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Journal of Clinical Virology 131 (2020) 104614

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

SARS-CoV-2 sample-to-answer nucleic acid testing in a tertiary care emergency department: evaluation and utility

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ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
PCR
sample-to-answer

ABSTRACT

Background: Rapid sample-to-answer tests for detection of SARS-CoV-2 are emerging and data on their relative performance is urgently needed.
Objectives: We evaluated the analytical performance of two rapid nucleic acid tests, Cepheid Xpert® Xpress SARS-CoV-2 and Mobidiag Novodiag® Covid-19, in comparison to a combination reference of three large-scale PCR tests. Moreover, utility of the Novodiag® test in tertiary care emergency departments was assessed.
Results: In the preliminary evaluation, analysis of 90 respiratory samples resulted in 100% specificity and sensitivity for Xpert®, whereas analysis of 107 samples resulted in 93.4% sensitivity and 100% specificity for Novodiag®. Rapid SARS-CoV-2 testing with Novodiag® was made available for four tertiary care emergency departments in Helsinki, Finland between 18 and 31 May, coinciding with a rapidly declining epidemic phase. Altogether 361 respiratory specimens, together with relevant clinical data, were analyzed with Novodiag® and reference tests: 355/361 of the specimens were negative with both methods, and 1/361 was positive in Novodiag® and negative by the reference method. Of the 5 remaining specimens, two were negative with Novodiag®, but positive with the reference method with late Ct values. On average, a test result using Novodiag® was available nearly 8 hours earlier than that obtained with the large-scale PCR tests.
Conclusions: While the performance of novel sample-to-answer PCR tests need to be carefully evaluated, they may provide timely and reliable results in detection of SARS-CoV-2 and thus facilitate patient management including effective cohorting.

1. Introduction

Patients with COVID-19 disease can present with a number of unspecific symptoms. Thus, the diagnosis of COVID-19 relies on molecular testing of SARS-CoV-2, typically from respiratory specimens [1]. Several methods are available for this purpose [2–7], both large-scale testing platforms and simple cartridge-based tests for rapid examination of one or few samples at a time.

Rapid and reliable laboratory testing is essential for patient management and infection control of COVID-19 and it is a prerequisite for appropriate patient cohorting within hospitals. Rapid SARS-CoV-2 molecular testing that can be performed near the healthcare facility is urgently needed. A number of such tests have now become available, and variable performance values have been reported for them [8–15].

We aimed to evaluate the analytical performance of two sample-to-answer rapid PCR tests for the detection of SARS-CoV-2 infection, Cepheid Xpert® Xpress SARS-CoV-2 and Mobidiag Novodiag® Covid-19, and to assess the usefulness of such tests at tertiary care emergency departments. Patients who become hospitalized through emergency departments are among those who will benefit the most from quickly available test results. Here we describe the utility of a rapid test compared to large-scale testing platforms in such a patient care setting.

2. Materials and methods

The study was conducted at the Helsinki University Hospital Laboratory (HUSLAB), Finland, according to permit HUS/157/2020 (Helsinki University Hospital, Finland).

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https://doi.org/10.1016/j.jcv.2020.104614
Received 7 July 2020; Received in revised form 24 August 2020; Accepted 26 August 2020
Available online 27 August 2020

Table 1
Features of the evaluated and reference tests. LDT, laboratory developed test; LoD, limit of detection, TCID50, 50 percent tissue culture infective dose.

	Evaluated tests		Reference tests		
	Cepheid Xpert® Xpress SARS-CoV-2	**Mobidiag Novodiag® Covid-19**	**Roche Diagnostics Cobas® SARS-CoV-2**	**Mobidiag Amplidiag® Covid-19 kit**	**LDT**
Intended use	Nasopharyngeal, oropharyngeal, nasal, or mid-turbinate swab and/or nasal wash/ aspirate	Nasopharyngeal sample	Nasal, nasopharyngeal or oropharyngeal swab samples	Nasopharyngeal sample	Nasal, nasopharyngeal, oropharyngeal swab, nasopharyngeal/tracheal aspirate, sputum or faeces.
Sample volume µl	300	250	350	360	250
Targets	E and N2	orf1ab and N	orf1ab and E	orf1ab and N	N
Internal controls	Sample processing control, probe check control	Sampling control, process control	Process control	Sampling control	no
External controls	Not included, but recommended by the manufacturer	Not included, but recommended by the manufacturer	Negative control and a low titer positive control	Negative and positive controls	2 negative controls (H_2O, no-template control), positive control
LoD, as reported by the manufacturer	250 c/ml	313 c/ml	0,009 TCID50/ml (ORF1/a)/ 0,003 TCID50/ml (E)	1250 c/ml	
Assay run time	~45 min	~1 h 15 min	~3 h	~2,75h	~2 h + extraction ~1 h

2.1. Test methods

The evaluated tests were Cepheid Xpert® Xpress SARS-CoV-2, software version 1.0, later referred to as Xpert®, and Mobidiag Novodiag® Covid-19, software version v1.0.1, later Novodiag®. Both of these tests are cartridge-based platforms that perform sample preparation, nucleic acid extraction, amplification, and detection of the target sequences.

The three platforms used in our laboratory for routine diagnostics of SARS-CoV-2 were deployed as reference tests: the WHO recommended laboratory-developed test (LDT), modified from Corman and others [2], cobas® SARS-CoV-2 test kit on the cobas® 6800 platform (Roche Diagnostics, Basel, Switzerland), and Amplidiag® COVID-19 test on the Amplidiag® Easy platform (Mobidiag, Espoo, Finland). We have separately evaluated the performance of the three reference methods used in our laboratory, and shown a good agreement between them [7]. See Table 1 for the main features of the tests.

2.2. Patient samples and proficiency samples for the analytical evaluation

107 nasopharyngeal or oropharyngeal swab specimens were included in the evaluation: all were tested with Novodiag®, and 90 with Xpert®, as well. Of the 107 specimens, 97 were sent to HUSLAB for SARS-CoV-2 testing between March and May 2020, and 10 were sent due to suspicion of other respiratory virus infection in 2019 or early 2020. Sixty-one were SARS-CoV-2 positive and 46 negative in the reference SARS-CoV-2 PCR tests. All specimens were analyzed by at least one of our reference tests. Those specimens that gave discrepant results were analyzed with at least the cobas® SARS-CoV-2 test.

Of the 10 samples originally sent for other than SARS-CoV-2 testing, 8 were tested by Allplex Respiratory Panel 1/2/3 (Seegene, Seoul, Republic of Korea) and two by xTAG RVP Fast (Luminex Diagnostics, Toronto, Canada). One was positive for human coronavirus (CoV) OC43, and one for CoV 229E and human rhinovirus. The remaining samples were positive for other potentially interfering respiratory viruses: parainfluenzavirus 1 (1 sample), parainfluenza virus 2 (1), parainfluenza virus 3 (1), adenovirus (1), human metapneumovirus (1), human rhinovirus and bocavirus (1), respiratory syncytial virus (RSV; 1), influenza virus A (pdm09; 1) and influenza virus B (1).

To assess the comparative sensitivity of the two tests, we pooled positive patient samples and made a dilution series in a pool of negative samples. All were nasopharyngeal swabs in 0.9% NaCl. We tested triplicates of dilution 10^{-3}, 10^{-4} and 10^{-5}, and duplicates of dilution 10^{-6} with Novodiag® and Xpert®, and duplicates of dilution 10^{-7} and one sample of 10^{-8} with Xpert®.

In addition, 8 proficiency samples of the QCMD 2020 Coronavirus Outbreak Preparedness EQA Pilot Study (Glasgow, Scotland, UK) containing CoVs SARS-CoV-2 (5 samples), OC43 (1) and NL63 (1) were analyzed with Novodiag®.

2.3. Patient samples from emergency departments

This study was conducted with specimens from the emergency departments of the following tertiary care hospitals in Helsinki, Finland: Meilahti Tower Hospital, Haartman Hospital, Malmi Hospital, and the New Children's Hospital. 362 nasopharyngeal specimens were sent to our laboratory for rapid PCR testing from these emergency departments between 18 to 31 May 2020, coinciding with a declining phase in the epidemic in Finland. Three of these emergency departments are located within 1 km and one at 13 km from our laboratory. Rapid testing was primarily targeted for those patients who were likely to be hospitalized, and were requested according to clinical assessment. The specimens first underwent rapid PCR testing with Novodiag®, and the result was immediately reported. Directly after pipetting the Novodiag® cassette, the specimens were subjected to one of the three reference tests for confirmation and for the clinical evaluation.

2.4. Statistical analysis

Concordance of the results obtained by the Novodiag® and Xpert® assays in comparison to a combination reference of the three large-scale PCR tests was examined in McNemar's test. Statistical significance was set at $P < 0.05$. To assess the agreement between the methods by chance, Cohen's kappa coefficient (κ) was computed. Mann-Whitney U test was used to compare the Ct value medians, and the turnaround times of Novodiag® and the three large-scale PCR tests was examined using Wilcoxon signed ranks test. Statistical analysis was performed using SPSS/PASW statistical program package, version 25 (IBM SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Analytical evaluation

The results of the analytical evaluation are summarized in Table 2a. The performance of the Xpert® and Novodiag® tests was assessed in analysis of 90 and 107 upper respiratory samples, respectively. Xpert® yielded a valid result for all specimens, and they were 100% (90/90 specimens) consistent compared to the reference with kappa value of 1.000 ($P < 0.001$). Novodiag® yielded a valid result for all but one specimen (invalid rate of 0.93%) and an agreement of 96.2 % (102/106), kappa value of 0.924 ($P < 0.001$) with the reference. The four samples with discordant results were positive with the reference tests

Table 2a
Number of tested samples and performance of the Novodiag® Covid-19 assay and the Xpress® SARS-CoV-2 assay in the initial evaluation.

Reference		Novodiag® Covid-19							Xpert Xpress® SARS-CoV-2						
		Pos	Neg	Inv	Total	Agr	Sens (95% CI)	Spec (95% CI)	Pos	Neg	Inv	Total	Agr	Sens (95% CI)	Spec (95% CI)
LDT	Pos	29	0	0	29	100%			28	0	0	28	100%		
	Neg	0	26	0	26	100%			0	11	0	11	100%		
cobas® SARS-CoV2	Pos	19	4	0	23	82%			23	0	0	23	100%		
	Neg	0	7	1	8	89%			0	7	0	7	100%		
Amplidiag® COVID-19	Pos	9	0	0	9	100%			9	0	0	9	100%		
	Neg	0	12	0	12	100%			0	12	0	12	100%		
Total	Pos	57	4	0	61	92%			60	0	0	60	100%		
	Neg	0	45	1	46	98%			0	30	0	30	100%		
	Total	57	49	1	107		93.4 (84.3-97.4)	100.0 (92.1-100)	60	30	0	90		100.0 (94.0-100)	100.0 (88.6-100)

LDT; laboratory developed test; Pos, positive; Neg, negative, Inv, invalid; Agr, agreement; Sens, sensitivity; Spec, specificity; CI, confidence interval.

Table 2b
Number of tested samples and performance of the Novodiag® Covid-19 assay at the tertiary care emergency department evaluation.

Reference		Novodiag® Covid-19				
		Pos	Neg	Inv	Total	Agreement
LDT	Pos	0	2	0	2	0%
	Neg	0	166	1	167	99%
cobas® SARS-CoV-2	Pos	3	0	0	3	100%
	Neg	1	127	0	128	99%
Amplidiag® COVID-19	Pos	0	0	0	0	na
	Neg	0	62	0	62	100%
Total	Pos	3	2	0	5	60%
	Neg	1	355	1	357	100%
	Total	4	357	1	362	

LDT; laboratory developed test; Pos, positive; Neg, negative, Inv, invalid; na, not applicable.

and Xpert® but remained negative with Novodiag®. Discrepant samples are listed in Table 3. No difference of statistical significance between the results of the Novodiag® and the reference tests was found (P = 0.125). For the samples positive with cobas® SARS-CoV-2 test, the median Ct value of SARS-CoV-2 specific target 1 was significantly higher in the four samples with discordant results (31.9) than that for the 19 concordant results (21.6, P = 0.002). In analysis of the proficiency samples, Novodiag® failed to detect two SARS-CoV-2 containing samples with 3.3 log_{10} and 2.3 log_{10} copies/ml, the lowest concentrations in the panel. For proficiency samples, interpretation of the results was performed manually, as the samples included no target for the sampling control of the assay required for valid interpretation of negative results by the software.

In the patient sample dilution series experiment, Xpert® gave positive results until the dilution 10^{-7}, whereas 2/3 samples diluted 10^{-4}, 1/3 diluted 10^{-5}, and 0/2 diluted 10^{-6} were positive with Novodiag® (Table 4).

Other respiratory viruses, including seasonal coronaviruses OC43 and 229E, did not cause false positive test results.

3.2. *Evaluation of the utility of the Novodiag® test with specimens from tertiary care emergency departments*

The clinical evaluation included 362 samples analyzed by Novodiag® and reference PCR test from 356 patients attending tertiary care emergency departments, see Table 2b. One specimen was excluded from further analyses due to invalid sampling control detected by Novodiag®. The remaining 361 samples were from 356 patients (median age 72 years). The patients consisted of 34 children (median age 5 years) and 322 adults (median age 74 years), with ages ranging from 2 weeks to 16 years and 19 to 99 years, respectively. Altogether, 356/361 samples were negative according to a reference test. One of these was positive with Novodiag®, so the specificity of Novodiag® in this setting was 99.7%. Of the five reference-test positive samples, three were positive by Novodiag®. The two false-negatives by Novodiag® had high Ct values of N gene target in the reference LDT (37.62 and 38.48). The discrepant samples are listed in Table 3.

The prevalence of SARS-CoV-2 PCR positivity among these patients, including people attending tertiary care emergency departments due to other reasons than suspicion of COVID-19, was 1.4%. Fever, respiratory, and gastrointestinal symptoms were recorded at attendance, see Table 5.

Table 3
Discrepant samples.

Sample	Reference			Novodiag® COVID-19			Xpert® Xpress SARS-CoV-2		
	Test	Result	Ct[1] (pos samples)	Result	N	orf1ab	Result	Ct E (pos samples)	Ct N (pos samples)
1	cobas® SARS-CoV-2	Posit	33.15/36.77	Negat	Negat	Negat	Posit	0	39.9
2	cobas® SARS-CoV-2	Posit	32.32/34.46	Negat	Negat	Negat	Posit	0	39.8
3	cobas® SARS-CoV-2 Amplidiag® COVID-19	Posit Posit	31.53/33.41 38.1/0	Negat	Negat	Negat	Posit	32.1	35.6
4	cobas® SARS-CoV-2	Posit	28.14/28.09	Negat	Negat	Negat	Posit	27.3	30
5	cobas® SARS-CoV-2 LDT	Negat Negat		Invalid			ND		
6	LDT	Posit	37.62	Negat	Negat	Negat	Negat		
7	LDT	Posit	38.48	Negat	Negat	Negat	Negat		
8	cobas® SARS-CoV-2	Negat		Posit	Negat	Posit	Negat		
9	LDT	Negat		Invalid			ND		

Samples 1-5: samples that gave discrepant result using Novodiag® and reference test in the initial evaluation. Samples 6-9: samples that gave discrepant result using Novodiag® and reference test in the emergence department utility evaluation. Sample 3 was reference tested by both cobas and Amplidiag tests. Sample 5 was reference tested by both cobas and LDT. [1]Reference test Ct values when sample positive in reference test: for cobas®: target 1/ Target 2, for Amplidiag®: N/orf1ab, for LDT: N. LDT, laboratory developed test, ND, not done.

Table 4
Dilution series of positive patient sample pool.

	Xpert®	Ct N2/E	Novodiag®	orf1ab/N
1:1000	Posit	27.6/25.4	Posit	posit/posit
	Posit	27.3/24.9	Posit	posit/posit
	Posit	27.3/25.2	Posit	posit/posit
1:10000	Posit	30.3/28.1	Posit	posit/negat
	Posit	30.1/28.1	Posit	posit/posit
	Posit	31/28.6	Negat	negat/negat
1:100000	Posit	32.9/30.5	Posit	negat/posit
	Posit	35.1/32.1	Negat	negat/negat
	Posit	34.7/31.8	Negat	negat/negat
1:1000000	Posit	38.4/35.3	Negat	negat/negat
	Posit	39.7/35.8	Negat	negat/negat
1:10000000	Posit	41.4/0	N. D.	N. D.
	Posit	42.8/0	N. D.	N. D.
1:100000000	Negat	0/0	N. D.	N. D.

Ct N2/E, Ct values of N2 and E gene targets by Xpert®. orf1ab/N, result of Novodiag® system gene targets orf1ab and N. N.D., not done.

Table 5
Clinical characteristics of the adult patients at the first evaluation at the emergency department. Some patients presented with multiple symptoms.

Number of patients (n)	322
Females n (%)	143 (44.4)
Males n (%)	179 (55.6)
Median age (years)	74 (range 19-99)
Median age females (years)	78 (range 19-99)
Median age males (years)	72 (range 21-97)
Symptoms	
Fever	
High fever (>38.5 °C) n (%)	42 (13.0)
Moderate fever n (%)	82 (25.5)
Low fever (37.0-37.5 °C) n (%)	67 (20.8)
No fever n (%)	131 (40.7)
Respiratory symptoms	
Dyspnea ± coughing n (%)	87 (27.0)
Cough without dyspnea n (%)	17 (5.3)
Rronchi n (%)	3 (0.9)
Upper respiratory symptoms n (%)	1 (0.3)
Sore throat n (%)	1 (0.3)
No information n (%)	1 (0.3)
No respiratory symptoms n (%)	212 (65.8)
Gastro-intestinal symptoms	
Diarrhea n (%)	32 (9.9)

86 patients had no clear symptoms pointing towards COVID-19. Patients positive for SARS-CoV-2 according to a reference test were

1) 97-year-old male, slight temperature (37 °C), reduced general condition. No respiratory or gastro-intestinal symptoms. Patient's sample was negative with Novodiag® and positive with LDT with high Ct value (37.62).
2) 45-year-old male, high fever (39.9 °C) and shortness of breath. Positive with Novodiag® and cobas® SARS-CoV-2 with low Ct values (26.47 for target 1 and 27.20 for target 2).
3) 84-year-old male, no fever, no respiratory or gastro-intestinal symptoms. Had fallen at home and brought to hospital. Died after a week in the hospital. Negative with Novodiag® and positive with LDT with high Ct value (38.48).
4) 71-year-old male, slight temperature (37 °C), shortness of breath, coughing, and diarrhea. Several underlying diseases (type II diabetes, liver cirrhosis, hypertension, psoriasis). He succumbed to the infection after 2 days in the hospital. Novodiag® positive, cobas® SARS-CoV-2 positive with low Ct values (26.89 and 27.06 for targets 1 and 2, respectively).
5) 16-year-old male, whose medical data is not available. Positive with Novodiag® and cobas® SARS-CoV-2 (Ct values 29.47 and 31.25 for targets 1 and 2, respectively).

The one patient who was positive for SARS-CoV-2 according to Novodiag® but negative in a reference test, was a 53-year-old man with acute myocardial infarction, no symptoms suggesting COVID-19.

All of the clinical evaluation samples were analyzed with one of the reference tests on large-scale PCR platforms immediately after the Novodiag® cassette was pipetted. The Novodiag® assay resulted in statistically significant acceleration of diagnostics by enabling results with median turnaround time of 3 h 54 min as compared to the median turnaround time of 11 h 44 min obtained with the reference tests ($P < 0.001$). These times include transportation of the samples from the emergency departments to the laboratory.

4. Discussion

The current epidemiological situation underlines the need for rapid SARS-CoV-2 diagnostic tests with comparable performance with the more time-consuming, technically demanding and labor-intensive tests. Implementing rapid, easy to use diagnostic approaches is especially important in remote locations where distance to specialized microbiological laboratories may cause severe delays in specimen transportation and diagnosis of COVID-19 patients, and in closed settings such as hospitals, where appropriate cohorting of patients is essential for controlling the risk of nosocomial infections. The evaluated cartridge-based rapid PCR tests, Xpert® and Novodiag®, provide automated analysis of results and storage of data therefore reducing the level of expertise required. Moreover, the tests require no batching of samples or processing of sample prior to analysis, therefore offering relatively short turnaround times with minimal equipment.

In the analytical performance assessment of this study, Xpert® showed complete concordance of results with the reference and the kappa value of 1.00 implied an almost perfect agreement. The high sensitivity and specificity observed for Xpert® in this study has also been shown in previous reports [8–10].

For Novodiag®, the results obtained were 96.2% concordant with the reference. The kappa value of 0.924 also referred to an almost perfect agreement, which was further supported by McNemar's test. Together with the two false negative low-concentration proficiency samples, the high median Ct value of 31.9 for the false negative patient samples may point towards a limited ability of the Novodiag® to detect positive samples with low viral loads, which was further supported by the dilution series experiment (Tables 3, 4 and 6). Another weakness of Novodiag® system is that it does not easily enable evaluation of the amplification curves nor other data from the analysis. It would be of

Table 6
Performance of the Novodiag® Covid-19 assay and the Xpress® SARS-CoV-2 assay in the preliminary evaluation.

		Agreement compared to combination reference			
		Novodiag® Covid-19, n=106		Xpress® SARS-CoV-2, n=90	
		No/ reference	Agreement % (95% CI)	No/ reference	Agreement % (95% CI)
Posit	Total	57/61	93.4 (84.3-97.4)	60/60	100 (94.0-100)
	Ct < 20	15/15	100 (79.6-100)	15/15	100 (79.6-100)
	Ct 20-30	38/39	97.4 (86.8-99.5)	38/38	100 (90.8-100)
	Ct > 30	4/7	57.1 (25.0-84.2)	7/7	100 (64.6-100)
Negat	No Ct	45/45	100 (92.1-100)	30/30	100 (88.6-100)

high importance especially now, when diagnostic tests worldwide have been set up so promptly [7]. Nonetheless, with specificity of 100% and sensitivity of 93.4%, and low invalid rate of 0.9%, the Novodiag® was chosen for the utility assessment of rapid SARS-CoV-2 testing in the clinical setting of emergency departments. Due to the inactivation protocol included in the sample preparation step of the Novodiag®, there is no need for placing the Novodiag® instrument inside a biosafety cabinet. This, together with potentially foreseeable challenges in the availability of Xpert® test cassettes, encouraged us to choose Novodiag® for the clinical utility study.

The utility of rapid SARS-CoV-2 testing with Novodiag® was assessed prospectively in the analysis of 362 samples from four tertiary care emergency departments in Helsinki, Finland, in May 2020. At that time, the number of new cases was declining (on the average 28 cases per day in the Helsinki and Uusimaa hospital district (incidence 11.6/100000)) [16] and approximately 2% of all specimens sent to HUSLAB were positive [17]. As expected, a slightly lower positivity rate of 1.4 % was observed for the patients at the emergency departments, the majority of whom sought health care services primarily due to reasons other than COVID-19. Together with the clinical profiles of the positive patients, this epidemiological snapshot on the frequency of COVID-19 infections showed cases of COVID-19 patients with unspecific clinical picture. This emphasizes the need for a rapid SARS-CoV-2 testing in emergency departments and hospital settings.

As a response to the current need for extensive SARS-CoV-2 testing, several commercial nucleic acid detections assays have become available, all of which have their advantages and limitations. Timely results are required to facilitate efficient patient flow. Subclinical COVID-19 infections do occur [18] and could potentially lead to spread of the disease within a hospital. Prompt diagnosis is of especially high priority for patients admitted to the hospital through the emergency departments and therefore the possibility for rapid SARS-CoV-2 testing was first offered to these settings. Indeed, implementation of Novodiag® provided results nearly 8 hours faster as compared to the large-scale PCR tests.

A limitation of this study is the use of three large-scale PCR tests for reference, as analysis of all samples on one platform was not possible due to the global shortage in testing supplies and a heavy load of samples to be tested. Furthermore, two out of four adults, who were tested SARS-CoV-2 positive by reference test at the emergency department utility study, were negative in Novodiag®. These two did not present with symptoms clearly pointing towards COVID-19, and had high Ct values in reference test. We cannot definitely verify if one or both of these samples were true or false positives in the reference test.

In conclusion, the Xpert® showed high sensitivity and specificity, and a reasonable sensitivity and high specificity was achieved for the Novodiag® assay. The possible limited ability of the Novodiag® to detect low viral load samples is a drawback, which may be overcome by confirmatory testing depending on the clinical context. Taken together, with the acceleration of diagnostics and the ease of use, rapid sample-to-answer PCR tests may provide timely results with a positive impact on the management of patient flow and infection control in the prevention of nosocomial COVID-19 infections.

CRediT authorship contribution statement

Pia Jokela: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Anu E. Jääskeläinen:** Conceptualization, Data curation, Formal analysis, Project administration, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Hanna Jarva:** Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Tanja Holma:** Methodology, Validation, Writing - review & editing. **Maarit J Ahava:** Data curation, Writing - review & editing. **Laura Mannonen:** Methodology, Writing - review & editing. **Maija Lappalainen:** Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Writing - review & editing. **Satu Kurkela:** Conceptualization, Writing - original draft, Writing - review & editing. **Raisa Loginov:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Acknowledgements

We would like to thank the nursing staff at our laboratory, especially Jonna Keijama and Esa Koivistoinen, for the valuable technical assistance.

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