

Evaluation of eleven rapid tests for detection of antibodies against SARS-CoV-2

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Published April 24th, 2020

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1 Summary

Background

SARS-CoV-2, causing COVID-19, has emerged to cause a human pandemic. Molecular diagnostic tests were rapidly developed, and detection of SARS-CoV-2 in respiratory samples by using PCR is the standard laboratory diagnostic tool. A number of rapid (point-of-care) tests for detection of antibodies against SARS-CoV-2 have also become available, detecting immunoglobulins type M (IgM) and/or type G (IgG). In most cases, the tests come with limited documentation and without independent evaluation.

Objective

Our aim was to perform a limited evaluation of the diagnostic performance of eleven rapid tests for detection of antibodies against SARS-CoV-2 and compare their ability to indicate present and past infection in selected clinical settings.

Methods

All participants fulfilled the Norwegian testing criteria for COVID-19, and samples collected by a swab from the upper airways were tested with PCR against E-gen SARS-CoV-2 at a clinical microbiology laboratory. We evaluated the antibody detecting rapid tests' performances in three arms; 1) 20 hospitalized patients with PCR-confirmed COVID-19, 2) 23 recovered participants with previously PCR-confirmed COVID-19, who had not required hospitalization, and 3) 49 participants with suspected COVID-19 presenting at a primary care emergency room. User-friendliness was evaluated by the biomedical laboratory scientists performing the tests.

Results

All the eleven tests detected IgM and/or IgG antibodies in hospitalized COVID-19 patients, though with varying sensitivities. In participants who had recovered from COVID-19, there were differences between tests in the IgG positivity rates, with five tests having a sensitivity below 65%. In participants with suspected COVID-19 infection, who were tested simultaneously with PCR and rapid tests, the rapid tests had very low sensitivities, but high specificities. Despite comparable sensitivities, the tests did not necessarily give the same result in all participants. With some exceptions, most rapid tests were reported easy to perform and interpret.

Conclusions and recommendations

In this assessment, rapid tests did not seem to be suited as stand-alone tests to detect present infection in a Norwegian primary care emergency room population, as sensitivity in the early stages of disease was too low. Future investigations may show if rapid tests have a supplemental role in the acute phase.

All the rapid tests were able to detect SARS-CoV-2 antibodies, although positivity rates varied and were generally higher in the study arm of more severely affected participants. To confirm past infection, we recommend the use of rapid tests with high IgG sensitivity and specificity in recovered COVID-19 patients. We also recommend using tests that are user-friendly and with a low proportion of invalid/inconclusive tests. Our sample size was limited, and our results are therefore preliminary and must be interpreted with caution, but tests A, B, D, and possibly K (Table 1), seem to fulfill these recommendations.

2 Background

In December 2019, Wuhan city in Hubei Province, China, became the center of an outbreak of a severe pneumonia, later identified as caused by a novel coronavirus SARS-CoV-2 [1]. Human-to-human transmission of SARS-CoV-2 occurs primarily through respiratory droplets. Due to the rapid spread of the virus WHO declared SARS-CoV-2 a worldwide pandemic by February 2020. As of April 23rd, there were 2.5 million confirmed cases worldwide and 176 000 reported deaths [2]. The clinical presentation of COVID-19 varies from asymptomatic disease, via mild upper respiratory infection to severe pneumonia with respiratory failure and death.

Laboratory methods for diagnosing COVID-19

Currently in Norway, COVID-19 is diagnosed by detection of SARS-CoV-2 RNA by PCR in a sample collected by a swab from the upper airways. PCR is performed at medical microbiology laboratories, requiring advanced analytical instruments and trained personnel. Together with growing concerns regarding shortage of sampling equipment and necessary reagents, this limits the number of people currently being tested for COVID-19.

Detecting humoral immune response to the virus is a different analytical approach. Generally, immunoglobulin type M (IgM) is produced during the early stages of an infection, usually followed by production of immunoglobulin type G (IgG). For infection with the SARS-CoV-2 virus, however, there is some evidence that IgG may be detected at the same time as IgM, or even earlier [3].

Several enzyme immune assays (EIA-methods) detecting and quantifying antibodies against SARS-CoV-2, both commercial and in-house, will shortly be available in Norwegian hospital laboratories. At the same time, a substantial number of point-of-care rapid test kits are currently being marketed. These rapid tests are for professional use, they make use of capillary or venous whole blood, plasma or serum, and they are designed to qualitatively detect IgM and/or IgG antibodies against SARS-CoV-2. The results are read visually after 10-15 minutes. Even though most of the rapid tests are CE/IVD approved, they generally come with very limited documentation on test performance, and with a few exceptions without any manufacturer independent evaluation [4, 5]. To determine a rapid test's ability to detect past infection, its performance with regard to IgG antibodies is emphasized by the United Kingdom Medicines & Healthcare products Regulatory Agency [6].

3 Objectives

Our main objective was to perform a limited evaluation of the diagnostic accuracy of a selection of rapid test for COVID-19 entering the Norwegian market. In particular, we aimed to evaluate if the tests could be used to confirm past infection. The project was designed as a quality assurance study to compare the performance of the tests in selected clinical settings. Furthermore, we wanted to evaluate the user-friendliness of the rapid tests.

4 Methods

The evaluation was organized as a collaboration between the municipality of Kristiansand, the Norwegian Institute of Public Health, and the Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus). Sørlandet hospital in Kristiansand, Oslo University hospital, Ullevål, and Bergen municipality primary care emergency room also contributed.

The eleven rapid tests chosen for evaluation was a convenience sample, consisting of the tests that could be delivered to Noklus before the set deadline of April 1st, 2020 (Table 1). Suppliers provided their tests free of charge to Noklus and did not pay for the evaluation. In sending the tests, they consented to having the results published. All rapid tests were performed in accordance with manufactures' instructions under optimal and standardized conditions, and by experienced biomedical laboratory scientists, using venous blood samples with K₂-EDTA anticoagulant.

Study design

We evaluated the performance of the point-of-care rapid tests in three study arms:

1. 20 patients hospitalized at Oslo University hospital, Ullevål, with PCR-confirmed COVID-19.
Days since onset of symptoms:
 - <7 days for one patient
 - 7-13 days for three patients
 - 14+ days for 16 patients
2. 23 participants with previously PCR-confirmed COVID-19 in the municipality of Kristiansand, who had not required hospitalization.
 - Median days since onset of symptoms was 30 (range 27-36)
3. 49 participants fulfilling the criteria for being PCR-tested for COVID-19 at the primary care emergency room of Bergen municipality.
 - Median days since onset of symptoms was 8 (range 2-34)

In arms 2 and 3, participants consented to having drawn one tube of K₂-EDTA whole blood to be used for evaluation of the rapid tests. In arm 1, surplus K₂-EDTA whole blood left over from hematology analyses was used. In arms 1 and 2, PCR-confirmed COVID-19 was the inclusion criterion, but in arm 3, PCR results were collected in addition to the rapid test results. We also collected the date and laboratory used for the PCR test, and the date of onset of symptoms (in arm 1 in categories <7, 7-13 and 14+ days).

Statistical analyses

PCR results from the clinical microbiology laboratories were used as comparison when investigating diagnostic accuracy of the rapid tests. In all arms, we calculated the tests' sensitivities (positivity rates). Sensitivity was defined as the proportion of patients diagnosed with COVID-19 using PCR on respiratory samples, who had detectable IgM or IgG antibodies on the rapid tests. In arm 3, we also calculated specificity, defined as the proportion of participants with negative PCR tests who were also antibody negative. Further, in arm 3, we stratified positivity rates according to days since onset of symptoms (<7 or 7+ days). IgM and IgG test results were evaluated separately, except for test E, which detected "total antibodies". Because sample sizes were small, 80% confidence intervals for binomial proportions were calculated using the adjusted Wald method [7].

We also report the number of invalid/inconclusive tests, as well as user-friendliness reported by biomedical laboratory scientists performing the tests.

Ethical considerations

The project was approved by the Data protection officer at each test site. Oral consent was obtained from participants in study arms 2 and 3 at collection of blood samples.

5 Results

Results from hospitalized participants (arm 1) showed that the eleven tests detected IgM and/or IgG antibodies in this population, though with varying sensitivities (Tables 2 and 3).

Arm 2 consisted of participants who had recovered from PCR-confirmed COVID-19 without requiring hospitalization. In this population, tests A, B, C, and D had higher IgG positivity rates than tests E, F, H, I, and J. Confidence intervals (80%) for test K were overlapping with the others (Table 3). Five of the tests had a sensitivity below 65% for IgG.

Of the 49 participants with suspected COVID-19 (arm 3), 23 had positive PCR tests, and 26 tested negative. In this population, the rapid tests had very low sensitivities when compared to PCR (Tables 2 and 3). Positivity rates however, especially for IgM, increased with increasing number of days since onset of symptoms (Table 4), although numbers were too small to draw firm conclusions. Since few rapid tests were positive in participants with negative PCR tests, calculated specificities were high.

Not all participants with confirmed COVID-19 had detectable antibodies. Also, despite comparable sensitivities, the rapid tests did not necessarily give the same result in all participants. For test K, IgM and IgG results were identical in all participants in arms 1 and 2, and in 46 out of 49 participants in arm 3, leaving the question of whether the test distinguishes between IgM and IgG. In arm 2, tests I and J had higher positivity rates for IgM than IgG, even though all samples were collected more than 14 days after onset of symptoms.

Tests G and H were judged as less user-friendly (Table 1), both when performing the tests and reading the results. In addition, they had a high proportion of inconclusive or invalid tests. Tests C and E were judged easy to perform but difficult to read. Test C additionally had a high proportion of inconclusive or invalid tests.

6 Discussion

PCR for detection of viral RNA and antibody detection tests use different test principles and are not interchangeable. Early in the infection, we expect PCR to be positive and antibody detection tests to be negative. As the infection progresses and clears, most patients will develop detectable antibodies, while the virus is gradually cleared from the airways. Thus, even under the best of circumstance, PCR is far from an ideal “gold standard” for comparison of the rapid tests.

If a participant with PCR-confirmed COVID-19 has no detectable antibodies, there are several possibilities: (i) the stage of the infection is too early for antibodies to have been formed, (ii) the level of antibodies produced is too low to be detected, (iii) the participant does not form antibodies ([3, 8]), (iv) a false negative rapid test result, or v) a false positive PCR result (wrong labeling for instance). Similarly, if a participant with negative SARS-CoV-2 PCR has detectable antibodies on a rapid test, there are a number of plausible explanations: (i) false positive rapid test result (for instance cross reaction with other antibodies), (ii) false negative PCR result (pre-analytical or analytical issues), or (iii) the participant recovered from COVID-19 and cleared the virus prior to PCR testing. Comparing results from several rapid tests with each other may provide some clue as to which is the most likely explanation in each case, but until we have a gold standard method for antibody detection, we cannot be certain which is true.

Most tests had higher IgG positivity rates in arm 1 (hospitalized patients) than in arm 2 (recovered, community treated participants). This is to be expected if the tests have different detection limits; hospitalized patients are likely more severely affected, and more severe infection has been associated with higher levels of antibodies [3, 9]. It is worth noticing that according to manufacturers’ information, most of the rapid tests have been evaluated in samples from hospitalized populations.

Most COVID-19 recovered participants (arm 2) should have had sufficient time to develop IgG antibodies, as median seroconversion time has been reported at around 13-14 days after onset of symptoms [3, 9]. The rapid tests displayed varying degrees of IgG positivity rates in this population. One might speculate that antibody levels were lower in this group, who were less severely affected than patients in study arm 1, which may affect rapid test performance. We were not able to evaluate the tests’ performances in a population that had been through a COVID-19 infection with very little or no symptoms.

In arm 3, most participants had a short duration of symptoms. All of the rapid tests in our study had low sensitivities compared to PCR in this population, confirming *a priori* expectations. It is possible that the rapid tests, and IgM in particular, may still have a supplemental role in diagnosing COVID-19 in the acute phase. In any case, an isolated positive IgM result should be followed by a second sample to detect IgG-seroconversion and thereby rule out the possibility of an unspecific IgM result. Furthermore, a negative result in the acute phase of infection should never be used to exclude COVID-19.

In arm 3, we also calculated specificities of the rapid tests. We do not know if a participant with a negative PCR test and a positive IgG rapid test is someone who has recovered from COVID-19, or if the rapid test result is a false positive. We therefore have to be cautious when interpreting calculated specificities, and in the present study, we do not evaluate the tests based on this parameter.

7 Conclusions and recommendations

All tests were able to detect SARS-CoV-2 antibodies in participants with PCR-confirmed COVID-19, although positivity rates varied and were generally higher in the study arm of more severely affected patients. In the population with suspected COVID-19, the rapid tests did not have any diagnostic value. As the sample size was small, further studies are needed to assess the usefulness of antibody rapid tests in the acute phase of COVID-19 as a supplement to PCR.

When a rapid test is used to confirm past COVID-19 infection, we recommend using a test with high IgG positivity rates in recovered COVID-19 patients, in line with the specification criteria for serology point of care tests published by the United Kingdom Medicines & Healthcare products Regulatory Agency [6]. We also recommend using tests that are user-friendly and have a low proportion of invalid/inconclusive tests. In our study, it seems that tests A, B, D, and possibly K (Table 1) fulfill these recommendations, under the assumption that their specificities are high. In a population where the prevalence of COVID-19 is low, however, there is a risk of false positive results, which we cannot at present quantify because of the lack of knowledge of the tests' specificities. We acknowledge this limitation of the study, in addition to the limited sample size, and our results are therefore preliminary and must be interpreted with caution.

As a negative antibody test performed during the early phase of infection cannot rule out COVID-19, we recommend not using a rapid test until at least two weeks after onset of symptoms. A negative test may be repeated, but not all COVID-19 infected patients develop antibodies, and not all antibodies are necessarily detected by the rapid test. Thus, a negative rapid test does not rule out current nor past COVID-19 disease.

Many rapid tests are now marketed with very limited documentation. Our results show varying sensitivity and user-friendliness, and we highly recommend performing an independent evaluation before using a test. It is important to evaluate the test performance in the population it is intended for. Thus, when a rapid test is to be used to detect past infection in people who have not required hospitalization, it is not sufficient to validate the test in a hospitalized population. As more rapid tests are emerging and EIA becomes increasingly available, our group will continue to evaluate tests. We will use EIA methodology as a comparison method in addition to PCR, and also test in sera collected before the COVID-19 pandemic. This will allow us to investigate diagnostic accuracy and analytical properties of the rapid tests more thoroughly.

8 References

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9 Tables

Table 1. Rapid tests included and user-friendliness.

Test acronym	Test name	Manufacturer	User-friendliness
A	Acro 2019-nCoV IgG/IgM Rapid Test	Acro Biotech Inc, USA	Easy to perform test. Easy to read results.
B	ONsite Covid-19 IgG/IgM Rapid Test	CTK Biotech, Inc, USA	Hard to avoid air bubbles in buffer vial. Easy to read result. Light pink background not optimal for reading weak positive results.
C	COVID-19 IgG/IgM Rapid Test Kit	WuHanUNscience Biotechnology Co., China	Ran out of buffer early at one test site. Difficult to read result due to colored background. Blood drawn into the IgM test area on several tests. 21% invalid/inconclusive tests.
D	A Rapid IgM-IgG Combined Antibody Test Kit for SARS-CoV-2	Jiangsu Medomics medical technology Co., China	Easy to perform test. Easy to read results.
E	Wantai SARS-CoV-2 Ab Rapid Test Kit	Beijing Wantai Biological Pharmacy Enterprise Co, China	Easy to perform test. Strong pink background made it difficult to read weak positive results.
F	Novel coronavirus 2019-nCoV) IgM/IgG Antibody Combo Test Kit	Hangzhou Laihe Biotech Co, China. (LYHER)	Easy to perform test. Easy to read results.
G	Novel Coronavirus (SARS-CoV-2) IgM Antibody Detection Ki	RayBiotech, USA	Buffer vial spills easily. Requires mixing of blood and buffer pre analyses and a pipette for analyses. Difficult to read results due to blood drawn into the test area. 16% invalid/inconclusive tests.
H	Novel Coronavirus (SARS-CoV-2) IgG Antibody Detection Kit	RayBiotech, USA	Buffer vial spills easily. Requires mixing of blood and buffer pre analyses and a pipette for analyses. Difficult to read results due to blood drawn into the test area. 23% invalid/inconclusive tests.
I	Lumiratek COVID-19 IgG/IgM Hurtigtest kassett	Hangzhou Biotest Biotech Co., China	Easy to perform test. Easy to read results.
J	Covid-19 IgG/IgM Rapid Test Cassette	SureScreen Diagnostics, UK	Easy to perform test. Easy to read results.
K	SARS-CoV-2 IgG/IgM Rapid Test	Zhuhai Encode Medical Engineering Co., China	Easy to perform test. Easy to read results.

Table 2. Test results, IgM.

	Arm 1 (N=20)	Arm 2 (N=23) ^a	Arm 3 (N=49) ^b		Inconclusive tests
	Sensitivity	Sensitivity	Sensitivity	Specificity	N (arm 1,2,3)
A	0.30 (0.19-0.44)	0.52 (0.39-0.65)	0.35 (0.23-0.48)	0.85 (0.73-0.92)	0,0,0
B	0.80 (0.66-0.89)	0.87 (0.75-0.94)	0.22 (0.13-0.35)	0.92 (0.82-0.97)	0,0,0
C	0.35 (0.23-0.49)	0.48 (0.35-0.61)	0.00 (0.00-0.22)	0.75 (0.56-0.88)	9,4,4
D	0.65 (0.51-0.77)	0.60 (0.46-0.73)	0.24 (0.13-0.39)	0.87 (0.75-0.94)	0,1,0
F	0.80 (0.66-0.89)	0.91 (0.80-0.97)	0.48 (0.35-0.61)	0.88 (0.78-0.95)	0,0,0
G	0.15 (0.07-0.28)	0.43 (0.31-0.57)	0.27 (0.14-0.47)	0.68 (0.54-0.80)	6,3,3
I	0.80 (0.66-0.89)	0.83 (0.70-0.91)	0.30 (0.20-0.44)	0.88 (0.78-0.95)	0,0,0
J	0.65 (0.51-0.77)	0.83 (0.70-0.91)	0.30 (0.20-0.44)	0.85 (0.73-0.92)	0,0,0
K	0.80 (0.66-0.89)	0.74 (0.61-0.84)	0.22 (0.13-0.35)	0.96 (0.87-0.99)	0,0,0

^aN for test D: 20^bN for test C: 15, for test D: 40, for test G: 30**Table 3. Test results, IgG.**

	Arm 1 (N=20)	Arm 2 (N=23) ^a	Arm 3 (N=49) ^b		Inconclusive tests
	Sensitivity	Sensitivity	Sensitivity	Specificity	N (arm 1,2,3)
A	0.90 (0.78-0.96)	0.87 (0.75-0.94)	0.17 (0.09-0.30)	0.92 (0.82-0.97)	0,0,0
B	0.85 (0.72-0.93)	0.83 (0.70-0.91)	0.04 (0.01-0.14)	1.00 (0.97-1.00)	0,0,0
C	0.80 (0.66-0.89)	0.87 (0.75-0.94)	0.00 (0.00-0.22)	0.67 (0.48-0.81)	3,1,3
D	0.85 (0.72-0.93)	0.85 (0.72-0.93)	0.06 (0.01-0.19)	0.91 (0.80-0.97)	0,0,0
E ^c	0.65 (0.51-0.77)	0.52 (0.39-0.65)	0.04 (0.01-0.14)	0.96 (0.87-0.99)	0,0,0
F	0.75 (0.61-0.85)	0.39 (0.27-0.52)	0.04 (0.01-0.14)	1.00 (0.97-1.00)	0,0,0
H	0.60 (0.46-0.73)	0.48 (0.35-0.61)	0.09 (0.02-0.27)	0.79 (0.65-0.89)	4,7,6
I	0.80 (0.66-0.89)	0.52 (0.39-0.65)	0.04 (0.01-0.14)	1.00 (0.97-1.00)	0,0,0
J	0.80 (0.66-0.89)	0.52 (0.39-0.65)	0.04 (0.01-0.14)	1.00 (0.97-1.00)	0,0,0
K	0.80 (0.66-0.89)	0.74 (0.61-0.84)	0.13 (0.06-0.25)	1.00 (0.97-1.00)	0,0,0

^aN for test C: 20^bN for test C: 15, for test D: 40, for test H: 30^cTotal antibodies

Arm 1 - Oslo University Hospital, Ullevål

Arm 2 – Kristiansand municipality

Arm 3 – Bergen municipality primary care emergency room

Table 4. Sensitivity stratified by days since onset of symptoms, study arm 3.
Median number of days was 5.

Test	IgM		IgG	
	<7 days (N=13)	7+ days (N=10)	<7 days (N=13)	7+ days (N=10)
A	0.31 (0.18-0.49)	0.40 (0.23-0.60)	0.00 (0.00-0.06)	0.40 (0.23-0.60)
B	0.08 (0.01-0.23)	0.40 (0.23-0.60)	0.00 (0.00-0.06)	0.10 (0.02-0.29)
C	0.00 (0.00-0.30)	0.00 (0.00-0.47)	0.00 (0.00-0.30)	0.00 (0.00-0.49)
D	0.10 (0.02-0.29)	0.43 (0.23-0.66)	0.00 (0.00-0.08)	0.14 (0.03-0.39)
E*			0.00 (0.00-0.06)	0.10 (0.02-0.29)
F	0.38 (0.23-0.56)	0.60 (0.40-0.77)	0.00 (0.00-0.06)	0.10 (0.02-0.29)
G	0.00 (0.00-0.15)	0.50 (0.27-0.73)		
H			0.00 (0.00-0.15)	0.17 (0.04-0.44)
I	0.15 (0.06-0.32)	0.50 (0.31-0.69)	0.00 (0.00-0.06)	0.10 (0.02-0.29)
J	0.15 (0.06-0.32)	0.50 (0.31-0.69)	0.00 (0.00-0.06)	0.10 (0.02-0.29)
K	0.00 (0.00-0.06)	0.50 (0.31-0.69)	0.00 (0.00-0.06)	0.30 (0.15-0.50)