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Evidence and regulation for COVID-19 self-tests

Evidências e regulação para autotestes de COVID-19

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ABSTRACT

Introduction: The development of new diagnostic tests for SARS-CoV-2 is a strategic component for the prevention and control of COVID-19. To regulate the market for SARS-CoV-2 antigen detection self-tests, the regulatory agency issued a resolution that provided for the introduction of self-tests in Brazil. **Objective:** To perform a comparison between the new technical requirements of antigen self-tests for COVID-19 with data and information available in the literature. **Method:** This is a systematic literature review to carry out a comparative study between the scientific evidence and the new technical requirements for the commercialization of antigen self-tests for COVID-19 in Brazil. The search was performed in October 2021, and updated in January 2022. **Results:** Of the 517 studies identified, nine were included. The studies reported adequate sensitivity and specificity results for most self-tests performed in symptomatic people. The studies bring a variety of tests available and one of them was registered for commercialization in Brazil. Based on this outcome, national regulation follows standards that favor the promotion of self-monitoring by the population, which can contribute to a public health policy. **Conclusions:** The technical requirements contained in the new regulation and at the national level are consistent with the evidence found, which ensures reliability for decision-making by consumers, clinicians and service providers. It is necessary to continue with studies on self-test coverage for new variants, biological material disposal policies and how the use of self-tests can contribute to the role of consumers in health surveillance actions.

KEYWORDS: COVID-19; SARS-CoV-2; Self-testing; Home Based Testing; Regulation

RESUMO

Introdução: O desenvolvimento de novos testes diagnósticos para o vírus SARS-CoV-2 é uma etapa estratégica para a prevenção e o controle da COVID-19. Para regular o mercado dos autotestes de detecção de antígenos do SARS-CoV-2, a agência regulatória brasileira emitiu resolução que oportunizou a introdução de autotestes no Brasil. **Objetivo:** Realizar uma comparação entre os novos requisitos técnicos de autotestes de antígeno para a COVID-19 com dados e informações disponíveis na literatura. **Método:** Trata-se de uma revisão sistemática da literatura para a realização de um estudo comparativo entre as evidências científicas e os novos requisitos técnicos para comercialização de autotestes de antígeno para COVID-19 no Brasil. A busca foi realizada em outubro de 2021 e atualizada em janeiro de 2022. **Resultados:** Dos 517 estudos identificados, nove foram incluídos. Os estudos reportaram resultados de sensibilidade e especificidade adequados para maioria dos autotestes realizados em pessoas sintomáticas. Os estudos trazem uma variedade de testes disponíveis e um deles foi registrado para comercialização no Brasil. Baseados nesse desfecho, a regulação nacional segue os padrões que favorecem a promoção de automonitoramento por parte da população, o que pode contribuir para uma política de saúde pública. **Conclusões:** Os requisitos técnicos contidos na nova regulação e no plano nacional estão condizentes com as evidências encontradas, o que assegura confiabilidade para a tomada de decisão tanto dos consumidores, clínicos e prestadores de serviços. Necessário continuar com estudos sobre cobertura de autotestes para novas variantes, políticas de descarte de material biológico e como o uso de autotestes podem contribuir para o papel dos consumidores nas ações de vigilância em saúde.

PALAVRAS-CHAVE: COVID-19; SARS-CoV-2; Autoteste; Testes Domiciliares; Regulação

INTRODUCTION

According to the World Health Organization (WHO), as of February 25, 2022, 430,257,564 cases of COVID-19 and 5,922,049 deaths have been confirmed worldwide. In the Americas, the number of cases to date has been 146,449,862 and 2,618,433 deaths; in Brazil, the number of cases has been 28,484,820 and 646,419 deaths[1].

The virus that transmits COVID-19, SARS-CoV-2, belongs taxonomically to the coronavirus family, which contains several other species that cause mild to severe human diseases[2], and is transmitted to humans after mutations appear in the *spike* glycoprotein (S protein) and N protein of the nucleocapsid[3].

The development of new diagnostic tests for SARS-CoV-2 is a strategic component for the monitoring and control of COVID-19[4]. Currently, diagnosis can be carried out using the antigen self-test[5]. In order to regulate the market for SARS-CoV-2 antigen detection self-tests, the Brazilian National Health Surveillance Agency (Anvisa) published Anvisa Collegiate Board Resolution (RDC) No. 595, of January 28, 2022[6], which defined:

> §1º A self-test for the detection of the SARS-CoV-2 antigen is understood to be a medical device for *in vitro* diagnosis whose intended use is to provide a guiding result, but not conclusive for the diagnosis, carried out by a lay user [...].

According to the National Plan for the Expansion of Testing (PNE-test) for COVID-19, the rapid antigen test (TR-Ag) contributes to the expansion of diagnosis and monitoring of the epidemiological situation of COVID-19[7]. Rapid antigen tests use upper respiratory tract samples to detect viral proteins and may offer a faster and less expensive way of detecting active SARS-CoV-2 infection when compared to nucleic acid amplification tests (NAAT)[8]. The WHO recommends the use of TR-Ag with a performance ≥ 80% sensitivity and ≥ 97% specificity. The use of TR-Ag should be prioritized in symptomatic individuals, asymptomatic individuals at high risk of infection or in places where NAAT capacity is limited[8].

Potential variants of concern (VOC) are regularly evaluated based on the risk posed to global public health. Currently, SARS-CoV-2 is characterized by the predominance of the Delta and Omicron variants, with a trend towards the decline of Alpha, Beta, and Gamma. As of December 14, 2021, the Omicron variant has been confirmed in 76 countries. The diagnostic accuracy of polymerase chain reaction (PCR) assays and rapid antigen testing does not appear to be affected by the Omicron[9].

The fight against COVID-19 can still be considered incipient, as effective and clinically validated treatments are still being investigated. In this context, self-test *kits* can help diagnose the disease[10], reducing the COVID-19 contamination cycle.

In view of the recent publication of RDC No. 595/2022, the aim of this study was to compare the clinical performance of COVID-19 VOC self-tests identified in a systematic review with the new technical requirements for marketing COVID-19 antigen self-tests published by Anvisa.

METHOD

This is a systematic review of the literature to carry out a comparative study between the scientific evidence identified and the new technical requirements for marketing COVID-19 antigen self-tests proposed by Anvisa.

The study question was structured based on the acronym "PECO"[11], with: (P) population; (E) exposure; (C) comparator; (O) outcomes. The question was "What is the clinical performance of self-tests for COVID-19 variants of concern?", considering the entire population, whether or not they were reactive to COVID-19; exposed to COVID-19 self-tests compared to the gold standard *real-time polymerase chain reaction* (RT-PCR) test or tests comparing clinical performance between self-tests and tests carried out by health professionals. The following measures were considered as clinical performance outcomes of the self-tests: sensitivity, specificity, positive predictive value, negative predictive value, as presented by the authors.

For conceptual purposes[12,13,14], indicators were defined as: (i) accuracy - the probability of the test giving reliable results; (ii) sensitivity - the proportion of sick individuals who test positive; (iii) specificity - the proportion of healthy individuals who test negative; (iv) true positive proportion (PPV) - the proportion of individuals who test positive out of the total number of sick people, according to the gold standard and (v) true negative proportion (TRP) - the proportion of individuals who test negative and are healthy, according to the gold standard.

A search was carried out for studies describing diagnostic self-tests for COVID-19 that analyzed accuracy for the variants: Alpha, Beta, Gamma, and Delta.

The first searches were carried out in October 2021 and updated in January 2022. Six databases were used: PubMed, Embase, Cochrane *Library*, *Web of Science*, Scopus, and OVID. The search for gray literature was carried out by tracing and identifying bibliographic references of the included studies, government *websites* and Google Scholar.

The search strategy used the terms "COVID-19", "*Self-testing*", and their respective synonyms, adapted according to the specificities of each database. At the time of the search, attempts were made to include VOC descriptors, but no articles were found. It was therefore decided to broaden the search to minimize the loss of studies that did not mention the variants in the title and abstract.

The Mendeley® reference manager was used to remove duplicates and organize the identified studies. The selection of included articles was carried out in two stages (title and abstract, and full reading) and was independently assessed by

two reviewers using the Rayyan® tool. Differences were resolved by a third reviewer.

Inclusion and exclusion criteria were predefined for the search and selection of studies. Studies that evaluated self-tests, supervised or not, with data collection carried out from 2021 onwards were included, since the aim was to identify the performance of self-tests for COVID-19 VOCs. There was no year or language filter. Studies that did not evaluate the clinical performance of self-tests for VOCs that emerged in 2021; antibody self-test studies, as they lacked diagnostic validity; and studies without a description of clinical performance were excluded.

The following information was collected from the studies: characterization of the study (author/year, title, objective, results, recommendations), characterization of the test (manufacturer, trade name, collection, sample, population), clinical performance (reactive/positive result for COVID-19, sensitivity, specificity), according to the findings reported by the authors.

To analyze the quality of the evidence, the QUADAS 2 *checklist* was used, specifically for evaluating diagnostic tests[15]. The systematic review was registered on the *openScience* platform, under the title "Rapid review to evaluate the clinical performance of COVID-19 self-tests (antigens)", available at: <osf.io/pnfyd>.

The analysis focused on the narrative description of the studies found in the literature on diagnostic self-tests for COVID-19 that analyzed the accuracy of the Alpha, Beta, Gamma, and Delta variants, comparing them with the technical requirements described in RDC No. 595/2022[6], and the PNE-test for COVID-19 of 2022[7].

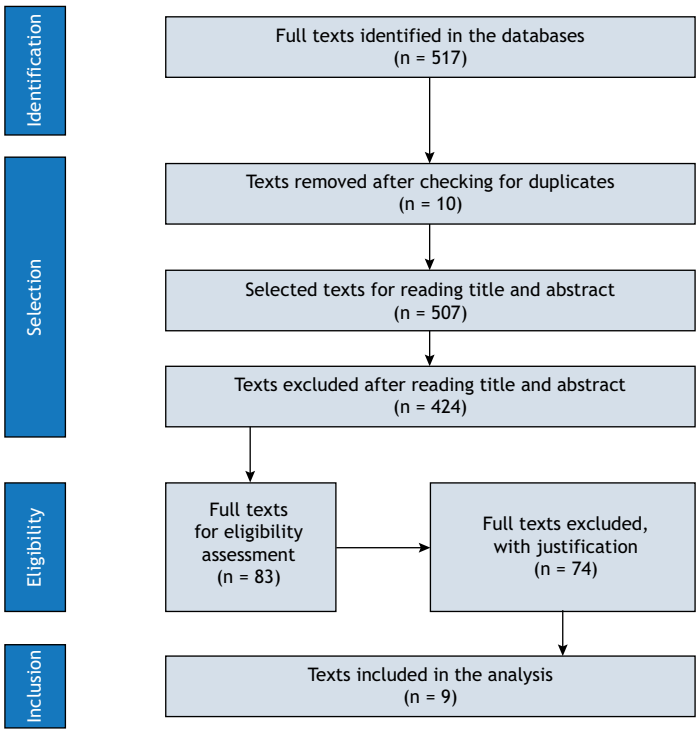
RESULTS

Literature review

A total of 517 studies were identified in the six databases used and, after removing duplicates, 507 studies were selected for reading the titles and abstracts. After reading the titles and abstracts, 83 studies were selected for reading the full texts based on the predefined inclusion and exclusion criteria. Of these, 52 did not have a collection period of the year 2021, 14 did not present clinical performance, seven did not present the expected outcome and one was an expanded conference abstract. In the end, nine studies were included[16,17,18,19,20,21,22,23,24] (Figure).

Chart 1 shows the main characteristics of the included studies. The assessment of the quality of the studies according to the criteria of the QUADAS 2 *checklist* is shown in Chart 2.

As far as the applicability of TR-Ag is concerned, the study by Jungnick et al.[20] cannot be considered for clinical validation, as it is a laboratory-based *in vitro* investigation, the aim of which was to detect the analytical performance of the self-test (no real-life clinical samples were used). It should be noted that performance was tested with infectious SARS-CoV-2 samples derived from cell



Source: Prepared by the authors, 2022.

Figure. Study selection flowchart.

Chart 1. Characteristics of the included studies.

Author	Objective of the study	Main findings	Limitations of the study
Jungnick et al.[20]	To investigate the performance of four TR-Ag for VOC of SARS-CoV-2 [B.1.1 (non-VOC), B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta).	All TR-Ag were able to detect all variants of the virus at least up to a dilution of 1:1,000 (corresponding to 2-5 x 10^6 RNA copies/mL).	Dilution steps can interfere with the analytical limits of detection. Small variations in the initial concentrations of SARS-CoV-2 virus samples can occur.
Sakai-Tagawa et al.[21]	To evaluate the sensitivity of TR-Ag available in Japan for the detection of the Delta variant (lineage B.1.617.2) of SARS-CoV-2.	Compared to the gold standard (RT-qPCR), the data showed that the sensitivity for the Delta variant is relatively high. Eight of the 27 tests analyzed were able to detect the virus (detection limit: 750 $TCID5_{0/mL}$).	Differences in sensitivity can exist between batches and, as only one batch was tested, the authors recommended re-evaluating the sensitivity of the test with different batches to confirm the consistency of the results.
Regan et al.[22]	To analyze the sensitivity of the Abbott BinaxNow TR-Ag used in the United States for use with the Omicrom variant of SARS-CoV-2.	For the Delta and Omicron variants, four samples with concentrations of 100,000 *copies/swab* or more were positive. For lower concentrations, the sensitivity of the test was decreased by 1/4 for the Omicron variant and 1/3 for the Delta variant. At concentrations of 2,500 *copies/swab*, all tests were negative.	This is data from research that is still in progress.
Ogtrop et al.[24]	Compare the performance of TR-Ag PanBio for diagnosis in SARS-CoV-2 variants B.1.1.7 (Alpha) versus non-variants B.1.1.7.	The overall sensitivity of the TR-Ag was 62.7% (47/75 healthcare professionals). The sensitivity of the Ag test was 89.0% for non-B.1.1.7 variants and 53.0% for B.1.1.7 variants, with an odds ratio (OR) of 6.8 (95%CI 1.9 to 23.8) for the chance of a B.1.1.7 variant being negative compared to that of a non-B.1.1.7 variant being negative.	It is likely that the nucleocapsid mutations associated with B.1.1.7 are responsible for the lower sensitivity observed for the B.1.1.7 variants and not the characteristic B.1.1.7 N501Y mutation in the S glycoprotein.
Bekliz et al.[23]	To investigate the analytical performance of 11 TR-Ag to detect VOC Delta in comparison with the Alpha, Beta and Gamma variants of SARS-CoV-2.	A single TR-Ag, *Sure Status* showed greater sensitivity for the Alpha, Beta and Gamma variant than for the Delta variant. On the other hand, *Flowflex* showed greater sensitivity for Delta compared to other *kits*.	It did not mention any limitations, however, we would point out that the text used the words sensitivity and accuracy but did not give the respective values.
Osmanodja et al.[16]	Evaluate the sensitivity and specificity for a TR-Ag with a supervised and self-collected anterior nasal *swab* sample compared to the RT-PCR reference standard collected from an oropharyngeal (OP)/ nasopharyngeal (NP) *swab*.	In total, 379 patients were included in the analysis (273 symptomatic and 106 asymptomatic). In the 61 symptomatic patients with medium or high viral concentration (≥ 1 million RNA copies), TR-Ag sensitivity was 96.7% (59/61 positive RT-PCR detected 95%CI 88.7-99.6%).	Due to organizational reasons in setting up the test, the OP/NP test for RT-PCR was performed before TR-Ag, which could transfer the virus from the nasopharyngeal space to the anterior nose. Another limitation is that the estimation of viral concentration is highly dependent on the quality of the sample.
Willeit et al.[19]	To evaluate the performance of the screening program based on the use of TR-Ag to detect SARS-CoV-2 infections in Austrian schools.	When a perfect positive predictive value of 100% was assumed, the sensitivity ranges were 17.0%-44.0% in elementary school, 13.3%-59.4% in secondary schools and 28.7%-86.6% when testing teachers.	The findings cannot be generalized to other countries. Furthermore, the health authorities were unable to provide data on the frequency with which a positive rapid antigen test was confirmed with RT-qPCR.
Homza et al.[17]	To compare the diagnostic performance of TR-Ag using three sampling methods: one nasopharyngeal test (NPS) collected by a healthcare professional in a hospital environment, two anterior nasal *swab* (ANS) sample tests collected by a healthcare professional in a hospital environment, and four self-collected saliva tests in school and work environments.	In 480 nasopharyngeal *swab* samples, the sensitivity was 80.60% (95%CI 73.5-86.5) and the specificity 98.50% (95%CI 96.4-99). In 488 anterior nasal *swab* samples, the sensitivity was 46.50% (95%CI 37.7-55.5) and the specificity 99.40% (95%CI 98.0-99.9). For 407 saliva samples, the sensitivity was 32.80% (95%CI 25.8-40.3) and the specificity 89.30% (95%CI 84.6-92.9).	It could not be guaranteed whether the patients followed the recommendations not to eat, drink, smoke, or chew for a certain period before the saliva tests were carried out. In addition, the study was financed by the distributors of self-tests in the Czech Republic, with the companies remaining anonymous.
Poukka et al.[18]	Evaluate the sensitivity of three alternative methods for collecting self-collected samples.	Gargle samples collected had a sensitivity of 0.97 (95%CI 0.92-1.00) and specificity of 0.50 (95%CI 0.00-1.00); sputum showed a sensitivity of 0.94 (95%CI 0.83-1.00) and specificity was not calculated, and ; sputum collected in the morning had a sensitivity and specificity of 1.00 (95%CI 1.00-1.00).	Further studies need to be carried out, as it has been observed that the efficiency of different RNA extraction methods can vary significantly between sample materials.

Source: Prepared by the authors, 2022.
OP/NP: oropharyngeal/nasopharyngeal; RT-qPCR: *quantitative reverse transcription PCR*; TR-Ag: rapid antigen test; VOC: variants of concern; OR: odds ratio; CI: confidence interval.

Chart 2. Quality of evidence assessed using the QUADAS 2 *checklist*.

Study		Jungnicket et al.[17]	Tagawa et al.[18]	Regan et al.[19]	Ogtrop et al.[21]	Bekliz et al.[20]	Osmanodja, et al.[13]	Homza et al.[14]	Poukka et al.[15]	Willeit et al.[16]
Risk of bias	Selection of participants	high risk	high risk	high risk	high risk	high risk	low risk	low risk	high risk	low risk
	Index test	low risk	low risk	low risk	low risk	low risk	low risk	low risk	low risk	low risk
	Reference standard	low risk	low risk	low risk	low risk	low risk	low risk	low risk	low risk	low risk
	Flow and time	low risk	low risk	high risk	low risk	high risk	low risk*	low risk**	low risk	low risk
Applicability	Selection of participants	high risk	high risk	high risk	high risk	high risk	low risk	low risk	low risk	low risk
	Index test	low risk	low risk	low risk	low risk	low risk	low risk	low risk	low risk	low risk
	Reference standard	low risk	low risk	low risk	low risk	low risk	high risk	low risk	low risk	low risk

Source: Prepared by the authors, 2022.
* The study was stopped early due to insufficient recruitment and the sponsor's decision after 70 participants tested positive for RT-PCR.
** The study was stopped early due to the low sensitivity of the saliva tests evaluated.

culture that were diluted in *Dulbecco's* modified *Eagle's* medium (DMEM) and saliva from SARS-CoV-2 negative volunteer donors by *quantitative reverse transcription PCR* (RT-qPCR). However, none of the TR-Ag tested in the study are currently approved for use with saliva by their manufacturers.

The study by Sakai-Tagawa et al.[21] pointed out that cell culture-derived SARS-CoV-2 samples, which did not come from clinical samples, may have been compromised due to some biological components derived from human or indigenous microflora that could interfere with the detection of viral antigens or cause a false-positive reaction.

The study by James Regan et al.[22] (*preprint*) carried out laboratory validation of the BinaxNow TR-Ag with anterior nasal (AN) *swab* samples from COVID-19 PCR positive participants from the COVID-19[25] virology study. Samples of two variants were included in the study, Omicron and Delta at different dilutions. Regarding the applicability of TR-Ag BinaxNow, it is suggested that the test can detect SARS-CoV-2 infections of the Omicron variant, however, future work should further evaluate the diagnostic validity and detection range of the assay for this new variant, as well as its performance in clinical and public health settings.

Regarding the applicability, in the study by van Ogtrop et al.[24], the exact sensitivity of the PanBio TR-Ag for SARS-CoV-2 B.1.1.7 (Alpha) variants could not be reliably estimated. In addition, the study was not set up as a prospective study with the aim of comparing the performance of the TR-Ag in populations infected with the non-B.1.1.7 variant and the B.1.1.7 variant. It was observed that the sensitivity and performance of the PanBio TR-Ag decreased over time, which led to its discontinuation for infection control purposes in the hospital.

The study by Meriem Bekliz et al.[23] (*preprint*) evaluated 11 TR-Ag to detect cultured variants of SARS-CoV-2. The data found do not replace clinical evaluations. TR-Ag proved to be effective in detecting all VOCs, including the Delta variant, and can assist in the diagnosis and control of SARS-CoV-2.

The study by Osmanodja et al.[16] showed that TR-Ag, when compared with RT-PCR results, had a sensitivity of 88.6% (62/70 positive PCR detected 95%CI 78.7%-94.9%) and specificity among symptomatic patients was 99.5% (203/204 95%CI: 97.3-100.0%). With regard to variants, 44 participants were diagnosed with VOC B.1.1.7 and 26 participants had no VOC detected. The sensitivity of the TR-Ag among those patients with VOC Alpha was 88.6% (39/44), which did not differ significantly (p = 0.9075) from those without VOC, in whom the sensitivity was 84.6% (22/26).

The prospective study by Willeit et al.[19] reported lower sensitivity but similar specificity in children compared to previous studies in adults. Sample collection was not carried out by trained medical staff, but by 1st to 8th graders and their teachers, which can substantially impact the detection rate. In addition, the sensitivity of antigen-based tests is higher in symptomatic patients, as the viral load is higher.

In the study by Homza et al.[17] 2,287 samples were collected and analyzed. The sensitivity and specificity of the tests carried out by healthcare professionals (nasopharyngeal sample, NPS, and anterior nasal *swab* sample, ANS) were higher than the self-collection tests (saliva). Regardless of the manufacturer of the saliva test, a low sensitivity (< 40%) was observed, while the specificity of these self-tests was over 89% in symptomatic or asymptomatic patients. The saliva sample self-tests showed low sensitivity (< 45%) and high specificity (> 90%).

In the study by Poukka et al.[18], the authors compared the *cycle threshold* (Ct) values obtained from self-collected samples with the NPS sample collected by a healthcare professional. The NPS had the lowest Ct value (22.07 SD, 4.63), although it was not significantly lower than the values for mucus sputum (25.82 [SD, 9.21] p = 0.28) and sputum collected in the morning (23.51 [SD, 4.57] p = 0.11). Both gargle samples showed significantly higher Ct values compared to the NPS collection done by the healthcare professional.

Chart 3. Criteria of Anvisa's RDC No. 595/2022 and the Ministry of Health's National Plan for the Expansion of Testing (PNE-Teste).

Criteria of Anvisa's RDC No. 595/20226	PNE-test/MS criteria[7]
• TR-Ag SARS-CoV-2: risk class III and subject to registration.	• All components must appear on the external labeling and the results must be easy to read/interpret.
• Sensitivity ≥ 80% and specificity ≥ 97%.	• Sensitivity ≥ 80% and specificity ≥ 97%.
• Instructions for use, storage and disposal of the product: clear drawings on how to obtain the sample, perform the test and read the result.	• The package leaflet or test instructions provided by the manufacturer must contain the information needed to carry out the self-test and guidance on how to proceed afterwards.
• External label for all *kit* components.	• In symptomatic individuals: from the 1st to the 7th day of symptom onset. • In asymptomatic individuals: from the 5th day of contact with an individual with SARS-CoV-2 infection.
	• Self-testing through saliva collection.
	• Self-testing through nasal collection.
	• The test's package insert should include the number of the toll-free health hotline, 136, from which individuals can obtain information.
	• The test registration applicant must provide a telephone communication channel, free of charge, available during business hours, for user support throughout the country.

Source: Prepared by the authors, 2022.

Brazilian public health policies

In January 2022, ANVISA published RDC No. 5956, which set out the requirements and procedures for applying for registration, distribution, marketing and use of medical devices for *in vitro* diagnosis as self-tests for detecting SARS-CoV-2 antigen. In the same month, the Ministry of Health published the PNE-Test[7] which dealt with the expansion of COVID-19 diagnosis by TR-Ag with the aim of monitoring the pandemic in the national territory (Chart 3).

Of the self-tests identified in this review, only one test was registered with Anvisa as of March 23, 2022, Abbott's Panbio COVID-19 Ag RAPID (sensitivity and specificity declared by the manufacturer of 98.1% [95%CI 93.2%-99.8%] and 99.8% [95%CI 98.6%-100.0%], respectively). The clinical performance of Panbio COVID-19 Ag RAPID was evaluated in four included studies[20,21,23,24].

DISCUSSION

The results found in the studies showed that one of the TR-Ag identified in the studies included in this systematic review was registered with Anvisa in the period studied, so consumers should be aware of the tests offered on the Brazilian market. The rules for registration in Brazil require the producer to submit an application to be marketed in the country, which is why there are tests cited in the articles that are not registered. We should also consider the recent authorization to market tests with self-collection of biological material for COVID-19 diagnosis, a factor that may influence the number of TR-Ag identified in the literature with registration with Anvisa.

In the study by Osmanodja et al.[16], the sensitivity of TR-Ag was 96.7%, which differs from the results found in the literature. Lee et al.[25] carried out a systematic review of 24 studies, totaling 14,188 patients, which used rapid antigen detection tests (RADT), identifying an overall combined sensitivity of 0.68 (95%CI, 0.59-0.76). Anvisa's RDC No. 595/2022 and the PNE-test recommend sensitivity ≥ 80% and specificity ≥ 97%. In the study by Willeit et al.[19], the sensitivity of the self-test ranged from 17.0%-44.0% in elementary school, 13.3%-59.4% in secondary schools and 28.7%-86.6% in teachers,

Homza et al.[17] evaluated the accuracy of the self-test using two types of sample: for NPS samples, the sensitivity was 80.60% (95%CI 73.5-86.5) and the specificity was 98.50% (95%CI 96.4-99); for saliva samples, the sensitivity was 32.80% (95%CI 25.8-40.3) and the specificity was 89.30% (95%CI 84.6-92.9). Anvisa recently ordered the withdrawal of AG-RTs from the Brazilian market that used saliva as a sample due to the low sensitivity identified. In the literature, Homza et al.[17] strongly advised the independent evaluation of saliva-based self-tests before the distribution and use of these tests for mass testing of the population, a recommendation similar to that made by Brümmer et al.[26].

Poukkaet et al.[18] evaluated self-collected gargle samples, identifying a sensitivity of 0.97 (95%CI 0.92-1.00) and a specificity of 0.50 (95%CI 0.00-1.00).

The study by Jungnick et al.[20] showed that all the TR-Ag investigated were able to detect the VOC B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) with a performance comparable to the non-VOC B.1.1, although small variations in the limit of detection (LoD) were observed. The study by Sakai-Tagawa et al.[21] evaluated the sensitivity of the Delta variant of SARS-CoV-2 in 27 TR-Ag. The authors identified that eight of them showed sensitivity to detect Delta variants, however, the information provided by the TR-Ag manufacturers suggests low sensitivity against the Delta variant.

Although the study by James Regan et al.[22] (*preprint*) did not aim to identify a detection limit for this assay, the data suggested that the BinaxNow assay has a LoD of approximately 2.0 x 10^4-7.0 x 10^4 viral copies/swab.

Most of the TR-Ags performed well in detecting the Delta variant *and* were comparable to the other variants. A single test, *Sure Status Ag Test* (*Premier Medical Corporation* Ltd.), showed greater sensitivity for the Alpha, Beta and Gamma variants than for the Delta variant. The TR-Ag Flowflex Ag Test (ACON) showed greater sensitivity for the Delta variant[23].

In the study in question, the authors evaluated the accuracy of 11 TR-Ag. Despite the small differences in sensitivity, TR-Ag remains, in principle, effective for detecting all VOCs, including the Delta variant, and can be used for diagnosis in order to monitor the spread of SARS-CoV-2[23].

Among the barriers pointed out in the studies for the implementation of the tests in Brazil is the reliability of the information on the accuracy of the tests. There is a need for independent validations since results have been identified that do not reflect the data reported by the manufacturers. A meta-analysis published in *The Lancet* identified sensitivity of 0.97 (95%CI 0.92-0.99) and specificity of 0.97 (95%CI 0.92-0.99) for the combined nasal and throat (oropharyngeal) *swab* self-tests and sensitivity of 0.85 (95%CI 0.69-0.96) and specificity of 0.98 (95%CI 0.92-1.00) for the nasal *swab* sample self-tests, both compared to collection by a healthcare professional[27].

The moderate sensitivity of nasal *swab* self-tests (~85%) suggests a potential risk of missing 15% of infected cases. In a pandemic context, the implications of a false diagnosis influence the severity of the pandemic (in cases of false negatives) or expose healthy users to unnecessary medical procedures, including the possibility of undue hospitalization[27].

In the regulatory context, the COVID-19 pandemic has accelerated the evaluation processes for the commercialization and/or incorporation of technologies, a point defended by many researchers as an advance in regulatory policy[28]. Although some questions about the COVID-19 self-test remain unanswered, such as possible language barriers, how to mitigate them and how the self-test disposal flow will occur[29], the new regulations provide space for consumers to self-monitor in the event of symptoms.

In Brazil, there is the prerogative of exceptionality for COVID-19 self-tests, since RDC No. 36 of August 26, 2015, which deals with *in vitro* diagnostics, states that products whose purpose is to test samples for the presence of or exposure to pathogenic organisms cannot be classified as self-tests[30]. With the publication of the new RDC (No. 595), is there a prerogative for industries to request the registration of other self-tests? What impact will this decision have on regulatory policy? These questions are important for public health decisions and future regulatory actions. This work has methodological limitations, such as: the scarcity of studies correlating the availability of TR-Ag on the market and the independent validation of the tests in clinical populations, and in response to viral variants.

At the same time, the review provides an overview of the tests that were evaluated in the period studied, emphasizing that Anvisa's role in regulating the marketing of self-tests in Brazil was important, given that more and more consumers and users are learning about the disease and can self-monitor as a way of taking individual measures to prevent transmission.

Overall, there was adequate sensitivity and specificity of antigen-based self-tests compared to PCR tests for COVID-19, especially in symptomatic individuals. This makes it easier to obtain rapid results, even as a form of screening, for both consumers and professionals in primary care.

In addition, self-tests are useful for countries with inadequate vaccination coverage and a high incidence of COVID-19. From the point of view of research and development, the offer of different tests and new alternatives and rapid diagnostic techniques are promising for future epidemics.

CONCLUSIONS

In general, self-tests based on anterior nasal swabs seem to be ideal. The use of saliva is not recommended by many manufacturers due to the impossibility of standardizing the sample. The collection of self-tests appears to be simple and feasible to carry out in real life; however, it should be noted that the safety of self-tests was not the subject of this review.

The sensitivity of the self-tests presented in most of the studies has been investigated at laboratory level, thus requiring more precise clinical studies, however two studies in the *preprint* phase have preliminarily evaluated samples from specific populations and indicate that the tests have promising potential for VOC. This evidence supports the national regulatory decision.

Based on the evidence identified, the use of self-tests as screening strategies is recommended, as long as they meet local regulatory policy recommendations. In the current scenario of the pandemic, in which educational and work activities are returning to the face-to-face modality, self-testing can have a significant impact on controlling the transmission of SARS-CoV-2, especially among the unvaccinated population or even due to reinfections in vaccinated populations.

REFERENCES

1. World Heatlh Organization – WHO. WHO coronavirus (COVID-19) dashboard. Geneva: World Heatlh Organization; 2021.
2. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019;17(3):181-92. https://doi.org/10.1038/s41579-018-0118-9
3. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: evidence for virus evolution. J Med Virol. 2020;92(4):455-9. https://doi.org/10.1002/jmv.25688

4. Vandenberg O, Martiny D, Rochas O, van Belkum A, Kozlakidis Z. Considerations for diagnostic COVID-19 tests. Nat Rev Microbiol. 2021;19(3):171-83. https://doi.org/10.1038/s41579-020-00461-z
5. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta. 2020;510:475. https://doi.org/10.1016/j.cca.2020.08.019
6. Agência Nacional de Vigilância Sanitária - Anvisa. Resolução RDC Nº 595, de 28 de janeiro de 2022. Dispõe sobre os requisitos e procedimentos para a solicitação de registro, distribuição, comercialização e utilização de dispositivos médicos para diagnóstico *in vitro* como autoteste para detecção de antígeno do SARS. Diário Oficial União. 29 jan 2022.
7. Ministério da Saúde (BR). Plano nacional da testagem para COVID-19/PNE-teste. Brasília: Ministério da Saúde; 2022.
8. World Heatlh Organization – WHO. Antigen-detection in the diagnosis of SARS-CoV-2 infection. Geneva: World Heatlh Organization; 2021[acesso 4 nov 2021]. Disponível em: https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays
9. Stanley S, Hamel DJ, Wolf ID, Riedel S, Dutta S, Cheng A et al. Limit of detection for rapid antigen testing of the SARS-CoV-2 omicron variant. medRxiv. 30 jan 2022. https://doi.org/10.1101/2022.01.28.22269968
10. Yüce M, Filiztekin E, Özkaya KG. COVID-19 diagnosis: a review of current methods. Biosens Bioelectron. 2021;172. https://doi.org/10.1016/j.bios.2020.112752
11. Camargo EB, Pereira ACES, Gliardi JDM, Pereira DR, Puga ME, Silva ET et al. Judicialização da saúde: onde encontrar respostas e como buscar evidências para melhor instruir processos. Cad Ibero-Am Direito Sanit. 2017;6(4):27-40. https://doi.org/10.17566/ciads.v6i4.410
12. Ferreira JC, Patino CM. Entendendo os testes diagnósticos parte 1. J Bras Pneumol. 2017;43(5):330-1. https://doi.org/10.1590/S1806-37562017000000330
13. Patino CM, Ferreira JC. Entendendo os testes diagnósticos parte 2. J Bras Pneumol. 2017;43(6):408. https://doi.org/10.1590/S1806-37562017000000424
14. Ferreira JC, Patino CM. Entendendo os testes diagnósticos parte 3. J Bras Pneumol. 2018;44(1):4. https://doi.org/10.1590/S1806-37562018000000017
15. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB et al. Quadas-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36. 1 https://doi.org/0.7326/0003-4819-155-8-201110180-00009
16. Osmanodja B, Budde K, Zickler D, Naik MG, Hofmann J, Gertler M et al. Accuracy of a novel SARS-CoV-2 antigen-detecting rapid diagnostic test from standardized self-collected anterior nasal swabs. J Clin Med. 2021;10(10):4-11. https://doi.org/10.3390/jcm10102099
17. Homza M, Zelena H, Janosek J, Tomaskova H, Jezo E, Kloudova A, et al. Performance of seven SARS-CoV-2 self-tests based on saliva, anterior nasal and nasopharyngeal swabs corrected for infectiousness in real-life conditions: a cross-sectional test accuracy study. Diagnostics. 2021;11(9):1-12. https://doi.org/10.3390/diagnostics11091567
18. Poukka E, Mäkelä H, Hagberg L, Vo T, Nohynek H, Ikonen N et al. Detection of SARS-CoV-2 infection in gargle, spit, and sputum specimens. Microbiol Spectr. 2021;9(1):1-9. https://doi.org/10.1128/Spectrum.00035-21
19. Willeit P, Bernar B, Zurl C, Al-Rawi M, Berghold A, Bernhard D et al. Sensitivity and specificity of the antigen-based anterior nasal self-testing programme for detecting SARS-CoV-2 infection in schools, Austria, March 2021. Euro Surveill. 2021;26(34):1-5. https://doi.org/10.2807/1560-7917.ES.2021.26.34.2100797
20. Jungnick S, Hobmaier B, Mautner L, Hoyos M, Haase M, Baiker A et al. *In vitro* rapid antigen test performance with the SARS-CoV-2 variants of concern b.1.1.7 (alpha), b.1.351 (beta), p.1 (gamma), and b.1.617.2 (delta). Microorganisms. 2021;9(9):1-8. https://doi.org/10.3390/microorganisms9091967
21. Sakai-Tagawa Y, Yamayoshi S, Halfmann PJ, Kawaoka Y. Comparative sensitivity of rapid antigen tests for the delta variant (B.1.617.2) of SARS-CoV-2. Viruses. 2021;13(11):1-9. https://doi.org/10.3390/v13112183
22. Regan J, Flynn JP, Choudhary MC, Uddin R, Lemieux J, Boucau J et al. Detection of the omicron variant virus with the abbott binaxnow SARS-CoV-2 rapid antigen assay. medRxiv. 27 dez 2021. https://doi.org/10.1093/ofid/ofac022
23. Bekliz M, Adea K, Essaidi-Laziosi M, Escadafal C, Sacks JA, Kaiser L et al. Analytical performance of eleven SARS-CoV-2 antigen-detecting rapid tests for Delta variant. medRxiv. 7 out 2021. https://doi.org/10.1101/2021.10.06.21264535
24. van Ogtrop ML, van de Laar TJW, Eggink D, Vanhommerig JW, van der Reijden WA. Comparison of the performance of the panbio COVID-19 antigen test in SARS-CoV-2 B.1.1.7 (Alpha) variants versus non-B.1.1.7 variants. Microbiol Spectr. 2021;9(3):1-6. https://doi.org/10.1128/Spectrum.00884-21
25. Lee J, Song JU, Shim SR. Comparing the diagnostic accuracy of rapid antigen detection tests to real time polymerase chain reaction in the diagnosis of SARS-CoV-2 infection: a systematic review and meta-analysis. J Clin Virol. 2021;144:104985. https://doi.org/10.1016/j.jcv.2021.104985
26. Brümmer LE, Katzenschlager S, Gaeddert M, Erdmann C, Schmitz S, Bota M, et al. Accuracy of novel antigen rapid diagnostics for SARS-CoV-2: A living systematic review and meta-analysis. PLOS Med. 2021;18(8):1-41. https://doi.org/10.1371/journal.pmed.1003735
27. Tsang NNY, So HC, Ng KY, Cowling BJ, Leung GM, Ip DKM. Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. Lancet Infect Dis. 2021;21(9):1233-45. https://doi.org/10.1016/S1473-3099(21)00146-8

28. Kersh EN, Shukla M, Raphael BH, Habel M, Park I. At-home specimen self-collection and self-testing for sexually transmitted infection screening demand accelerated by the COVID-19 pandemic: a review of laboratory implementation issues. J Clin Microbiol. 2021;59(11):1-13. https://doi.org/10.1128/JCM.02646-20

29. Nundy S, Patel KK. Self-service diagnosis of COVID-19: ready for prime time? JAMA Heal Forum. 2020;1(3). https://doi.org/10.1001/jamahealthforum.2020.0333

30. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC Nº 36, de 26 de agosto de 2015. Dispõe sobre a classificação de risco, os regimes de controle de cadastro e registro e os requisitos de rotulagem e instruções de uso de produtos para diagnóstico *in vitro*, inclusive seus instrumentos e dá outras providências. Diário Oficial União. 27 ago 2015.

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Authors' Contribution

Camargo EB, Ramos MC - Conception, planning (study design), acquisition, data interpretation, and writing of the work. Elias FTS - Acquisition, data interpretation, and writing of the work. All the authors approved the final version of the work.

Conflict of Interest

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