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OPINION ARTICLE

The Role of Antigen Rapid Diagnostic Test in COVID-19 Diagnosis

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Abstract:

Since the emergence of a novel infection due to the SARS-CoV-2 virus (COVID-19), the World Health Organization has urged countries to develop diagnostic tests to combat the pandemic. Molecular assays were developed following the release of the gene sequence of the virus in January 2020. Reverse transcription-quantitative PCR (RT-qPCR) is taken as the gold standard for the diagnosis of COVID-19. However, due to its limitations, highly sensitive methods for detecting antigens (antigen rapid diagnostic tests) have been developed that would help in a timely and accurate diagnosis. Antigen rapid diagnostic tests (Ag-RDTs) can help guide patient management at the point of care by random screening, re-testing, and timely decision-making in the field of public health. When the affordability and validity of the diagnostic assay are involved, no assay can show 100% correct results. Further studies need to be done to better understand the response of the Ag-RDTs in different settings. Nevertheless, Ag-RDTs can play a complementary role in the response and case management of COVID-19.

Keywords: COVID-19, SARS-CoV-2, Antigen rapid diagnostic test, Sensitivity, Specificity, PCR.

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1. INTRODUCTION

Coronavirus disease 2019, COVID-19, emerged from the Wuhan province of China at the end of 2019 [1], and the World Health Organization (WHO) declared it as a pandemic on March 11th, 2020 [2]. To combat the pandemic, Tedros Adhanom Ghebreyesusm, the Director-General of WHO, appealed to countries to perform extensive testing [3]. Rapid identification and isolation of patients were needed for curbing the spread of COVID-19 [1]. The gene sequence of SARS-CoV-2, which was responsible for COVID-19, was published in January 2020 [4].

Most of the tests that were developed to detect SARS-CoV-2 relied on viral RNA amplification. The tests typically use polymerase chain reaction (PCR) to detect viral RNA. These molecular tests are highly sensitive and specific. Reverse transcription-quantitative PCR (RT-qPCR) through nasopharyngeal swabs, throat swabs, or saliva is considered the gold standard for the diagnosis of COVID-19 [5]. Most of these tests require robust laboratory infrastructure and highly skilled laboratory personnel. The test results are usually available within 2 hours but may extend up to 7 days due to obvious reasons [6]. This led to the need for highly sensitive immunological diagnostic methods, which detect on-site viral antigens in clinical specimens that would help in early and accurate diagnosis of COVID-19 [7].

Ag-RDTs diagnose SARS-CoV-2 active infection by the detection of viral proteins in different types of specimens. These are lateral flow, single-use, rapid tests that are processed or visually read using a small compact device [4]. Ag-RDTs can be performed in various settings, including off-laboratory, by following the manufacturer's instructions and the result can be achieved within 15-20 min. These tests can be carried out at a much faster rate and are also cheaper for extensive implementation [4]. Even though these rapid tests are very specific, they are not as sensitive as molecular assays [4]. Despite having lesser sensitivity than molecular tests, Ag-RDT appears beneficial in guiding patient management at the point of care and also for random screening or re-testing; this helps in making timely public health decisions in order to curb the transmission of the virus [8].

Table **1** shows some of the available COVID-19 Ag-RDTs made available by different manufacturers, their sensitivity & specificity, and specimens on which these tests can be performed. As of March 2021, the rapid tests that received US Food and Drug Administration (FDA) Emergency Use Authorization (EUA) is shown in Table (**2**) [9].

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Table 1. Some of the available COVID-19 antigen rapid diagnostic tests [4].

Manufacturer	Sensitivity/ Specificity*	Specimen Collected	US FDA Emergency Use Authorization (EUA)	WHO Emergency Use Listing
Abbott BinaxNOW, USA	97%/99%	Nasal swab	Yes	Yes
Abbott Panbio, USA	93%/99%	Nasal swab, nasopharyngeal swab	-	Yes
Access Bio CareStart, USA	88%/100%	Nasal swab, nasopharyngeal swab	Yes	-
BD Veritor, USA	84%/100%	Nasal swab	Yes	-
LumiraDx, UK	98%/97%	Nasal swab	Yes	-
Quidel Sofia Flu and SARS Antigen Fluorescent Immunoassay, USA	95%/100%	Nasal swab, nasopharyngeal swab	Yes	-
SD Biosensor, South Korea	97%/100%	Nasal swab, nasopharyngeal swab	-	Yes
Ellume COVID-19 Home Test, Australia	95%/97%	Nasal swab	Yes	-
Clip COVID Rapid Antigen Test, luminostics, Inc. USA	97%/100%	Nasal swab	Yes	-

Table modified from the article published by Peeling *et al*. [4].
FDA: Food and Drug administration *Data from manufacturers.

Table 2. Antigen rapid diagnostic tests that received US FDA Emergency Use Authorization (EUA) [9].

Manufacturer	Antigen Rapid Diagnostic Tests	EUA Originally Issued Date	Characteristics
Quidel Corporation	QuickVue At-Home COVID-19 Test	3/1/2021	Lateral Flow, Visual Read, Prescription Home Testing
Princeton BioMeditech Corp.	Status COVID-19/Flu	2/4/2021	Lateral Flow, Visual Read, Multi-analyte
Quidel Corporation	QuickVue SARS Antigen Test	12/18/2020	Lateral Flow, Visual Read
Abbott Diagnostics Scarborough, Inc.	BinaxNOW COVID-19 Ag Card Home Test	12/16/2020	Lateral Flow, Visual Read, Prescription Home Testing
Ellume Limited	Ellume COVID-19 Home Test	12/15/2020	Lateral Flow, Fluorescence, Instrument Read, Over the Counter (OTC) Home Testing, Screening
Luminostics, Inc.	Clip COVID Rapid Antigen Test	12/7/2020	Lateral flow immunoluminescent assay, instrument read
Access Bio, Inc.	CareStart COVID-19 Antigen test	10/8/2020	Lateral Flow, Visual Read
Quidel Corporation	Sofia 2 Flu + SARS Antigen FIA	10/2/2020	Lateral Flow, Fluorescence, Instrument Read, Multi-Analyte
Abbott Diagnostics Scarborough, Inc.	BinaxNOW COVID-19 Ag Card	8/26/2020	Lateral Flow, Visual Read
LumiraDx UK Ltd.	LumiraDx SARS-CoV-2 Ag Test	8/18/2020	Microfluidic Immunofluorescence Assay, Instrument Read
Becton, Dickinson and Company (BD)	BD Veritor System for the Rapid Detection of SARS-CoV-2	7/2/2020	Chromatographic Digital Immunoassay, Instrument Read

Adapted from US Food and Drug Administration, Individual EUAs for Antigen Diagnostic Tests for SARS-CoV-2 [9].

Even though the Ag-RDTs approved by WHO or US FDA for emergency use show a consistent performance constant, the independent Ag-RDTs evaluation carried out by the foundation for innovative new diagnostics (FIND) showed that their performance differs in different countries based on the assessment panel and the viral load in the study samples [4, 10].

Several Ag-RDT studies have been conducted globally. Lambert-Niclot *et al*. reported a sensitivity of 50% with COVID-19 Ag Respi-Strip (Coris) compared to RT-PCR. They stated that the test was more sensitive to high viral loads and can be used within a few days of the onset of symptoms [7]. Whereas a study from Belgium reported that Coris COVID-19 Ag Respi-Strip rapid test showed a higher antigen detection rate that correlates with higher viral loads, but this study also suggested that the test's low sensitivity precludes its use as the first-line test for COVID-19 [11]. Mak *et al*. in China, evaluated the performance of BIOCREDIT COVID-19 Ag test with RT-PCR for SARS-CoV2. According to them, the rapid test detected between 11.1% and 45.7% of RT-PCR-positive samples. They suggested the use of the rapid test as an additional test to RT-PCR [12]. Another study by Kruttgen *et al*. compared the Ag-RDTs to RT-PCR kit and concluded that the sensitivity and specificity of the antigen assay are lower than the PCR assay. Nevertheless, they concluded that rapid antigen testing is a quick and easy-to-use approach that permits individuals who are contagious for SARS-CoV-2 to be separated from less or non-contagious individuals [13]. A field study by Albert *et al*. [14] found Panbio™ COVID-19 Ag-RDT to perform well in primary health centers for the early diagnosis of COVID-19. Notably, their data indicated that

Table 3. Some field studies on rapid antigen diagnostic tests.

Studies	Rapid Antigen Test Kits Used	Results	Conclusion
Peto *et al*. (2021) [23]	Deepblue, orient Gene, Abbott and Innova SARS-CoV-2 Antigen Rapid Qualitative Test	Viral antigen sensitivity was 78.8% (156/198, 95% CI: 72.4 - 84.3)	Lateral Flow Devices results are promising for large-scale population testing and identifying infectious positive individuals.
Yin *et al*. (2021) [24]	Panbio™ COVID-19 Ag Rapid Test Device, BD Veritor™ SARS-CoV-2, COVID-19 Ag Respi-Strip and SARS-CoV-2 Rapid Antigen Test (SD Biosensor)	All the rapid tests showed a sensitivity of 83.3% (95% CI: 78.2-87.4%).	Rapid tests can be used to cover a large target population by considering into account the ease to use, readiness of reagents and the rapid result, and molecular assays can be used for severely ill patients.
Matsuda *et al*. (2021) [25]	COVID-19 Ag ECO Test and Panbio COVID-19 Ag Rapid Test Abbott	Both the rapid tests' overall sensitivity was 87%, and specificity was 96%.	The rapid tests have an important role in improving testing strategies, notably in resource-constrained regions.
Francis VR and Muthugala MARV (2021) [26]	STANDARD Q COVID-19 Ag test, SD Biosensor,	The overall sensitivity of the kit was 58.5% (95% CI: 44, 72) and specificity was 100%.	The rapid antigen test can be used as a primary screening test for community surveillance.

patients with RT-PCR-proven Ag-RDT negative for COVID-19 are highly doubtful to be infectious. They reported that false-negative Ag-RDT results may be uncertain from a public health perspective, but a diagnostic approach that missed the RT-PCR confirmation of negative Ag-RDT tests in non-hospitalized patients might reduce laboratory workloads when there is a shortage of RT-PCR tests [14]. Some other field studies on Rapid Antigen tests are summarized in Table **3**.

A study in Spain reported the overall sensitivity of 48.1% with the Panbio™ COVID-19 Ag-RDT for the identification of SARS-CoV-2-infected individuals among asymptomatic close contacts of confirmed COVID-19 cases [15], which was similar to the data published by Linares *et al*. (54.5%) [16], Fenollar *et al*. (45.4%) [17], Bulilete *et al*. (59.0%) [18]. Porte *et al*. [19] evaluated the fluorescence immunochro-matographic SARS-CoV-2 antigen test (Bioeasy Biotechnology Co., Shenzhen, China) during the first weeks of the outbreak in Chile, through oropharyngeal and nasopharyngeal swabs from suspected COVID-19 patients. They concluded that Ag-RDT carried on samples during the first week of symptoms and with high viral loads showed high sensitivity and specificity. They also proposed the use of Ag-RDT as an important tool for the early diagnosis of SARS-CoV-2, particularly when the molecular assays are limited [19]. A study from Thailand reported that SARS-CoV-2 Ag-RDT (StandardTM Q COVID-19 Ag kit) showed similar sensitivity (98.33%; 95% CI, 91.06-99.96%) and specificity (98.73%; 95% CI, 97.06-99.59%) with the RT-PCR assay. They suggested the use of Ag-RDT as a screening test, mainly in highly prevalent regions [20]. Many rapid antigen tests currently lack robust analytical sensitivity data when compared to reverse transcription-quantitative PCR (qRT-PCR). Perchetti *et al*. used SARS-CoV-2-positive samples to assess the analytical sensitivity of the Abbott BinaxNOW COVID-19 Ag card, and they noticed that BinaxNOW COVID-19 Ag card was roughly equivalent to a generic qRT-PCR cycle threshold (CT) value of 29 to 30 [21]. Another study by Eshghifar *et al*. reported that rapid antigen tests have low analytical and clinical sensitivity for identifying asymptomatic patients (low viral load). As a result, they proposed that the analytical sensitivity of rapid antigen tests be thoroughly assessed before being used in clinical settings [22].

CONCLUSION

To ensure proper patient management and public health action, countries need to maintain a balance between benefits and risk outcomes of rapid Ag-RDT. When the affordability and validity of the diagnostic assay are involved, no assay can show 100% correct results. More research is needed to better understand the validity of rapid Ag-RDTs in various settings and to know how often and when to use these tests. This would support testing strategies and health policies and would disrupt the transmission of disease. However, antigen rapid diagnostic tests can play a supporting role in the management of the COVID-19 pandemic.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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