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

Ronni Mol Joji¹ and Mohammad Shahid*¹

¹Department of Microbiology, Immunology & Infectious Diseases, College of Medicine & Medical Sciences, Arabian Gulf University, Manama, Kingdom of Bahrain

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.

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].
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 BIOCREST 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
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], Bulilet et al. (59.0%) [18], Porte et al. [19] evaluated the fluorescence immuno-chromatographic 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 (rRT-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

Not applicable.

### FUNDING

None.

### CONFLICT OF INTEREST

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

### ACKNOWLEDGEMENTS

Declared none.

### REFERENCES

1. Yamayoshi S, Sakai-Tagawa Y, Koga M, et al. Comparison of rapid antigen tests for COVID-19. Viruses 2020; 12(12):1420. [http://dx.doi.org/10.3390/v12121420] [PMID: 33322035]
2. Lee J-K. We cannot go back to the old world, before global pandemic declaration of the COVID-19 pandemic: Developing new normal practices in society. Osong Public Health Res Perspect 2020; 11(4):147-8. [http://dx.doi.org/10.24171/j.phrp.2020.11.4.01] [PMID: 32864303]
3. WHO. Director general’s opening remarks at the March 16, 2020 media briefing 2020. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19---16-march-2020
4. Pooling RW, Olliaro PL, Boeras DI, Fongwen N. Scaling up COVID-19 rapid antigen tests: Promises and challenges. Lancet Infect Dis 2021; 21(9): e290-5. [http://dx.doi.org/10.1016/S1473-3099(21)00048-7] [PMID: 33636148]
COVID-19 Rapid Antigen Tests

The Open COVID Journal, 2021, Volume 1

[5] Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA 2020; 323(22): 2249-51. [PMID: 32374370]

[6] McGarry BE, Steel/Fisher GK, Grabowski DC, Barnett ML. COVID-19 test result turnaround time for residents and staff in us nursing homes. JAMA Intern Med 2020; 180(4): 556-9.

[7] Lambert-Niclot S, Cufell A, Le Pape S, et al. Evaluation of a rapid diagnostic assay for detection of SARS-CoV-2 antigen in nasopharyngeal swabs. J Clin Microbiol 2020; 58(8): e00977-20. [PMID: 32404480]

[8] Centers for Disease Control Prevention (CDC). Interim guidance for rapid antigen testing for SARS-CoV-2 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-test-s-guidelines.html

[9] US food and drug administration. Coronavirus disease 2019 (COVID-19) emergency use authorizations for medical devices 2020. Available from: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covi-d-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-eua#individual-antigen

[10] FIND. Field evaluation of SARS-CoV-2 Available from: https://www.fndx.org/COVID-19/sarscov2-eval/

[11] Scohy A, Anantharajah A, Bodeu M, Kabambu-Mukadi B, Verroken M, Vander Elst E, et al. Field evaluation of a rapid antigen test (Panbio™ COVID-19 Ag rapid test device) for SARS-CoV-2 virus. J Clin Virol 2020; 129: 104455.

[12] Mak GC, Cheng PK, Lau SS, et al. Evaluation of rapid antigen test for detection of SARS-CoV-2 virus. J Clin Virol 2020 Aug 1; 129: 104500.

[13] Krüttgen A, Cornelissen CG, Dreher M, Horneck MW, Imböl M, Kleines M. Comparison of the SARS-CoV-2 rapid antigen test to the real star Sars-CoV-2 RT PCR kit. J Virol Methods 2021; 288: 114024. [PMID: 33227341]

[14] Albert E, Torres I, Bueno F, Huntley D, Molla E, Fernández-Fuentes MÁ, et al. Field evaluation of a rapid antigen test (Panbio™ COVID-19 Ag Rapid Test Device) for COVID-19 diagnosis in primary healthcare centres. Clin Microbiol Infect 2020; S1189-743X(20): 30697-2.

[15] Torres I PS, Albert E, Colomina J, Navarro D. Evaluation of a rapid antigen test (Panbio™ COVID-19 Ag rapid test device) for SARS-CoV-2 detection in asymptomatic close contacts of COVID-19 patients. Clin Microbiol Infect 2021; 27(4): 636. e1-e4

[16] Linares M, Pérez-Tancorao R, Carrero A, et al. Panbio antigen rapid test is reliable to diagnose SARS-CoV-2 infection in the first 7 days after the onset of symptoms. J Clin Virol 2020; 133: 104659. [PMID: 33160179]

[17] Fenollar F, Bouam A, Ballouche M, Fuster L, Prudent E, Colson P, et al. Evaluation of the Panbio COVID-19 rapid antigen detection test device for the screening of patients with COVID-19. J Clin Microbiol 2020; 59(2): e02589-20. [PMID: 33139420]

[18] Baulite O, Lorente P, Leiva A, Carandell E, Oliver A, Rojo E, et al. Evaluation of the Panbio rapid antigen test for SARS-CoV-2 in primary healthcare centers and test sites medRivx 2020. [PMID: 32497809]

[19] Porte L, Legarrarra P, Vollrath V, et al. Evaluation of a novel antigen-based rapid detection test for the diagnosis of SARS-CoV-2 in respiratory samples. Int J Infect Dis 2020; 99: 328-33. [PMID: 32497809]

[20] Chaimayo C, Kaewnaphan B, Tanieng N, et al. Rapid SARS-CoV-2 antigen detection assay in comparison with real-time RT-PCR assay for laboratory diagnosis of COVID-19 in Thailand. Virol J 2020; 17(1): 177. [PMID: 33187528]

[21] Perchetti GA, Huang M-L, Mills MG, Jerome KR, Greninger AL. Analytical sensitivity of the abbott BinaxNOW COVID-19 Ag card. J Clin Microbiol 2021; 59(3): e00880-20. [PMID: 3310764]

[22] Eshghifar N, Busheri A, Shretha R, Beqq S. Evaluation of analytical performance of seven rapid antigen detection kits for detection of SARS-CoV-2 Virus. Int J Gen Med 2021; 14(14): 435-40. [PMID: 3360450]

[23] Peto T, Affron D, Aforough B, et al. COVID-19: Rapid antigen detection for SARS-CoV-2 by lateral flow assay: A national systematic evaluation of sensitivity and specificity for mass-testing. E Clinical Medicine 2021 May 30; 100924. [PMID: 34101770]

[24] Yin N, Debuyschere C, Decroly M, et al. SARS-CoV-2 Diagnostic Tests: Algorithm and field evaluation from the near patient testing to the automated diagnostic platform. Front Med (Lausanne) 2021; 8(380): 650581. [PMID: 3388587]

[25] Mateuda EM, de Campos IB, de Oliveira IP, Colpas DR, Carmo AMDS, Bridigo LFM. Field evaluation of COVID-19 antigen tests versus RNA based detection: Potential lower sensitivity compensated by immediate results, technical simplicity, and low cost. J Med Virol 2021; 93(7): 4405-10. [PMID: 34101770]

[26] Francis VR, Muthugula MARV. Field evaluation of a commercially available COVID-19 rapid antigen test kit. Sri Lankan J Infec Dis 2021; 11(1): 13-7. [PMID: 34101770]