9,10].

AgTR is based on the sensitization of antibodies conjugated to colloidal gold that capture specific SARS-CoV-2 proteins in samples collected from saliva and the upper respiratory tract, such as those taken by swab from infected individuals, forming an antigen-antibody complex that migrates by capillarity along the nitrocellulose membrane housed in a test device.

The registration of *in vitro* diagnostic products in Brazil follows the guidelines based on the Resolution of the Collegiate Board (RDC) of the Brazilian National Health Surveillance Agency (Anvisa) No. 36, of August 26, 2015, updated by Anvisa RDC No. 830, of December 6, 2023. The criteria established by this standard encompass performance and efficacy assessments related to the use of *in vitro* diagnostic products[11].

In Brazil, efforts to tackle COVID-19 were initiated in January 2020 by Anvisa[12]. With the declaration of the COVID-19 pandemic by the WHO and the need to make tests for the diagnosis of SARS-CoV-2 available and feasible in the national market, Anvisa published RDC No. 348 on March 18, 2020, which established extraordinary and temporary rules to speed up the evaluation of new products, by prioritizing the analysis of applications for registration of tests for the detection of the new coronavirus[13]. The measure was part of strategic actions to make products that could be used to tackle the COVID-19 pandemic more viable and maintain safety and efficacy criteria[3,12].

RDC No. 348/2020 allowed emergency registration to be granted for up to one year for products that demonstrated diagnostic effectiveness for COVID-19, provided that there was technical justification for the lack of studies or that there was evidence of restricted data on the product[13]. At the end of one year, the validity of the registration could be extended to the regular term of ten years, counted from the initial grant, provided that the relevant documentation was complemented[15]. In this way, access to various commercial products was made possible, and it was possible to verify the performance information declared by the manufacturers in the instructions for use of the products made available on the Anvisa portal. Anvisa did not set minimum performance limits (sensitivity and specificity) for the analysis of the products, but the information should be clearly set out in the instructions for use of each product evaluated[12].

In the area of laboratories, Anvisa has coordinated several integrated strategies with the National Institute for Quality Control in Health (INCQS) and with entities of the National Health

Surveillance System (SNVS). The analytical monitoring program for COVID-19 diagnostic kits was established and coordinated by Anvisa in partnership with INCQS and included the participation of local Health Surveillance agencies in the collection of samples for tax analyses. In addition, guidelines for sending samples of COVID-19 diagnostic kits to INCQS were published on the agency's website[12].

On April 30, 2020, ANVISA published RDC No. 379, which amended RDC No. 356/2020, which provided for the manufacturing requirements, importation and acquisition of medical devices identified as a priority for use in health services, due to the international public health emergency related to SARS-CoV-2[15]. According to RDC No. 379/2020, those responsible for importing diagnostic products should send a sample of at least 100 units of each imported batch to INCQS for analysis within a maximum of five days from the date the cargo is cleared[14]. The dashboard created on the Power BI platform available on Anvisa's portal promoted the consultation and dissemination of the results of the analysis of products released by INCQS as of April 6, 2020.

Thus, the purpose of this paper is to present the analysis of the results of the post-market monitoring of RTs for the detection of the SARS-CoV-2 antigen carried out between April 6, 2020 and December 28, 2021, made available on Anvisa's Power BI Platform panel. The tests were evaluated for clinical or diagnostic sensitivity (S) and specificity (E), in compliance with Law No. 6,360, of September 23, 1976, Law No. 6,437, of August 20, 1977, RDC No. 830/2023, and RDC No. 379/2020.

METHOD

Data was collected from the "Post-market monitoring of the quality of COVID-19 *in vitro* diagnostic devices: laboratory analyses" prepared on the Microsoft® Business Intelligence platform (Microsoft® Power BI) available on the Anvisa website at: https://app.powerbi.com/view?r=eyJrIjoiZjQzMDE0NGUtN2M4Yi00NTZiLTliN2MtMzA2YTZkMjcyNDRhIiwidCI6ImI2N2FmMjNmLWMzZjMtNGQzNS04MGM3LWI3MDg1ZjVlZGQ4MSJ9, which included data on product analyses carried out between April 6, 2020 and December 28, 2021.

Of the different COVID-19 diagnostic products available on the platform, the RTs for antigen research (AgTR) in the proposed period were selected. To analyze the results, the raw data extracted from the panel was organized into Microsoft® Excel spreadsheets consisting of information on the products: trade name, manufacturer, batch, analytical report number issued by INCQS, sensitivity, and clinical or diagnostic specificity values declared by the manufacturer and the values obtained after laboratory analysis.

Tests which, after laboratory analysis, showed sensitivity (S) and specificity (E) values greater than or equal to those declared by the manufacturers in the instructions for use (IU) were considered compliant, while those which showed lower values were considered non-compliant.

It is worth noting that only the performance values of the product batches that showed non-compliant results were presented on the platform and included in the spreadsheet.

The laboratory analyses were carried out by the Laboratory of Blood and Blood Products (LSH) of the Immunology Department (DI) of the INCQS in compliance with current legislation.

RESULTS AND DISCUSSION

A total of 504 results were verified regarding the performance analysis of COVID-19 diagnostic tests. Among them, 366 (72.6%) RT, 56 (11.1%) CLIA, 31 (6.15%) molecular tests (RTqPCR), 22 (4.37%) ELISA, as well as 29 (5.75%) other auxiliary products for COVID-19 diagnosis.

Of the 366 RT results, 304 (83.06%) corresponded to AcTR and 62 (16.94%) to AgTR. The 62 AgTR results corresponded to the analysis of 50 batches of products, 42 different importers referring to guidance analysis, tax analysis and counter-proof for batches with unsatisfactory results (when requested). Of the 62 results, 49 (79.1%) obtained a compliant report and 13 (20.9%) a non-compliant report.

Since Anvisa has not published minimum sensitivity and specificity criteria for approving registrations, the values stated in the instructions for use for each product were used as criteria. This measure ensured that different products and methodologies were available on the domestic market. Non-compliant products had lower values than those declared.

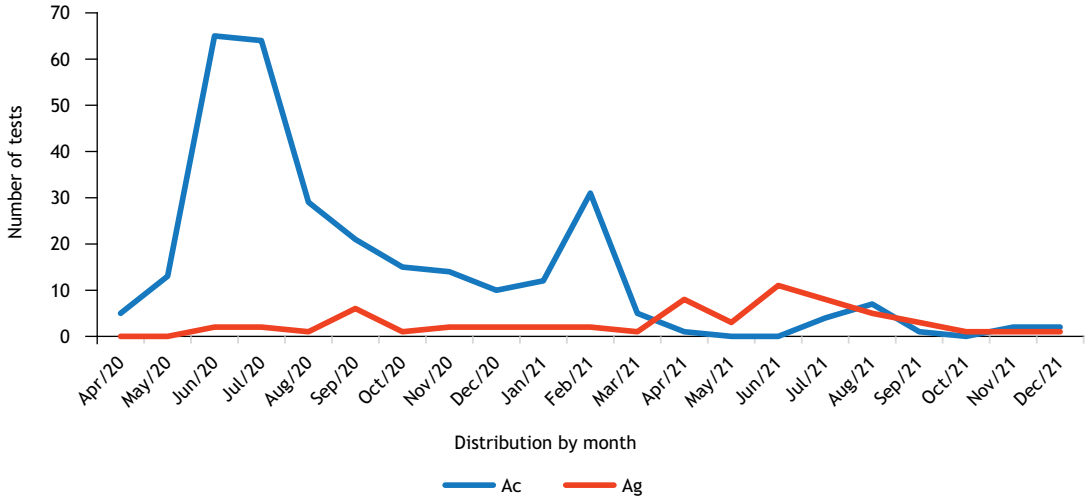
During the initial period of the pandemic, the Ministry of Health made more AcTR tests available than AgTR tests, except for the period from April to July 2021 (Graph). With the spread of cases in Brazil, and considering that molecular tests would not be largely applied due to their complexity, technology costs, execution time, and need for specific inputs, space was opened up for AcTR. In addition, according to the Ministry of Health's Epidemiological Bulletin No. 58, the curve of new confirmed cases and deaths during the pandemic has shown an intense increase since February 2021[15]. The increase in the number of cases and deaths that occurred in April 2021 increased the search for early diagnosis of the disease and, therefore, the use of AgTR was intensified in some regions of the country[16].

The Table shows the performance results of the non-compliant AgTRs as well as the sensitivity values declared by the manufacturer and those obtained in the laboratory analysis. Of the total of 13 results, six (46.5%) were unsatisfactory for Sensitivity, four (30.8%) for Specificity, and three (23.1%) for both.

The 13 non-compliant AgTR results corresponded to eight products (16%) from manufacturers in Asia and North America.

As part of Anvisa's analytical monitoring programs, the AgTRs were sent to INCQS for analysis of the requested guidance. The other AgTRs underwent fiscal analysis, as defined in Law

No. 6.360/1976, and only AgTR B, D, G, and H were sent for counter-proof expertise[17]. The counter-evidence analysis is the appeal requested by the company, in accordance with Law No. 6.437/1977, when it disagrees with the result of the tax analysis[18]. This analysis must be scheduled in advance with Anvisa and the health surveillance agency that collected the product and the laboratory. The analytical procedure is strictly similar to that carried out in the tax analysis, which justifies the reproducibility of the results presented in the Table. The counter test also involves drawing up minutes containing all the



Source: Prepared by the authors, 2022.

Graph. Distribution of the number of rapid tests for detecting COVID-19 antigens (AgTR) and antibodies (AcTR) in the period from 04/06/2020 to 12/28/2021.

Table. Performance results obtained in the evaluation of non-compliant products (NC) for antigen detection (AgTR) distributed by type of analysis.

Type of Analysis	AgTR Manufacturer Country	Sensitivity		Specificity		NC
		Declared (95%CI)	Obtained	Declared (95%CI)	Obtained	
Guidance	A- Korea	92.0% (NI)	82.1%	NI (NI)	NI	S
Guidance	A- Korea	92.0% (NI)	82.1%	NI (NI)	NI	S
Tax	B- China	96.1% (96.4%-98.4%)	80.5%	NI (NI)	NI	S
Counter-evidence	B- China	96.1% (96.4%-98.4%)	90.6%	99.7% (98.4%-99.9%)	93.8%	S/E
Tax	C- China	96.1% (NI)	85.1%	NI (NI)	NI	S
Tax	D- China	NI (NI)	NI	99.2% (95.9%-99.8%)	73.6%	E
Counter-evidence	D- China	NI (NI)	NI	99.2% (95.9%-99.8%)	77.3%	E
Tax	E- China	NI (NI)	NI	99.2% (95.9%-99.8%)	76.0%	E
Tax	F- China	NI (NI)	NI	99.2% (95.9%-99.8%)	91.5%	E
Tax	G- USA	92.0% (NI)	76.3%	> 99.9% (NI)	86.5%	S/E
Counter-evidence	G- USA	92.0% (NI)	80.0%	> 99.9% (NI)	92.5%	S/E
Tax	H- USA	87.8% (80.0%-95.7%)	69.0%	NI (NI)	NI	S
Counter-evidence	H- USA	87.8% (80.0%-95.7%)	73.9%	NI (NI)	NI	S

Source: Prepared by the authors, 2022.
NI: Not informed; CI: Confidence interval; NC: Non-compliant; S: Sensitivity; E: Specificity.

information pertinent to this activity, in front of the representatives appointed by the company to witness the test[18].

CONCLUSIONS

The COVID-19 pandemic has become a public health emergency of international importance. The measures to prevent and deal with it have so far imposed challenges of all kinds on health and health surveillance systems and services around the world.

The monitoring of products subject to health surveillance begins when they are approved by Anvisa for marketing and use. This activity is an essential part of the work of health regulation, since it allows us to verify, in reality, the relevant impacts of the use of products on the health of the population.

The initiative to make the results of the monitoring of post-market products and the daily update of the performance of COVID-19 diagnostic tests by Anvisa available on the Power BI platform dashboard has made it possible to be transparent about the analyses carried out. This is in addition to the tools used to guarantee the quality of the products sold in the country, since the products that did not comply were not made available on the domestic market.

Post-registration evaluation has made a significant contribution to the country's public health during the pandemic and, consequently, should be a quality tool for compliant products marketed in the country. This contributes to protecting the health and safety of consumers, minimizing the risk of harm and promoting a safer consumer environment.

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Authors' Contributions

Conceição GR - Conception, acquisition, data interpretation, and writing of the paper. Adati MC, Borges HCBG - Planning (study design), writing of the paper. All the authors approved the final version of the paper.

Conflict of Interest

The authors inform that there is no potential conflict of interest with peers and institutions, political or financial, in this study.