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Original Article

The Performance of Antigen-detecting Rapid Diagnostic Test Among COVID-19 Outbreaks in North-Eastern Peninsular Malaysia

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Abstract

Background and aims: Accurate and timely diagnosis is crucial for coronavirus disease 2019 (COVID-19) outbreaks. Antigen-detecting rapid diagnostic tests (Ag-RDTs) are easily accessible and affordable, producing rapid results. They are an alternative to the limited gold-standard real-time reverse-transcription polymerase chain reaction (rRT-PCR) tests. This study assessed the performance of Ag-RDTs for COVID-19 outbreaks in institutional settings with high disease prevalence in Kelantan State, Malaysia.

Methods: This study analyzed a total of 303 individuals from five institutional outbreaks with paired nasopharyngeal specimens tested for COVID-19 by Ag-RDTs and rRT-PCR. The diagnostic performance of Ag-RDTs was evaluated through rRT-PCR as the gold standard based on cycle threshold (Ct) value, disease prevalence, and manufacturers.

Results: There was a moderate agreement between Ag-RDTs and RT-PCR ($\kappa = 0.603$; 95% CI: 0.520-0.686; $P < 0.001$). The overall specificity was 97.9% (95% CI: 94.1%-99.6%), sensitivity was 63.3% (95% CI: 55.3%-70.8%), accuracy Ag-RDTs was 81.2% (95% CI: 76.4%-85.5%), while positive and negative predictive value was 96.6% (95% CI: 90.2%-98.9%) and 74.1% (95% CI: 70.0%-77.9%), respectively. Further, lower median Ct was reported in 100 (33.0%) true-positive cases compared to 58 (19.1%) false-negative cases (20.3 vs 31.4, $P < 0.001$). The sensitivity was higher ($P < 0.001$) in those with high viral load (Ct value ≤ 25.0) with better performance and a prevalence > 10%. In addition, no significant difference was observed between the studied manufacturers.

Conclusion: The Ag-RDTs performed well in diagnosing COVID-19 among outbreaks with higher viral load and disease prevalence. High-risk cases tested negative by Ag-RDTs may have low viral load and require confirmation by rRT-PCR.

Keywords: Accuracy, COVID-19, Diagnostic performance, Rapid antigen test

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was identified in December 2019, causing the coronavirus disease 2019 (COVID-19) pandemic with over 273 million confirmed cases and 5.3 million reported deaths worldwide.[1] An accurate and timely diagnosis of COVID-19 is crucial for effective prevention and controlling strategy of the COVID-19 pandemic. It is vital to correctly identify those diagnosed with the disease to assure that appropriate public health interventions are being carried out.[2] A false-negative result not only hinders the treatment for the infected individual, but more importantly, it will contribute to the spreading of the disease.[2] It is also important to rule out those without the disease to avoid unnecessary treatment, quarantine, or exposure to other confirmed cases that are being quarantined at the same place.[3] Although diagnostic accuracy plays an important role in managing the said pandemic, diagnostic efficiency is just as important. In addition, laboratory testing is also required for screening and surveillance purposes.

The gold standard for the diagnosis of COVID-19 is the highly accurate nucleic acid amplification tests (NAATs), especially the real-time reverse-transcription polymerase chain reaction (rRT-PCR) that is based on the detection of unique sequences of virus RNA.[4] The process of doing rRT-PCR is complex and requires costly experimental devices, testing reagents, and highly trained personnel, often limiting the test only to centralized laboratories. Although the laboratory turnaround time is only around 4-6 hours, the logistic requirement for the samples to be sent to the respective laboratories and

later processed in batches causes delays in obtaining the result, often exceeding 24 hours.[5] Computed tomography was suggested to be able to detect COVID-19 disease with around 87% sensitivity and 46% specificity, with higher sensitivity reported in the pneumonia stage, but it is costly and not widely available.[6,7]

More modalities are coming forward and being made commercially available. The antigen-detecting rapid diagnostic tests (Ag-RDTs) are suggested to be reliable alternatives to NAATs in diagnosing COVID-19.[3] The Ag-RDTs are less expensive, are simple to use, can be done in a wide range of setting to achieve high coverage of testing, and produce rapid results.[8,9] However, the performance of Ag-RDTs varies in different circumstances influenced by viral loads, age, symptoms, the timing of sampling based on the duration of symptoms, and manufactures.[3,10] The sensitivity of Ag-RDTs was also reported to be higher for upper respiratory samples compared to the sensitivity of other clinical specimens.[11] The management of the patient through any Ag-RDTs result is not only dependent on the test performance but also on the disease prevalence since low positive predictive values are often observed in a low transmission setting.[3]

Kelantan is a state located in north-eastern Peninsular Malaysia that has experienced surges of COVID-19 cases since early 2021. An increasing number of outbreaks occurring at multiple institutions associated with high transmission rates was observed. As the cases increased, the number of laboratory testing was amplified, causing overburdens on centralized state laboratories running the rRT-PCR and resulting in delays in achieving the result. Ag-RDTs are useful tools to support the investigation, especially in managing outbreaks with higher transmission rates, as large-scale screening and rapid case detections allow early implementation of appropriate infection control measures and case management.[12,13] Although Ag-RDTs were very advantageous in this setting, the data on their field performance was quite limited at the time of conducting this study. Nonetheless, the reliability of Ag-RDTs must be evaluated thoroughly. The WHO target product profile for Ag-RDTs aimed at sensitivities over 80% and specificities over 97%.[14] The center for disease control along with the Malaysia Ministry of Health recommended that independent and setting-specific evaluations be made before carrying out the widespread implementation of Ag-RDTs as diagnostic testing.[15,16] This study aimed at evaluating the diagnostic performance of Ag-RDTs for COVID-19 diagnosis among individuals exposed to SARS-CoV-2 infection during institutional outbreaks in Kelantan, specifically to assess the variation of performance based on different disease prevalence, viral load, and manufacturers.

Materials and Methods

Study Design

An analytical cross-sectional study was carried out in Kelantan from February 2021 to June 2021. As part of the routine contact tracing activities and outbreak investigations, 310 individuals that were epidemiologically linked to randomly selected active COVID-19 institutional outbreaks were identified. These institutions were a prison, a correctional facility, and three boarding schools in Kelantan with no previous positive results within three months. Three individuals with inconclusive rRT-PCR results and four individuals with invalid Ag-RDTs results were further excluded from statistical analysis.

Specimen Collection

The randomly selected individuals had paired nasopharyngeal swabs taken in the same setting on the same day with a couple of hours gap but with at least an hour interval between the two specimens. All of the samples included in this analysis were collected by trained government health personnel that were following specific instructions of sampling for each test and wearing adequate personal protective equipment. The clinical specimen tested by Ag-RDTs were obtained using the swab provided along with the respective Ag-RDTs kit. Conversely, another sample obtained from the nasopharyngeal swabs using the standard flocked swabs was placed into sterile tubes containing the virus transport media and further transported to the centralized laboratories on the same day to be tested by rRT-PCR for the SARS-CoV-2 virus.

Testing by Ag-RDTs

The nasopharyngeal swabs collected at the site were transported to the nearest government health clinics that adhered to the bio-safety requirements on the same day. The obtained samples were tested for SARS-CoV-2 virus by either one of the two commercially produced Ag-RDTs that were widely available at government health clinics. Both kits are lateral flow chromatographic immunoassays for the qualitative detection of SARS-CoV-2 antigens. The samples were processed for the Ag-RDTs test by trained medical lab technicians according to the test-specific instructions by the manufacturer with a specified reagent used for a specific kit. The result was interpreted and verified by trained healthcare personnel and further reported to the health authorities via the national public health laboratory reporting system. An Ag-RDT was interpreted as positive based on the guideline provided by the manufacturers.

Testing by rRT-PCR

The collected samples were transported to one of two centralized laboratories that were certified to run rRT-PCR tests for SARS-CoV-2 detection. The nucleic acid extraction process was performed using either manual or automated extraction based on the magnetic beads principle and processed immediately or stored at -80°C. The specific rRT-PCR assay was performed by targeting the RdRP, S, N, E, or ORF1ab genes using either an in-house method or a commercial kit (GenoAmp® Real-Time

RT-PCR SARS-CoV-2 or LyteStar 2019-nCoV RT-PCR). The genome amplification was performed on a Bio-Rad CFX96 machine. The SARS-CoV-2 virus was considered detectable by rRT-PCR when at least two different targeted viral genes were detected by the test based on the manufacturer's recommendations.

Data Entry and Statistical Analysis

The sample size was calculated with an estimated area under the curve (AUC) of 0.836,[17] precision level of 0.05, 95% confidence interval (CI), and expected sensitivity of around 85%.[18] The true positive (TP) + false negative (FN) were calculated for sensitivity and the true negative (TN) + false positive (FP) for specificity through the following equation: $TP+FN=Z^2\ x\ Sensitivity\ (1-Sensitivity)\ /W^2$; where Z, the normal distribution value, was set to 1.96 as corresponding with the 95% CI, and W, the maximum acceptable width of the 95% CI, was set to 10%.[19] The required sample size was further calculated using the following equations: $(TP+FN)/P$.[19] Further, the variance of nonparametric AUC (Wilcoxon statistic) used in sample size calculation based on AUC was estimated using the methods proposed by Bamber using exponential approximation through Hanley and McNeil formula.[20]

The data were handled in line with the guidelines by the Malaysia Ministry of Health. The relevant demographic data (e.g., age, gender, symptomatic or asymptomatic, risk categories, and epidemiological link with any outbreak/confirmed cases), sampling, testing, and the results were registered in the National Crisis Preparedness and Response Centre (CPRC) database and the nation-wide E-COVID portal. The relevant information concerning the outbreaks included in the study was obtained from the outbreak reports produced by the state CPRC. The data were extracted from both databases and collated into a line listing by Microsoft Excel version 2019. The cleaned data were then imported to SPSS version 25.0 for statistical analysis.

The agreement between Ag-RDTs and rRT-PCR was measured using Cohen's kappa score. The diagnostic accuracy of Ag-RDTs was reflected by the sensitivity, specificity, negative predictive value, positive predictive value, and likelihood ratios, and the respective 95% CI was estimated using rRT-PCR as the reference standard. The receiving operative characteristic curve was constructed using the overall sensitivity (TP rate) vs 1-specificity (FP rate), and the respective AUCs were calculated. Sensitivity was also evaluated according to the cycle threshold (Ct) value for different intervals (high viral load: Ct ≤ 25.0; medium viral load: Ct = 25.1-29.9; low viral load: Ct ≥ 30.0).[21] Any variation of sensitivity among outbreaks with different disease prevalence was also observed. The linear relationship between sensitivity and Ct value as well as disease prevalence was measured by the Pearson correlation test. The predictive values were estimated using the disease prevalence for each outbreak and were determined based on the result of rRT-PCR test carried out prior to the study as part of the initial outbreak investigation. The turnaround time was measured by the day difference between sample collections and test results. Further, descriptive data were expressed as mean and standard deviation (SD) for normally distributed variables or median with interquartile range (IQR) for skewed data, while categorical data were expressed as frequency and percentage. The student t-test was used to compare means, while the Mann-Whitney U test was used to compare median. Then, categorical variables were compared using the chi-square or Fisher's exact test. A 2-sided $P < 0.05$ was considered statistically significant.

Results

A total of 303 eligible individuals from five different institutional outbreaks were included in the analysis. The characteristics of the studied population are presented in Table 1. A total of 103 (34.0%) individuals had positive Ag-RDTs, while 158 (52.1%) had positive rRT-PCR. One of the three individuals excluded from statistical analysis due to inconclusive rRT-PCR results had a positive Ag-RDT test, whereas all four individuals with invalid Ag-RDTs results had a negative rRT-PCR test. The turnaround time for Ag-RDTs was less than a day for all samples. Meanwhile, the average turnaround time for rRT-PCR was two days. Further, the result was obtained from sample collection within a day for 103 (30.4%) individuals, two days for

Table 1. The Characteristic of the Study Population (n = 303)

Characteristics		n (%)
Age, years		16.0 (16.0)*
Gender	Male	206 (68.0)
	Female	97 (32.0)
Symptoms	Symptomatic	51 (16.8)
	Asymptomatic	201 (66.4)
	Unknown	51 (16.8)
Outbreaks	A (boarding school)	56 (18.4)
	B (boarding school)	46 (15.2)
	C (boarding school)	49 (16.2)
	D (correctional facility)	49 (16.2)
	E (prison)	103 (34.0)
Ag-RDTs results	Positive	103 (34.0)
	Negative	200 (66.0)
RT-PCR results	SARS-CoV-2 detected	158 (52.1)
	SARS-CoV-2 not detected	145 (47.9)
Ct value (all cases)		25.1 (10.9)*
	Outbreak A	21.0 (7.3)*
	Outbreak B	25.1 (9.5)*
	Outbreak C	20.4 (14.9)*
	Outbreak D	20.3 (7.8)*
	Outbreak E	30.9 (4.9)*

Note. Ag-RDTs: Antigen-detecting rapid diagnostic tests; RT-PCR: Reverse transcription polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; Ct: Cycle threshold.
*Median (Interquartile range).

154 (50.8%) individuals, and three days for 46 (15.2%) individuals. As Figure 1 illustrates, the transportation distance from the collected samples to the laboratories to be processed was significantly shorter for Ag-RDTs testing (M = 9.8 km, SD =10.8 km) compared to that for rRT-PCR (M = 29.2 km, SD = 9.8 km, t (4) = 2.4, P = 0.043).

Overall Diagnostic Performance of Ag-RDTs

There was a moderate agreement between Ag-RDTs and rRT-PCR in overall samples (κ = 0.603, 95% CI: 0.520-0.686, P < 0.001), but the agreement was significant among cases with high viral load (Ct value ≤ 25) samples (κ = 0.899, 95% CI: 0.839-0.960, P < 0.001). The absolute number of the positive and negative results by both Ag-RDTs and rRT-PCR along with the true- and false-negative and positive results were summarized in Table 2. The overall specificity of Ag-RDTs in this study was 97.9% (95% CI: 94.1%-99.6%), sensitivity was 63.3% (95% CI: 55.3%-70.8%), and accuracy was 81.2% (95% CI: 76.4%-85.5%). Moreover, the positive and negative likelihood ratios were 30.6 (95% CI: 9.9-94.3) and 0.4 (95% CI: 0.3-0.5), respectively, and the receiving operative characteristic curve showed an AUC of 0.806 (95% CI: 0.755-0.857). These findings suggested that the Ag-RDTs had overall good accuracy.

Diagnostic Performance of Ag-RDTs Based on Ct Value

The median Ct value for all positive rRT-PCR cases (n = 158) in this study was 25.2 with 48.7% of the study population having a high viral load (Ct value ≤ 25). As depicted in Figure 2, the median Ct value was lower among concordant (TP) samples at 20.3 (IQR = 7.22) compared to discordant (FN) samples at 31.4 (IQR = 6.07) at a P < 0.001 significance level. A Pearson correlation coefficient was computed to assess the linear relationship between the sensitivity of Ag-RDTs and Ct value. The results of Table 3 indicated a strong negative correlation between the two variables (r = -0.95, P = 0.014). The sensitivity significantly varied among different Ct value intervals, indicating the highest sensitivity in high viral load samples.

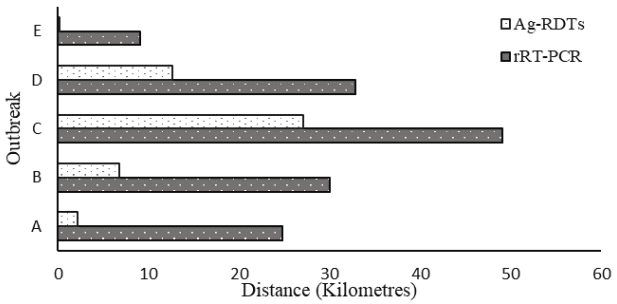

Figure 1. The Transportation Distance From Sample Collection to Procession for Ag-RDTs and rRT-PCR Test for Each Studied Outbreak. *Note.* Ag-RDTs: Antigen-detecting rapid diagnostic tests; rRT-PCR: Real-time reverse-transcription polymerase chain reaction

Table 2. Summary of the Performance Comparison Between Ag-RDTs and RT- PCR for COVID-19 Diagnosis (n = 303)

Ag-RDTs	RT-PCR		
	Detected	Not Detected	Total
Positive	TP = 100	FP = 3	103
Negative	FN = 58	TN = 142	200
Total	158	145	303

Note. COVID-19: Coronavirus Disease 2019; Ag-RDTs: Antigen-detecting rapid diagnostic tests; RT-PCR: Reverse transcription polymerase chain reaction; TP: True-positive; FP: False positive; TN: True negative; FN: False negative.

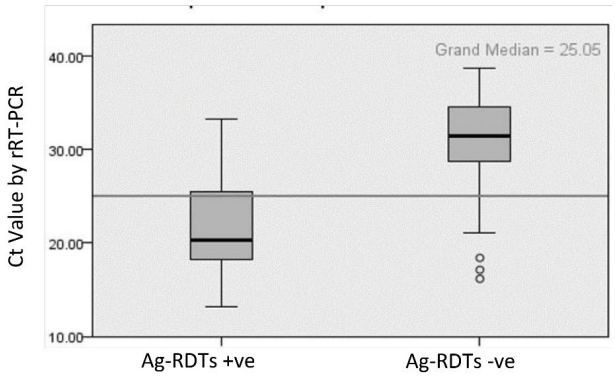

Figure 2. The Distribution of Ct Value of TP and FN Ag-RDTs Samples With Regard to Positive rRT-PCR (n = 158). *Note.* TP: True positive; FN: False negative; Ct: Cycle threshold; Ag-RDTs: Antigen-detecting rapid diagnostic tests; rRT-PCR: Real-time reverse-transcription polymerase chain reaction

Diagnostic Performances Based on Disease Prevalence

Table 4 presents the diagnostic performance of Ag-RDTs based on pre-test prevalence of different outbreaks. As evident, there was a strong positive correlation between the two variables (r = 0.899, P = 0.038). The positive and negative predictive values were 96.6% (95% CI: 90.2%-98.9%) and 74.1% (95% CI: 70.0%-77.9%), respectively, at 48.2% disease prevalence. The predictive values were estimated at various simulated prevalence (Figure 3). The positive predictive values were constantly above 80% when the prevalence was over 10%, while the negative predictive values reduced to below 80% when the disease prevalence was highly over 45%.

Diagnostic performance of Ag-RDTs Based on Manufacturers

Regarding the performance based on different manufacturers, the specificity ranged from 97% (95% CI: 89.4%-99.2%) to 100% (95% CI: 94.5%-100%), whereas, the sensitivity ranged from 75.0% (95% CI: 19.4%-99.4%) to 92% (95% CI: 83.0%-96.9%) in high viral load samples and 12% (95% CI: 1.5%-36.4%) to 14% (95% CI: 2.9%-34.9%) in low viral samples. However, there was no significant difference in terms of sensitivity and specificity between manufacturers in different categories of Ct values (P = 1.000, the Fisher's exact test).

Discussion

As evident by this study, Ag-RDTs produced a faster turnaround time compared to rRT-PCR which would

Table 3. The Sensitivity of Ag-RDTs Based on Different Ct Value Intervals (n = 158)

Viral Load (Ct Value)	TP	FN	n (%)	Ct Value, Mean (SD; 95% CI)	Sensitivity (95% CI)	*P* Value
High (≤25.0)	70	7	77 (48.7)	19.2 (2.6; 18.6-19.8)	90.9% (82.2%-96.3%)	
Medium (25.1 - 29.9)	25	17	42 (26.6)	27.5 (1.6; 27.0-28.0)	59.5% (43.3%-74.4%)	<0.001[a]
Low (≥30.0)	5	34	39 (24.7)	33.9 (2.4; 33.2-34.8)	12.8% (4.3%-27.4%)	

Note. TP: True positive; FN: False negative; SD: Standard deviation; CI: Confidence interval.
[a] Analysis by Chi-square test.

Table 4. The Performance of Ag-RDTs Based on Disease Prevalence of Different Outbreaks

Outbreak	Prevalence[a]	Sensitivity %(95% CI)[b]	Specificity % (95% CI)[b]	PPV % (95% CI)[c]	NPV % (95% CI)[c]	Accuracy % (95% CI)[b]
A	51.0%	71.0 (52.0-85.8)	100 (86.3-100)	100 (n/a)	76.8 (65.6-85.2)	85.2 (73.2-93.3)
B	52.2%	80.6 (62.5-92.6)	86.7 (59.5-98.3)	86.9 (64.3-96.0)	80.4 (66.1-89.6)	83.5 (69.7-92.8)
C	46.9%	65.4 (44.3-82.8)	100 (85.2-100)	100 (n/a)	76.6 (65.9-84.7)	83.8 (70.5-92.7)
D	70.9%	76.7 (57.7-90.1)	94.7 (74.0-99.9)	97.3 (83.9-99.6)	62.5 (46.3-76.9)	81.9 (68.3-91.5)
E	20.0%	32.5 (18.6-49.1)	100 (94.3-100)	100 n/a	85.6 (82.7-88.0)	86.5 (78.4-92.4)
Overall	48.2%	63.3 (55.3-70.8)	97.9 (94.1-99.6)	96.6 (90.2-98.9)	74.1 (70.0-77.9)	81.2 (76.4-85.5)

Note. Ag-RDTs: Antigen-detecting rapid diagnostic tests; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; rRT-PCR: Real-time reverse-transcription polymerase chain reaction; 95% CI: 95% Confidence interval;
[a] Pre-test prevalence for each outbreak based on standard reference (rRT-PCR); [b] 95% CI were estimated using the Clopper-Pearson method; [c] 95% CI were estimated using standard logit confidence intervals.

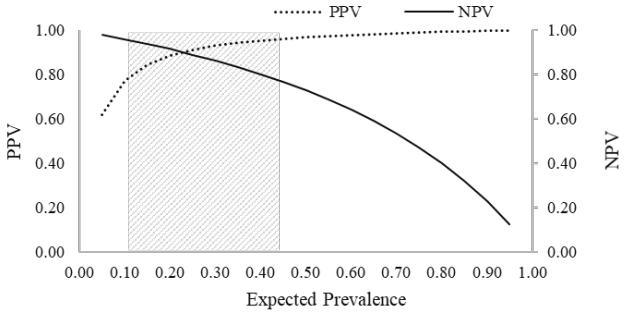

Figure 3. Positive and Negative Predictive Values of Ag-RDTs at Different Simulated Prevalence. *Note*. Ag-RDTs: Antigen-detecting rapid diagnostic tests; PPV: Positive predictive value; NPV: Negative predictive value; *The shaded area denote the respective prevalence associated with predictive values of above 80%

be very useful to control the transmission in highly transmissible settings like institutions and semi-closed communities. Ag-RDTs are reliable alternatives to rRT-PCR in diagnosing COVID-19 with some crucial caveats to be considered. The specificities of Ag-RDTs in this study were constantly high, but the sensitivity varied in different settings. Reviews on the diagnostic accuracy of Ag-RDTs against the performed RT-PCR have documented a high variability of sensitivity estimates (range: 0% - 94%) with constantly high specificity (range: 90% - 100%).[10,22,23] The Ag-RDTs were found to be highly specific, allowing prompt identification of highly infectious individuals. On the other hand, the sensitivity is often reported to be suboptimal in general and is greatly affected by viral loads and disease prevalence, among other factors. The highest sensitivity was observed among cases with high viral loads when the Ct value was ≤ 25.0.[13,18,24] Although this suggested that cases tested negative by Ag-RDTs are likely to be non-infectious at the time of testing, the test may compromise the diagnosis of people during the early or late phase of the infection due to its low sensitivity among those with low viral load. The viral load was reported to be low during the early phase of SARS-CoV-2 infection and rapidly increasing, especially during the infectious period. Hence, high-risk individuals with negative Ag-RDTs who are consciously exposed to SARS-CoV-2 infection may need further confirmation by rRT-PCR or to undergo quarantine and repeat the Ag-RDTs test at a later time based on clinical considerations.

The performance of Ag-RDTs is affected by the disease prevalence.[25] The positive predictive value (PPV) increased with an increase in the prevalence.[10] This study suggested that positive Ag-RDTs could be confirmatory when the disease prevalence is over 10%, which is consistent with the recommendations that were later published by WHO[3] and the national guidelines.[16] An FN result is likely in a high-prevalence setting; hence, further confirmation by RT-PCR is recommended.[10,13] However, in a low-prevalence setting, despite high specificities consistently reported for Ag-RDTs, the FP result is a concern. In such settings, individuals with positive Ag-RDTs should be asked for further confirmation by NAATs to avoid unnecessary quarantine, and they should not be quarantined with TP cases. The sensitivity and specificity may vary with disease prevalence which may be attributable to clinical variations and patient's spectrum.[26] It was reported that a lower specificity and higher sensitivity are often observed in higher prevalence setting.[26] Therefore, it is important for policymakers to rely on studies that would closely match their current setting for decision-making before conducting a widespread implementation of testing policies or strategies.

Although both studied kits were found to be highly specific, the overall sensitivities were lower than the manufacturers' claimed data of over 97% which is also observed in several reviews.[10,23] A Cochrane review

reported the variation of sensitivities from 34.1% to 88.1% among different brands with high specificities for most brands.[10] Nonetheless, there was no significant difference in performance between the two studied kits. These kits were recommended by the Medical Devices Authorities of Malaysia Ministry of Health based on the consensus of the COVID-19 Test Kit Expert committee that thoroughly evaluated the manufacturer reported clinical and analytical performance based on the criteria set by the clinical experts.[27] Hence, the use of any Ag-RDT kit recommended by the above-mentioned authority would be suggested. A very low sensitivity was reported for both kits in low viral load samples when the Ct value was high (≥ 30), suggesting that the studied Ag-RDTs are not reliable for diagnosing COVID-19 when the viral load is low.[10,22]

Strengths and Limitations

This study reflected the real-life evaluation of Ag-RDTs as diagnostic tools in outbreak settings. One limitation was that two swabs were taken from each individual that could be regarded as two different samples, but it was taken by trained healthcare personnel at least an hour later to improve the yields. Moreover, rather than testing a single specific kit, the overall performance was assessed by combining the result of two kits. However, the kits were widely used in the studied facilities with similar reported accuracy. Each participant was only tested with one of the two selected manufacturers; therefore, only indirect comparisons could be made. Further, the data on symptoms and age of individuals from prison and correctional facilities were limited in this study. It is reported by researchers that the sensitivity of Ag-RDTs is lower among asymptomatic and younger individuals.[24]

This study has immediate clinical implications. It has been used to include Ag-RDTs as confirmatory tests for diagnosing COVID-19 in Kelantan permitted by the National CPRC. In outbreaks with a disease prevalence of > 10%, confirmation of positive Ag-RDTs by rRT-PCR was not necessary, while negative Ag-RDTs test was further confirmed by rRT-PCR at clinical discretion. This significantly increased the local testing coverage with rapid results leading to more efficient implementations of public health interventions. As the cases and sampling reduced to its centralized laboratories' capacity, the NAATs, mainly rRT-PCR was selected as the preferred diagnostic test.

Conclusion

To summarize, Ag-RDTs are reliable alternatives, especially in a highly transmissible setting requiring large-scale screenings, and when the rRT-PCR is limited or not easily accessible. It allows rapid identification of highly infectious cases, making it a useful tool for diagnosing COVID-19 with some considerations. Positive Ag-RDTs could be confirmatory in settings where the disease prevalence is > 10% and among individuals with high viral load. However, in a setting with high transmissions, cases tested negative by Ag-RDTs may require confirmation by rRT-PCR. For high-risk individuals with negative Ag-RDTs, confirmation by rRT-PCR or subsequent Ag-RDTs at a later time is recommended due to its low sensitivities among cases with low viral load.

Conflict of Interest Disclosures

None of the authors has any conflict of interest.

Ethical Approval

This study was registered and ethically approved by the National Medical Research and Ethics Committee (Register No. NMRR-20-1624-55900) and was conducted as part of the routine outbreak investigation for COVID-19; hence, no patients consent was needed.

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