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Accuracy of point-of-care Panbio™ SARS-CoV-2 antigen-detection test in a socioeconomically vulnerable population in Brazil

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Background: Development and validation of point-of-care (POC) diagnostic tests with high accuracy is critical for underrepresented populations, allowing for wider access to diagnosis. Here, we evaluate the performance of the Panbio™ antigen-rapid test device (Ag-RTD) for SARS-CoV-2, our index test, having RT-qPCR as the reference standard.

Methods: This phase III validation study was conducted concomitantly with a primary health care center routine tending to a low-income Brazilian population. Eligibility criteria were residing at Cidade Estrutural and presenting flu-like/respiratory symptoms for 3-10 days.

Results: Among the 505 participants, 45.15% (228/505) tested positive for RT-qPCR and 54.85% (277/505) for the Ag-RTD. Overall sensitivity was 76.32% (CI95% 70.39-81.37) and specificity was 98.92% (96.02-99.82).

Conclusions: Our results show that the Panbio™ Ag-RTD does not meet the minimum performance requirements established by the World Health Organization (≥ 80% sensitivity and ≥ 97% specificity compared to a reference test in suspected COVID-19 cases). Thus, we do not recommend the implementation of Panbio™Ag-RTD as a single diagnostic tool in

underrepresented and disadvantaged populations. Finally, we discuss a possible setting for the use of Panbio™Ag-RTD under combined sensitivity.

KEYWORDS

accuracy, antigen rapid detection test, socioeconomically vulnerable population, COVID-19, diagnostics

Introduction

The coronavirus disease-2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Host biological and socioeconomic factors, in addition to health conditions and other risk factors, are positively associated with the spread and unfavorable outcomes of COVID-19 (1–4). The current pandemic disproportionately affects historically underrepresented, disadvantaged groups, and exacerbates preexisting and current social inequalities (5).

In Brazil, populations from municipalities with higher socioeconomic vulnerability experienced higher death rates from COVID-19 and greater disease spread during the initial phase of the epidemic; moreover, socioeconomic inequalities appear to have had stronger effects on the epidemic rather than biological and other risk factors for COVID-19 (6). Publicly available state-level reports also revealed a strong positive correlation between mortality and socioeconomic vulnerability in a Brazilian pediatric population (7). Controlling the spread and reducing negative outcomes of COVID-19 require early and rapid detection for isolation of symptomatic patients and close contact tracing; nevertheless, health care and proper diagnostic tools are often unavailable for underrepresented populations.

Real-time reverse-transcription polymerase chain reaction (RT-qPCR) from nasopharyngeal (NP) samples is the reference standard test for the detection of SARS-CoV-2 (8). Specialized instruments, trained human resources, and equipped and safe laboratories are required to conduct the high-cost RT-qPCR essays, limiting testing availability and posing an obstacle to mass testing. Point-of-care (POC) SARS-CoV-2 antigen rapid test devices (Ag-RTDs), such as Panbio™ Ag-RTD, emerge as rapid, easy, and less expensive and laborious alternatives to diagnose ongoing SARS-CoV-2 infections in several settings.

The World Health Organization's interim guidance from October 2021 advises the use of SARS-CoV-2 Ag-RTDs that meet a minimum performance of ≥80% sensitivity and ≥97% specificity compared to RT-qPCR (8). Sensitivity of the Panbio™ Ag-RTD evaluated at POC in symptomatic patients ranges from ~50 to 100%, whereas specificity ranges from ~80 to 100% (9–30). However, all but three studies with small samples and/or insufficient description of the sampled population (10, 17, 27) evaluated Panbio™ Ag-RTD in populations from high-income countries, and none of them included disadvantaged populations.

The case of the COVID-19 pandemic has raised concerns that the lack of representation of disadvantaged groups might bias investigation (31), as well as the perception of health and access to diagnosis and treatment. Thus, it is crucial to validate diagnostic tools for early detection of COVID-19 in underrepresented, disadvantaged groups and to account for patient characteristics such as race/ethnicity/ancestry, sex, age, and preexisting medical conditions. Here, we aimed to assess the accuracy of the Panbio™ Ag-RTD performed at POC at a primary health care center tending to an urban area inhabited by underrepresented groups in Brazil. Populations such as this, presenting flu-like/respiratory syndrome symptoms for 3 to 10 days, would benefit from opportune, accurate, fast, and cheaper diagnostic tools, as long as those tools meet WHO's interim guidance from October 2021 for the adoption of rapid antigen detection tests.

Materials and methods

We conducted a prospective diagnostic accuracy study, type phase III (32), for the validation of a diagnostic test for the detection of SARS-CoV-2 in patients with flu-like/respiratory syndrome symptoms who sought medical assistance at a primary health center. This work was conducted in accordance with the Ethical Principles for Medical Research in Human Subjects (Declaration of Helsinki) and the Brazilian regulations on ethics in human research. Data and sample collection were approved by the Research Ethics Committee of the Faculty of Medicine at University of Brasília (CEP-FM/UnB, CAAE 39892420.7.1001.5558; CAAE 40557020.6.3001.5553) and Fundação de Ensino e Pesquisa em Ciências da Saúde (FEPECS/SES/DF, CAAE 40557020.6.3001.5553). All participants were volunteers and informed about research goals and confidentiality of data, and signed instruments of consent previously to data and sample collection. This study was conducted according to the updated Standards for Reporting Diagnostic Accuracy Studies (STARD) (33). A checklist of STARD essential items is presented in S1 Checklist.

Study population

Cidade Estrutural (RA XXV SCIA/Estrutural, DF, Brazil; Figure 1) is inhabited by a socioeconomically vulnerable population occupying a stretch of land bordered by highly degraded and preserved environments (Figure 1). It was founded as an irregular occupation area, which until 2017, housed an enormous untreated refuse disposal site known as "lixão da Estrutural" (Estrutural dump), where around 4,000 people worked scavenging waste (34). Today, the refuse disposal site has been turned into an official rubble receiving unit (URE, Unidade de Recebimento de Entulho), though different dumping sites often emerge in Estrutural. Furthermore, Estrutural borders the Brasília National Park (a 423.60 km^2 conservation area), the Brasília National Forest, the Cabeceira do Valo river and its area of relevant ecological interest a.k.a ARIE (i.e., small extension area of sustainable use, protected by law, which houses rare specimens of fauna and flora). Even though Cidade Estrutural was founded during the 50's, it is still expanding into surrounding areas, mostly nature preserves. Neighborhoods vary widely in urban infrastructure. On one extreme, Santa Luzia, the most socioeconomically vulnerable neighborhood, is situated on the border with the Brasilia National Park, making it susceptible to spillovers and outbreaks, as well as to political tension concerning its expansion. Streets are not paved, and there is no sanitation infrastructure. On the other hand, Setor Leste is a long-consolidated neighborhood and has a better infrastructure (Figure 1). Cidade Estrutural is inhabited by over 35,000 people (35) all tended to by a single public primary health care center, where our samples were collected. According to official data (35), sociodemographic data depicts a population with low income (R$ 573,00 or US$ 112,00 per capita), low education (6.4% are illiterate, 9.6% have completed only elementary school), and low Human Development Index (HDI, 0.616) in a Federative Unit (the Brazilian Federal District - DF) with a Gini coefficient of 0.553 (36). The resident population identifies mostly as black (15%) and mixed race (62%), and most of the remaining self-declared white. The age-sex pyramid is characteristic of developing populations (35).

Sample size

Sample size was calculated as $N= Z^2 [(p(1-p)]/(D^2)]$, in which p was the frequency of the expected event and D was the semi-amplitude of a bi-caudal precision. According to the Abbott Panbio™ Ag-RTD insert, test sensitivity was 0.91 and specificity was 0.98. To calculate the sample size to assess sensitivity, we used 0.91 as the frequency of the expected event and a precision of 4%, resulting in a sample size of approximately 196 participants. To calculate the sample size to assess specificity, we used 0.98 as the frequency of the expected event and a precision of 4%, which resulted in a sample size of 188 participants. Therefore, our final sample size was at least 384 volunteers.

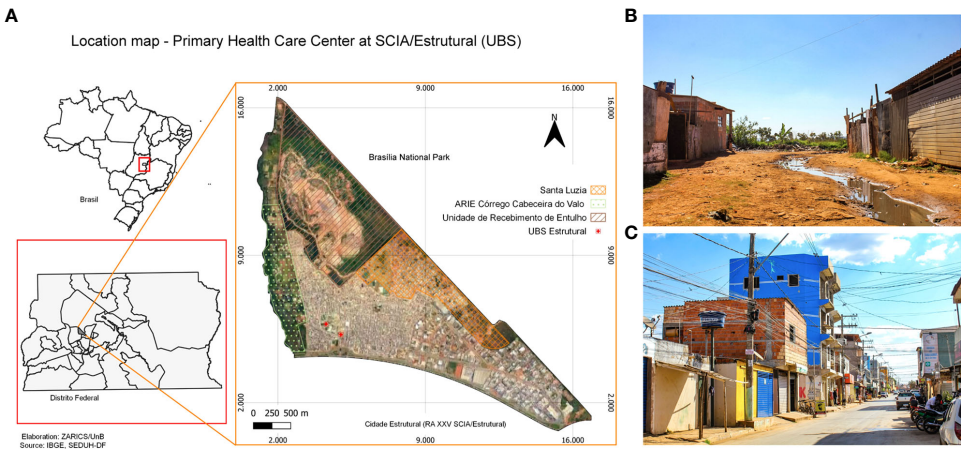

FIGURE 1
Characterization of Estrutural. **(A)** Location map of the primary health care center at Estrutural. The primary health care center (UBS) is pointed in red; Santa Luzia, Cabeceira do Valo river and its ecological conservation unit (Unidade de Conservação Área de Relevante Interesse Ecológico do Córrego Cabeceira do Valo (ARIE), Brasília National Park and the rubble receiving unit (URE - Unidade de Recebimento de Entulho) are also highlighted. **(B)** Santa Luzia, the most socioeconomically vulnerable neighborhood in Estrutural. The photograph depicts the border between Estrutural and the Brasília National Park. **(C)** A street in Setor Leste, a neighborhood with better urban infrastructure.

Clinical assessment and eligibility criteria

Eligibility criteria were: 1. residing in Cidade Estrutural; 2. presenting flu-like/respiratory syndrome symptoms for 3 to 10 days as defined by the Brazilian Ministry of Health (37); and 3. seeking assistance at the Cidade Estrutural primary health care center. All patients with flu-like/respiratory syndrome symptoms referred for medical care were invited to participate in the study (Figure S1). All participants were informed about research goals and confidentiality of data and signed instruments of consent previously to data and sample collection.

Data collection

In March 2021, our research team joined efforts with the Cidade Estrutural primary health care center staff and became responsible for the surveillance system for COVID-19. Primary data were collected by semi-structured interviews utilizing standardized, pre-tested questionnaires using the data capture software Research Electronic Data Capture (REDCap) (38) hosted at the University of Brasília. Beginning on March 16th, 515 patients agreed to participate in our validation study.

Sample collection for RT-qPCR reference standard test and case definition

Our trained staff collected NP swab specimens for diagnosis by RT-qPCR reference standard test from each participant at the Cidade Estrutural primary health care center. A single sterile swab was introduced in both nostrils until nasopharyngeal resistance was met, rotated 5 times, and stored in a viral transport medium (VTM - LaborClin, Brazil). Samples were transported at 4-6°C to the Laboratório de Diagnóstico Molecular (Laboratory of Molecular Diagnosis) at Hospital Universitário de Brasília (HUB), University of Brasília (UnB), where RT-qPCR assays were performed. All patients with flu-like symptoms plus SARS-CoV-2 RNA detected by RT-qPCR were considered COVID-19 cases, whereas patients with flu-like symptoms and undetected SARS-CoV-2 RNA were considered non-cases.

Execution of RT-qPCR reference standard test

RT-qPCR assays were performed by blinded, trained technical staff who had no prior knowledge of the clinical presentation of patients. SARS-CoV-2 RNA was isolated using the EXTRACTA 32 kit (MVXA-P016 FAST) in a Loccus automated extractor following the manufacturer's instructions. SARS-CoV-2 was detected by the RT-qPCR Allplex™ 2019-nCoV Assay (Seegene Inc.) for the amplification of genes *E*, *RdRP*, *N*, as well as an internal control gene, according to the manufacturer's protocol. RT-qPCR results were considered positive (SARS-CoV-2 RNA detected) when the internal control and at least two genes were amplified, negative (SARS-CoV-2 RNA not detected) when the internal control and none or only one gene was amplified, and inconclusive when the internal control did not amplify. Inconclusive RT-qPCR reactions were repeated once.

Over the months since the first sample collection, results of the ongoing analyses (RT-qPCR for diagnosis) were informed to the participants and to the public health services that attend to the community for follow-up and treatment, and for epidemiologic bulletins.

Sample collection and execution of the Panbio™ Antigen Rapid Test Device

Abbott's Panbio™ Ag-RTD contains a swab to collect NP specimens, a buffer solution where the swab must be inserted immediately after the NP specimens collection, and an apparatus to run the test. This apparatus contains a membrane strip pre-coated with antibodies to detect the nucleo-capsid (N) protein of SARS-CoV-2 in human NP swab specimens. NP specimens were collected from both nostrils immediately after swab collection for RT-qPCR at POC (the primary health care center at Cidade Estrutural). Specimens were immediately inserted into the test buffer and then dripped on the spot indicated in the membrane strip as per the manufacturer's instructions. A visible control line is required to validate the test result. A second line indicates a positive result, and its absence, a negative result. The absence of a control line defines an invalid test, which should be canceled, and the participant excluded from the study. All tests were performed according to the manufacturer's protocol and each test was evaluated by two independent observers at the same time.

Statistical analysis

Test results and patient data were tabulated and analyzed using SPSS version 22 (39). Patients with missing data were excluded from the study. Data were plotted using RStudio version 1.1.463 (40) and the ggplot2 package (41). The overall sensitivity, specificity, and likelihood ratios of the Panbio™ Ag-RTD and their respective 95% confidence intervals (CI95%) were calculated in Microsoft Excel; we also calculated these values for the test regarding the self-reported symptoms and days from symptom onset. The kappa index was

used to test for agreement between the results reported by two independent observers. For all statistical analyses, the first observer results were used.

Results

From March 16th to July 1st of 2021, 1118 patients with flu-like/respiratory syndrome symptoms sought medical care at the primary healthcare center at Cidade Estrutural and were invited to join our research. A total of 515 patients consented to participate and signed consent instruments, as described above. RT-qPCR results for 10 participants remained inconclusive even after repeating RNA extraction and RT-qPCR essay, and were therefore excluded from the accuracy analysis of the index test. Thus, the sample size for the accuracy analysis of the index test was 505 participants (Figure 2).

Sample description

Out of the 505 participants, 61.39% (310/505) were female and 79.60% (402/505) self-declared mixed-race or black. Age ranged from 5 to 73 years old (median age 33 and quartiles 24-42.25). A total of 43.56% (220/505) participants declared to have at least one comorbidity; hypertension was the most common self-reported comorbidity (15.25%, 77/505). Descriptive analysis of the sample characteristics according to RT-qPCR and Panbio™ Ag-RTD results are summarized in Table 1, and additional information on other self-reported coexisting conditions is shown in Table S1.

Headache was the most reported symptom (75.64%, 382/505), followed by fever (67.33%, 340/505) and cough (66.93%, 338/505). Headache, cough, and fever were also the most commonly reported symptoms among the 228 participants that tested positive for RT-qPCR (72.37%, 165/228; 69.74%, 159/228; 68.42%, 156/228), as well as among participants with positive results for the Panbio™ Ag-RTD (headache: 71.19%, 126/177; cough: 70.62%, 125/177; fever: 67.80%, 120/177). Out of the 136 participants that reported ageusia, 63.23% (86/136) tested positive with RT-qPCR, and 53.68% (73/136) tested positive with the Ag-RTD. Similarly, anosmia was reported by 131 patients, 68.70% of which tested (90/131) positive with RT-qPCR and 57.25% (75/131) tested positive with Panbio™ Ag-RTD. Self-reported symptoms are summarized in Table 2, and additional information on other self-reported symptoms/signs/discomforts is presented in Table S1.

Overall Panbio™ Ag-RTD accuracy

Considering our sample size of 505 participants, the Panbio™ Ag-RTD obtained 54.85% (277/505) positive results, whereas the reference standard test (RT-qPCR) obtained 45.15% (228/505). Accuracy assessment (Table 3) showed sensitivity of 76.32% (CI95% 70.39-81.37) and specificity of 98.92% (CI95% 96.02-99.82). Positive likelihood ratio was 70.46 (CI95% 22.81-217.64) and negative likelihood ratio was 0.24 (CI95% 0.19-0.30). There were no inconclusive results in the Panbio™ Ag-RTD. The raw concordance between results was 97.82% (494/505), and the kappa index for the Panbio™ Ag-RTD evaluating the agreement between results of two independent observers was 0.96.

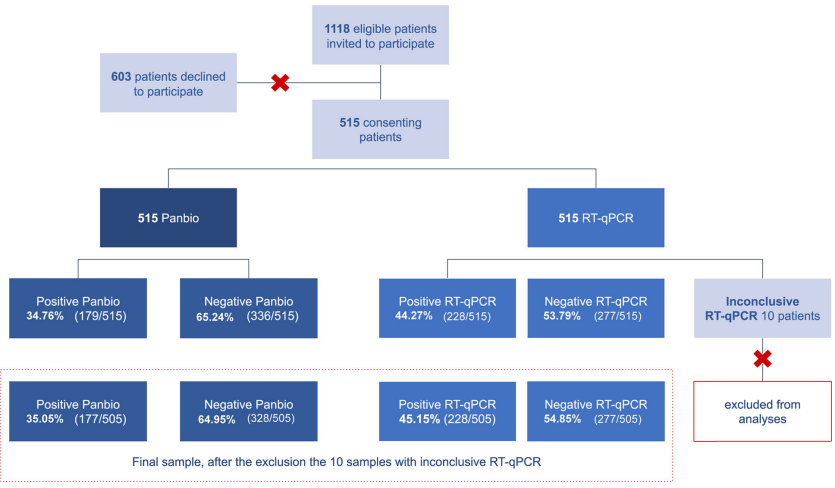

FIGURE 2
Flowchart showing enrollment of participants in research and test results.

TABLE 1 Baseline characteristics of the 505 participants enrolled in Panbio™ antigen-rapid test devices (Ag-RTD) accuracy assessment.

		Reference standard test (RT-qPCR)		Panbio™ Ag-RTD	
	Total	**Positive**	**Negative**	**Positive**	**Negative**
Sample size	505	228	277	177	328
%		45.15%	54.85%	35.05%	64.95%
Sex					
Female	310	132	178	107	203
	61.39%	57.89%	64.26%	60.45%	61.89%
Male	195	96	99	70	125
	38.61%	42.11%	35.74%	39.55%	38.11%
Age					
Range	5-73	5-73	5-68	5-73	5-68
Mean	34.06	35.38	32.98	36.03	33
s.d.	12.65	13	12.28	13.25	12.21
Median	32	35	31	35	31
Quartiles	24.00 – 42.25	25.00 – 44.00	23.50 – 41.00	25 – 44.50	22.00 – 41.00
Race					
Not declared	4	3	1	1	3
	0.79%	1.32%	0.36%	0.56%	0.91%
Mixed race	300	133	167	102	198
	59.41%	58.33%	60.29%	57.63%	60.37%
White	71	36	35	32	39
	14.06%	15.79%	12.64%	18.08%	11.89%
Black	102	44	58	32	70
	20.20%	19.30%	20.94%	18.08%	21.34%
Asian	21	9	12	7	14
	4.16%	1.32%	1.44%	1.69%	1.22%
Indigenous American	7	3	4	3	4
	1.39%	1.32%	1.44%	1.69%	1.22%
Comorbidities					
Obesity	26	14	12	9	17
	5.15%	6.14%	4.33%	5.08%	5.18%
Diabetes	31	17	14	16	15
	6.14%	7.46%	5.05%	9.04%	4.57%
Hypertension	77	42	35	36	41
	15.25%	18.42%	12.64%	20.34%	12.50%
High cholesterol	14	8	6	6	8
	2.77%	3.51%	2.17%	3.39%	2.44%
HIV/AIDS	5	1	4	1	4
	0.99%	0.44%	1.44%	0.56%	1.22%
Transplanted organs	0	1	2	3	4
	0.00%	0.44%	0.72%	1.69%	1.22%
Chronic kidney disease	5	1	4	1	4
	0.99%	0.44%	1.44%	0.56%	1.22%
Depression/Anxiety	62	25	37	17	45
	12.28%	10.96%	13.36%	9.60%	13.72%
Other psychiatric conditions	5	2	3	1	4
	0.99%	0.88%	1.08%	0.56%	1.22%
Asthma	9	4	5	3	6
	1.78%	1.75%	1.81%	1.69%	1.83%

(Continued)

TABLE 1 Continued

		Reference standard test (RT-qPCR)		Panbio™ Ag-RTD	
	Total	Positive	Negative	Positive	Negative
None declared	285	126	159	99	186
	56.44%	55.26%	57.40%	55.93%	56.71%

*Four participants declared to have been previously vaccinated with CoronaVac (Sinovac Biotech, China). They received the last vaccine shot at least 11 days before the onset of symptoms. Other self-reported coexisting conditions are presented in Table S1.

Panbio™ Ag-RTD accuracy regarding symptoms and symptoms onset

The days from symptom onset to medical assistance at the primary health care center and, hence, the diagnosis, were similar between volunteers with positive RT-qPCR and Panbio™ Ag-RTD. Average days of self-reported symptoms for RT-qPCR positive participants was 5.47 days (SD 1.94), whereas for Panbio™ Ag-RTD it was 5.45 days (SD 1.93) (Figure S2). Sensitivity of Panbio™ Ag-RTD slightly increased in patients with ≤5 days from symptom onset to 77.17% (CI95% 69.13-83.60), whereas specificity virtually did not change 99.41% (CI95% 98.54-100) (see Table 3). In patients with >5 from symptom onset, sensitivity and specificity (75.25%, 66.01-82.64 and 98.13% 96.29-99.97, respectively) slightly decreased. We also found that the Panbio™ Ag-RTD sensitivity was improved to 81.55% (CI95% 72.98-87.86) in patients who declared having anosmia and/or ageusia; in these cases, specificity slightly decreased to 98.39% (CI95% 96.47-100).

Discussion

Our results show that the Panbio™ Ag-RTD has overall sensitivity and specificity of 76.32% (CI95% 70.39-81.37) and 98.92% (CI95% 98.02-99.82), respectively, compared to the reference standard RT-qPCR test for patients with mild to moderate flu-like/respiratory symptoms. The kappa index for agreement between results evaluated by two independent observers was 0.96, which is labeled as a strong agreement.

Other Panbio™ POC accuracy studies with symptomatic patients reported variable sensitivity and specificity values ranging from ~50-100% and ~80-100%, respectively (9–30). Although these are all phase III studies (32), such wide ranges are noteworthy. Possible explanations relate to the origin and collection of the samples used for RT-qPCR reference standard tests and index Ag-RTD. Some authors performed RT-qPCR as reference test from NP and/or oropharyngeal (OP) swab samples (11–13, 19, 23, 24, 30), whereas others used saliva or combined saliva and NP samples for the reference test or for the Panbio™ Ag-RTD (9, 16, 17). Akingba et al., 2021 (10) performed RT-qPCR using a single NP swab sample for both RT-qPCR and Panbio™ testing instead of collecting two NP swab samples from each nostril – one for RT-qPCR and another for Ag-RTD, as other authors chose to do (18, 22, 26, 28). Nsoga et al., 2021 (20) used OP swab samples to perform the Panbio™ Ag-RTD tests and NP samples for the RT-qPCR. Furthermore, other authors did not specify whether NP swab samples were collected from one or two nostrils (14, 15, 21, 25).

In the present study, we first collected a NP swab sample from both nostrils for diagnosis by RT-qPCR, and then collected a second one from each nostril for the Panbio™ Ag-RTD. By doing so, we expect to have established a more robust methodological approach for the accuracy study for two main reasons. First, the chosen workflow ensures the collection of a biological sample even in the eventuality of nasal obstruction due to anatomical variation (i.e., deviated septum), which might prevent a swab from reaching the nasopharynx. Second, the chosen method ensures that the two samples are collected exactly in the same way and excludes variation in sample collection as a factor for disagreement between RT-qPCR and Ag-RTD.

To our knowledge, this is the first Panbio™ Ag-RTD accuracy study carried out at POC in socioeconomically vulnerable, disadvantaged groups. All but three of the studies mentioned above were performed in populations from high-income countries (10, 17, 27). The study by Akingba and colleagues (2021) (10) does not fully describe the sampled population and given the high inequality rates in South Africa (Gini index 0.63) (42) it is not possible to ascertain whether high or low-income groups were included. The same problem was found in the other two studies in populations from São Paulo, Brazil (17, 27). Four out of six studies reporting Panbio™ Ag-RTD sensitivity >80% (12, 18, 20, 25) were carried out in European populations from Spain, Germany, or Switzerland. Although two studies found an overall sensitivity >80% in a population from Brazil (17, 27), they evaluated the Panbio™ accuracy in a very small sample (n=127 and 112, respectively). Moreover, the Matsuda et al., 2021 study (17) comprised patients from public and private hospitals – in addition to using saliva combined with NP swab samples to perform RT-qPCRs – whereas Faíco-Filho and colleagues (2021) (27) did not describe the population nor the hospital where samples were collected.

Unlike previously reported by Merino et al., 2021 and Bulilete et al., 2021 (18, 25), we did not see a great increase

TABLE 2 Symptoms reported by the 505 participants enrolled in the Panbio™ antigen-rapid test devices (Ag-RTD) accuracy assessment.

Self-reported symptoms		Reference standard test (RT-qPCR)		Panbio™ Ag-RTD	
	Total	Positive	Negative	Positive	Negative
	505	**228**	**277**	**177**	**328**
Cough	338	159	179	125	213
	66.93%	69.74%	64.62%	70.62%	64.94%
Fever	340	156	184	120	220
	67.33%	68.42%	66.43%	67.80%	67.07%
Runny nose	258	117	141	89	169
	51.09%	51.32%	50.90%	50.28%	51.52%
Sore throat	242	98	144	68	174
	47.92%	42.98%	51.99%	38.42%	53.05%
Headache	382	165	217	126	256
	75.64%	72.37%	78.34%	71.19%	78.05%
Difficulty breathing	53	22	31	14	39
	10.50%	9.65%	11.19%	7.91%	11.89%
Anosmia	131	90	41	75	56
	25.94%	39.47%	14.80%	42.37%	17.07%
Ageusia	136	86	50	73	63
	26.93%	37.72%	18.05%	41.24%	19.21%
Nausea	34	12	22	11	23
	6.73%	5.26%	7.94%	6.21%	7.01%
Vomit	35	18	17	14	21
	6.93%	7.89%	6.14%	7.91%	6.40%
Diarrhea	80	38	42	32	48
	15.84%	16.67%	15.16%	18.08%	14.63%
Tiredness	80	40	40	28	52
	15.84%	17.54%	14.44%	15.82%	15.85%
Hyperoxia	22	8	14	7	15
	4.36%	3.51%	5.05%	3.95%	4.57%
Dyspnea	65	27	38	22	43
	12.87%	11.84%	13.72%	12.43%	13.11%
Abdominal pain	26	13	13	10	16
	5.15%	5.70%	4.69%	5.65%	4.88%
Chills	22	11	11	11	11
	4.36%	4.82%	3.97%	6.21%	3.35%
Myalgia	279	128	151	102	177
	55.25%	56.14%	54.51%	57.63%	53.96%
Fatigue	52	26	26	21	31
	10.30%	11.40%	9.39%	11.86%	9.45%
Adynamia	24	12	12	11	13
	4.75%	5.26%	4.33%	6.21%	3.96%
Prostration	13	7	6	3	10
	2.57%	3.07%	2.17%	1.69%	3.05%
Persistent thoracic pressure	25	11	14	8	17
	4.95%	4.82%	5.05%	4.52%	5.18%
Cyanosis	1	0	1	0	1
	0.20%	0.00%	0.36%	0.00%	0.30%
Mental confusion	1	0	1	0	1
	0.20%	0.00%	0.36%	0.00%	0.30%

(Continued)

TABLE 2 Continued

Self-reported symptoms		Reference standard test (RT-qPCR)		Panbio™ Ag-RTD	
	Total	Positive	Negative	Positive	Negative
Exanthem (rash)	0	0	0	0	0
	0.00%	0.00%	0.00%	0.00%	0.00%
Back pains	52	26	26	21	31
	10.30%	11.40%	9.39%	11.86%	9.45%
Conjunctivitis	0	0	0	0	0
	0.00%	0.00%	0.00%	0.00%	0.00%
Arthritis	6	1	5	1	5
	1.19%	0.44%	1.81%	0.56%	1.52%
Arthralgia	11	0	11	0	11
	2.18%	0.00%	3.97%	0.00%	3.35%
Petechiae	0	0	0	0	0
	0.00%	0.00%	0.00%	0.00%	0.00%
Retro-orbital pain	75	36	39	25	50
	14.85%	15.79%	14.08%	14.12%	15.24%
Nasal obstruction	19	7	12	6	13
	3.76%	3.07%	4.33%	3.39%	3.96%
Asymptomatic	0	0	0	0	0
	0.00%	0.00%	0.00%	0.00%	0.00%

Other self-reported symptoms. signs and discomforts are presented in Table S1.

in sensitivity for Panbio™ Ag-RTD in patients with ≤ 5 days from symptom onset. Even though the relationship between viral load in COVID-19 (estimated by Cycle threshold [Ct] values) and days from symptom onset are not yet clear, a higher viral load is expected early in the course of the disease [e.g (18, 25)] – and, hence, a higher sensitivity of the test. However, it is important to stress that the precision of information like days from symptom onset in a population might affect the results of accuracy evaluation. Moreover, disadvantaged populations like those in our study, which in

TABLE 3 Accuracy assessment of the Panbio™ antigen-rapid test devices (Ag-RTD).

Reference testRT-qPCR	Positive	Negative	Sensitivity (CI95%)	Specificity (CI95%)	Positive likelihood ratio (CI95%)	Negative likelihood ratio (CI95%)
Overall accuracy n = 505						
Ag-RTD Test Positive	174	3	76.32% (70.39-81.37)	98.92% (98.02-99.82)	70.46 (22.81-217.64)	0.24 (0.19-0.30)
Ag-RTD Test Negative	54	274				
Accuracy in patients with ≤ 5 days from symptoms onset n = 297						
Ag-RTD Test Positive	98	1	77.17% (69.13-83.60)	99.41% (98.54-100)	131.18 (18.54-928.02)	0.23 (0.17-0.32)
Ag-RTD Test Negative	29	169				
Accuracy in patients with >5 days from symptoms onset n = 208						
Ag-RTD Test Positive	76	2	75.25% (66.01-82.64)	98.13% (96.29-99.97)	40.26 (10.15-159.61)	0.25 (0.18-0.35)
Ag-RTD Test Negative	25	105				
Accuracy in patients with ageusia and/or anosmia n = 165						
Ag-RTD Test Positive	84	1	81.55% (72.98-87.86)	98.39% (96.47-100)	50.56 (7.22-354.07)	0.19 (0.12-0.28)
Ag-RTD Test Negative	19	61				

Brazil are mostly black/mixed race, are overall underrepresented in investigations on health, as well as on accuracy assessment of diagnostic tools like Panbio™ Ag-RTD. Such studies are worldwide centered on European and European-derived populations, which might introduce biases derived from ancestry and socioeconomic and sociodemographic characteristics. In spite of that, it should be noted that the presence of anosmia and ageusia, commonly reported in European COVID-19 patients (43), seems to improve the sensitivity of the Panbio™ Ag-RTD in our study population.

Development and validation of POC diagnostic tests with high accuracy would be pivotal for populations like that of Estrutural, Brazil, allowing for quick, efficient, and cheaper diagnosis, as well as mass testing. Tests such as the Panbio™ Ag-RTD could theoretically be used as a mass screening tool and aid a physician to identify and treat infected patients, given its high positive likelihood ratio (LR); nevertheless, its negative LR speaks against it. In scenarios in which patients have negative results in Panbio™ Ag-RTD, a second diagnostic tool (like the RT-LAMP test with 91% of sensitivity described by Jiang et al. (2020) (44), would increase sensitivity by 20%. Regardless, a combination of different diagnostic tools like this (i.e., combined sensitivity) is not feasible for most underrepresented and disadvantaged populations and should always be carefully evaluated before being implemented.

Caveats

It is important to note that our study included mild-to-moderate symptomatic patients; asymptomatic and severe cases were not assessed. However, Brazilian health care centers do not routinely test asymptomatic patients and collecting the two NP swabs from each nostril might not be possible in severe cases. Therefore, we tested the accuracy of the Panbio™ Ag-RTD in a real scenario of primary health care in a socioeconomically vulnerable area in Brazil.

During the collection of NP samples, we faced a methodological conundrum: could the amount of virus in the first swab be greater than the amount of virus in the second swab and, hence, affect the test sensitivity? We cannot answer this question without measuring the viral load in the swabs destined for RT-qPCR and Panbio™ Ag-RTD. Another possibility would be comparing our study and others that used a similar approach for sample collection. However, to our knowledge, the order of swab collection – and if it was collected from one or two nostrils – has not been addressed in any accuracy studies of the Panbio™ Ag-RTD, which limits our capacity to answer that question.

Our collection strategy might have diminished patient enrollment in the study because of the discomfort of NP swab collection. In spite of a large number of refusals, all patients who agreed to participate in our study i) reported symptoms of a very well-described flu-like syndrome, ii) had mild-to-moderate symptoms, and ii) all NP samples for both tests (reference and index) were collected at the same time – which, therefore, discards the possibility of introducing a selection bias based on prior knowledge of the patient's condition of being infected or not infected by SARS-CoV-2. Therefore, we stand behind our choice for the reasons described above, as we followed a rigorous methodology for evaluating the test's accuracy, ensuring biological material from all patients – mainly those who have nasal obstruction due to anatomical variation – was properly collected. In addition, samples collected for RT-qPCR were immediately stored in VTM and kept at 4-6°C until processed on the next day, guaranteeing sample integrity. Samples collected for Panbio™ Ag-RTD were immediately inserted into the test buffer and then dripped on the spot indicated in the membrane strip as per manufacturer's instructions. Finally, our methodological approach for collection and processing ensures biological material from all patients was collected and processed exactly the same way.

Conclusions

Our results show that the Panbio™ Ag-RTD does not meet WHO's interim guidance from October 2021 in our study population. Its sole use at POC could mislead patients with false negative results, who would in turn refrain from adopting isolation and other preventative recommendations. Hence, the apparent benefits from fast, cheap testing are outweighed by the possible harms precipitated by a false sense of security and health, and might hinder control of the spread of SARS-CoV-2 even further in populations where actual isolation and social distancing are nearly unattainable. Therefore, even though Panbio™ Ag-RTD might be useful in specific scenarios (as those recommended by WHO), we do not recommend its implementation as a single diagnostic tool in underrepresented and disadvantaged populations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the Faculty of Medicine at University of Brasília (CEP-FM/UnB, CAAE 39892420.7.1001.5558; CAAE 40557020.6.3001.5553) and

Fundação de Ensino e Pesquisa em Ciências da Saúde (FEPECS/SES/DF, CAAE 40557020.6.3001.5553). The procedures used in this study adhere to the tenets of the Ethical Principles for Medical Research in Human Subjects (Declaration of Helsinki) and the Brazilian regulations on ethics in human research. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

CG: Conceptualization and design of the study, Data acquisition and curation, Formal analysis and interpretation of data, Investigation, Methodology, Validation, Writing (Original draft, Review & Editing), Final approval. RB: Conceptualization and design of the study, Data acquisition and curation, Formal analysis and interpretation of data, Investigation, Methodology, Validation, Writing (Original draft, Review & Editing), Final approval. AT: Conceptualization and design of the study, Data acquisition and curation, Formal analysis and interpretation of data, Investigation, Methodology, Validation, Writing (Original draft, Review & Editing), Final approval. GR: Conceptualization and design of the study, Interpretation of the data, Validation, Resources, Funding acquisition, Writing (Review & Editing), Final approval. PP: Data acquisition, Writing (review & editing), Final approval. WR: Data acquisition, Resources, Funding acquisition, Writing (Review & Editing), Final approval. RH: Data acquisition, Resource, Funding acquisition, Writing (Review & Editing), Final approval. EN: Data acquisition, Resource, Funding acquisition, Writing (Review & Editing), Final approval. WA: Conceptualization and design of the study, Interpretation of data, Investigation, Methodology, Validation, Resource, Funding acquisition, Writing (Review & Editing), Final approval. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fitd.2022.929524/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Flowchart showing the route a patient seeking medical attention with flu-like/respiratory syndrome follows at the primary healthcare center where our study was conducted. The diagram shows the route from triage to enrollment in research (or decline) to diagnosis by RT-qPCR and Panbio™ Ag-RTD testing. *Flu-like/respiratory syndrome is characterized by the presence of at least two non-specific symptoms, such as coughing, sore throat, runny nose, anosmia, ageusia, diarrhea, abdominal pain, fever, chills, myalgia, fatigue, headache

SUPPLEMENTARY FIGURE 2
Violin and boxplots showing results obtained from RT-qPCR and Panbio™ Ag-RTD, as well as agreement/disagreement of said tests over days from symptom onset. Dates were self-declared. Samples were collected from participants within a 3-10 days of symptoms interval

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