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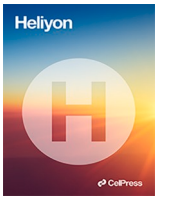

Research article

Performance characteristics of INDICAID antigen rapid diagnostic test on SARS-CoV-2 samples during the omicron wave in Cameroon

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ABSTRACT

Background: WHO recommends the use of COVID-19 antigen rapid diagnostic tests (Ag-RDT) with at least 80 % sensitivity and 97 % specificity. In the era of Omicron variants, we sought to ascertain the performance of the INDICAID™ Ag-RDT compared to real-time PCR (RT-PCR) as the gold standard.

Methods: A laboratory-based study was conducted among consenting individuals tested for COVID-19 at the virology laboratory of the Chantal BIYA International Reference Centre, Yaoundé-Cameron. The samples were processed by INDICAID™ Ag-RDT and DaAn Gene real-time PCR according to the manufacturer's instructions, and PCR-results were interpreted as per cycle thresholds (CT). The sensitivity, specificity, positive and negative predictive values (PPV and NVP) of INDICAID™ Ag-RDT were evaluated according to PCR CT-values.

Results: A total of 565 nasopharyngeal swabs were collected from participants (median age [IQR]: 40 [31–75]; M/F sex-ratio was 1.2 and 380 were vaccinated). Following PCR, overall COVID-19 positivity was 5.66 %. For CT $<$ 37, INDICAID™ Ag-RDT sensitivity was 21.9 % (95%CI: [8.3–39.9]), specificity 100 % (95%CI: [99.3–100]); PPV 100 % (95%CI: [59.0–100]), NPV 95.5 % (95%CI: [93.4–97.1]) and kappa = 0.34 (95%CI: [0.19–0.35]). For CT $<$ 25, sensitivity was 100 % (95%CI: [47.8–100.0]), specificity 99.6 % (95%CI: [98.7–99.9]); PPV 94.4 % (95%CI: [51.7–100]), NPV 100 % (95%CI: [99.3–100]) and kappa = 0.83 (95%CI: [0.6–1.0]). COVID-19 sequences generated were all Omicron BA.1 subvariants.

Conclusion: For patients infected with high viral loads (CT $<$ 25), INDICAID™ Ag-RDT has high intrinsic (sensitivity and specificity) and extrinsic (predictive values) performances for COVID-19 diagnosis. Due to its simplicity and short turnaround time, INDICAID™ Ag-RDT is, therefore a reliable tool to prevent the spread of COVID-19 at community level in the current era of Omicron subvariants.

1. Introduction

The global COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a significant burden on society and health systems since late 2019 when this emerging virus was initially recognized in Wuhan, China[1–4]. According to the World Health Organization, more than 768,983,095 confirmed cases and 6,953,743 deaths have been reported worldwide by August 2nd, 2023, indicating ongoing transmission though at lower levels and with limited severity [5]. In Cameroon, there were 125,110 confirmed cases of COVID-19 with 3,693,678 people who had received at least one dose of vaccine, representing 26.2 % of the target population [6,7].

The detection of the first cases of Omicron sub-lineages in November 2021 was accompanied by the fourth wave of the pandemic in Cameroon, with a rapid transmission at community level. Of note, the effective reproduction number (R_0) for Omicron is around 3.4, assuming no immune evasion [8–10]. Omicron is antigenically distant to the ancestral strain of SARS-CoV-2, which leads to a lower vaccine effectiveness against mild infections but also raises concerns about accurate detection of SARS-CoV-2 using some existing diagnostic assays. This is particularly true as Omicron remains a highly transmissible viral strain at community level, requiring accurate/rapid diagnostic assays to test, track and treat cases timeously [9–13]. Reverse transcription polymerase chain reaction (RT-PCR), based on the molecular detection of viral genetic material from a nasopharyngeal swab, has been routinely used to detect SARS-CoV-2 infection in standard molecular biology laboratories [11–15]. However, large-scale RT-PCR assays, while having excellent analytical sensitivity and specificity, also have major drawbacks, such as long turnaround times and the need for sophisticated equipment and highly trained personnel[16]. In this frame, using a rapid diagnostic tool with a high reliability in detecting community transmission of Omicron variants becomes essential to limit the viral propagation, both in resource-limited and high-income settings. Thus, rapid but highly sensitive testing is needed to quickly identify individuals who may transmit SARS-CoV-2 and thus contribute to the spread of the infection [11,12,14–19]. The World Health Organization (WHO) recommended using antigenic tests for quick diagnosis of SARS-CoV-2, with a sensitivity of at least 80 % and a specificity of at least 97 % [16,19,20]. The INDICAID™ Ag-RDT is a lateral flow immunoassay designed to qualitatively detect SARS-CoV-2 antigens in direct nasal swab samples [21–23]. Most positive results are reported between 20 and 25 min and not after that indicated in the manufacturer's instructions [23]. The INDICAID™ Ag-RDT detects SARS-CoV-2 virus antigens and can screen for COVID-19 during active infection. SARS-CoV-2 antigens are present in patients with an optimal concentration around 5–7 days after symptom onset or following infection, before the production of specific antibodies [23].

Prior to the present study, the Cameroonian Ministry of Public Health had equipped accredited centres for COVID-19 diagnosis with the DaAn Gene kit for SARS-CoV-2 real-time RT-PCR (rRT-PCR) and the INDICAID™ Ag-RDT for rapid screening at population-level. The clinical performance of the INDICAID™ Ag-RDT (sensitivity, specificity, positive and negative predictive values) was therefore prospectively evaluated among consenting individuals being tested for SARS-CoV-2 infection in the era of Omicron variants within the Cameroonian context.

2. Material and methods

2.1. Study design and setting

Within the frame of the EDCTP PERFECT-Study(https://edctp-perfect-study.com), an observational laboratory-based study was conducted from March to August 2022 among consenting individuals attending the virology laboratory of the Chantal BIYA International Reference Centre (CIRCB), to be tested for SARS-CoV-2 infection.

The CIRCB is a government reference institution of the Ministry of Public Health dedicated to viral research and patient monitoring, among which: (a) HIV early infant diagnosis in the frame of the national PMTCT program; (b) diagnosis of co-infections with HIV; (c) viral load measurement; (d) CD4 and CD8 T lymphocytes counts; (e) biochemical and haematological tests for drug safety; (f) genotypic resistance testing (GRT) for HIV; (g) molecular diagnostic and genomic surveillance of SARS-CoV-2; with regular participation to external quality control programs conducted in partnership with Quality Assessment and Standardization of Indicators (QASI), African Society for Laboratory Medicine (ASLM)/Africa Centres for Disease Control and Prevention (Africa CDC), Viral Quality Assurance (VQA) of WHO, the College of American Pathologists (CAP), and other international agencies (http://www.circb.cm/btc_circb/web/).

Nasopharyngeal swabs were collected from individuals aged 21 years and older after obtaining written consent. Age, sex, vaccination status, symptoms, and time since onset of symptoms were collected for each participant. Nasopharyngeal samples were processed by both INDICAID™ COVID-19 Ag-RDT (investigative assay) and the DaAn Gene real-time PCR (gold standard) according to manufacturers' instructions.

2.2. Nucleic acid extraction, amplification and detection with DaAn gene platform

For DaAn gene rRT-PCR assay, viral RNA was manually extracted from 140 μL nasopharyngeal sample (i.e. the swabs contained within the viral transport medium) using the QIAamp Viral RNA Mini Kit (Qiagen Inc, Valencia, CA, USA) as per manufacturer's instructions. Amplification was performed using the DaAn gene detection kit for 2019-nCoV (PCR fluorescence) (https://en.daangene.com/uploads/file/detection-kit-for-2019-novel-coronavirus-2019-ncov-rna-pcr-fluorescence-probing.pdf) on the Quant Studio 5 (Thermofisher™) thermocycler. The protocol used probes targeting the open reading frame (ORF1ab) gene and the nucleocapsid (N) protein gene, with a lower detection limit of 500 copies/mL and an amplification reaction of 45 cycles. Briefly, 3 μl of enzyme (solution B) and 5 μl of SARS-CoV-2 RNA were added into 17 μl of master-mix (solution A). The total (master mix and biological sample) was then placed into a thermocycler for reverse transcription (at 50 °C, 15min); Taq pol activation (95 °C, 15min); and finally amplification during 45 cycles (94 °C,15sec and 55 °C, 45sec).

2.3. Results interpretation

For comparison of different positivity cycle threshold (CT) values, RT-PCR positivity was interpreted for each sample with CT-values <40 (manufacturer's instructions) (BIC Medical, n.d.); CT values < 37 (national guidelines)[24]; and or CT values < 25 (threshold for high-risk of transmission)[11,25–27].

2.4. Interpretation of INDICAID immune-chromatographic assay

Samples for the INDICAID™ Ag-RDT were processed immediately on-site after collection with no storage as per the manufacturer's protocol. Results of the INDICAID™ Ag-RDT were interpreted by the test operators and recorded as "Positive," "Negative", or "Invalid" based on the visual presence or absence of the control and test lines on the developed test strip after 20 min [23,28].

2.5. Statistical analysis

Statistical analyses were performed using Graph-Pad v.6; correlation analyses were done using spearman's correlation test. INDICAID performance characteristics (sensitivity, specificity, positive and negative predictive values) were described against RT-PCR according to different CT values: CT < 40 represents the manufacturer's instructions [23]; CT < 37 which represents our national threshold for positivity [24] and CT < 25 which represents the threshold for high viral loads related to high-risk of viral transmission [11,25–27]. The concordance in diagnosis was evaluated following Cohen's kappa (k) value at all these thresholds.

2.6. Ethical considerations

The present research was approved by the Cameroon national committee for human health research (N°2020/05/1227/CNERSH/SP); the CIRCB General Directorate issued administrative authorization for the study; data were collected using the standard case reporting forms was conducted on anonymous samples. All information, including, demographic and clinical data was recorded in an anonymized database, with limited access to unauthorized persons.

3. Results

3.1. Sociodemographic characteristics

Of the 565 nasopharyngeal samples collected from individuals aged ≥21 years, 380 (67.25 %) patients were vaccinated against Covid-19. We counted about 54.51 % (308/565) males and the median age was 40 [interquartile range (IQR): 38–55] years. See Table 1 for baseline features of study participants.

3.2. Positivity rates and diagnostic performances

Overall positivity rates of SARS-CoV-2 with RT-PCR was 10.09 % (57/565), 5.66 % (32/565) and 0.88 % (5/565) considering respectively the manufacturer's instructions (CT < 40), our national guidelines (CT < 37) and high positivity threshold (CT < 25) versus 1.24 % (7/565) with INDICAID™ Ag-RDT (see Table 2).

- **At CT<40**, (mean CT = 35.6 ± 2.75), sensitivity was 12.28 % (95%CI: [5.1–23.7]); specificity was 100 % (95%CI: [99.3–100.0]); PPV was 100 % (95%CI: [31.3–97.2]) and NPV was 95.0 % (95%CI: [92.8–96.7]). The positive concordance between the two assays was 12.28 % and the negative concordance was 100 %, with a kappa = 0.2 ([95%CI: 0.0–0.4]), suggesting a poor agreement between the PCR and the rapid test.
- **At CT<37**, (mean CT = 33.1 ± 3.86), sensitivity of INDICAID™ AgRDT was 21.9 % (95%CI: [8.3–39.9]); specificity was 100 % (95%CI: [99.3–100]); PPV was 100 % (95%CI: [59.0–100]) and NPV was 95.5 % (95%CI: [93.4–97.1]). The positive concordance between the two assays was 21.87 %, and the negative concordance was 100 %, with a kappa = 0.346 (95%CI: [0.19–0.35]), also suggesting a poor agreement between the PCR and the rapid test.
- **At CT<25**, (mean CT = 21.2 ± 2.34), sensitivity was 100 % (95%CI: [47.8–100.0]); specificity was 99.6 % (95%CI: [98.7–99.9]); PPV was 94.4 % (95%CI: [51.7–100]) and NPV was 100 % (95%CI: [99.3–100]). The positive concordance between the two assays was 100 % and the negative concordance was 99.64 %, with a kappa = 0.832 ([95%CI: 0.6–1.0]), suggesting an excellent agreement between PCR and rapid test.

Importantly, following sequencing of PCR positive SARS-CoV-2 sample with eligible CT-value, the seven COVID-19 sequences generated were 100 % of the OMICRON lineage BA.1.H sub-variants.

4. Discussion

As early and accurate detection of SARS-CoV-2 infection is key in stopping the transmission of the virus at community level, the need for highly precise rapid tests has grown considerably, and several antigenic tests have been introduced on the market. This study evaluated the diagnostic performances of INDICAID™ Ag-RDT on clinical samples in a context where COVID-19 burden/incidence, as reported by the reference diagnostic method (i.e. real-time RT-PCR), was very low [29–31].

Our findings showed an overall low prevalence of SARS-CoV-2 infection in Cameroon (i.e. ~10 % following the manufacturer's instructions and <6 % following our national guidelines), in line with the global trend at the moment [5]. On the other hand, detection of SARS-CoV-2 antigens through INDICAID™ Ag-RDT was even lower (~1 %), indicating the presence of very few active cases at community level. Interestingly, these results also prove that the current state of the pandemic is mostly driven by low-level viremia (CT > 25) and, thus low symptomatology in our context [11,25–27]. This is not surprising at all, as all sequences obtained were omicron BA.1.H sub-variants; which has been associated with very few symptoms worldwide[8,9,32,33]. However, previous reports highlighted that rapid COVID-19 tests miss 90 % of asymptomatic cases [34,35]. In effect, on the day of infection onset, rapid tests detected almost 60 % of infected participants who had COVID-19 symptoms, but only 10 % of those who didn't; with more than 75 % of diagnosis among asymptomatic participants after repeating the test 3 times at 48 h intervals [34,35]. Thus, Ag-RDT are much more reliable at detecting COVID-19 in symptomatic people than their asymptomatic pairs, with serial testing (48 h apart) improving the diagnosis among asymptomatic individuals. Consequently, the low symptomatology of COVID-19 at the moment may call for a revision of diagnosis strategies while implementing Ag-RDT-based testing for rapid screening at community level.

Secondly, a comparison between the two assays demonstrated an excellent agreement between PCR and INDICAID™ Ag-RDT at high viral loads (CT < 25), in line with the highest intrinsic and extrinsic performances of this Ag-RDT at this threshold. Of note, the

Table 1
Baseline characteristics of study participants.

Characteristics	Total	Vaccinated	Non-vaccinated
Total, n (%)	565	380	185
Gender distribution, n (%)			
Male	308(54.51)	207(54.47)	101(54.59)
Female	257(45.48)	155(45.52)	84(45.40)
Median age (interquartile range), years	40(38–55)	42(33–52)	36(30–46)
Median CT value (interquartile range)	36.12(32.34–38.40)	36.36(33.03–38.58)	36.36(33.03–38.58)

Table 2
Comparison of PCR vs. RDT positivity according to various PCR thresholds of <40, <37 and < 25 respectively the manufacturer's threshold, national positivity threshold and a high viral loads threshold).

PCR Positivity at CT < 40				
		Positive	Negative	
INDICAID™ Ag-RDT	POSITIVE	7	0	7
	NEGATIVE	50	508	558
		57	508	565
PCR Positivity at CT < 37				
		Positive	Negative	
INDICAID™ Ag-RDT	POSITIVE	7	0	7
	NEGATIVE	25	533	558
		32	533	565
PCR Positivity at CT < 25				
		Positive	Negative	
INDICAID™ Ag-RDT	POSITIVE	5	2	7
	NEGATIVE	0	558	558
		5	560	565

gold standard for detecting SARS-CoV-2 infection has always been the RT-PCR, based on its excellent analytical sensitivity and specificity [11–15,36]. With this result, INDICAID™ Ag-RDT appears to be perfectly suited for timely diagnosis/tracking of active and symptomatic cases of COVID-19; which is essential in reducing the spread of the disease [13,14,16,19,22,20,37]. Also, the ease of use and the short turn-around-time of rapid antigen tests such as INDICAID™ Ag-RDT, could not be over emphasized for large-scale screening of individuals in schools, markets, workplaces and other crowded, thus limiting COVID-19 transmission in the community [14,15,22].

Intriguingly while processing the samples, we noticed an incompatibility between the RDT's buffer and the extraction kit, resulting in falsely negative PCR results. This was corrected by collecting two swabs from every participant at enrolment in the study, one for the INDICAID™ Ag-RDT and the other one destined to the RT-PCR. In the meantime, it is important to recall that excellent agreement at CT < 25 was observed in spite of the very few cases at this threshold; which was due to the low pathogenicity of omicron-driven infection as described elsewhere [8,9,32,33].

5. Conclusion

For the surveillance of SARS-CoV-2 cases with high risk of transmission at the community- or population level, INDICAID™ Ag-RDT shows an excellent diagnosis performance for COVID-19 patients with high viral loads. Thus, with its simplicity and short turn-around-time, INDICAID™ Ag-RDT is therefore a reliable tool for timely management and for preventing the spread of COVID-19 at community-level, alongside vaccination strategies and other preventive measures, even in the era of Omicron variants.

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CRediT authorship contribution statement

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Declaration of competing 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.

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