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Clinical impact of molecular point-of-care testing for suspected COVID-19 in hospital (COV-19POC): a prospective, interventional, non-randomised, controlled study

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Summary

Background The management of the COVID-19 pandemic is hampered by long delays associated with centralised laboratory PCR testing. In hospitals, these delays lead to poor patient flow and nosocomial transmission. Rapid, accurate tests are therefore urgently needed in preparation for the next wave of the pandemic.

Methods We did a prospective, interventional, non-randomised, controlled study of molecular point-of-care testing in patients aged 18 years or older presenting with suspected COVID-19 to the emergency department or other acute areas of Southampton General Hospital during the first wave of the pandemic in the UK. Nose and throat swab samples taken at admission from patients in the point-of-care testing group were tested with the QIAstat-Dx Respiratory SARS-CoV-2 Panel. Samples taken from patients in a contemporaneous control group were tested by laboratory PCR. The primary outcome was time to results in the full cohort. This study is registered with ISRCTN (ISRCTN14966673) and is completed.

Findings Between March 20 and April 29, 2020, 517 patients were assessed for eligibility, of whom 499 were recruited to the point-of-care testing group and tested by the QIAstat-Dx Respiratory SARS-CoV-2 Panel. 555 contemporaneously identified patients were included in the control group and tested by laboratory PCR. The two groups were similar with regard to the distribution of sex, age, and ethnicity. 197 (39%) patients in the point-of-care testing group and 155 (28%) in the control group tested positive for COVID-19 (difference 11·5% [95% CI 5·8–17·2], p=0·0001). Median time to results was 1·7 h (IQR 1·6–1·9) in the point-of-care testing group and 21·3 h (16·0–27·9) in the control group (difference 19·6 h [19·0–20·3], p<0·0001). A Cox proportional hazards regression model controlling for age, sex, time of presentation, and severity of illness also showed that time to results was significantly shorter in the point-of-care testing group than in the control group (hazard ratio 4023 [95% CI 545–29 696], p<0·0001).

Interpretation Point-of-care testing is associated with large reductions in time to results and could lead to improvements in infection control measures and patient flow compared with centralised laboratory PCR testing.

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Introduction

The management of suspected COVID-19 respiratory disease, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is severely hampered by the long turnaround times associated with centralised laboratory PCR testing, which can take several days to generate results. In acute hospitals, these delays can lead to poor patient flow through clinical areas, with suspected patients grouped into assessment areas until their results are available. In addition, shortages of single-occupancy rooms mean that COVID-19-negative patients in these assessment areas might acquire infection from patients who do have the disease before results are available. Hospital-acquired infection is a hallmark metric for quality of care in hospitals and UK National Health Service (NHS) data suggest that large proportions of COVID-19 cases diagnosed in hospital during the first wave were acquired nosocomially.[1,2] Rapid, accurate diagnostic tests that can be done in admission areas are therefore urgently required.

In previous work, we showed that the routine use of point-of-care molecular testing for influenza and other respiratory viruses is associated with improvements in antiviral use and infection control measures, and that these effects are dependent on very short turnaround times that are not achievable in centralised laboratory testing.[3,4] Several rapid molecular platforms that can test for SARS-CoV-2 at the point of care have now been developed and are likely to reduce time to results, but there is little evidence for their clinical effect and real-world diagnostic accuracy.[5–8] The aim of this trial was to assess the clinical impact and real-world diagnostic accuracy of point-of-care testing using the QIAstat-Dx Respiratory SARS-CoV-2 Panel (Qiagen,

Research in context

Evidence before this study

We searched PubMed, the Cochrane Controlled Clinical Trials Register, and the ClinicalTrials.gov and ISRCTN trial databases for relevant published articles and ongoing trials assessing the clinical impact of molecular point-of-care testing for COVID-19 in hospitals. We used the search terms "point-of-care testing" or "rapid PCR testing" or "rapid molecular testing" or "near patient testing" and "COVID-19" or "SARS-CoV-2" and "hospital" and "clinical trial" or "randomised controlled trial" or "trial" or "study". We limited the search to studies published between Jan 1, 1980, and July 22, 2020, in English. We excluded studies reporting only diagnostic accuracy. We found no Cochrane systematic reviews for point-of-care testing for COVID-19. We found no published studies evaluating the clinical impact of point-of-care testing for COVID-19.

Added value of this study

This prospective, non-randomised, controlled trial of routine point-of-care testing for COVID-19 in hospital shows the feasibility of point-of-care testing with the QIAstat-Dx Respiratory SARS-CoV-2 Panel, and shows clinical benefits across a range of outcome measures including time to results, infection control measures, and recruitment into clinical trials compared with a control group tested by centralised laboratory PCR. It also shows that the real-world diagnostic accuracy of the QIAstat-Dx Respiratory SARS-CoV-2 Panel test was high compared to our composite PCR reference standard.

Implications of all the available evidence

Routine point-of-care testing for severe acute respiratory syndrome coronavirus 2 in hospitalised adults is feasible, accurate, and improves the time to results compared with laboratory PCR. Point-of-care testing is associated with improvements in the use of infection control measures, patient flow, and enrolment of patients into clinical trials. Efforts should now focus on improving access to and implementation of point-of-care testing for acute admission to secondary care, in preparation for a second wave of COVID-19.

Hilden, Germany) in adults presenting with suspected COVID-19 during the first wave of the pandemic in the UK.

Methods

Study design

We did a single-centre, prospective, interventional, non-randomised trial, with a contemporaneous control group, in a secondary care facility in the UK. The study design was selected because a randomised trial was considered likely to be unacceptable to many patients in the context of a pandemic caused by an organism of unknown lethality at the time. The trial took place during the first wave of the pandemic in the UK, from March 20 to April 29, 2020. All patients were recruited from the acute medical unit, emergency department, or other acute areas of Southampton General Hospital, a large acute teaching hospital in Southampton, UK. The hospital serves a population of 650 000 for secondary care, and is run by the University Hospital Southampton NHS Foundation Trust, which sponsored the trial. The study was approved by the South Central—Hampshire A research ethics committee (reference 20/SC/0138) on March 16, 2020. The protocol is available online.

One protocol amendment (notified May 29, 2020; granted June 23, 2020) was made to change the control group from a pre-implementation control group to a contemporaneous control group. This change was made in recognition of the fact that most patients tested for COVID-19 before the start of the trial were ambulatory community patients who were tested in hospital as part of the containment phase of the pandemic, and were therefore not comparable to patients presenting with acute respiratory illness who were recruited into the intervention group of the trial.

Participants

For the intervention group, eligible participants were those who met the following criteria: age 18 years or older; capacity to give written informed consent (or, where capacity was lacking, consultee assent could be obtained); a provisional decision had been made by the assessing clinical team to admit the patient to hospital; located in either the acute medical unit, emergency department, or other acute areas; could be recruited within 24 h of presentation; and had an acute respiratory illness, or did not have acute respiratory illness but was suspected to have COVID-19 according to the current Public Health England (PHE) case definition. An episode of acute respiratory illness was defined as a provisional diagnosis of acute pulmonary illness—including pneumonia, bronchitis (non-pneumonic lower respiratory tract infection), and influenza-like illness—or an acute exacerbation of a chronic respiratory illness (including exacerbation of chronic obstructive pulmonary disease, asthma, or bronchiectasis). Patients were excluded if they declined nasal or pharyngeal swabbing, or had previously been included in the study and were presenting again within 14 days after the previous enrolment. The protocol originally allowed for recruitment of symptomatic members of hospital staff; however, this provision was abandoned after only a single staff member was enrolled.

For the **study protocol** see https://eprints.soton.ac.uk/439309/2/CoV_19POC_Protocol_v2_0_eprints.pdf

The contemporaneous control group consisted of adults aged 18 years or older who presented with acute respiratory illness or suspected COVID-19 to the emergency department or acute medical unit during the study period (March 20 to April 29, 2020). These patients were eligible for inclusion in the intervention group but were not enrolled because of the capacity of the research team—we had insufficient research staff to

recruit all patients with suspected COVID-19 during the day and did not have resources to deploy research teams overnight. Patients in this group were not asked to provide consent, and we collected routinely obtained, fully de-identified data (including demographic, clinical, and outcome data) retrospectively from hospital systems after local data protection assessment and approval.

Procedures

Before recruitment began, a brief validation phase took place in which the QIAstat-Dx Respiratory SARS-CoV-2 Panel was evaluated using control material, under biosafety level 2 conditions within a class 2 medical safety cabinet, as per PHE guidance. The panel received CE marking on March 18, 2020.[9]

Patients were recruited by research staff between March 20 and April 29, 2020, from 0800 h until 1800 h, 7 days a week. After obtaining informed consent, combined nose (mid-turbinate) and throat swabs were obtained from patients by research staff and placed directly into Sigma Molecular Medium to rapidly inactivate viruses. Samples were then tested on the QIAstat-Dx platform using the Respiratory SARS-CoV-2 Panel, in a dedicated testing hub located in the acute medical unit, following local risk assessment and approval. The QIAstat-Dx Respiratory SARS-CoV-2 Panel detects two gene targets, ORF1b and the E gene, in a single assay, and detection of either gene is reported as positive. A full list of the pathogens detected by the panel is shown in the appendix (p 2).[10,11]

See Online for appendix

Laboratory PCR testing for SARS-CoV-2 on an additional combined nose and throat swab (collected contemporaneously) was done for all patients in the on-site PHE microbiology laboratory. Initially, laboratory PCR testing used the PHE RdRp gene assay alone and subsequently used the PHE RdRp and E gene assays combined.[12,13] COVID-19-positive status was defined as PCR positivity for SARS-CoV-2 on either assay.

To allow an assessment of diagnostic accuracy in the point-of-care testing group, if results were discordant between point-of-care and laboratory PCR testing, further PCR testing was done with two additional CE-marked SARS-CoV-2 assays (COVID-19 genesig Real-Time PCR assay [Primerdesign, Chandler's Ford, UK] and VIASURE SARS-CoV-2 Real Time PCR Detection Kit [CerTest Biotec, Zaragoza, Spain) in another regional laboratory, with operators masked to the original results.

Demographic and clinical data were collected at enrolment and outcome data collected retrospectively from case notes and electronic systems. The ALEA and BC platforms were used for data capture and management.

Outcomes

The primary outcome measure was the time to results, defined as time from COVID-19 testing being requested (ie, the time of recruitment for the point-of-care testing group and the time laboratory testing was requested for control patients) to the result being available to clinical teams, assessed in the full cohort. Prespecified secondary outcomes included time from admission to arrival in a definitive clinical area (ie, a designated COVID-19-positive or COVID-19-negative ward) based on test results, among patients admitted for more than 24 h; total number of bed moves before arrival in the correct definitive clinical area based on test results, among patients admitted for more than 24 h; duration of hospitalisation; proportion of patients treated with antibiotics; proportion of patients admitted to an intensive care unit (ICU); in-hospital and 30-day mortality; sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy of the QIAstat-Dx Respiratory SARS-CoV-2 Panel; and reliability of the QIAstat-Dx system (proportion of tests with run failures). Given the rapidly changing nature of admission pathways and other factors during the pandemic, various secondary outcomes prespecified in the protocol became redundant or impractical to assess, and are therefore not included in this report (appendix p 10).

As post-hoc measures, we assessed the proportion of COVID-19-positive patients enrolled into other clinical trials, and time from admission to enrolment in other clinical trials among COVID-19-positive patients.

All outcomes were measured for the duration of hospitalisation or up to 30 days (whichever was shortest), unless otherwise specified.

Statistical analysis

The sample size of 500 patients in the point-of-care testing group was chosen pragmatically, based on the availability of the QIAstatDx Respiratory SARS-CoV-2 Panel test kits. The control group consisted of all contemporaneously identified patients who presented in the same time period as the intervention and fulfilled the inclusion criteria in the same admission pathways. It was anticipated that the number included in the control group would be similar, based on the time periods for recruitment to point-of-care testing and the proportion of potentially eligible patients who were recruited. These numbers were considered to be sufficient to provide enough power for comparisons between groups and to estimate the diagnostic accuracy with acceptable precision. Although not formalised in the study design, this sample size corresponds to more than 90% power for a hazard ratio (HR) of 1·25 for turnaround time (equivalent to decreasing the median time to results from 24 h to <20 h, or increasing the proportion of patients with results within 24 h from 50% to 58%). Because the prevalence of COVID-19 during the study was highly speculative at the time of study conception, a formal sample size calculation for the evaluation of diagnostic accuracy was not done. However, a sample size of 500 patients in the point-of-care testing group would provide 80% power to give an approximately 90% chance of achieving a 95% CI width

	Point-of-care testing*	Control*	Between-group difference (95% CI)†
Characteristics			
Age, years			
Median	68 (51 to 81)	70 (51 to 81)	−2 (−3 to 2)
<50	117/499 (23%)	133/555 (24%)	−1% (−6 to 5)
50–59	67/499 (13%)	66/555 (12%)	1% (−2 to 6)
60–69	77/499 (15%)	78/555 (14%)	1% (−3 to 6)
70–79	99/499 (20%)	124/555 (22%)	−2% (−7 to 2)
≥80	139/499 (28%)	154/555 (28%)	0% (−5 to 5)
Sex			
Male	262/499 (53%)	303/555 (55%)	−2% (−8 to 4)
Female	237/499 (47%)	252/555 (45%)	··
Ethnicity			
White British	406/477 (85%)	442/518 (85%)	0% (−4 to 4)
White other	19/477 (4%)	23/518 (4%)	0% (−2 to 3)
Black	13/477 (3%)	9/518 (2%)	1% (−1 to 3)
Asian	37/477 (8%)	30/518 (6%)	2% (−1 to 5)
South Asian	14/477 (3%)	18/518 (3%)	0% (−2 to 3)
Other Asian	23/477 (5%)	12/518 (2%)	2% (−1 to 4)
Other	2/477 (<1%)	14/518 (3%)	−2% (−4 to 1)
Pregnant			
Yes	4/494 (1%)	5/555 (1%)	0% (−1 to 2)
No	490/494 (99%)	550/555 (99%)	··
Duration of symptoms, days	4 (1 to 10)	3 (1 to 7)	1 (0 to 1)
Comorbidities			
Hypertension			
Yes	175/475 (37%)	247/554 (45%)	−8% (−14 to 2)
No	300/475 (63%)	307/554 (55%)	··
Chronic obstructive pulmonary disease			
Yes	93/481 (19%)	85/554 (15%)	4% (−1 to 9)
No	388/481 (81%)	469/554 (85%)	··
Asthma			
Yes	84/478 (18%)	95/554 (17%)	1% (−4 to 5)
No	394/478 (82%)	459/554 (83%)	··
Renal disease			
Yes	38/473 (8%)	85/554 (15%)	−7% (−11 to 3)
No	435/473 (92%)	469/554 (85%)	··
Liver disease			
Yes	24/476 (5%)	43/554 (8%)	−3% (−6 to 1)
No	452/476 (95%)	511/554 (92%)	··
Diabetes			

(Table 1 continues in next column)

(Continued from previous column)

	Point-of-care testing*	Control*	Between-group difference (95% CI)†
Yes	108/478 (23%)	135/554 (24%)	−1% (−7 to 3)
No	370/478 (77%)	419/554 (76%)	··
Cancer			
Yes	40/479 (8%)	36/554 (6%)	2% (−1 to 5)
No	439/479 (92%)	518/554 (94%)	··
Dementia			
Yes	56/481 (12%)	57/554 (10%)	2% (−2 to 6)
No	425/481 (88%)	497/554 (90%)	··
Observations at admission			
Temperature at admission, °C			
Median	36·8 (36·4 to 37·6)	36·7 (36·4 to 37·5)	0·1 (0·0 to 0·2)
≥38	92/493 (19%)	92/552 (17%)	2 (−3 to 7)
<38	401/493 (81%)	460/552 (83%)	··
Pulse rate, beats per min	95 (82 to 109)	92 (78 to 106)	3 (0 to 5)
Respiratory rate, breaths per min	24 (20 to 28)	21 (18 to 26)	3 (0 to 2)
Oxygen saturation, %	96 (94 to 98)	96 (94 to 98)	0 (0 to 1)
Supplementary oxygen used			
Yes	174/499 (35%)	128/555 (23%)	12 (6 to 17)
No	325/499 (65%)	427/555 (77%)	··
Systolic blood pressure, mm Hg	134 (120 to 150)	133 (119 to 150)	1 (−3 to 4)
NEWS2 score	5 (3 to 6)	4 (2 to 6)	1 (0 to 1)
Laboratory and radiological parameters			
C-reactive protein concentration, mg/L	52 (12 to 125)	55 (12 to 129)	−3 (−6 to 4)
White blood cell count, $\times 10^9$/L	9·3 (6·8 to 13·2)	9·3 (6·7 to 13·2)	0·0 (−0·5 to 0·7)
Neutrophil count, $\times 10^9$/L	7·1 (4·6 to 11·1)	7·0 (4·8 to 10·5)	0·1 (−0·5 to 0·6)
Lymphocyte count, $\times 10^9$/L	1·0 (0·7 to 1·6)	1·1 (0·7 to 1·7)	−0·1 (−0·1 to 0·1)
Chest x-ray done			
Yes	488/498 (98%)	507/555 (91%)	7 (4 to 9)
No	10/498 (2%)	48/555 (9%)	··
Infiltrates or consolidation on chest x-ray			
Yes	277/488 (57%)	136/507 (27%)	30 (24 to 36)
No	211/488 (43%)	371/507 (73%)	··

NEWS2=National Early Warning Score 2. *Data are n/N (%) or median (IQR). †Point-of-care testing group minus control group.

Table 1: **Baseline characteristics of patients**

no larger than 10%, based on a sensitivity of 90% and a prevalence of 30%.

Statistical analysis was done by a dedicated medical statistician from the University of Southampton Clinical Trials Unit (SE) who was independent from the study team. Analysis was done with GraphPad Prism (version 7.0) and Stata (version 16) software. The use of multiple imputation was planned if missing data were to exceed 5% for the primary outcome or for key secondary outcomes, but was not needed.

Baseline characteristics and outcomes were compared between groups with use of χ^2 tests for equality of proportions for binary data, and with

	Point-of-care testing*	Control*	Between-group difference (95% CI)†	p value
Time to results, h	1·7 (1·6 to 1·9)	21·3 (16·0 to 27·9)	−19·6 (−19·0 to −20·3)	<0·0001
COVID-19 positive	197/499 (39%)	155/555 (28%)	11·5% (5·8 to 17·2)	0·0001
Admitted for >24 h	428/499 (86%)	421/555 (76%)	10·0% (5·0 to 14·7)	<0·0001
Transferred from assessment area to correct definitive clinical area on the basis of test result‡	313/428 (73%)	242/421 (57%)	15·7% (9·1 to 22·0)	<0·0001
Time from admission to arrival in a definitive clinical area‡, h	8·0 (6·0 to 15·0)	28·8 (23·5 to 38·9)	−20·8 (−18·4 to −21·2)	<0·0001
Bed moves between admission and arrival in definitive clinical area‡	··	··	··	<0·0001
0	43/313 (14%)	0/236	··	··
1	244/313 (78%)	163/236 (67%)	··	··
2	26/313 (8%)	56/236 (23%)	··	··
3	0/313	12/236 (5%)	··	··
4	0/313	4/236 (2%)	··	··
5	0/313	1/236 (<1%)	··	··
Mean (SD)	0·9 (0·5)	1·4 (0·7)	−0·5 (−0·4 to− 0·6)	<0·0001
COVID-19-positive patients enrolled into other COVID-19 trials	124/197 (63%)	104/155 (67%)	−4·2% (−14·0 to 5·9)	0·42
Time from admission to enrolment into other COVID-19 trials, days	1·0 (1·0 to 3·0)	3·0 (2·0 to 4·5)	−2·0 (−1·0 to −2·0)	<0·0001
Antibiotics used	418/496 (84%)	387/555 (70%)	14·6% (9·5 to 19·5)	<0·0001
Length of stay, days	5·1 (2·0 to 9·2)	4·2 (1·2 to 9·6)	0·9 (0 to 1·0)	0·017
Intensive care unit admission	64/499 (13%)	42/555 (8%)	5·2% (0·2 to 8·9)	0·0039
In-hospital mortality	67/494 (14%)	69/555 (12%)	1·1% (−2·9 to 5·2)	0·58
30-day mortality	80/440 (18%)	86/555 (15%)	2·6% (−2·0 to 7·3)	0·26

*Data are n/N (%) or median (IQR), unless otherwise specified. †Point-of-care testing group minus control group. ‡Assessed in patients admitted for >24 h; definitive clinical area refers to a designated COVID-19-positive or COVID-19-negative ward.

Table 2: **Primary and secondary outcome measures**

independent-samples *t* tests (for mean values) or Mann–Whitney *U* tests (for median values) as appropriate for continuous data. Time to results and time to definitive ward arrival had no censoring. For duration of hospitalisation, deaths were right-censored at 30 days. Median differences and corresponding CIs were calculated with the Hodges-Lehmann estimate. Enrolment into other COVID-19 studies was only evaluated in COVID-19-positive patients.

For the assessment of diagnostic accuracy (point-of-care testing group only), measures were calculated on the basis of a composite reference standard of PCR positivity by any assay when confirmed by a second assay. Results are presented as sensitivity, specificity, likelihood ratios, and predictive values. CIs for sensitivity, specificity, and accuracy are exact Clopper–Pearson CIs, and for the likelihood ratios CIs were calculated using the Log method.

Further analyses were carried out for the primary outcome (time to results) and key secondary outcome (time to arrival at a definitive ward). Timing of events are presented graphically using the Kaplan-Meier failure function. In addition, multivariable analysis was done based on a Cox proportional hazards model to adjust for confounding variables in view of the non-randomised nature of the study. Based on a directed acyclic graph, time of presentation (in light of the point-of-care testing group being enrolled between 0800 h and 1800 h) and severity of disease (based on National Early Warning Score 2 [NEWS2]), alongside age and sex, were identified as confounding variables to be controlled for, represented using the R package dagitty (appendix p 3). These variables were identified before analysis among the research team based on scientific rationale and clinical experience.

CIs for comparison of proportions are based on the Newcombe–Wilson method. CIs for individual proportions are based on the Wilson–Brown method except for measures of diagnostic accuracy as above.

This study was prospectively registered with the ISRCTN on March 18, 2020 (ISRCTN14966673).

Role of the funding source

The funders of the study had no role in the study conception, design, conduct, data analysis, or manuscript preparation. The corresponding author had full access to all data and the final responsibility to submit for publication.

Results

Between March 20 and April 29, 2020, 517 patients were assessed for eligibility and 500 were recruited to the point-of-care testing group, including one participant who was subsequently excluded because they were a member of staff rather than a patient (appendix p 6). In addition, 555 contemporaneously tested patients were identified for inclusion in the control group. The trial period included the upslope, peak, and downslope of the first wave of the pandemic in our locality (appendix p 7). Baseline characteristics are shown in table 1. The point-of-care testing group had a higher median NEWS2 score (5 [IQR 3–6]) than that of the control group (4 [2–6]; difference 1 [95% CI 0–1], p=0·041), as well as a higher frequency of patients requiring supplementary oxygen (174 [35%] 499 *vs* 128 [23%] of 555; difference 12% [6–17], p<0·0001), and a higher proportion of patients with infiltrates or consolidation on chest x-ray (277 [57%] of 488 *vs* 136 [27%] of 507; difference 30% [24–36], p<0·0001).

The turnaround times for laboratory PCR results before and during the trial are shown in the appendix (p 8). Median time to results during the study was 1·7 h (IQR 1·6–1·9) in the point-of-care testing group and 21·3 h (16·0–27·9) with laboratory PCR in the control group (difference 19·6 h [95 % CI 19·0–20·3], p<0·0001, Mann–Whitney *U* test; table 2). The large difference between

groups remained after controlling for age, sex, time of presentation, and severity of illness in a Cox proportional hazards regression model (HR 4023 [95% CI 545–29 696], p<0·0001; figure 1; appendix p 3). 197 (39%) of 499 patients in the point-of-care testing group were PCR positive for SARS-CoV-2, compared with 155 (28%) of 555 patients in the control group (difference 11·5% [5·8–17·2], p=0·0001; table 2).

Of those patients admitted to hospital for at least 24 h, 313 (73%) of 428 in the point-of-care testing group and 242 (57%) of 421 in the control group were transferred from assessment areas to the correct definitive clinical area (ie, a COVID-19-positive or COVID-19-negative ward) on the basis of their test results (difference 15·7% [95% CI 9·1–22·0], p<0·0001; table 2; appendix p 9). The median time from presentation to arrival in a definitive clinical area was 8·0 h (IQR 6·0–15·0) in the point-of-care testing group and 28·8 h (23·5–38·9) in the control group (difference 20·8 h [18·4–21·2], p<0·0001, Mann–Whitney *U* test; table 2). Based on a Cox proportional hazards model controlling for age, sex, time of presentation and severity of illness, time to arrival in a definitive clinical area was significantly quicker in the point-of-care testing group than in the control group (HR 10·2 [8·0–13·0], p<0·0001; figure 2; appendix p 3).

The mean total number of bed moves between admission and definitive ward arrival was 0·9 (SD 0·5) in the point-of-care testing group and 1·4 (0·7) in the control group (difference 0·5 [95% CI 0·4–0·6], p<0·0001; table 2). 43 (14%) of 313 patients in the point-of-care testing group were transferred directly from the emergency department to a definitive ward area without going to an assessment area, compared with 0 of 241 in the control group (difference 13·7% [10·0–18·0], p<0·0001).

124 (63%) of 197 COVID-19-positive patients in the point-of-care testing group and 104 (67%) of 155 in the control group were recruited into other COVID-19 clinical trials (difference 4·2% [95% CI –5·9 to 14·0], p=0·42). Median time to enrolment into trials was 1·0 days (IQR 1·0 to 3·0) in the point-of-care testing group and 3·0 days (2·0 to 4·5) in the control group (difference 2·0 days [1·0 to 2·0], p<0·0001; table 2). There was more antibiotic use, a longer length of stay, and a higher ICU admission rate in the point-of-care testing group than in the control group, whereas in-hospital mortality and 30-day mortality were similar between groups (table 2).

In the point-of-care testing group, 24 patients did not have laboratory PCR done and six samples were unavailable for discrepancy analysis. Therefore, 469 were evaluated for diagnostic accuracy (table 3). The QIAstat-Dx Respiratory SARS-CoV-2 Panel returned positive results for SARS-CoV-2 in 176 of 177 positive cases (sensitivity 99·4% [95% CI 96·9–100]) and negative results in 288 of 292 negative cases (specificity 98·6% [96·5–99·6]), using a composite reference standard of detection by any PCR assay with confirmation by a second assay to determine true positive and negative cases for comparison. Laboratory PCR in the point-of-care testing group had an overall sensitivity of 85·9% (79·9–90·7; 152 of 177 cases) and specificity of 99·0% (97·0–99·8; 289 of 292 cases). During the first 7 days of the study, the sensitivity of the laboratory PHE RdRp assay was found to be very poor

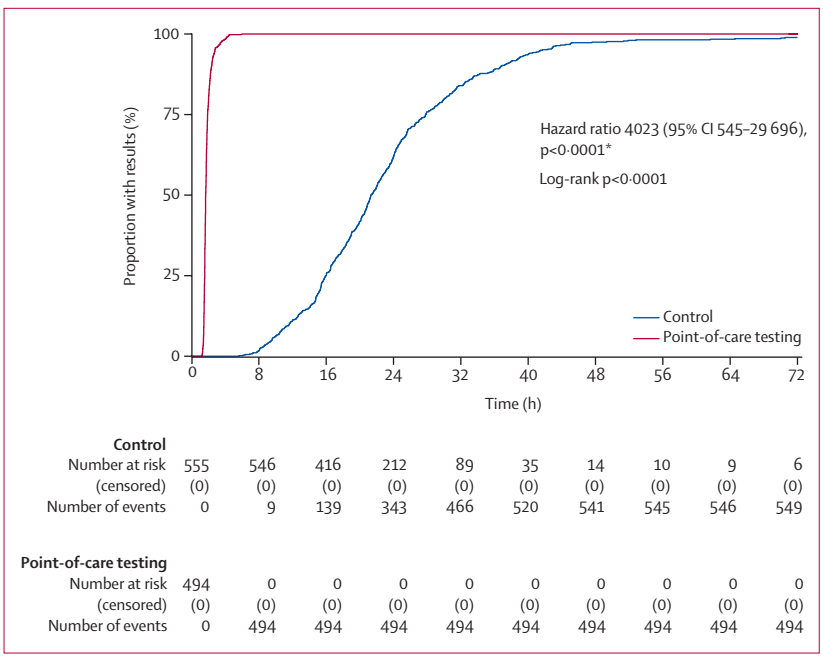

Figure 1: **Time-to-event curve for time to results**
*Cox proportional hazards regression model controlling for age, sex, time of presentation, and severity of illness.

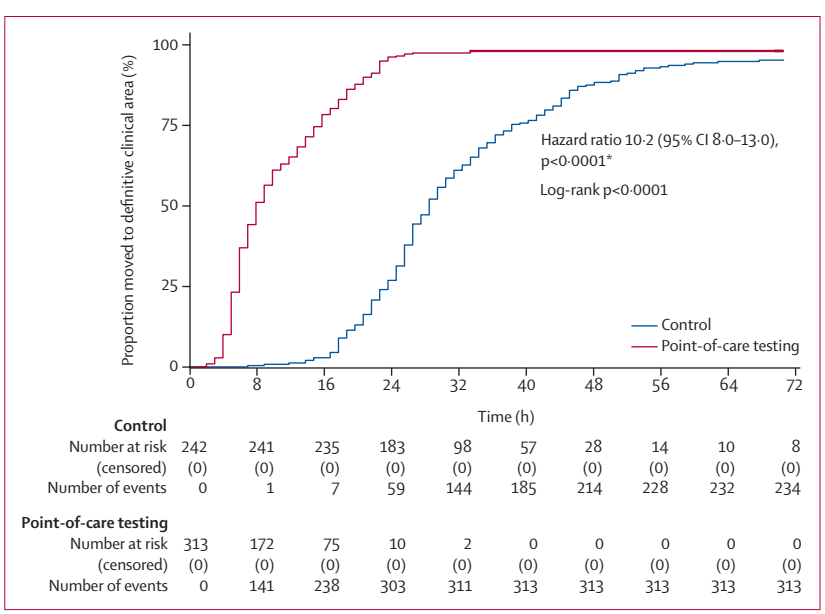

Figure 2: **Time-to-event curve for time to arrival in a definitive clinical area (ie, COVID-19-positive or COVID-19 negative area)**
*Cox proportional hazards regression model controlling for age, sex, time of presentation, and severity of illness.

	QIAstat-Dx SARS-CoV-2 assay		Laboratory PCR	
	n/N	% (95% CI)	n/N	% (95% CI)
Positive results	180/469	38·4% (34·0–42·9)	155/469	33·0% (28·8–37·5)
True (positive predictive value)	176/180	97·8% (94·3–99·2)	152/155	98·1% (94·3–99·4)
False	4/180	2·2% (0·6–5·6)	3/155	1·9% (0·4–5·6)
Negative results	289/469	61·6% (57·1–66·0)	314/469	67·0% (62·5–71·2)
True (negative predictive value)	288/289	99·7% (97·6–99·9)	289/314	92·0% (88·5–94·8)
False	1/289	0·3% (0·0–1·9)	25/314	8·0% (5·2–11·5)
Sensitivity	176/177	99·4% (96·9–100·0)	152/177	85·9% (79·9–90·7)
Specificity	288/292	98·6% (96·5–99·6)	289/292	99·0% (97·0–99·8)
Positive likelihood ratio	··	72·6% (27·4–192·1)	··	83·6% (27·1–258·1)
Negative likelihood ratio	··	0·01% (0·0–0·04)	··	0·14% (0·1–0·21)
Overall accuracy	464/469	98·9% (97·5–99·7)	441/469	94·0% (91·5–96·0)

Results from each assay were compared against a composite reference standard (PCR assay with confirmation by a second assay), which showed 177 positive cases (prevalence 37·7% [33·3–42·3]) and 292 negative cases.

Table 3: **Diagnostic accuracy measures for QIAstat-Dx Respiratory SARS-CoV-2 Panel and laboratory PCR in the point-of-care testing group (n=469)**

(62·5% [40·6–81·2]; 15 of 24 cases) compared with the QIAstat-Dx Respiratory SARS-CoV-2 Panel. The RdRp assay was then optimised and a second gene target added (E gene, with detection of either gene target being considered positive), improving the sensitivity to 89·5% (83·6–93·9; 137 of 153 cases) measured over the remainder of the study. Full details of discrepancy analysis are provided in the appendix (p 4). 29 (6%) of 499 patients in the point-of-care testing group had other respiratory pathogens detected by the panel (appendix p 5). Because of reagent shortages, PCR for other respiratory viruses was not done in the control group. Overall, 26 (5%) of 499 cases tested by the QIAstat-Dx Respiratory SARS-CoV-2 Panel had initial run failures.

Discussion

The long delays associated with centralised laboratory PCR testing are recognised as a major challenge for hospitals in effectively responding to the COVID-19 pandemic, and mitigation strategies are urgently required in preparation for the probable second wave this winter.[14] To our knowledge, this study is the first to assess the clinical impact of molecular point-of-care testing for COVID-19 for acute admissions, and shows that routine use of point-of-care testing can deliver rapid, accurate, and actionable results to clinical and infection control teams. The use of point-of-care testing led to a large reduction in the time to availability of results compared with laboratory PCR, and this reduction was associated with improvements in infection control measures and patient flow, with patients spending around 1 day less in assessment areas and having fewer bed moves before arriving in definitive COVID-19-positive or COVID-19-negative clinical areas. Less time spent in assessment areas means that non-infected patients spend less time unknowingly exposed to infected patients and are therefore less likely to acquire nosocomial infection. In addition, the rapid identification of COVID-19 patients in assessment areas could mean that health-care workers are less likely to be exposed and infected because COVID-19-positive patients would be rapidly moved to COVID-19-positive areas rather than staying in assessment areas for more than 24 h, where personal protective equipment recommendations are less stringent.[15] The fewer bed moves in the point-of-care testing group equates to a cost and time saving for hospitals because each bed space must be decontaminated after a patient has vacated it, and cleaning staff are also less likely to be exposed to heavily contaminated environments. Some patients who received point-of-care testing received their results while still in the emergency department and were transferred directly to definitive clinical areas, bypassing the assessment cohort wards entirely. If an even quicker turnaround time for results could be achieved, it is possible that all patients could have their results returned while still in the emergency department so that assessment cohort areas would become unnecessary.

Compared with the control group, patients positive for COVID-19 in the point-of-care testing group were recruited 2 days earlier into other clinical trials. Recruitment of COVID-19-positive patients into trials is an international priority, and the early identification of patients for inclusion is vital because antiviral therapies are most likely to be effective when given early in the course of the disease.[16,17] The utility of routine point-of-care testing in facilitating early enrolment into clinical trials has not been fully recognised and should be highlighted. Although there were no approved therapeutic agents available during the current study, subsequently both the antiviral agent remdesivir and the corticosteroid dexamethasone have been shown to be efficacious in treating patients with COVID-19-associated pneumonia who require supplementary oxygen or respiratory support.[18,19] Routine point-of-care testing will enable the early identification of patients with COVID-19 as they are being admitted to hospital, facilitating rapid directed therapy with these agents in a test-and-treat paradigm maximising therapeutic benefit.

In addition to testing symptomatic acute admissions to hospital, point-of-care testing could also be used for assessing elective hospital admissions, primary care patients, hospital staff, and care home staff and residents, as well as for airport screening, school screening, and even population-level screening. However, because of the insufficient availability of suitable point-of-care testing platforms for all these uses at present, prioritisation is necessary and should initially be given to acute admission to hospitals to prevent nosocomial infections.

In this study, the diagnostic accuracy of the QIAstat-Dx Respiratory SARS-CoV-2 Panel assay was found to be high, and initiating point-of-care testing alongside laboratory

PCR alerted us to the poor sensitivity of the nationally recommended PHE RdRp screening assay early in the course of the first wave, preventing the release of many additional false-negative results. Multiple groups across the world have now reported on the insensitivity of the RdRp as a gene target in PCR assays for SARS-CoV-2.[20,21] The findings of this study highlight the shortcomings inherent to instituting PCR assays based on a single gene target for a novel virus, without the availability of robust quality-assurance systems. Not all point-of-care testing platforms that are currently available have been shown to be sufficiently sensitive for use in secondary care, where the consequences of false-negative result can be very serious.[5] Point-of-care testing platforms with appropriate levels of accuracy must be selected based on the intended use case. We would also point out that point-of-care testing must be undertaken under a robust overarching governance structure that includes all elements of the testing process, including pre-analytic and post-analytic steps.

The detection of other respiratory viruses by the QIAstat-Dx Respiratory SARS CoV-2 Panel was infrequent during this study, presumably because of reduced circulation of viruses resulting from physical distancing measures, or because of viral interference from SARS-CoV-2. In Europe, COVID-19 incidence is currently low; however, a second wave is expected this winter which could coincide with seasonal epidemics of other viral infections, including influenza and respiratory syncytial virus infections. Therefore, the use of syndromic point-of-care testing for SARS-CoV-2 and other viruses will be vital for hospitals to rapidly differentiate the causes of acute respiratory illnesses and manage patients appropriately.

This study had a number of limitations, the most important of which was its non-randomised nature. The groups differed at baseline in terms of their respiratory symptoms and signs and NEWS2 scores, which can be explained by the higher prevalence of COVID-19 in the point-of-care testing group compared with the control group. Similarly, this higher prevalence can also explain the longer length of stay and higher rate of antibiotic use and ICU admission in the point-of-care testing group. Patients in the point-of-care testing group were recruited during the day by research staff and eligible patients were highlighted initially by clinical staff in the emergency department. It is likely that patients considered to be at high likelihood of COVID-19 were prioritised for point-of-care testing by clinical staff, leading to these differences.

We attempted to control for bias through the use of multivariable analyses for key outcomes. The multivariable analyses were based on a directed acyclic graph representing the research team's knowledge of variables related to group assignment and time to results or definitive ward arrival, allowing us to identify and control for confounding variables while avoiding spurious associations between group and outcome. However, it is possible that other unrecognised confounders could exist that affect the relationships between group and outcome. We believe the plausibility and magnitude of effect for these outcomes make it highly unlikely that the process of group assignment would significantly alter the conclusions of the study. Although the results of this study are compelling, they are not fully definitive and ideally should be confirmed with a randomised trial. However, the relatively low incidence of COVID-19 in the UK makes conducting such a randomised trial difficult. In addition, there remain uncertainties around the ideal implementation model for point-of-care testing in hospitals. Different models for deployment include nurse-delivered point-of-care testing and laboratory technician-delivered testing, and the most appropriate and cost-effective models will vary between health-care institutions.

Another limitation of this study was that the same swab could not be used for both point-of-care testing and laboratory testing, meaning that a second swab was obtained contemporaneously for laboratory testing, which could have contributed to the differences in diagnostic accuracy in terms of swabbing technique. Our estimates of diagnostic accuracy are also complicated by the use of the PHE RdRp assay as our comparator. Because of the poor sensitivity of the RdRp assay, we cannot be sure that the QIAstatDx Respiratory SARS-CoV-2 Panel did not generate false-negative results that were also not detected by the RdRp assay but would have been detected by a more sensitive assay. In addition, several samples identified as positive by point-of-care testing could not be tested by the RdRp assay because samples were not sent to the laboratory, which could have affected the overall measures of performance. Finally, because this study was done in symptomatic adults presenting to hospital, the effect of point-of-care testing in other patient groups such as children, community-dwelling adults, and those who are asymptomatic or pauci-symptomatic, is currently unknown.

In summary, routine use of point-of-care testing for emergency admissions was associated with a large reduction in time to results and improvements in infection control measures, patient flow, and recruitment into other clinical trials, compared with laboratory PCR testing. The QIAstat-Dx Respiratory SARS-CoV-2 Panel had high diagnostic accuracy for the detection of COVID-19. Resources should urgently be made available to support the implementation of appropriate point-of-care testing platforms in emergency departments and admission units in hospitals in preparation for the next phase of the pandemic.

Contributors

NJB assisted with the design of the study, screened and recruited patients, and collected data. SP, VVN, CTM, NJN, HW, and LP screened and recruited patients and collected and collated data. SK and NJC did the discrepancy analysis of samples for PCR testing. FB and HP were responsible for data extraction and management. GB collected and processed samples. BV did the independent performance evaluation for

the QIAstatDx Respiratory SARS-CoV-2 Panel. SE analysed the data. TWC reviewed the medical literature, conceived and designed the study, oversaw the conduct of the study, participated in the interpretation of data, and drafted and wrote the manuscript. All authors reviewed and contributed to the manuscript during its development.

Declaration of interests

TWC has received speaker fees, honoraria, travel reimbursement, and equipment and consumables free of charge for the purposes of research outside of this submitted study from BioFire Diagnostics and BioMerieux; consultancy fees from Synairgen Research, Randox Laboratories, and Cidara Therapeutics; is a member of an advisory board for Roche and a member of two independent data monitoring committees for trials sponsored by Roche; and has acted as the UK chief investigator for an investigational medicinal product study sponsored by Janssen. All other authors declare no competing interests.

Data sharing

The data analysed and presented in this study are available from the corresponding author on reasonable request, providing the request meets local ethical and research governance criteria.

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References

1 Harding L, Campbell D. Up to 20% of hospital patients with COVID-19 caught it at hospital. May 17, 2020. https://www.theguardian.com/world/2020/may/17/hospital-patients-england-coronavirus-covid-19 (accessed July 22, 2020).

2 BBC. Coronavirus: hundreds caught virus in hospitals in Wales. July 22, 2020. https://www.bbc.co.uk/news/uk-wales-53501223 (accessed July 22, 2020).

3 Brendish NJ, Malachira AK, Armstrong L, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. *Lancet Respir Med* 2017; **5:** 401–11.

4 Brendish NJ, Malachira AK, Beard KR, Ewings S, Clark TW. Impact of turnaround time on outcome with point-of-care testing for respiratory viruses: a post hoc analysis from a randomised controlled trial. *Eur Respir J* 2018; **52:** 1800555.

5 Zhen W, Smith E, Manji R, Schron D, Berry GJ. Clinical evaluation of three sample-to-answer platforms for detection of SARS-CoV-2. *J Clin Microbiol* 2020; **58:** e00783–20.

6 Visseaux B, Le Hingrat Q, Collin G, et al. Evaluation of the QIAstat-Dx Respiratory SARS-CoV-2 Panel, the first rapid multiplex PCR commercial assay for SARS-CoV-2 detection. *J Clin Microbiol* 2020; **58:** e00630–20.

7 Smithgall MC, Scherberkova I, Whittier S, Green DA. Comparison of Cepheid Xpert Xpress and Abbott ID Now to Roche cobas for the rapid detection of SARS-CoV-2. *J Clin Virol* 2020; **128:** 104428.

8 Rhoads DD, Cherian SS, Roman K, Stempak LM, Schmotzer CL, Sadri N. Comparison of Abbott ID Now, DiaSorin Simplexa, and CDC FDA emergency use authorization methods for the detection of SARS-CoV-2 from nasopharyngeal and nasal swabs from individuals diagnosed with COVID-19. *J Clin Microbiol* 2020; **58:** e00760–20.

9 Qiagen. QIAstat-Dx® Respiratory SARS-CoV-2 Panel instructions for use (Handbook). September, 2020. https://www.fda.gov/media/136571/download (accessed Sept 23, 2020).

10 Parčina M, Schneider UV, Visseaux B, Jozić R, Hannet I, Lisby JG. Multicenter evaluation of the QIAstat Respiratory Panel–a new rapid highly multiplexed PCR based assay for diagnosis of acute respiratory tract infections. *PLoS One* 2020; **15:** e0230183.

11 Leber AL, Lisby JG, Hansen G, et al. Multicenter evaluation of the QIAstat-Dx Respiratory Panel for detection of viruses and bacteria in nasopharyngeal swab specimens. *J Clin Microbiol* 2020; **58:** e00155–20.

12 Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill* 2020; **25:** 2000045.

13 NHS England, NHS Improvement. Guidance and standard operating procedure: COVID-19 virus testing in NHS laboratories. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/guidance-and-sop-covid-19-virus-testing-in-nhs-laboratories-v1.pdf (accessed July 22, 2020).

14 Academy of Medical Sciences. Preparing for a challenging winter 2020/21—full report. July 14, 2020. https://acmedsci.ac.uk/file-download/51353957 (accessed July 22, 2020).

15 Public Health England. Guidance—COVID-19: investigation and initial clinical management of possible cases. https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection (accessed July 30, 2020).

16 Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med* 2014; **2:** 395–404.

17 Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: a 5-year analysis of oseltamivir timing and clinical outcomes. *Clin Infect Dis* 2019; **69:** 52–58.

18 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—preliminary report. *N Engl J Med* 2020; published online May 22. https://doi.org/10.1056/nejmoa2007764.

19 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med* 2020; published online July 17. https://doi.org/10.1056/nejmoa2021436.

20 Colton H, Ankcorn M, Yavuz M, et al. Improved sensitivity using a dual target, E and RdRp assay for the diagnosis of SARS-CoV-2 infection: experience at a large NHS Foundation Trust in the UK. *J Infect* 2020: published online May 28. https://doi.org/10.1016/j.jinf.2020.05.061.

21 Chan JF, Yip CC, To KK, et al. Improved molecular diagnosis of COVID-19 by the novel, highly sensitive and specific COVID-19-RdRp/Hel real-time reverse transcription-PCR assay validated in vitro and with clinical specimens. *J Clin Microbiol* 2020; **58:** e00310–20.