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ORIGINAL ARTICLE



SARS-CoV-2 antigen rapid immunoassay for diagnosis of COVID-19 in the emergency department

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ABSTRACT

Background: In the emergency department (ED) setting, rapid testing for SARS-CoV-2 is likely associated with advantages to patients and healthcare workers, for example, enabling early but rationale use of limited isolation resources. Most recently, several SARS-CoV-2 rapid point-of-care antigen tests (AGTEST) became available. There is a growing need for data regarding their clinical utility and performance in the diagnosis of SARS-CoV-2 infection in the real life setting EDs.

Methods: We implemented AGTEST (here: Roche/SD Biosensor) in all four adult and the one paediatric EDs at Charité – Universitätsmedizin Berlin in our diagnostic testing strategy. Test indication was limited to symptomatic suspected COVID-19 patients. Detailed written instructions on who to test were distributed and testing personnel were trained in proper specimen collection and handling. In each suspected COVID-19 patient, two sequential deep oro-nasopharyngeal swabs were obtained for viral tests. The first swab was collected for nucleic acid testing through SARS-CoV-2 real-time reverse transcriptase (rt)-PCR diagnostic panel (PCRTEST) in the central laboratory. The second swab was collected to perform the AGTEST. Analysis of routine data was prospectively planned and data were retrieved from the medical records after the inclusion period in the adult or paediatric ED. Diagnostic performance was calculated using the PCRTEST as reference standard. False negative and false positive AGTEST results were analysed individually and compared with viral concentrations derived from the calibrated PCRTEST.

Results: We included $n = 483$ patients including $n = 202$ from the paediatric ED. $N = 10$ patients had to be excluded due to missing data and finally $n = 473$ patients were analysed. In the adult cohort, the sensitivity of the AGTEST was 75.3 (95%CI: 65.8/83.4)% and the specificity was 100 (95%CI: 98.4/100)% with a SARS-CoV-2 prevalence of 32.8%; the positive predictive value was 100 (95%CI: 95.7/100)% and the negative predictive value 89.2 (95%CI: 84.5/93.9)%. In the paediatric cohort, the sensitivity was 72.0 (95%CI: 53.3/86.7)%, the specificity was 99.4 (95%CI: 97.3/99.9)% with a prevalence of 12.4%; the positive predictive value was 94.7 (95%CI: 78.3/99.7)% and the negative predictive value was 96.2 (95%CI: 92.7/98.3)%. Thus, $n = 22$ adult and $n = 7$ paediatric patients showed false negative AGTEST results and only one false positive AGTEST occurred, in the paediatric cohort. Calculated viral concentrations from the rt-PCR lay between 3.16 and 9.51 log₁₀ RNA copies/mL buffer. All false negative patients in the adult ED cohort, who had confirmed symptom onset at least seven days earlier had less than 5×10^5 RNA copies/mL buffer.

Conclusions: We conclude that the use of AGTEST among symptomatic patients in the emergency setting is useful for the early identification of COVID-19, but patients who test negative require confirmation by PCRTEST and must stay isolated until this result becomes available. Adult patients with a false negative AGTEST and symptom onset at least one week earlier have typically a low SARS-CoV-2 RNA concentration and are likely no longer infectious.

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Introduction

The COVID-19 pandemic requires sophisticated test strategies. From the beginning, a specific and highly sensitive reverse transcriptase polymerase chain reaction (rt-PCR) test was available (Corman *et al.* 2020a) and is the standard diagnostic tool to diagnose COVID-19. Nevertheless, the rt-PCR has a turn-around time of 6–8 hours under optimal circumstances and therefore a clinical need for more rapid diagnostic testing remains. Several companies developed SARS-CoV-2 antigen rapid immunoassays (Corman *et al.* 2020b) using lateral flow techniques, which can be used at patient bedside with a turn-around time of under 30 min. The price of speed is lower sensitivity and specificity compared to the rt-PCR test. The WHO test strategy suggests use of these tests in the community.

In the emergency department (ED), a wide spectrum of COVID-19 manifestations occur, including many patients who stay as outpatients after an initial diagnostic swab. Most of these patients are discharged before the test result is available. On the other hand, patients who require admission require isolation until the test result is available. Often, these patients remain in and crowd the ED. In some cases, special diagnostic wards have been set up, at the cost of a long and less efficient admission process. Therefore, we implemented rapid antigen immunoassay testing with the goal of early triage of patients to non-COVID-19 or COVID-19 wards. The current paper reports the first experiences with this strategy in the real-life setting of five EDs.

Clinical significance

- We provide data of the clinical use of rapid SARS-CoV-2 antigen tests (AGTEST) in symptomatic ED patients.
- It is shown that false negative test results may occur in patients with high viral concentrations, who are likely infectious.
- False positives are rare in this population.
- Thus, the recommended use of AGTEST is the early identification of symptomatic patients with COVID-19, but not the exclusion of infection in screening.

Methods

The study uses routine data within the EPICS-14 study (DRKS00019207) between 12 October 2020 and 24 November 2020, in four adult and the one paediatric EDs of the Charité.

The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin (EA1/163/20).

Patients

Patients were consecutively included based on a standard operating procedure established before the start of the test use. Test inclusion criteria were:

- Acute respiratory symptoms and/or loss of smell or taste.
- Contact with a confirmed COVID-19 case up to a maximum of 14 days before onset of any COVID-19 symptoms

(cough, fever, rhinorrhea, sore throat, dyspnoea, headache, muscle ache, loss of appetite, loss of body weight, nausea, abdominal pain, vomiting, diarrhoea, conjunctivitis, skin efflorescence, lymphadenopathy, apathy or somnolence).

- Clinical or radiological signs of viral pneumonia in the context of an outbreak in nursing homes or hospitals.

Contraindications for the use of the rapid antigen test in this setting were:

- Screening of asymptomatic patients.
- Screening of asymptomatic staff.
- Screening of asymptomatic persons returning from regions at risk.

The data were retrieved from the electronic medical records, pseudonymized, and analysed by Charité – Universitätsmedizin Berlin scientists.

Testing

Two oro-nasopharyngeal swabs were obtained from patients who met the inclusion criteria. The first was sent to the laboratory for a SARS-CoV-2 rt-PCR. The ED nurse, who took the swabs, according to the AGTEST instructions, immediately processed the second swab. Personal protective equipment (PPE) for this person included gloves, gown, an FFP-2 (N95) mask and protection goggles. A core ED team alongside written instructions trained the ED nurses.

During the study time, we applied the Roche SARS-CoV-2 rapid antigen test (Penzberg, Germany), manufactured by SD Biosensor following the manufacturer's instructions. After the drops of the swab fluid were applied to the test device, it was inserted in a prepared clear plastic bag, which was sealed and labelled with the name of the patient. A timer was set and the result, obtained after 15–30 min, was controlled by a second medical professional and both need to reach consensus on the interpretation of the test (four eyes principle). The test result was documented digitally in the hospital information system or on a separate paper list, allowing later data retrieval for the current analysis.

The rt-PCR interpretation was conducted without knowledge of the AGTEST result.

Viral concentration

rt-PCR testing was performed with the Roche cobas SARS-CoV-2 assay (Penzberg, Germany) on the Roche cobas® 6800 or 8800 system or the Roche MagNA Pure 96 System for RNA purification and the SARS-CoV-2 E-gene assay from TibMolbiol (Berlin, Germany) upon availability in one central laboratory. Viral RNA concentrations were calculated using assay-specific cycle threshold (Ct)-values and serial diluted cell culture supernatants. Quantification of viral RNA was done using photometrically quantified *in vitro* RNA transcripts and reference samples quantified by droplet digital PCR (<https://doi.org/10.2807/1560-7917.ES.2020.25.27>).

2001223; <https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045>). Due to different volumes present in different swab systems, e.g. 4.3 mL in cobas[®] PCR Media Uni Swab Kit or 1 mL in the Copan eSwab[™], viral concentrations are given in SARS-CoV-2 RNA copies per mL of sampling buffer.

Statistics

Descriptive data are given by the median and quartiles. Diagnostic test characteristics are calculated using 2×2 tables and listed with 95% confidence intervals. Comparison of median viral concentrations were done using the Wilcoxon test for unpaired samples. Calculations were performed using IBM[®] SPSS[®] Statistics, version 25 (Armonk, NY). Bayesian confidence intervals were calculated using available software (https://www.causascientia.org/math_stat/ProportionCI.html).

Results

Figure 1 shows the patient flow, from the number of retrieved patients to the analysis data set. Table 1 shows the

clinical characteristics of $n = 473$ analysed patients ($n = 271$ patients from the adult EDs and $n = 202$ from the paediatric ED). AGTEST results were available within 15–30 min. The median turnaround time and range (from laboratory registration to digital result communication) of the rt-PCR was 8.2 (3.8–39) hours.

Tables 2 and 3 show the 2×2 tables of the diagnostic accuracy of the rapid AGTEST in comparison with reference standard rt-PCR in the adult (Table 2) and paediatric (Table 3) patients.

Among the adult ED patients, $n = 22$ rapid AGTESTs were false negative, with no false positives; among the paediatric ED patients, $n = 7$ rapid AGTESTs were false negative, with $n = 1$ false positive. The false positive patient was an otherwise healthy two-year-old girl with mild respiratory symptoms (cough and rhinorrhea but no fever). Symptoms resolved after two days and her household tested SARS-CoV-2 negative with rt-PCR the same day.

Table 4 summarizes these patients with respect to the viral concentration derived from calibrated Ct levels of the reference rt-PCR, as described in the methods section.

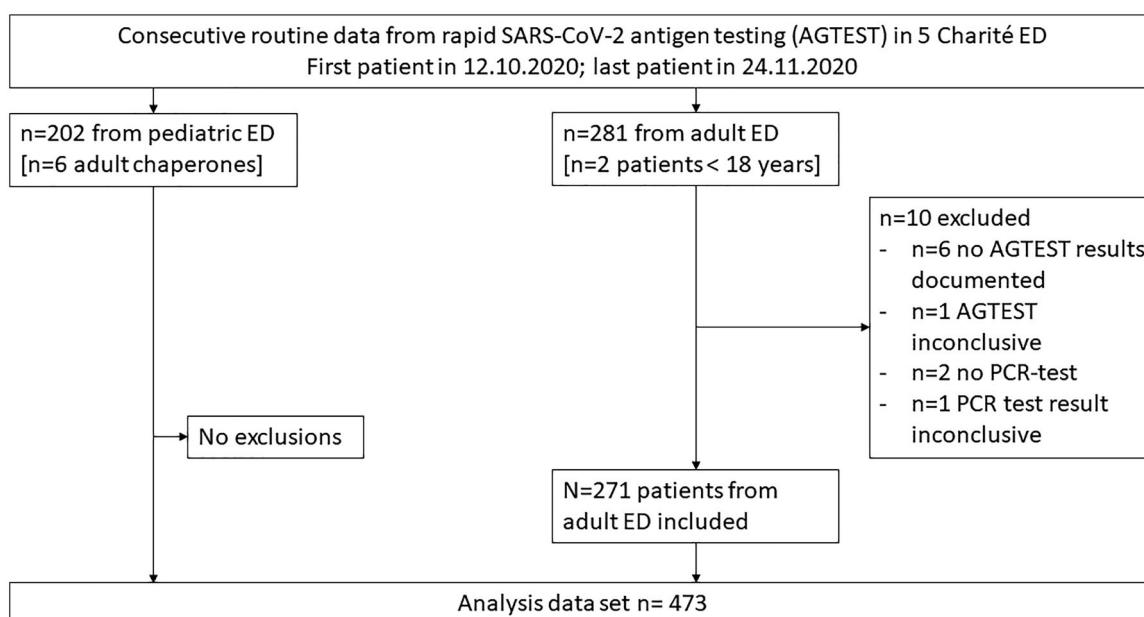


Figure 1. Patient flow diagram.

Table 1. Demographics, vital signs and frequency of the different inclusion criteria; values are medians and quartiles except adult age (mean, standard deviation and range).

	Adult ED (4 sites, $n = 271$)	Paediatric ED (1 site, $n = 202$)
Age (years)	59.7 SD 18 (21–98)	3 (1/9) ^a
Female sex (%)	41	45
Vital signs		
Respiratory rate (/min)	17 (15/21) nmiss = 80	23 (20/41) nmiss = 184
Temperature (°C)	37.2 (36.6/38.3) nmiss = 77	38.4 (37.3/39.7) nmiss = 50
Oxygen saturation (%)	97 (94/99) nmiss = 21	98 (96/100) nmiss = 148
Key inclusion criteria ^b (%)		
Respiratory symptoms	57.9	59.4
Loss of smell or taste	6.6	0.5
Contact to confirmed COVID-19 case and symptoms	12.2	18.3
Radiological signs of viral pneumonia	0.4	0.5
Other symptoms related to COVID-19	51.7	51.5
None	20.7	12.9

^a $n = 6$ chaperones for calculation of age excluded.

^bCompare to test indication in the methods section.

Figure 2 shows the viral concentration of true positive versus false negative AGTEST patients in both cohorts (adult ED, Figure 2(a); paediatric cohort Figure 2(b)). The false negative had significantly ($p < 0.001$ and $p = 0.017$, respectively) lower virus concentration compared to the true positive patients.

To assess their potential infectiousness, false negative patients, were analysed according to onset of symptoms, if available (see Table 4). Figure 3 shows the viral concentration depending on time since symptoms onset (as documented in the medical records) and labelled by the two cohorts. AGTEST negative but rt-PCR positive samples from adult patients with symptom onset at least one week earlier had viral RNA concentration below values for that successful virus

isolation in cell culture was regularly reported (Bullard *et al.* 2020, Cevik *et al.* 2021).

This is not true for the paediatric cohort, which may be due to uncertainties in symptom onset in this cohort.

Discussion

The current study analyses the routine use of rapid AGTEST in a cohort of symptomatic adult and paediatric patients from five university EDs, located in different catchment areas of Berlin, Germany. The sample represents the full spectrum of age and gender. We found a very high positive predictive value and conclude that the AGTEST is useful for early identification of COVID-19. Due to the number of false negative tests, with a broad variation in virus concentration, negative AGTEST results need to be interpreted with caution. At least in the adult cohort, knowledge of symptom onset, when reliable and available, seems to help in interpretation.

Test performance

The use of AGTEST in clinical routine differs in many regards from the evaluation in a virological laboratory. The quality of the individual swab, the use of fresh samples, and the performance of the test in the busy ED environment all influence test results. Recently, commercially available tests have been evaluated in the laboratory setting (Corman *et al.* 2020b) and revealed limits of detection between 2.08×10^6 and 2.88×10^7 copies per swab in six of seven tested products. Specificities ranged between 98.53% and 100% in five products, including the test used in our study. Thus, we

Table 2. Test characteristics and [95% confidence intervals]: sensitivity 75.3% [65.8/83.4], specificity 100% [98.4/100]; prevalence 32.8% [27.4/38.6]; positive predictive value 100% [95.7/100]; negative predictive value 89.2% [84.5/93.9].

	SARS-CoV-2 rt-PCR–	SARS-CoV-2 rt-PCR+	Total
SARS-CoV-2 Ag-Test–	182	22	204
SARS-CoV-2 Ag-Test+	0	67	67
Total	182	89	271

Table 3. Test characteristics and [95% confidence intervals]: sensitivity 72.0% [53.3/86.7], specificity 99.4% [97.3/99.9]; prevalence 12.4% [8.3/17.4]; positive predictive value 94.7% [78.3/99.7]; negative predictive value 96.2% [92.7/98.3].

	SARS-CoV-2 rt-PCR–	SARS-CoV-2 rt-PCR+	Total
SARS-CoV-2 Ag-Test–	176	7	183
SARS-CoV-2 Ag-Test+	1	18	19
Total	177	25	202

Table 4. Duration of any symptoms and viral concentrations in patients with false negative AGTEST.

Number	Age	Sex	COVID-19 related symptoms	Duration of symptoms (days)	Virus RNA Log10 copies/mL buffer
1	83	F	Yes	3	7.13
2	80	F	Yes	>7	4.41
3	58	M	No	n.a.	7.14
4	55	F	Yes	2	5.61
5	50	F	Yes	n.a.	4.93
6	45	M	Yes	2	5.67
7	24	M	Yes	1	9.51
8	70	M	Yes	7	4.76
9	77	F	Yes	>7	4.71
10	57	M	Yes	>7	4.40
11	50	M	Yes	0	7.27
12	56	M	No	n.a.	3.47
13	36	M	Yes	1	7.36
14	67	M	Yes	5	6.58
15	70	M	Yes	>7	3.16
16	64	F	Yes	5	3.16
17	84	M	Yes	>7	3.27
18	77	F	Yes	3	3.84
19	46	M	Yes	5	6.06
20	44	M	Yes	3	4.16
21	54	F	Yes	n.a.	5.56
22	75	F	Yes	7	4.71
23	11	F	Yes	2	5.46
24	17	M	Yes	7	5.62
25	17	F	Yes	>7	6.52
26	10	M	Yes	2	4.10
27	14	M	Yes	6	6.96
28	9	M	Yes	6	4.37
29	1	M	Yes	6	4.33

n.a.: not available.

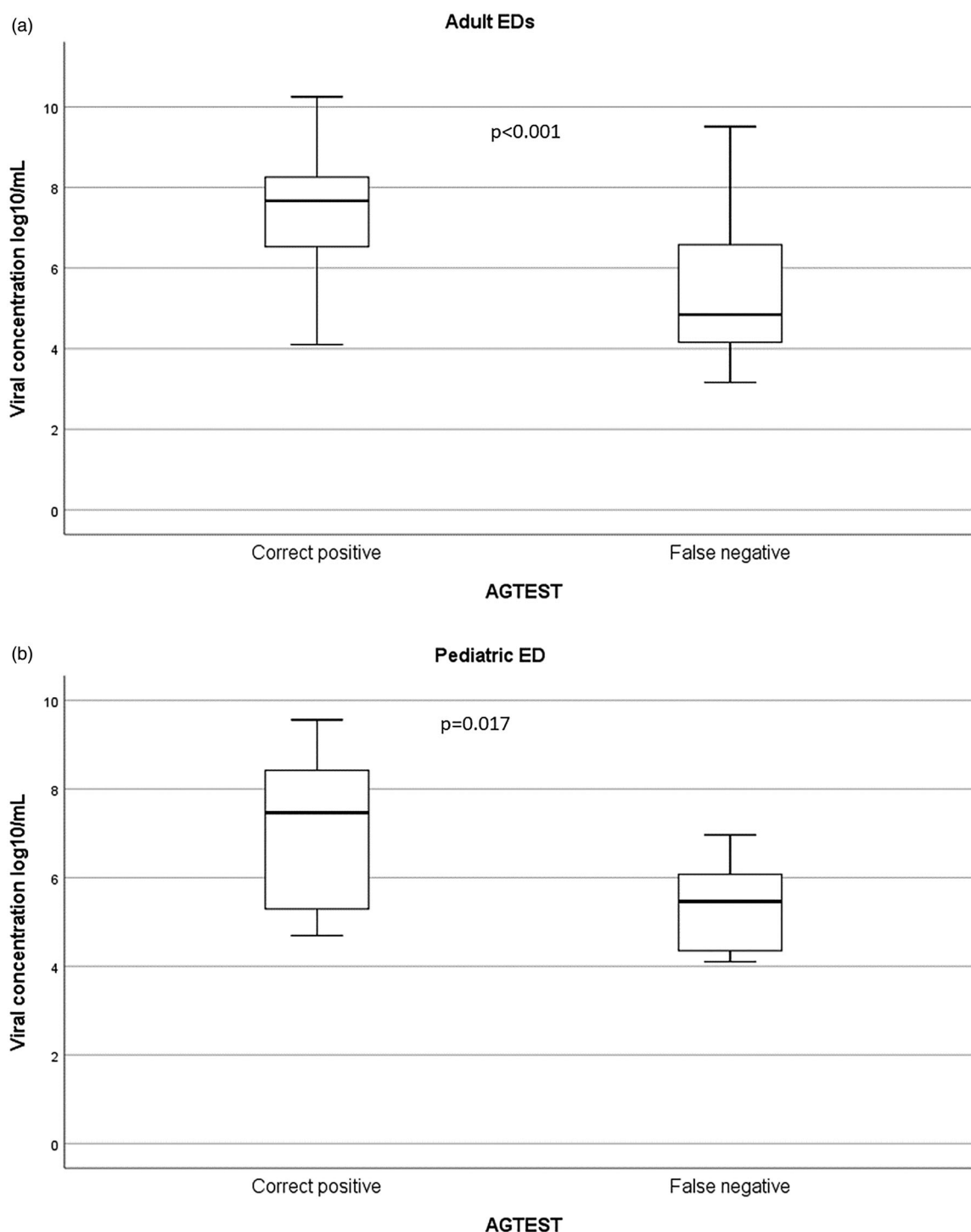


Figure 2. Viral concentration AGTEST true positives versus AGTEST false negatives (upper panel, adult ED; lower panel, paediatric ED).

confirm the test characteristics found in the laboratory in clinical practice use. Nevertheless, the observed false negative tests had viral concentrations, which in some cases exceed the detection limit cited above. This might be caused by different antigen expression in the early phase of the disease, as all false negative adults have levels below the detection once symptoms are known to have begun at least a week earlier. On the other hand, as this does not apply to the paediatric group, the information about symptom onset may be unreliable. Patients may report earlier symptoms,

which are unrelated to the actual disease or report only aggravation of pre-existing conditions. Therefore, in clinical practice, the theoretical view on rapid antigen tests cannot completely be confirmed (Mina *et al.* 2020).

We had only one false positive result in our cohort. We have previously shown before that false positive results of several rapid antigen test are not associated with any specific pathogen including other CoVs (Corman *et al.* 2020b) or characteristic, such as the presence of acids in the oral cavity resulting in positive signals. Regarding other respiratory viruses, the

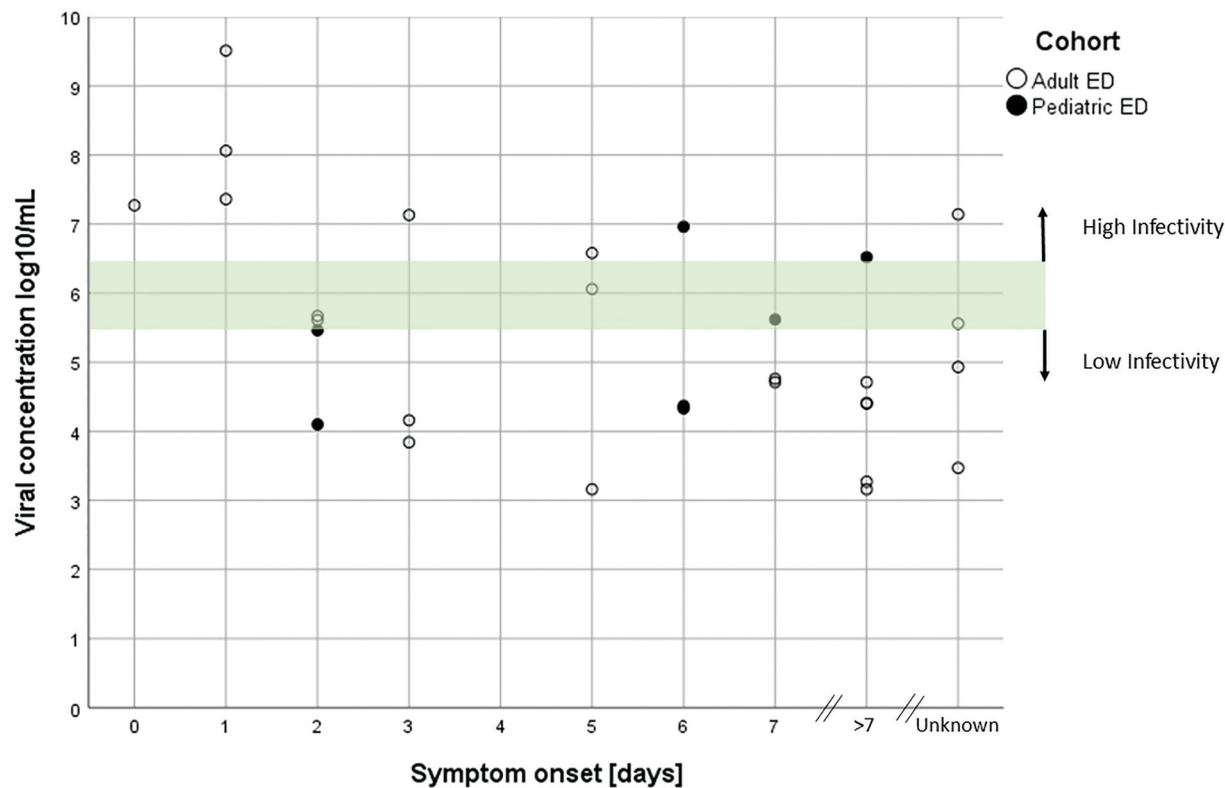


Figure 3. Viral concentration by time of symptom onset in false negative AGTEST.

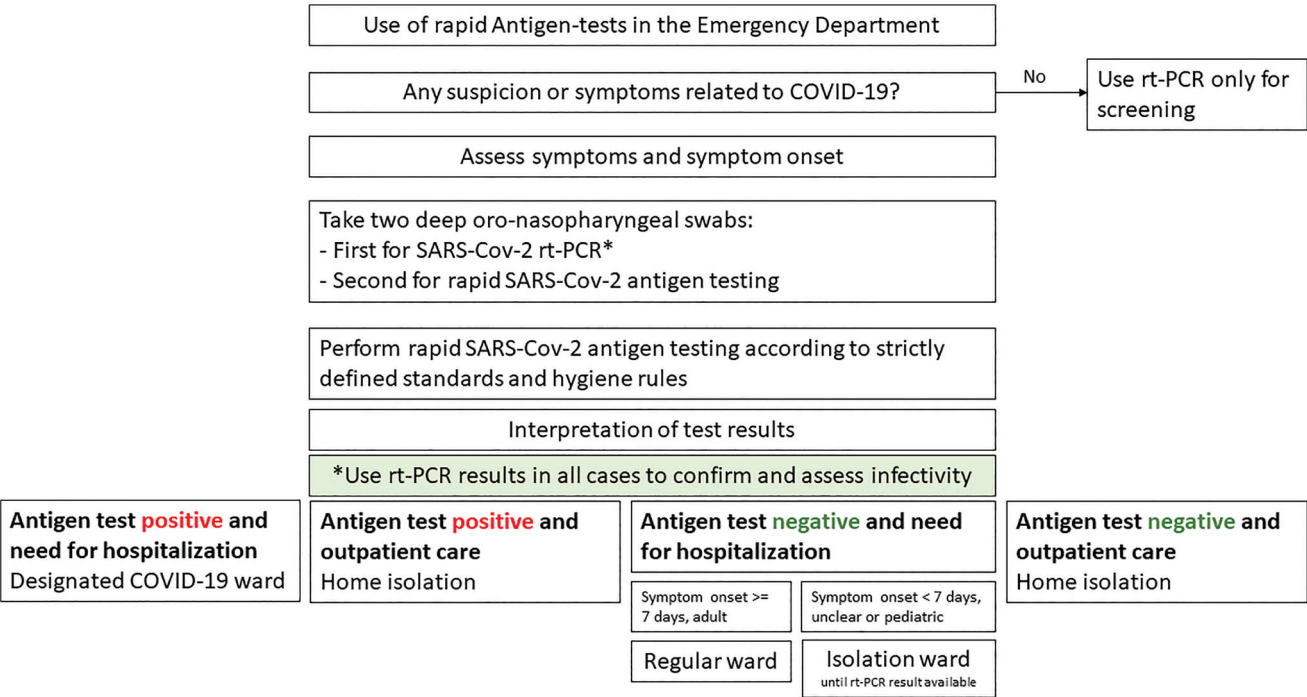


Figure 4. Use and interpretation of AGTEST in the ED setting.

weekly report of the influenza surveillance working group of Germany's public health institute (RKI) shows no significant activity of other respiratory infections during the study period (<https://influenza.rki.de/Wochenberichte.aspx>).

Assessment of virus concentration

The probability of successful virus cultivation from samples of the upper respiratory tract decreases significantly within the first week after onset of symptoms. In

immunocompetent patients, successful virus isolation is unlikely later than 10 days after onset of symptoms. Immunodeficient individuals, such as patients with hypogammaglobulinaemia or under rituximab, and severe COVID-19 cases are an exception to this rule with successful virus cultivation in isolated cases up to 20 days and longer after onset of symptoms (Moesker *et al.* 2016, Aydillo *et al.* 2020, Koff *et al.* 2020, Perera *et al.* 2020, Singanayagam *et al.* 2020, Wölfel *et al.* 2020).

The success of viral isolation correlates with viral RNA concentration quantified by rt-PCR. Often the cycle threshold (Ct) value has been used as a correlative measure of the viral concentration. However, variations of Ct values occur between different test systems, for reasons including different RNA extraction protocols, the use of different PCR reagents, and different PCR cyclers. Therefore, a comparison of Ct values between different studies has several shortcomings and a general threshold for estimation of infectiousness cannot be used. However, existing data indicate that isolation success below a viral RNA concentration of 10^6 to 10^7 copies/swab is infrequent. As shown here and elsewhere, the detection range of AGTEST overlaps with the time and the virus concentrations at which patients are likely to be infectious (Bullard *et al.* 2020, Cevik *et al.* 2021). Thus, taking a 1:5 predilution into account we concluded that in our setting an RNA load below 5×10^5 copies per mL buffer indicates that an individual is currently unlikely to be infectious. Reliable information about the time since onset of symptoms is crucial for the interpretation of AGTEST results. Presymptomatic patients sampled before peak viral concentration and corresponding infectiousness and symptomatic patients late in course, may both have viral concentrations below the limit of detection of AGTEST.

Therefore, by combining the AGTEST result and the knowledge of time of testing within the course of disease, and taking into account further information from patients medical history (e.g. underlying disease and living conditions), a good estimation regarding the potential infectiousness can be made, keeping in mind the limitations regarding symptom assessment mentioned above. Together with the excellent positive predictive value in symptomatic patients as shown here, this highlights AGTEST as a valuable tool in community healthcare settings and public health. Due to the highly vulnerable environment of a hospital, the fact that some patients with false negative AGTEST have high virus concentrations and are clearly infectious (see Table 4 and Figure 3), the use in the ED has to be strictly regulated and use for hospital admission screening in asymptomatic patients does not seem warranted. Furthermore, patients sampled late in course (>7 days post symptom onset) are more likely to be missed by AGTEST, so that, irrespective of reduced or absent of infectivity in these patients, an rt-PCR, e.g. from the lower respiratory tract, should be applied for confirmation of a potential COVID-19 diagnosis.

Interpretation and decision making in the ED

Combining the diagnostic test performance in a real-life setting of adult and paediatric EDs and the analysis of the viral

load in true positive and false negative AGTESTs, we created a flowchart for the use of AGTEST. We believe that in the setting of hospital-based emergency care, all AGTEST results should be validated by a second swab analysed with rt-PCR. AGTEST should be used ideally in symptomatic patients and may not detect pre-symptomatic individuals. In general, a negative AGTEST reduces the risk of being infected with SARS-CoV-2, but does not mean that infection is absent. A repetition of the test after 1–2 days may be a strategy to gain more information in settings, where rt-PCR is not available (Figure 4).

Limitations

The current paper uses routine data. The main advantage is that no selection bias occurs and one disadvantage is that the different steps of the procedure are done in the clinical context of a busy ED. As two different swabs were used for the rapid AGTEST and the rt-PCR, this may have partly influenced test results in an unclear direction.

Conclusions

We conclude that the use of AGTEST among symptomatic patients in the emergency setting is useful for the early identification of COVID-19, but patients who test negative require confirmation by PCRTTEST and must stay isolated until this result becomes available.

Adult patients with a false negative AGTEST and symptom onset at least one week earlier have typically a low SARS-CoV-2 RNA concentration and have likely passed the infectious period.

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Disclosure statement

The authors report no conflicts of interest related to this paper.

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