PERFORMANCE OF STANDARD™ Q COVID-19 AG AND STANDARD™ F COVID-19 AG FIA COMPARED TO GENES DETECTED BY RT-PCR IN BURKINA FASO

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Abstract

Introduction: Antigen rapid diagnosis tests (Ag RDT) are an alternative to molecular tests for SARS-CoV-2 detection in a context of limited resources. This study aimed to assess the performance of two Ag RDTs compared to the genes detected by RT-PCR.

Methods: This study was conducted during the COVID-19 pandemic from January to May 2021 at the Institut de Recherche en Sciences de la Santé, Burkina Faso. A total of 156 samples were collected, of which 86 tested positive and 70 negative by RT-PCR. It consisted of a technical evaluation of two antigenic rapid diagnostic tests, Standard™ Q COVID-19

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Ag and Standard™ F COVID-19 Ag FIA, compared to the FastPlex™ SARS-CoV-2 detection RT-PCR.

Results: The number of positives detected with each Ag RDT was higher for a single gene than for the two genes detected by RT-PCR (31 vs. 18 and 26 vs. 19). In the presence of two genes (ORF1ab and N), both Ag RDTs are less sensitive (43.9% and 46.3%) than when RT-PCR detects a single ORF1ab or N gene (68.9% and 57.8%). For each Ag RDT, the most positives were detected for samples with high viral loads (Ct<29). Although sensitivities were low, the sensitivity of each Ag RDT was better for higher viral loads.

Conclusion : This study showed a poor performance of the two RDTs, especially in comparative sensitivity and when the RT-PCR detected two genes. Their use should be limited in the context of the high endemicity of COVID-19 and samples with low viral load.

Keywords: SARS-CoV-2, gene ORF1ab, gene N, RDT, RT-PCR, performance

Résumé

Introduction : Les tests de diagnostic rapide (TDR) des antigènes sont une alternative aux tests moléculaires pour la détection du SARS-CoV-2 dans un contexte de ressources limitées. Cette étude visait à évaluer les performances de deux TDR antigéniques par rapport au RT-PCR.

Méthodes : Cette étude a été menée pendant la pandémie de COVID-19 de Janvier à Mai 2021 à l'Institut de Recherche en Sciences de la Santé. Au total, 156 échantillons ont été collectés, dont 86 testés positifs et 70 négatifs par RT-PCR. Elle a consisté en une évaluation de Standard™ Q COVID-19 Ag et Standard™ F COVID-19 Ag FIA, comparés au kit FastPlex™ SARS-CoV-2 detection RT-PCR.

Résultats : Le nombre de positifs détectés avec chaque TDR Ag était plus élevé pour un seul gène que pour les deux gènes détectés par RT-PCR (31 vs. 18 et 26 vs. 19). En présence de deux gènes (ORF1ab et N), les deux tests sont moins sensibles (43,9% et 46,3%) que lorsque la RT-PCR détecte un seul gène ORF1ab ou N (68,9% et 57,8%). Le plus grand nombre de positifs a été détecté avec les échantillons ayant un Ct<29. Bien que les

sensibilités soient faibles, la sensibilité de chaque TDR Ag était meilleure pour les charges virales élevées.

Conclusion : Cette étude a montré une faible performance des deux TDR Ag, en particulier lorsque la RT-PCR a détecté deux gènes. Leur utilisation devrait être limitée dans un contexte de forte endémicité de COVID-19 et des échantillons à faible charge virale.

Mots-clé : SARS-CoV-2, gène ORF1ab, gène N, RDT, RT-PCR, performance

1. INTRODUCTION

COVID-19 is a worldwide pandemic that has plunged thousands of families into mourning, with economic, social, and other consequences [1]. Having had its epicenter in Wuhan, China, the disease quickly spread to the rest of the world [2, 3]. The disease is caused by a virus known as Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV 2), previously unknown to scientists worldwide [4]. Many antigenic rapid diagnostic tests (RDTs) have been developed to facilitate the diagnosis of COVID-19, even in the most remote geographical areas of various countries [5].

Many commercial tests for detecting SARS-CoV-2 RNA (nucleic acid tests or NAT) or viral antigen are currently available, as are serological tests for SARS-CoV-2-specific antibodies. The different types of tests can be used for a variety of purposes. Many hold the CE-IVD certificate indicating compliance with the European directive on in vitro diagnostics (98/79/EC). They can therefore be marketed in European Union (EU) and European Economic Area (EEA) countries [6]. However, choosing the tests best suited to the local context is essential in countries with limited resources. To this end, technical evaluations of the various RDTs are needed to provide data on their performance and facilitate the right decisions [7].

NAT generally requires well-equipped laboratories, many reagents, sample orientation systems, and qualified personnel. Yet

only some countries have such facilities, especially those with limited resources. RDTs, however, are rapid, easy-to-use tests that can be used at the point of care or in peripheral health facilities without the need for expensive laboratory facilities or equipment [8, 9].

Clinical management of infected subjects depends on the quality of SARS-CoV-2 antigen or antibody RDTs and viral load. The need to evaluate these RDTs arises in high RDT circulation. Several studies have already assessed the performance of the Standard™ Q COVID-19 Ag and/or Standard™ F COVID-19 Ag FIA tests, but without making a comparison according to the genes detected by the reverse transcriptase polymerase chain reaction (RT-PCR) used as the gold standard [10-12]. However, for the gold standard used (FastPlex ™ SARS-CoV-2 detection (PreciGenome, San Jose, USA), the diagnosis is positive if both genes are detected or if only one is detected. Comparison of Ag RDTs with RT-PCR could give different performances depending on the number of genes detected by RT-PCR. These results could provide essential additional information when choosing which RDTs to use. Studies have evaluated the performance of certain Ag RDTs, such as Abbott Panbio™ COVID-19 Ag, according to the genes detected by RT-PCR [13].

This study assessed the performance of two Ag RDT Standard™ Q COVID-19 Ag and Standard™ F COVID-19 Ag FIA compared to the genes detected by RT-PCR in Burkina Faso.

2. METHODS

2.1. Study setting

This was a cross-sectional study conducted during the COVID-19 pandemic from January to May 2021 at the Biomedical Research Laboratory (LaReBio) of the Institut de Recherche en Sciences de la Santé (IRSS) in Ouagadougou, Burkina Faso. All tests under evaluation, as well as the reference tests used in this study, were

obtained free of charge. The RDTs and RT-PCR tests were provided by the Ministry of Health for validation and routine diagnosis of

COVID-19 in Burkina Faso, respectively. This study was conducted according to ethics considerations. The Ministry fo health gave approval to use samples collected for the evaluation.

This study consisted of a technical evaluation of two antigenic rapid diagnostic tests, Standard^{TM} Q COVID-19 Ag and Standard^{TM} F COVID-19 Ag FIA (SD BIOSENSOR InC, Republic of Korea). Nasopharyngeal and oropharyngeal samples were collected from symptomatic or asymptomatic subjects in VTM (viral transport medium) tubes to diagnose COVID-19 by RT-PCR. A total of 156 samples were collected, of which 86 tested positive and 70 negative by RT-PCR. Data were collected through notification form.

2.2. Detection of SARS-CoV-2 antigens by RDT

Standard^{TM} Q COVID-19 Ag is a rapid immunochromatographic test for the qualitative detection of SARS-CoV-2-specific nucleoprotein antigens present in the human nasopharynx. It comprises two coated lines: "C" (control line) and "T" (test line) on the surface of the nitrocellulose membrane. Mouse monoclonal anti-SARS-CoV-2 antibodies coat the test line area, and mouse monoclonal anti-chicken IgY antibodies coat the control line area.

A colored test line should appear in the results window if SARS-CoV-2 antigens are present in the sample. If no SARS-CoV-2 antigen is present in the sample, no color will appear on the test line. The control line is procedural and should always appear if the test procedure is started correctly and the control line test reagents are valid. Reading time is 15-30 min. According to the manufacturer, the sensitivity and specificity of the Standard^{TM} Q COVID-19 Ag test are 96.52% and 99.68%, respectively.

Standard™ F COVID-19 Ag FIA is a fluorescent immunoassay for detecting SARS-CoV-2 viral nucleoprotein antigens in human nasopharyngeal swabs. The Standard™ F COVID-19 Ag FIA test was performed with the STANDARD F200 analyzer (SD BIOSENSOR InC, Republic of Korea). The Standard™ F COVID-19 Ag FIA has a test line coated with an anti-COVID-19 monoclonal antibody. The patient's sample is applied to the sample well of the test device, and the sample migrates through the membrane. If the SARS-CoV-2 antigen is present in the patent sample, it will react with the europium-conjugated anti-SRAS-CoV-2 monoclonal antibody in the conjugation buffer and form an antibody-antigen fluorescence particle complex. This complex moves towards the membrane to be captured by the anti-SARS-CoV-2 antibody on the test line and produce a fluorescence signal. The STANDARD F200 analyzer analyzes the intensity of the fluorescence light generated on the membrane. This device analyzes the presence of SARS-CoV-2 in the clinical sample, processing the results using pre-programmed algorithms and displaying the test result on the screen. The sample is said to be "positive" if the numerical representation of the fluorescence signal measurement (COI) is ≥ 1.0 and "negative" if COI<1.0. COI is a numerical representation of the fluorescence signal measurement. The result appears on the analyzer screen after 30 min. The sensitivity and specificity of the Standard™ F COVID-19 Ag FIA test are 100% and 100%, respectively, according to the manufacturer.

2.3. Détection of SRAS-CoV-2 RNA by RT-PCR (Gold Standard)

SARS-CoV-2 RNA was extracted from nasopharyngeal and oropharyngeal samples using the QIAmp viral RNA kit (QIAGEN, USA). Amplification and detection were performed using the FastPlex ™ SARS-CoV-2 detection kit (RT-PCR) (PreciGenome, San Jose, USA) on the HumaCycler thermocycler (Human GmH, Germany) according to the manufacter instrructions.

The FastPlex ™ SARS-CoV-2 detection (RT-PCR) kit is an assay designed for high-precision real-time detection of SARS-CoV-2. The primers and probe have been designed to detect SARS-CoV-2 RNA in patient samples. The test targets two genes, ORF1ab and N, with a detection limit of 285.7 copies/mL and a Ct threshold of 39. The total mix volume was 8µL containing 7µL of SARS-CoV-2-RT-PCR buffer and 1µL of SARS-CoV-2 enzyme mix. The amplification program was : 1 cycle with 50°C for 15 mn ; 1 cycle of 95°C for 1 mn following by 45 cycles of 95°C :15 sec, 60°c : 30 sec. In addition to the target genes, this test includes an internal control gene (RPP30) to validate the result. The result is "Positive" if the threshold value (Ct) ≤39 for each or both genes. The result is "Negative" if Ct>39.

2.4. Statistical analysis

Data were analyzed using OpenEpi software. The performance of each RDT was compared with the Gold Standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were determined with 95% confidence intervals and calculated using Openepi (https://www.openepi.com/). The sensitivity of each RDT was calculated according to the genes detected by RT-PCR and the Ct value categories: Ct ≤ 29 (strongly positive or high viral load): 30 ≤ Ct ≤ 37 (Moderately positive or medium viral load); 30 ≤ Ct ≤ 37 (Weakly positive or low viral load) [14].

3. RESULTS

3.1. Characteristics of the study population

In our study population, men were the most represented with 68.6% (107/156) and the most affected by COVID-19 with 55.1% among positive cases (59/107). Asymptomatic participants were most represented (88.5%).

Table 1: Socio-demographic and clinical characteristics of the study population

Characteristics	Total n=156 (%)	RT-PCR positive n=86 (%)	RT-PCR negative n=70 (%)
Gender			
Male	107 (68.6)	59 (55.1)	48 (44.9)
Female	45 (28.8)	23 (51.1)	22 (48.9)
Missing	4 (2.6)	4 (100)	0 (0.0)
Clinic			
Symptomatic	18 (11.5)	10 (55.6)	8 (44.4)
Asymtomatic	138 (88.5)	79 (55.1)	62 (44.8)

3.2. Comparison of Ag RDT results according to genes detected and Ct RT-PCR categories.

The number of positives detected with each Ag RDT is higher for a single gene than for the two genes detected by RT-PCR (31 vs. 18 and 26 vs. 19) (table 2). In the presence of two genes (ORF1ab and N), both Ag RDTs are less sensitive (43.9% and 46.3%) than when RT-PCR detects a single ORF1ab or N gene (68.9% and 57.8%). Diagnostic accuracy was also higher when only one gene was detected than when both genes were detected simultaneously. Overall, the performance of each Ag RDT is better when a single gene is detected than when both genes are detected simultaneously (Table 3). For each Ag RDT, the most positives were detected for samples with high viral loads (Ct<29) (Table 4). Although sensitivities are low, the sensitivity of each Ag RDT is better for higher viral loads. Overall, the lower the viral load, the lower the performance of each Ag RDT. The performance of Standard™ F COVID-19 FIA was slightly higher than that of Standard™ Q COVID-19 Ag (Table 5).

Table 2: RDT results by gene detected

	Standard™ Q COVID-19 Ag			Standard™ F COVID-19 FIA		
	Both Genes N and ORF1ab	Gene N or ORF1ab	Total	Both Genes N and ORF1ab	Gene N or RF1ab	Total
COVID-19 Ag Positive	18	31	49	19	26	45
COVID-19 Ag Negative	23	14	37	22	19	41
Total	41	45	86	41	45	86

Table 3: performance of RDT Ag compared with genes detected by RT-PCR

Parameters	Standard ™ Q COVID-19 Ag		Standard ™ F COVID-19 Ag FIA	
	Both Genes N and ORF1ab	Gene N or ORF1ab	Both Genes N and ORF1ab	Gene N or ORF1ab
	(95%CI)	(95%CI)	(95%CI)	(95%CI)
Sensitivity	43.9 (29.89 - 58.96)	68.9 (54.33 - 80.47)	46.3 (32.06 - 61.25)	57.8 (43.3 - 71.03)
Specificity	98.6 (92.34 - 99.75)	98.6 (92.34 - 99.75)	94.3 (86.21 - 97.76)	94.3 (86.21 - 97.76)
PPV	94.7 (75.36 - 99.06)	96.9 (84.26 - 99.45)	82.6 (62.86 - 93.02)	86.7 (70.32 - 94.69)
NPV	75 (65.27 - 82.72)	83.1 (73.66 - 89.68)	75 (65.04 - 82.87)	77.6 (67.71 -85.2)
Accuracy of diagnosis	78.4 (69.84 - 85.02)	87 (79.59 - 91.93)	76.6 (67.89 - 83.48)	80 (71.77 -86.29)
PLP	30.7 (3.77 - 250.7)	48.2 (6.60 - 352.3)	8.1 (4.41 - 14.92)	10.1 (5.86 - 17.44)
NLP	0.57 (0.52 - 0.62)	0.32 (0.27 - 0.36)	0.6 (0.52 - 0.62)	0.4 (0.40 - 0.50)
Kappa Coefficient	0.48 (0.31 - 0.64)	0.71 (0.53 - 0.89)	0.45 (0.27 - 0.62)	0.55 (0.38 - 0.73)

Legend : PPV : positive predictive value ; NPV : negative predictive value ; PLR : positive likelihood ratio ; NLP : negative likelihood ratio

Table 4: Standard™ Q COVID-19 Ag and Standard™ F COVID-19 Ag results compared with by Ct values category (viral load)

		Standard ™ Q COVID-19 Ag				**Standard ™ F COVID-19 Ag FIA**			
		Viral load				Viral load			
		High (Ct <29)	Moderate (Ct =30 – 37)	Low (Ct =38 – 39)	Total	High (Ct <29)	Moderate (Ct =30 – 37)	Low (Ct =38 – 39)	Total
COVID-19 Positive	**Ag**	24	17	8	49	26	11	8	45
COVID-19 Negative	**Ag**	14	17	6	37	12	20	9	41

Table 5: Performance of Standard Q COVID-19 Ag and Standard F COVID-19 Ag FIA compared to viral load

Parameters	Standard™ Q COVID-19 Ag			Standard™ F COVID-19 Ag FIA		
	High (Ct <29) (95%CI)	Moderate (Ct=30 – 37) (95%CI)	Low (Ct=38 – 39) (95%CI)	High (Ct <29) (95%CI)	Moderate (Ct=30 – 37) (95%CI)	Low (Ct=38 – 39) (95%CI)
Sensitivity	63.2 (47.28 - 76.62)	50 (34.07 - 65.93)	47.1 (26.16 - 69.04)	68.42 (52.54 - 80.92)	35.5 (21.12, 53.05)	47.1 (26.16, 69.04)
Specificity	94.3 (86.21 - 97.76)	94.3 (86.21- 97.76)	94.29 (86.21 - 97.76)	94.3 (86.21 - 97.76)	94.3 (86.21, 97.76)	94.3 (86.21, 97.76)
PPV	85.7 (68.51 - 94.3)	80.9 (60 - 92.33)	66.7 (39.06 - 86.19)	86.7 (70.32 - 94.69)	73.3 (48.05, 89.1)	66.7 ((39.06, 86.19)
NPV	82.5 (72.74 - 89.28)	79.5 (69.62 - 86.8)	88 (78.74 - 93.56)	84.6 (75.01 - 90.97)	76.7 (66.79, 84.41)	88 (78.74, 93.56)
Accuracy of diagnosis	83.3 (75.19 - 89.19)	79.8 (71.1 - 86.4)	85.1 (76.1 - 91.05)	85.2 (77.28 - 90.67)	76.2 (67.07, 83.48)	85.1 (76.1, 91.05)
PLR	11.05 (6.46 - 18.92)	8.75 (4.78 - 16.03)	8.23 (3.83 - 17.71)	11.97 (7.08 - 20.24)	6.21 (2.751 - 14.01)	8.23 (3.83 - 17.71)
NLP	0.39 (0.34 - 0.45)	0.53 (0.47 - 0.6)	0.56 (0.45 - 0.7)	0.33 (0.28 - 0.39)	0.68 (0.62 - 0.76)	0.56 (0.45 - 0.70)
Kappa Coefficient	0.61 (0.43 - 0.79)	0.49 (0.31 - 0.67)	0.46 (0.26 - 0.67)	0.66 (0.47 - 0.84)	0.35 (0.17 - 0.52)	0.46 (0.26 - 0.67)

Legend : PPV : positive predictive value ; NPV : negative predictive value ; PLR : positive likelihood ratio ; NLP : negative likelihood ratio

4. DISCUSSION

This study evaluated the performance of the StandardTM Q COVID-19 Ag and StandardTM F COVID-19 Ag FIA tests compared with RT-PCR in Burkina Faso. The sex male was the most represented and most affected in our study (68.8%). This confirms that men were the most affected by the COVID-19 pandemic [15, 16]. Asymptomatic subjects were the most numerous (88.5%). The results of the overall performance of the two Ag RDTs have been published, but their comparison according to the genes detected by RT-PCR has yet to be carried out [11]. These results gave a sensitivity of 57% (95% CI: 46.4- 66.9%) and a specificity of 98.6% (95% CI: 92.3- 99.8%) for the Standard™ Q COVID-19 Ag test. The sensitivity and specificity of the StandardTM F COVID-19 Ag FIA test were 52.3% (95%CI: 41.9-62.5) and 94.3% (95% CI: 86.2- 97.8), respectively [11]. The results discussed in this study continue those published in the previous study [11] but focused on the performance of the two Ag RDTs concerning the genes detected. Rapid tests must perform better if a single, two, or three target genes are required to confirm a positive diagnosis by RT-PCR. In this new comparison, we were able to show that both Ag RDTs were less sensitive (43.9% and 46.3%) when both genes were simultaneously detected (ORF1ab and N) than when only one gene (ORF1ab or N) was detected (68.9% and 57.8%). The FastPlex TM SARS-CoV-2 detection (RT-PCR) kit (PreciGenome, San Jose, USA) used as the gold standard targets two genes, ORF1ab and N, and RT-PCR is positive when two genes or a single gene is detected. This may be due to the higher number of positive cases detected with a single gene than with both genes simultaneously. Also, diagnostic accuracy was better for each of the two genes when a single gene was detected than when both were detected simultaneously. In contrast to our study, another study comparing the Abbott Panbio™ COVID-19 Ag test showed that test performance was better with two genes detected simultaneously than with a single gene with the gold Standard ARGENE SARS-CoV-2 R-GENE (BioMérieux, France), which

detects both N (nucleocapsid) and RdRp (RNA-dependent RNA polymerase) genes [13]. The availability of several confirmatory genes has compensated for the sensitivity and specificity of the targets [17]. Genetic mutations induced in these genes, leading to the appearance of SARS-CoV-2 variants, could influence the performance of Ag RDTs [18].

For each Ag RDT, the number of positive samples with a high viral load (Ct<29) was the most numerous. For the Standard™ Q COVID-19 Ag test, sensitivity was 63.2% (95%CI: 47.28 - 76.62) when the viral load was high (Ct<29) and 47.1% (95%CI: 26.16 - 69.04) when the viral load was low (Ct: 38 - 39). Also, for the Standard™ F COVID-19 Ag FIA test, sensitivity was 68.42% (95%CI: 52.54 - 80.92) at high viral load (Ct<29) and 47.1% (95%CI: 26.16, 69.04) at low viral load (Ct: 38 - 39). Overall, the lower the viral load, the lower the performance of each Ag RDT. This has also been observed in other studies [19-24]. These results show that both Ag RDTs have a low capacity to detect a genuine case with a low viral load, whether in the early stages of infection or the recovery phase of COVID-19. These tests may, therefore, diagnose false-negative individuals. Indeed, studies have shown false negatives with antigenic tests in people with lower viral loads [9, 25, 26]. Kappa values in our study indicated moderate agreement between the two AgRDT and RT-PCR. his shows that the two tests are not very reliable. So, using these tests in situations of high COVID-19 prevalence would not be recommended. This study, conducted in a laboratory context with stored samples for RDT, may be a limitation. Studies on specific populations, such as symptomatic, asymptomatic, or hospitalized cases, could provide more conclusive results on the performance of these two Ag RDTs in Burkina Faso.

5. CONCLUSION

This study investigated the performance of two Ag RDTs in a laboratory setting. The results showed the poor performance of the RDTs, especially in comparative sensitivity, and when the RT-PCR detected two genes (ORF1ab and N) of SARS-CoV-2. Also, these two Ag RDTs could have been more reliable regarding Kappa coefficient values. Their use should be limited in the context of the high endemicity of COVID-19 and asymptomatic individuals.

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CONFLIT OF INTEREST

The author declate they have no conflit of interest.

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