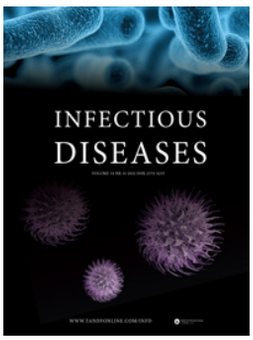

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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/infd20

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To cite this article: Eleonora Cottone, Frederik Van Hoecke, Geert Antoine Martens, Emmanuel De Laere, Roos De Smedt, Steven Vervaeke, Merijn Vanhee & Dieter De Smet (2022) Pitfalls of SARS-CoV-2 antigen testing at emergency department, Infectious Diseases, 54:10, 731-737, DOI: 10.1080/23744235.2022.2083226

To link to this article: https://doi.org/10.1080/23744235.2022.2083226

Published online: 30 May 2022.

Taylor & Francis
Taylor & Francis Group

INFECTIOUS DISEASES,
2022; VOL. 54,
NO. 10, 731–737

https://doi.org/10.1080/23744235.2022.2083226

ORIGINAL ARTICLE

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Pitfalls of SARS-CoV-2 antigen testing at emergency department

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ABSTRACT

Background: Current method for diagnosis of SARS-CoV-2 infection is an RT-PCR test on the nasopharyngeal or oropharyngeal swab. Rapid diagnosis is essential for containing viral spread and triage of symptomatic patients presenting to hospital ER departments. As a faster alternative to RT-PCR, we evaluated a SARS-Cov-2 Rapid Antigen test in symptomatic patients presenting to hospital ER departments.

Methods: We evaluated the diagnostic performance of the Roche SARS-CoV-2 Rapid Antigen test (SD Biosensor) for detection of SARS-CoV-2 compared to RT-PCR.

Results: Our study showed inferior performance of the SARS-CoV-2 Rapid Antigen test for detection of SARS-CoV-2. Firstly, because of the lack of specificity, which is potentially life-threatening due to the association of nosocomial-acquired SARS-CoV-2 infection. Secondly, with a sensitivity of 45.5%, it is impossible to rule out SARS-CoV-2 infection, resulting in reflex PCR-testing. Comparison of viral load in RT-PCR positive samples with corresponding antigen results showed a significant difference between antigen positive and negative samples. COVID-19 infection will not be detected in patients admitted to the hospital in an early or late phase, typically associated with low viral loads. Sensitivity increases when testing within 5–7 symptomatic days, but the implementation of this cut-off is impractical in ER settings. However, diagnostic performance is better to detect high viral load ($>= 5$ log10 copies/mL) linked with contagiousness.

Conclusion: Our study showed inferior performance of the Roche SARS-CoV-2 Rapid Antigen test (SD Biosensor) for detection of SARS-CoV-2 which limits its use as a diagnostic gatekeeper in ER departments, but is able to differentiate contagious individuals.

Abbreviations: SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Corona Virus Disease; RT-PCR: Reverse Transcription Polymerase Chain Reaction; LFA: Lateral Flow Assay; ER: Emergency Room; TAT: Turn Around Time; RMG: Belgian Risk Management Group; RAG: Belgian Risk Assessment Group; WHO: World Health Organisation

KEYWORDS
SARS-CoV-2
antigen test
ER-department
RT-PCR
LFA

ARTICLE HISTORY
Received 30 January 2022
Accepted 22 May 2022

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Introduction

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged and led to a global pandemic in March 2020. SARS-CoV-2 is an enveloped, single-stranded RNA virus. The viral RNA encodes for four major structural proteins: the envelope (E) protein, the spike (S) protein, the matrix (M) protein and the nucleocapsid (N) protein. It also encodes for a number of non-structural proteins, such as RNA-dependent RNA polymerase (RdRp) [1,2].

The current 'gold standard' method for the diagnosis of SARS-CoV-2 infection is a real-time reverse transcription polymerase chain reaction (RT-PCR) test on the nasopharyngeal or oropharyngeal swab. Commonly used targets for SARS-CoV-2 detection are S, E, N and RdRP genes as well as the Open Reading Frame 1ab (ORF1ab) region [3,4].

Rapid diagnosis of SARS-CoV-2 is essential for containing viral spread, but also for correct and fast triage of symptomatic patients presenting to hospital emergency (ER) departments. RT-PCR is an expensive, labour intensive and time-consuming laboratory test, which may cause a delay in the detection of infected patients. Fast PCR tests are available, but have low throughput capacity and are even more expensive [5]. In addition to PCR, rapid antigen tests also became available. Antigen tests target specific epitopes of SARS-CoV-2, mostly nucleocapsid protein, using lateral flow assays (LFA). LFA is relatively cheap and easy to execute, with expected results within 15–20 min. Trained professionals are still recommended to perform the assay, as inaccurate sample volumes reduce the precision of the LFA. The tests should be read out objectively to ensure that even weak positivity is accepted as positive [6–8].

In general, SARS-CoV-2 rapid antigen tests demonstrate high specificity, but variable sensitivity [7]. Many questions have been raised about their diagnostic performance in a hospital setting. In its statement on antigen detection for diagnosis of SARS-CoV-2, WHO does not specify how these tests should be used in hospitals [6]. Besides diagnostic use for COVID-19, antigen tests are also used in asymptomatic patients to detect contagious individuals, both in medical and non-medical settings. A patient is considered contagious if the SARS-CoV-2 viral load equals or exceeds 5 $\log_{10}$ ($=10^5$) copies/mL [9–14]. In this study, the diagnostic performance of the Roche SARS-CoV-2 rapid antigen test was evaluated as compared with RT-PCR results for 464 COVID-19 suspected patients admitted to the hospital ER department.

Materials and methods

Clinical specimens

Analyses were performed on nasopharyngeal swabs on UTM collected from 464 consecutive patients admitted to the ER department of AZ Delta General Hospital in Roeselare, Belgium between November 1 and December 2, 2020. The patient group consisted of 250 (54%) males and 214 (46%) females, with a median (IQR) age of 67 (47–81) years old. All patients were COVID-19 suspected with symptoms or anamnesis highly suggestive of COVID-19. Rapid antigen testing occurred immediately after sample arrival in the clinical laboratory, before RT-PCR testing. The number of symptomatic days prior to ER admission was also registered.

RNA extraction and RT-PCR for detection of SARS-CoV-2

RNA was extracted from nasopharyngeal swabs using the STARMag 96×4 Viral DNA/RNA 200 C kit, followed by real-time PCR using the Allplex™ 2019-nCoV assay (Seegene®, Seoul, Korea). Extraction and PCR setup was executed following the manufacturer's instructions on a Seegene Starlet pipetting robot. PCR amplification was run on a CFX96™ real-time thermocycler (Bio-Rad Laboratories, Hercules, California, USA) and data were analysed with the Sars-CoV-2 Viewer (Seegene). The assay simultaneously detects 3 different Sars-CoV-2 genes, resulting in separate Ct values for the E, RdRp and N genes.

PCR was calibrated with a reference virus stock (titer 7.73 $\log_{10}$ copies/mL) provided by the Belgian National Reference Centre for Covid-19 for estimation of viral load ($\log_{10}$ copies/mL). Viral load was calculated by Ct values as follows: *viral load ($\log_{10}$ copies/mL) = average* $((Ct^{E\text{-}gene} - 41.1)/-3.67;\ (Ct^{RdRp\text{-}gene} - 42.84)/-3.76;\ (Ct^{N\text{-}gene} - 42.78)/-3.44)$. Limit of detection (LOD) equals 1.7 $\log_{10}$ copies/mL. RT-PCR negative samples are presented as <1.7 $\log_{10}$ copies/mL.

Rapid antigen test

SARS-CoV-2 Rapid Antigen Test (SD-Biosensor distributed by Roche, Basel, Switzerland) is an LFA targeting viral nucleocapsid protein. Testing was performed by using the wet swab method following the manufacturer's specifications. 350 µL of nasopharyngeal swab transport medium was mixed with extraction buffer, included in the test kit. Three drops of the mixture were applied to

the LFA device. After 15–30 min at room temperature test results were manually read out. Samples showing both control and test lines were regarded as SARS-CoV-2 antigen positive, while samples only showing the control line were considered SARS-CoV-2 antigen negative. Re-analysis of false positive results was performed with Panbio® rapid antigen test (Abbott, Chicago, USA) and BioFire® Filmarray® (Biomérieux, Marcy l'Etoile, France).

Statistical analysis

Statistics were performed using Medcalc (software version 19.4.1, Mariakerke, Belgium). Diagnostic test (2×2) and receiver operating characteristic (ROC) curve analysis were used for the calculation of diagnostic performance. Mann-Whitney test was used to compare viral load or days of symptoms to antigen test results in the analysis. Correlation analysis was done by Spearman's Rank correlation. Differences were considered statistically significant if *P*-value was $<.05$.

Results

Diagnostic performance of SARS-CoV-2 rapid antigen test for detection of infection ("RT-PCR positivity")

Results are summarised in Table 1 and Figure 1(A, C). Of all 464 patients, 101 tested positive and 363 tested negative with RT-PCR. Rapid antigen testing yielded 55 false negative and 7 false positive results. ROC analysis showed an area under the curve (AUC) of 0.718 (95%CI 0.675 to 0.759, $p < .0001$). Sensitivity, specificity, positive and negative likelihood ratios (95% CI) for detection of SARS-CoV-2 infection were respectively 45.5% (35.6 to 55.8), 98.1% (96.1 to 99.2), 23.6 (11.0 to 50.7) and 0.56 (0.46 to 0.66).

Two out of 7 false positive antigen test results were re-analysed with another lot number of Roche rapid antigen tests, resulting in identical (false) positive results. Re-analysis with Panbio® rapid antigen test (Abbott, Chicago, USA) and BioFire® Filmarray® (Biomérieux, Marcy l'Etoile, France) showed a correct negative result, relating false positive results to the Roche rapid antigen test methodology.

Positive and negative predictive values (PPV/NPV) of the antigen test for detection of SARS-CoV-2 infection are dependent on virus circulation within the population in a specific time period (prevalence). Calculation of posttest probability in the function of pre-test probability (through the application of Bayes' theorem) is shown in Figure 1(C). PPV% (95% CI) is 86.8% (75.4 to 93.4) at the time of our study (midst of the second SARS-CoV-2 wave in Belgium with a prevalence of 21.8%), while NPV% (95% CI) is 86.6% (84.4 to 88.5). In between SARS-CoV-2 waves (prevalence is estimated at 5%) PPV% (95% CI) drops to 55.4% (36.7 to 72.7) and NPV% (95% CI) rises to 97.1% (93.1 to 97.2).

Diagnostic performance of SARS-CoV-2 rapid antigen test for detection of contagiousness (viral load $\geq$ 5 log_{10} SARS-CoV-2 RNA copies/mL)

Viral loads of antigen positive and antigen negative samples were significantly different ($p < .0001$), with respective medians (IQR) of 6.7 $\log_{10}$ copies/mL (5.7 to 7.9) and <1.7 $\log_{10}$ copies/mL (Figure 1(B)). ROC analysis for detection of contagiousness showed an AUC (95%CI) of 0.936 (0.910 to 0.956), significantly different from the AUC for detection of infection (Figure 1(A)). Sensitivity, specificity, positive and negative likelihood ratios (95% CI) for detection of contagiousness were respectively 89.6% (77.3 to 96.5), 97.9% (95.6 to 98.8), 37.3 (20.1 to

Table 1. Diagnostic performance characteristics of SARS-CoV-2 Rapid Antigen Test for detection of respectively infection and contagiousness at Emergency Department ($n = 464$).

Characteristic	Detection of infection (PCR positivity)		Detection of contagiousness (Viral load >5 $\log_{10}$ copies/mL)		
	PCR	Antigen (+)	Antigen (–)	Viral load	Antigen (+)	Antigen (–)
	PCR (+)	46	55	>5 $\log_{10}$ copies/mL	43	5
	PCR (–)	7	356	≤ 5 $\log_{10}$ copies/mL	10	406
Sensitivity, % (95% CI)		45.5 (35.6–55.8)			89.6 (77.3–96.5)	
Specificity, % (95% CI)		98.1 (96.1–99.2)			97.6 (95.6–98.8)	
AUC (95% CI)		0.72 (0.67–0.76)			0.94 (0.91–0.96)	
LR+ (95% CI)		23.6 (11.0–50.7)			37.3 (20.1–69.3)	
LR– (95% CI)		0.56 (0.46–0.66)			0.11 (0.05–0.24)	
Prevalence (95% CI)		21.8 (18.1–25.8)			10.3 (7.7–13.5)	
PPV, % (95% CI)		86.8 (74.7–94.5)			81.1 (68.0–90.6)	
NPV, % (95%)		86.6 (82.9–89.8)			98.8 (97.2–99.6)	
Accuracy, % (95% CI)		86.6 (83.2–89.4)			96.8 (94.7–98.0)	

AUC: area under the curve; LR+: positive likelihood ratio; LR–: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value.

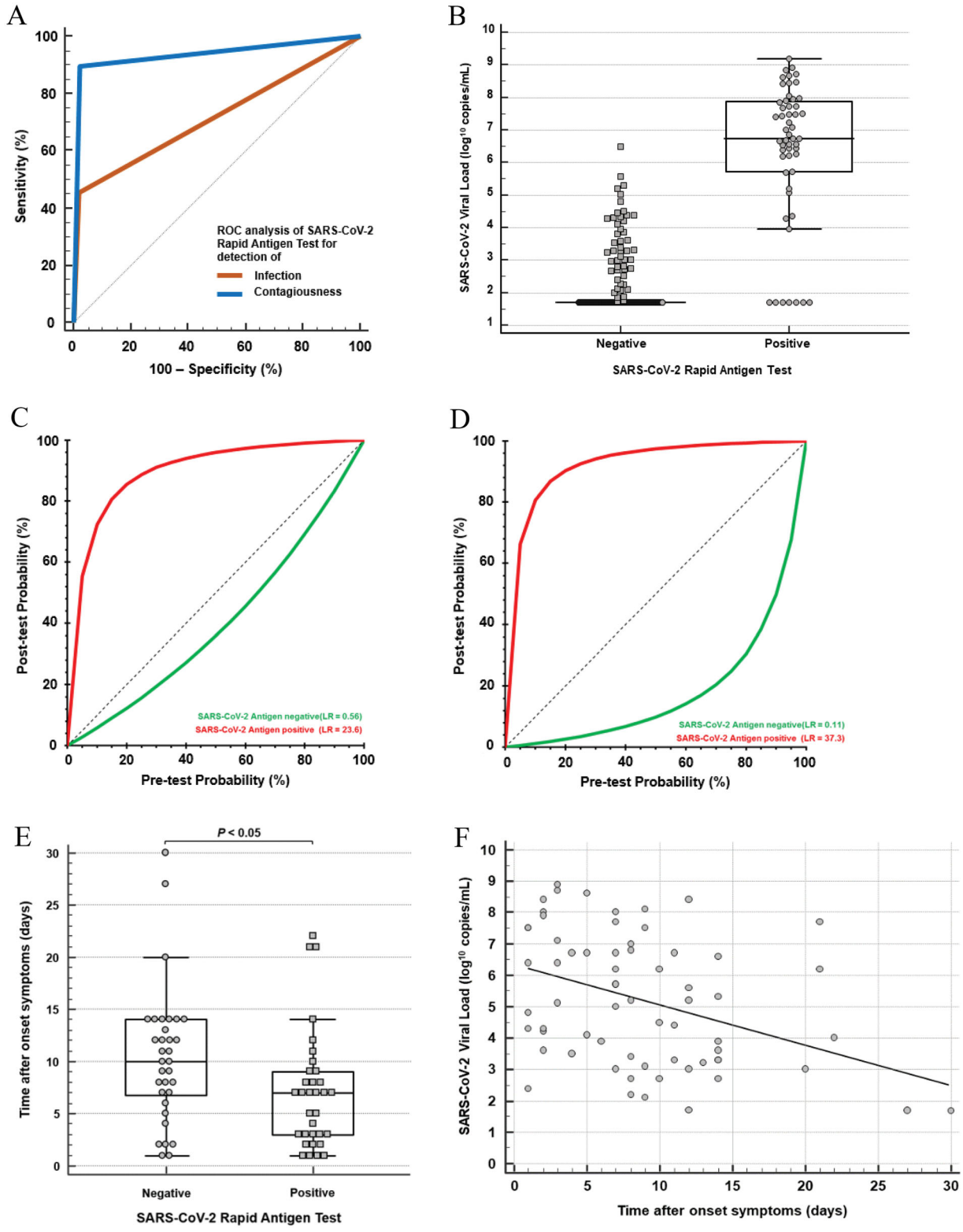

Figure 1. (A) Representation of ROC curves of SARS-CoV-2 Antigen Test for detection of Infection (orange) and contagiousness (blue). (B) SARS-CoV-2 viral load of samples compared to Antigen Test result; $n = 464$; $p < .05$. RT-PCR negative samples were presented as viral load <1.7 $\log_{10}$ copies/mL (=LOD). (C/D) Relations of posttest- and pre-test probabilities with the prevalence of SARS-CoV-2 used as pre-test probability, determining PPV & NPV for SARS-CoV-2 infection (C) and contagiousness (D). (E) Days after the onset of symptoms in relation to Antigen Test result; $n = 66$; $p < .05$. (F) Correlation between viral load and days after onset of symptoms; $n = 66$; r_s (95%CI) $= -0.372$ (-0.563 to -0.142).

69.4) and 0.11 (0.05 to 0.24). Figure 1(B). illustrates a sensitivity of 100% for viral load >7 $\log_{10}$ copies/mL and 0% for viral load <4 $\log_{10}$ copies/mL, suggestively corresponding to the LOD of the antigen test. The relation between post-test and pre-test probabilities is shown in Figure 1(D), where the prevalence of SARS-

Table 2. Impact of timing prior to testing after the onset of symptoms on the diagnostic performance of Rapid Antigen Test for detection of infection ($n = 66$).

Number of symptomatic days	Number of cases per antigen test result		Sensitivity of antigen test result, % (95% CI)
≤5 days	Antigen (+)	15	68.2 (50.0–86.4)*
	Antigen (–)	7	
>5 days	Antigen (+)	18	40. 9 (27.3–54.5)*
	Antigen (–)	26	
≤7 days	Antigen (+)	21	67.7 (51.6–83.9)**
	Antigen (–)	10	
>7 days	Antigen (+)	12	34.3 (20.0–51.4)**
	Antigen (–)	23	

*$p = .0380$.
**$p = .0072$.

CoV-2 can be taken as pre-test probability, to determine positive and negative predictive values for contagiousness. During our study, prevalence of contagiousness was 10.3%, which results in PPV% (95% CI) 81.1% (69.7 to 88.8) and NPV% (95% CI) 98.8% (97.3 to 99.5). When prevalence drops to 5%, PPV% (95% CI) is 66.2% (51.3 to 78.5) and NPV% (95% CI) is 99.4% (98.7 to 99.8).

Impact of timing prior to testing after onset of symptoms on diagnostic performance of rapid antigen test for detection of infection

Subset analysis was performed on 66 confirmed COVID-19 cases with available data on the timing of testing with regard to the onset of symptoms (Figure 1(E) and Table 2). Of the 66 included cases, 33 had a true positive antigen test and 33 had a false negative antigen test. True positive versus false negative antigen tested RT-PCR positive individuals differed significantly ($p < .05$) for the number of symptomatic days prior to testing with respective median (IQR) values of 7 (3 to 9) and 10 (7 to 14). Also, a negative correlation was found between viral load ($\log_{10}$ copies/ml) and symptomatic days before testing, with r_s (95% CI) of −0.372 (−0.563 to −0.142) (Figure 1(F)).

Sensitivities were calculated when considering 5 versus 7 symptomatic days as a maximum limit for use of rapid antigen testing. This resulted in sensitivities (95% CI) of 68.2% (50.0 to 86.4) when using the antigen test in patients with ≤5 symptomatic days and 67.7% (51.6 to 83.9) when using a cut-off of maximum of 7 symptomatic days. The sensitivities proved higher as compared with use without taking into account the number of symptomatic days. Also, sensitivities of using antigen tests with ≤5 versus >5 symptomatic days ($p = .0380$) and with ≤7 or >7 symptomatic days ($p = .0072$) differed significantly between themselves. No significant difference was found for the cut-off of 5 symptomatic days (sensitivity of 68.2) VS 7 symptomatic days (sensitivity of 67.7). Our data do not support a preference for 5 symptomatic days over 7, or vice versa.

Discussion

Our study showed inferior performance of the Roche Rapid Antigen test (SD Biosensor) for detection of SARS-CoV-2 infection which hampers its use as a diagnostic gatekeeper in the ER department [15]. With a sensitivity of 45.5%, it is not possible to confidently rule out SARS-CoV-2 infection, resulting in the compelling need for reflex PCR which generates an additional delay in the diagnostic and therapeutic workup. Comparison of median viral load in all tested samples with corresponding antigen results showed a significant difference between antigen positive (6.7 $\log_{10}$ copies/mL) and antigen negative (<1.7 $\log_{10}$ copies/mL) samples ($p < .0001$). As a consequence, one can conclude COVID-19 infection will not be detected in patients admitted to the hospital in an early or late phase, typically associated with low viral loads.

Further, the diagnostic value of a positive antigen test result with regard to detection of SARS-CoV-2 infection in ER department is very limited, even with a positive likelihood ratio of 23.6. A false positive rate (CI 95%) of 1.93% (1.43 to 4.41), regarding 7 false positive results, is potentially life-threatening due to its function as gatekeeper for admission to a COVID-19 cohort department and the associated high risk of nosocomial-acquired SARS-CoV-2 infection.

Diagnostic performance of rapid SARS-CoV-2 antigen tests for general use has been verified by others with extensive variability in reported sensitivities and specificities [16]. Sensitivity always seems to increase with lower Ct-values and higher viral load, hereby confirming our results. False positive Roche Rapid Antigen Test results were also found by other authors (specificity not 100%) [17,18]. Although, in other publications, a specificity of 100% was described with the same antigen test [19–21]. Antigen tests of other manufacturers seem to obtain a

specificity of 100% in a more consistent way, with both small and large sample sizes: Panbio by Abbott [7,19,20,22]; STANDARD Q COVID-19 Ag by SD-Biosensor [23], Clinitest Rapid COVID-19 Antigen Test by Siemens [19] and COVID-19 Ag Respi-strip by Coris BioConcept [24].

Hospital use of rapid antigen tests is accepted by the Belgian Risk Management Group (RMG) for COVID-19 suspected patients with a maximum of 5 days of symptoms. On the contrary, for patients with direct need for hospital admission or with symptoms >5 days, the use of fast RT-PCR-testing is recommended [25]. Also, WHO suggests 5–7 symptomatic days as a limit for use of rapid antigen tests. In case of unavailability of RT-PCR or if TAT exceeds 48 h, rapid antigen testing can be considered if minimal performance criteria (sensitivity >80%, specificity >97%) are met [6]. True positive and false negative patients differed significantly in days (median 7 versus 10) of symptoms before rapid antigen testing. Limitation of 5–7 symptomatic days before rapid antigen testing, resulted in increased sensitivities of approximately 68%; however still too low to meet WHO guidelines of >80% [6].

We showed that sensitive (89.6%) detection of contagious individuals is feasible with rapid antigen testing. WHO as well as RAG defined viral load of 5–6 $\log_{10}$ copies/mL as the cut-off for contagiousness. Contagiousness has been evaluated by linking viral load to viral replication on cell culture [26], and was determined as viral load $\geq$5 $\log_{10}$ copies/mL [6,10–13,27]. In a hospital setting, however, it remains important to identify infected patients, even with low viral load, because of their potential of becoming (more) contagious. Also, a viral load of 5 $\log_{10}$ copies/mL is not an absolute cut-off for contagiousness as patients might be contagious at lower viral loads and as some antigen tests were negative for samples with higher viral load (Figure 1(B)).

Previous studies share the same conclusion that rapid antigen tests have the potential of picking up "superspreaders" shedding viruses with high viral load and as consequence, with a higher likelihood of viral transmission to others [28]. This opens up possibilities for use of rapid antigen tests for events or short gatherings.

The INCREASE-study (Switzerland) confirms acceptable sensitivity of antigen tests at high viral load but stresses the risk of missing clusters of infected patients with viral loads < 5 $\log_{10}$ copies/mL. Also, progressive reduction in viral load over time among admitted patients was shown, highlighting the reduced sensitivity when using antigen tests after a symptomatic time period of more than 7 days. They recommend the use of rapid antigen testing within four symptomatic days for in and out hospital settings, and only during epidemic waves with the inadequate supply of fast PCR reagents, and followed by reflex RT-PCR [29]. Judicious use based on viral prevalence together with knowledge of days post onset of symptoms, improves diagnostic performance of antigen tests significantly.

To generate reliable test results, accurate sampling is indispensable. Our samples were obtained by nasopharyngeal swab collection and tests were performed and interpreted by professionals following standardised guidelines. Other sample types, such as saliva or self-taken superficial nasal swabs, or testing/interpretation carried out by non-professionals, are factors contributing to compromised antigen test performance [6,30].

In conclusion, our data show that the SARS-CoV-2 antigen test (SD Biosensor distributed by Roche) does not have added value as a diagnostic gatekeeper in ER department for rapid differentiation between SARS-CoV-2-infected and non-infected patients, regarding its low sensitivity and the substantial risk of false positivity. Also, a lot of patients enter ER department after a longer symptomatic period and with a more advanced disease stage, which hampers the use of a cut-off of a maximum of 5–7 symptomatic days. However, differentiation between contagious and non-contagious individuals is possible with rapid antigen testing, opening up possibilities for events or gatherings different from a hospital population. The limited period of validity of negative antigen test results should be emphasised.

Disclosure statement

The author(s) declare that there are no conflicts of interest.

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