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

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**Summary**

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

**Methods** We performed a prospective, interventional, non-randomised, controlled study of molecular point-of-care testing (POCT) in adults presenting to hospital with suspected COVID-19. Intervention group patients were tested using the QIAstat-Dx Respiratory SARS-CoV-2 Panel at the point-of-care and control patients were tested using laboratory PCR. The primary outcome was time to results. Secondary outcomes included infection control and diagnostic accuracy measures. This study is registered ISRCTN:14966673 and has completed.

**Findings** 499 patients were tested by POCT and 555 control patients were tested using laboratory PCR. Median (IQR) time to results with POCT was 1·7 (1·6 to 1·9) hours versus 21·3 (16·0 to 27·9) hours in the control group (difference of 19·6 hours, 95%CI 19·0 to 20·3; p<0·0001). 313/428 (73.1%) of patients were transferred from an assessment area to a definitive clinical area (i.e. COVID-19 positive or negative ward) in the POCT group versus 241/421 (57.2%) in the control group (difference of 15.9%, 95%CI 9.3 to 22.2; p<0.0001). Median (IQR) time to arrival in definitive clinical area was 8·0 (6·0 to 15·0) hours in the POCT group versus 28·8 (23·5 to 38·9) hours in the control group (difference of 20·8 hours, 96%CI 18·4 to 21·2; p<0·0001). The mean number of bed moves whilst in hospital was 0.9 (0.5) in the POCT group versus 1.4 (0.7) in the control group (difference of 0.5, 95%CI 0.4 to 0.6; p<0.0001). 124/197 (62.9%) SARS-CoV-2 positive patients were enrolled into other clinical trials in the POCT group versus 104/155 (67.1%) in the control group (difference of 4.2%, 95%CI -5.9 to 14.0; p=0.42). The time from admission to enrolment into other clinical trials was 1.0 (1.0 to 3.0) days in the POCT group versus 3.0 (2.0 to 4.5) days in the control group (difference of 2.0 days, 95%CI 1.0 to 2.0; p<0.0001) Sensitivity and specificity of the QIAstat-Dx SARS-CoV-2 assay was 176/177 (99·4%, 95%CI 96·9 to 100) and 288/292 (98.6%, 95%CI 96.5 to 99.6) compared to 152/177 (85·9%, 95%CI 79·9 to 90·7) and 289/292 (98.9%, 95%CI 97.0 to 99.8) with laboratory PCR.

**Interpretation** POCT was associated with large reductions in time to results and improvements in infection control measures, and had high diagnostic accuracy, compared to laboratory PCR testing.

**Funding** University Hospitals Southampton NHS Foundation Trust

**Introduction**

The management of suspected SARS-CoV-2-associated respiratory disease (COVID-19) 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 this leads to poor patient flow through clinical areas, as suspected patients are cohorted in assessment areas until their results are available. In addition, lack of single occupancy rooms means that COVID-19 negative patients in these assessment areas may acquire infection from positive patients before results are available. Hospital acquired infection is a hallmark metric for quality of care in hospitals and NHS data suggests that large proportions of COVID-19 cases diagnosed in hospital during the first wave were acquired nosocomially.1,2 Rapid, accurate diagnostics that can be performed in admission areas are therefore urgently required. In previous work we have shown that the routine use of molecular point-of-care testing (POCT) for influenza and other respiratory viruses is associated with improvements in antiviral use and infection control measures, and that this impact is dependent on very short turnaround times, not achievable in centralised laboratories.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 evidence for their clinical impact and real-world diagnostic accuracy are lacking.5-8 The aim of this trial was to assess the clinical impact and real-world diagnostic accuracy of POCT using the QIAstat-Dx Respiratory SARS-CoV-2 Panel, in adults presenting with suspected COVID-19, during the first wave of the pandemic.

**Methods**

**Study design and participants**

We performed a single centre, prospective, interventional, non-randomised, trial with a contemporaneous control group, in secondary care. The study design was selected as a randomised trial was felt likely to be unacceptable to many patients in the context of a pandemic due to an organism of unknown lethality at the time. The trial took place during the first wave of the pandemic, from 20th March to 29th April 2020. All patients were recruited from the Acute Medical Unit (AMU), Emergency Department (ED) or other acute areas of Southampton General Hospital, a large acute teaching hospital in the South of the UK serving a population of 650,000 for secondary care, run by University Hospital Southampton Foundation NHS Trust (UHSFT), who were the sponsor for the trial. The study was approved by the South Central - Hampshire A Research Ethics Committee: REC reference 20/SC/0138, on the 16th March 2020. The protocol is available at:

<https://eprints.soton.ac.uk/439309/2/CoV_19POC_Protocol_v2_0_eprints.pdf>

The protocol was amended a single time change the control group from a pre-implementation control group to a contemporaneous control group. This was due to recognition that the majority of patients tested for COVID-19 prior to the trial commencing were ambulatory community patients who were tested in hospital as part of the containment phase of the pandemic, and therefore not comparable to the patients presenting with acute respiratory illness who were recruited into the interventional arm of the trial.

**Intervention group**

Eligible patients were: aged 18 years or over; had the capacity to give informed, written consent or where capacity was lacking consultee assent was obtained; a provisional decision had been made to be admitted to hospital; located in either the AMU, ED or other acute areas; could be recruited within 24 hours of presentation; had an acute respiratory illness (ARI) or did not have ARI but were a suspected case of COVID-19 according to the current 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 - NPLRTI) and influenza-like illness (ILI), or an acute exacerbation of a chronic respiratory illness (including exacerbation of COPD, asthma or bronchiectasis). Exclusion criteria were: patient declined nasal/pharyngeal swabbing, or patient previously included in the study and re-presenting within 14 days after previous enrolment. There was originally provision in the protocol for symptomatic members of hospital staff to be recruited however this was abandoned after only a single member of staff was enrolled (see below).

**Procedures**

Prior to recruitment starting on the 20th March, a brief validation phase took place where 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 the 18th March.9 Patients were recruited from 20th March to 29th April by research staff, from 8am until 6pm, 7 days a week. Following 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 AMU, following local risk assessment and approval. The QIAstat-Dx SARS-CoV-2 assay detects two gene targets in a single assay; the Orf1b and the E gene and detection of either is reported as positive. A full list of the pathogens detected by the panel is shown in the appendix, p2.10,11 In addition, laboratory PCR testing for SARS-CoV-2 on an additional combined nose and throat swab (collected contemporaneously) was performed on all patients, in the on-site Public Health England (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. Demographic and clinical data was collected at enrolment and outcome data collected retrospectively from case note and electronic systems. The data management systems ALEA and BC platforms were used for data capture and management.

**Control group**

A contemporaneous control group of patients was identified, consisting of adults ≥18 years old presenting to hospital with ARI and/or suspected COVID-19 to the ED or AMU, during the same time period as the study (20th March to 29th April 2020). These patients were eligible for inclusion into the study but were not enrolled due to the limited capacity of the research team as we had insufficient research staff to recruit all patients with suspected COVID during the day and did not have resources to deploy research teams overnight, and were tested only by laboratory PCR. Control patient were not consented and routinely obtained fully de-identified data including demographic, clinical and outcome data were collected retrospectively from hospital systems after local data protection assessment and approval.

**Outcomes**

The primary outcome measure was the time to results, defined as time from COVID-19 testing being requested (for the POCT group this was the time of recruitment and for control patients the time laboratory testing was requested) to the result being available to clinical teams. Secondary outcomes included: time from admission to arrival in a definitive ward area (i.e. COVID-19 positive or negative ward), total number of bed moves before reaching definitive clinical area, proportion of COVID-19 positive patients enrolled into other clinical trials, time from admission to enrolment in other clinical trials, duration of hospitalisation, proportion of patients treated with antibiotics, proportion of patients with intensive care unit (ICU) admission, in-hospital and 30 day mortality, sensitivity, specificity, positive predicted value, negative predictive value, and overall diagnostic accuracy of QIAstat-Dx SARS-CoV-2 assay, and reliability of the QIAstat-Dx system (proportion of tests with run failures). All outcomes were measured for the duration of hospitalisation or up to 30 days (whichever is shortest) unless otherwise specified.

**Sample size**

The sample size of 500 patients in the POCT arm was chosen pragmatically based on the availability of the QIAstatDx Respiratory SARS-CoV-2 Panel test kits. The control arm 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 arm would be similar, based on the time periods for recruiting to POCT and the proportion of potentially eligible patient who were recruited. These numbers were thought sufficient to provide power for comparisons between arms, 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 of 1·25 for turnaround time (equivalent to decreasing median time to results from 24 hours to less than 20 hours, or increasing the percentage of those with results within 24 hours from 50 to 58%). The likely prevalence of COVID-19 during the study was highly speculative at the time of study conception, and so a formal sample size calculation for evaluation of diagnostic accuracy was not undertaken. However, a sample size of 500 patients in the POCT arm would have 80% power to give an approximately 90% chance of achieving a 95% confidence interval width no larger than 10% based on sensitivity of 90% and prevalence of 30%.

**Statistical analysis**

Statistical analysis was performed by a dedicated medical statistician from the University of Southampton Clinical Trials Unit (Dr Sean Ewings), independent from the study team. Analysis was carried out using Prism version 7.0 (GraphPad Software Inc; La Jolla, California), and Stata version 16 (StataCorp, College Station, Texas). The use of multiple imputation was planned should missing data exceed 5% for the primary outcome or for key secondary outcomes but was not needed. Summaries of all baseline characteristics are presented.

Baseline characteristics and outcomes were compared between the groups using chi-square tests for equality of proportions for binary data and using independent-samples t-tests (when presented with means) or Mann-Whitney U test (when presented with medians), as appropriate for continuous data. Time to results and time to definitive ward arrival had no censoring. For length of stay deaths were right censored at 30 days. Median differences and corresponding confidence intervals were calculated using the Hodges-Lehmann estimate. Enrolment into other COVID-19 studies was only evaluated in COVID-19 positive patients.

For assessment of diagnostic accuracy (POCT group only), measures were calculated based on a composite reference standard of PCR positivity by any assay when confirmed by a second assay. Therefore, where results were discordant between the POCT and laboratory PCR, further PCR testing was performed using two additional CE-marked SARS-CoV-2 assays (Primerdesign genesig COVID-19 RT-PCR assay and CerTest Viasure SARS-COV-2 RT-PCR) in another regional laboratory with operators blinded to the original results. Results are presented as sensitivity, specificity, likelihood ratios and predictive values. Confidence intervals for sensitivity, specificity and accuracy are ‘exact’ Clopper-Pearson confidence intervals and for the likelihood ratios are calculated using the ‘Log method’.

Further analyses were carried out for the primary outcome (time to results) and key the 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 carried out, 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 consenting the POCT arm between 8am to 6pm) and severity of disease (based on NEWS2 score), alongside age and sex, were identified as confounding variables to be controlled for, represented using the R package dagitty (appendix, p3). These variables were identified prior to analysis among the research team, based on scientific rationale and clinical experience.

Confidence intervals for comparison of proportions are based on the Newcombe/Wilson method. Confidence intervals 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 ISRCTN14966673 on the 18th March 2020.

**Role of funding source**

This study was funded by UHSFT who paid for the test kits. The laboratory work, nursing costs and consumables were supported by the NIHR Southampton Clinical Research Facility and NIHR Southampton Biomedical Research Centre. Statistical analysis was supported by Cancer Research UK core funding and NIHR CTU support funding at the Southampton Clinical Trials Unit. The study was supported by Qiagen with discounted equipment and consumables and they 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 20th March and 29th April 2020 500 patient-participants were recruited to the POCT arm and 555 contemporaneously tested patients were identified for inclusion into the control group. One participant in the POCT group was excluded as they were a member of staff rather than a patient presenting to ED with suspected COVID-19 (trial profile, appendix, p6). The trial period included the upslope, peak and downslope of the first wave of the pandemic in our locality (appendix, p7). Table 1 shows baseline characteristics for patients in the groups. Patients in the POCT group had a higher median NEWS2 score (5 [3-6] versus 4 [2-6], difference of 1, 95%CI 0 to 1; p=0.041), a higher frequency of requiring supplementary oxygen (135/499 [35%] versus 128/555 [23%], difference of 12%, 95%CI 6 to 17;p<0.0001) and having infiltrates or consolidation on chest X-ray (277/488 [57%] versus 136/507 [27%], difference 30%, 95%CI 24 to 36; p<0.0001).

The turnaround time for laboratory PCR results prior to, and during the trial is shown in the appendix, p8. Median (IQR) time to results with POCT was 1·7 (1·6 to 1·9) hours versus 21·3 (16·0 to 27·9) hours with laboratory PCR in the control group (difference of 19·6 hours, 95%CI 19·0 to 20·3; p<0·0001, Mann-Whitney U test). Figure 1 shows the time-to-event curve for test results in the groups (Log rank test, p<0·0001). 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 (hazard ratio [HR] = 4023, 95%CI 545 to 29696; p<0·0001), appendix, p3. 197 (39·5%) of 500 patients in the POCT group were PCR positive for SARS-CoV-2 compared to 155 of 555 (28·0%) patients in the control group (difference of 11·5%, 95%CI 5·8 to 17·2; p<0·0001). Of those patients admitted to hospital for at least 24 hours, 313 of 428 (73·1%) in the POCT group versus 241 of 421 (57·2%) in the control group were transferred from assessment areas to the correct definitive clinical area (i.e. COVID-19 positive or negative ward) according to their test results (difference of 15·9%, 95%CI 9·3 to 22·2; p<0·0001). The median (IQR) time from presentation to arrival in a definitive clinical area was 8·0 (6·0 to 15·0) hours in the POCT group versus 28·8 (23·5 to 38·9) hours in the control group (difference of 20·8 hours, 95%CI 18·4 to 21·2; p<0·0001, Mann-Whitney U test). Figure 2 shows the time to event curve for time to arrival in definitive clinical area (Log rank test, p<0·0001). The hazard ratio for group was 10·2 (95%CI 8·0 to 13·0; p<0·0001) in favour of the POCT arm arriving at a definitive clinical area earlier, based on a Cox proportional hazards model controlling for age, sex, time of presentation and severity of illness (appendix, p3). Further details of transfers to definitive ward areas are given in the appendix, p9. The mean (SD) total number of bed moves from admission before definitive ward arrival was 0·9 (0·5) in the POCT versus 1·4 (0·7) in the control group (difference of 0·5, 95%CI 0·4 to 0·6; p<0·0001). 43 of 313 (13·7%) patients in the POCT group were transferred directly from ED to a definitive ward area without going to an assessment area, compared to 0 of 241 (0%) in the control group (difference of 13·7%, 95%CI 10·0 to 18·0; p<0·0001). 124 of 197 (62·9%) COVID-19 positive patients were recruited into other COVID-19 clinical trials in the POCT group versus 104 of 155 (67·1%) in the control group (difference of 4·2, 95%CI -5·9 to 14·0; p=0.42). Median time to enrolment into trials was 1·0 (1·0 to 3·0) days in the POCT versus 3·0 (2·0 to 4·5) days in the control group, (difference of 2·0 days, 95%CI 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 POCT group compared to the control group, table 3.

***Diagnostic accuracy***

In the POCT group 24 patients did not have laboratory PCR performed and 6 samples were unavailable for discrepancy analysis, so a total of 469 were evaluated for diagnostic accuracy. The sensitivity of the QIAstat-Dx Respiratory SARS-CoV-2 Panel for detection of SARS-CoV-2 was 176/177 (99·4%, 95%CI 96·9 to 100) and specificity was 288/292 (98·6%, 95% CI 96·5 to 99·6) compared to the composite reference standard of detection by any PCR assay and confirmed by a second assay. The overall sensitivity of the laboratory PCR during the trial was 152/177 (85·9%, 95%CI 79·9 to 90·7) and specificity was 289/292 (98·9%, 95%CI 97·0 to 99·8). During the first 7 days of the study the sensitivity of the laboratory PHE RdRp assay was found to be very poor compared to QIAstat-Dx; 15/24 (62·5%, 95% CI 40·6 to 81·2). This assay was then optimised and a second gene target added (E gene, with detection of either gene target being considered positive) subsequently improving the sensitivity to 137/153 (89·5%, 95%CI 83·6 to 93·9) measured over the remainder of the study. Measures of diagnostic accuracy are given in table 4. Full details of discrepancy analysis is provided in the appendix, p4. 29 of 499 (5·8%) patients in the POCT group had other respiratory pathogens detected by the panel (appendix, p5). Due to reagent shortages PCR for other respiratory viruses was not performed in the control group. Overall there were 26 of 499 (5·2%) initial run failures on the QIAstat-Dx.

**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 a likely second wave this winter.14 To our knowledge this is the first study to assess the clinical impact of molecular POCT for COVID-19 for acute admissions, and demonstrates that routine use of POCT can deliver rapid, accurate, and actionable results to clinical and infection control teams. The use of POCT led to large reductions in time to availability of results compared with laboratory PCR and this was associated with improvements in infection control measures and patient flow, with patients spending around one day less in assessment areas and having fewer bed moves before arriving in definitive COVID-19 positive or negative clinical areas. Less time spent in assessment areas means that non-infected patients would spend less time unknowingly exposed to infected patients and are less likely to acquire nosocomial infection. In addition the rapid identification of COVID-19 patients in assessment area means that health care workers would be less likely to be exposed and infected, as positive patients were rapidly moved to positive areas rather than staying in assessment areas for over 24 hours, where PPE recommendations were less stringent.15 The fewer number of bed moves in the POCT group equates to a cost and time saving for hospitals as each bed space must be decontaminated after a patient has vacated it, and cleaning staff are less likely to be exposed to heavily contaminated environments. Some patients tested by POCT received their results whilst still in the ED and were transferred directly to definitive clinical areas, bypassing the assessment cohort wards entirely. It is likely that if an even quicker turnaround time for results could be achieved, all patients could have their results returned whilst still in the ED so that assessment cohort areas would become unnecessary.

COVID-19 patients in the POCT group were recruited 2 days earlier into other clinical trials. Recruitment of COVID-19 patients into trials is an international priority and the early identification of patients for inclusion is vital as antiviral therapies are most likely to be effective when given early in the course of the disease.16,17 The utility of routine POCT in facilitating early enrolment into clinical trials has not been fully recognised and should be highlighted. Whilst there were no approved therapeutic agents available during the COV19-POC trial, subsequently both the antiviral agent remdesivir and the corticosteroid dexamethasone have been proven to be efficacious in treating COVID-19 pneumonia patients requiring supplementary oxygen or respiratory support.18,19 Routine POCT will enable the early identification of COVID-19 patients as they are being admitted to hospital, facilitating rapid directed therapy with these agents in a ‘test and treat’ paradigm maximising therapeutic benefit.

There are many potential ‘use cases’ for point-of-care testing in addition to testing symptomatic acute admissions to hospital, including elective hospital admissions, primary care patients, hospital staff, care home staff and residents, airport screening, school screening and even population level screening. Due to the current lack of availability of suitable POCT platforms for all these use cases, prioritisation must be undertaken and should initially be given to acute admission to hospitals to prevent nosocomially acquired infection.

In this study the diagnostic accuracy of the QIAstat-Dx SARS-CoV-2 assay was found to be high and initiating POCT 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 shortcoming inherent to instituting PCR assays for a novel virus using a single gene target and without the availability of robust quality assurance systems. Not all POCT platforms that are currently available have been shown to be sufficiently sensitive for use in secondary care where the consequences false negative result may be very serious5. POCT platforms with appropriate levels of accuracy must be selected based on the intended use case. We would also point out that POCT must be undertaken under a robust overarching governance structure that includes all element so of the testing process including pre and post analytics steps.

The detection of other respiratory viruses by the QIAstat-Dx Respiratory SARS CoV-2 Panel was infrequent during this study, presumably due to reduced circulation of viruses resulting from social distancing measures or due to viral interference from SARS-CoV-2. In Europe COVID-19 incidence is currently low, however a second wave is expected this winter which may coincide with seasonal epidemics of other viruses including influenza and RSV. Therefore the use of syndromic POCTs that test for SARS-CoV-2 and other viruses will be vital for hospitals to rapidly differentiate the cause of acute respiratory illness and manage patients appropriately.

This study has a number of limitations, the most important of which is its non-randomised nature. There were differences between the groups at baseline in terms of their respiratory symptoms and signs and NEWS2 score that are explained by the higher prevalence of COVID-19 in the POCT group. Similarly the longer length of stay and higher rate of antibiotic use and ICU admission in the POCT group are also likely to be explained by this. Patients in the POCT group were recruited during the day by research staff and eligible patients were highlighted initially by clinical staff in the ED. It is likely that patients considered to be at high likelihood of COVID-19 were prioritised for POCT by clinical staff, leading to these differences.

We have 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 destination, allowing us to identify and control for confounding variables while avoiding spurious association between group and outcome. However, it is possible that other unrecognised confounders may exist that impact the relationship between group and outcome. We believe the plausibility and magnitude of the effect for the outcomes make it highly unlikely that the process of group assignment would significantly alter the conclusions of the study. Whilst the result of this study are compelling we do acknowledge that as a non-randomised study they are not fully definitive and ideally should be confirmed with a randomised trial. This would, however, be difficult to conduct currently in the UK due to the low incidence of COVID-19. In addition there remain uncertainties around the ideal implementation model for POCT in hospitals. There are several different models for deployment including nurse delivered POCT and laboratory technician delivered testing and the most appropriate and cost effective of these will vary between health care institutions.

The same swab could not be used for both the POCT and laboratory testing so a second swab was obtained contemporaneously for laboratory testing and this could have contributed to the differences seen 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. Due to the poor sensitivity of RdRp we cannot be sure that the QIAstatDx did not generate false negative results that were also not detected by RdRp but would have been detected by a more sensitive assay. In addition several POCT positive samples could not be tested by RdRp as samples were not sent to the laboratory, which could have affected the overall measures of performance. Finally, as this study was performed in symptomatic adults presenting to hospital, the impact of POCT 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 POCT 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 SARS-CoV-2 assay had high diagnostic accuracy for the detection of COVID-19. Resources should be urgently made available to support the implementation of appropriate POCT platforms in emergency departments and admission units in hospitals, in preparation for the next phase of the pandemic.

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**Author contributions**

TWC reviewed the medical literature, conceived of and designed the study, oversaw the conduct of the study, participated in the interpretation or data, drafted and wrote the manuscript. NJB assisted with the design of the study, screened and recruited patients and collected data. SP, CTM, NN, VVN, HW and LP screened and recruited patients, collected and collated data. HP and FB performed data extraction and management. SK and NC performed discrepancy analysis of samples for PCR testing, GB performed collection and processing of samples, BV performed independent performance evaluation for QIAstatDx SARS-CoV-2 assay, and SE analysed the data. All authors reviewed and contributed to the manuscript during its development.

**Declaration of competing 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 LLC and BioMerieux. TWC has received consultancy fees from Synairgen research Ltd, Randox laboratories Ltd and Cidara therapeutics. He a member of an advisory board for Roche and a member of two independent data monitoring committees for trials sponsored by Roche. He has acted as the UK chief investigator for an IMP study sponsored by Janssen. All other authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

**Data sharing**

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

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***Table 1*: Baseline characteristics of patients**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **POCT** **n=499** | **Control** **n=555** | **Difference 95%CI** |
| Age (years) | 68 (51 to 81)  | 70 (51 to 81) | 2 (-2 to 3)  |
|  <50  | 117 (23) | 133 (24) | 1 (-5 to 6)  |
|  50-59  | 67 (13) | 66 (12) | 1 (-2 to 6) |
|  60-69  | 77 (15) | 78 (14) | 1 (-3 to 6) |
|  70-79  | 99 (20) | 124 (22) | 2 (-2 to 7) |
|  ≥80  | 139 (28) | 154 (28) | 0 (-5 to 5)  |
| Sex |  |  |  |
|  Male | 262 (52) | 303 (54) | 2 (-4 to 8)  |
|  Female  | 237 (48) | 252 (46) |  |
| **Ethnicity**  |  |  |  |
|  White British  | 406 (85) | 442 (85) | 0 ( -4 to 4)  |
|  White other  | 19 (4) | 23 (4) | 0 (-2 to 3)  |
|  Black  | 13 (3) | 9 (2) | 1 (-1 to 3) |
|  Asian  | 37 (8) | 30 (6) | 2 (-1 to 5)  |
|  South Asian  | 14 (3) | 18 (3) | 0 (-2 to 3)  |
|  Other Asian | 23 (4) | 12 (2) | 2 (-1 to 4)  |
|  Other  | 2 (<1) | 14 (3) | 2 (1 to 4)  |
| Pregnant  |  |  |  |
|  Yes | 4 (1)  | 5 (1)  | 0 (-1 to 2)  |
|  No | 490 (99)  | 550 (99) |  |
| Duration of symptoms, days | 4 (1 to 10) | 3 (1 to 7)  | 1 (0 to 1)  |
| **Comorbidity**  |  |  |  |
| Hypertension  |  |  |  |
|  Yes | 175 (37)  | 247 (45) | 8 (2 to 14)  |
|  No | 300 (63) | 307 (55) |  |
| COPD |  |  |  |
|  Yes | 93 (19) | 85 (15) | 4 (-1 to 9)  |
|  No | 388 (81) | 469 (85)  |  |
| Asthma  |  |  |  |
|  Yes | 84 (18) | 95 (17) | 1 (-4 to 5)  |
|  No | 394 (82) | 459 (83) |  |
| Renal disease  |  |  |  |
|  Yes | 38 (8) | 85 (15) | 7 (3 to 11)  |
|  No | 435 (92) | 469 (85)  |  |
|  Liver disease  |  |  |  |
|  Yes | 24 (5) | 43 (8) | 3 (-1 to 6)  |
|  No | 452 (95) | 511 (92) |  |
|  Diabetes mellitus  |  |  |  |
|  Yes | 108 (22) | 135 (24) | 2 (-3 to 7)  |
|  No | 370 (77) | 419 (76) |  |
|  Cancer  |  |  |  |
|  Yes | 40 (8) | 36 (6) | 2 (-1 to 5)  |
|  No | 439 (92) | 518 (94) |  |
|  Dementia  |  |  |  |
|  Yes | 56 (12) | 57 (10) | 2 (-2 to 6)  |
|  No | 425 (88) | 497 (90) |  |
| **Observations at admission**  |  |  |  |
| Temperature, °C | 36·8 (36·4 to 37·6)  | 36·7 (36·4 to 37·5) | 0·1 (0 to 0·2)  |
|  Temperature ≥38°C  |  |  |  |
|  Yes | 92 (19) | 92 (17) | 2 (-3 to 7)  |
|  No | 401 (81) | 460 (83)  |  |
| Pulse rate, bpm  | 95 (82 to 109)  | 92 (78 to 106) | 3 (0 to 5)  |
| Respiratory rate, bpm  | 24 (20 to 28)  | 21 (18 to 26) | 3 (0 to 2)  |
| Oxygen saturations, %  | 96 (94 to 98)  | 96 (94 to 98)  | 0 (0 to 1)  |
| Supplementary O2 used  |  |  |  |
|  Yes  | 174 (35)  | 128 (23)  | 12 (6 to 17)  |
|  No | 325 (65) | 427 (77) |  |
| Systolic blood pressure, mmHg | 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**  |  |  |  |
| CRP, mg/L  | 52 (12 to 125)  | 55 (12 to 129)  | 3 (-4 to 6)  |
| WCC, x109/L  | 9·3 (6·8 to 13·2) | 9·3 (6·7 to 13·2 )  | 0·0 (-0·5 to 0·7)  |
| Neutrophils, x109  | 7·1 (4·6 to 11·1)  | 7·0 (4·8 to 10·5) | 0·1 (-0·5 to 0·6)  |
| Lymphocytes x109  | 1·0 (0·7 to 1·6)  | 1·1 (0·7 to 1·7) | 0·1 (-0·1 to 0·1)  |
| CXR performed |  |  |  |
|  Yes  | 488 (98)  | 507 (91) | 7 (4 to 9)  |
|  No | 10 (2) | 48 (9) |  |
| Infiltrates/consolidation on CXR  |  |  |  |
|  Yes  | 277 (57) | 136 (27) | 30 (24 to 36)  |
|  No | 211 (43) | 371 (73) |  |

Data are n (%) or median (IQR). POCT=point-of-care testing. CI=confidence interval,

COPD=chronic obstructive pulmonary disease, NEWS2=national early warning score 2,

CRP=C-reactive protein, WCC=white cell count, CXR=chest X-ray.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **POCT****n=499** | **Control** **n=555** | **Difference (95%CI)**  | **p value**  |
| Time to results (hours) | 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 (SARS-CoV-2) positive  | 197 (39·5)  | 155 (28·0)  | 11·5 (5·8 to 17·2)  | 0·0001 |
| Admitted for >24 hours | 428 (85·8) | 421 (75·8)  | 10·0 (5·0 to 14·7) | <0·0001 |
| Transferred from assessment (cohort) area to definitive ward (i.e. COVID-19 positive or negative)  | 313/428 (73·1)  | 241/421 (57·2)  | 15·9 (9·3 to 22·2) | <0·0001 |
| Time from admission to definitive ward arrival, hours | 8·0 (6 to 15)  | 28·8 (24 to 39)  | 20·8 (18·4 to 21·2)  | <0·0001 |
| Number of bed moves once admitted (mean, SD) | 0·9 (0·5)  | 1·4 (0·7) | 0·5 (0·4 to 0·6) | <0·0001 |
| Bed moves |  |  |  | <0·0001 |
| 0 | 43 (13·7) | 0 (0)  |   |  |
| 1 | 244 (77·9) | 163 (67·6) |  |  |
| 2 | 26 (8·3)  | 56 (23·2) |  |  |
| 3 | 0 (0) | 12 (5·0)  |   |  |
| 4 | 0 (0) | 4 (1·7)  |   |  |
| 5 | 0 (0) | 1 (0·4) |  |  |
| COVID-19 positive patients enrolled into other COVID-19 trials  | 124/197 (62·9) | 104/155 (67·1) |  4·2 (-5·9 to 14·0) | 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 |

Data are n (%) or median (IQR) expect where stated otherwise. POCT=point-of-care testing.

CI=confidence interval.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **POCT****n=499** | **Control** **n=555** | **Difference** **(95%CI)**  | **p value**  |
| Antibiotics used  | 418/496 (84·3)  | 387 (69·7) | 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 |
| ICU admission  | 64 (12·8)  | 42 (7·6) | 5·2 (0·2 to 8·9)  | 0·004 |
| In hospital mortality  | 67/494 (13·5) | 69 (12·4) | 1·1 (-2·9 to 5·2 | 0·58 |
| 30 day mortality  | 80/440 (18·2) | 86 (15·5) | 2·6 (-2·0 to 7·3) | 0·26 |

***Table 3:* Additional secondary outcome measures**

Data are n (%) or median (IQR) expect where stated otherwise. POCT=point-of-care testing, CI=confidence interval, ICU=intensive care unit.

***Table 4*: Diagnostic accuracy measures for QIAstat-Dx SARS-CoV-2 assay and Laboratory PCR in the POCT group, n=469**

|  |  |  |
| --- | --- | --- |
|  | **QIAstat-Dx SARS-CoV-2 assay** | **Laboratory PCR**  |
|  | n/n | % (95%CI)  | n/n | % (95% CI)  |
| Prevalence  | 177/469 | 37·7 (33·3 to 42·3) | 177/469 | 37·7 (33·3 to 42·3)  |
| Sensitivity  | 176/177 | 99·4 (96·9 to 100) | 152/177 | 85·9 (79·9 to 90·7) |
| Specificity  | 288/292 | 98·6 (96·5 to 99·6) | 289/292 | 98·9 (97·0 to 99·8) |
| Positive Likelihood ratio |  -  | 72·6 (27·4 to 192·1) |  -  | 83·6 (27·1 to 258·1) |
| Negative Likelihood ratio |  -  | 0·01 (0·0 to 0·04) |  -  | 0·14 (0·1 to 0·21) |
| Positive predictive value  | 176/180 | 97·8 (94·3 to 99·2) | 152/155 | 98·1 (94·3 to 99·4) |
| Negative predictive value  | 288/289 | 99·7 (97·6 to 99·9) | 289/314 | 92·1 (88·9 to 94·3)  |
| Overall accuracy  | 464/469 | 98·9 (97·5 to 99·7) | 441/469 | 94·0 (91·5 to 96·0) |
| CI=confidence interval  |

**Figure legends**

***Figure 1:* Time-to-event curve for time to results in the POCT and control groups**

***Figure 2:*** **Time-to-event curve for time to arrival in definitive clinical area (i.e. COVID-19 positive or negative) in the POCT and control groups**

**Supplementary appendix**

***Table S1:* Pathogens detected by QIAstat-Dx SARS-CoV-2 Respiratory Panel**

***Table S2:* Multivariate analysis for primary and key secondary outcome measures**

***Table S3*: Investigation of discrepant results between laboratory PCR and QIAstat-Dx SARS-CoV-2 Respiratory Panel, in the POCT group, n=469**

***Table S4*: Detection of respiratory viruses by QIAstat-Dx Respiratory SARS-CoV-2 Panel in the POCT group, n=499**

***Figure S1*. Directed acyclic graph representing theorised associations between variables related to group and outcomes**

***Figure S2*: Trial profile**

***Figure S3*: SARS-CoV-2 positivity rate during the study**

***Figure S4*: Turnaround time for laboratory PCR testing for SARS-CoV-2, before and during the study**

***Figure S5*: Details of patient transfers to definitive ward areas (COVID-19 positive or negative wards)**

**Research in context**

**Evidence before this study**

We searched PubMed, the Cochrane Controlled Clinical Trials Register, and ClinicalTrials.gov and ISRCTN trial databases, for relevant published articles and ongoing trials assessing the clinical impact of molecular POCT (POCT) 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 POCT for COVID-19. We found no published studies evaluating the clinical impact of POCT for COVID-19.

**Added value of this study**

This prospective, non-randomised, controlled trial of routine POCT for COVID-19 in hospital demonstrates the feasibility of POCT and shows clinical benefits across a range of outcome measures including infection control measure and recruitment into clinical trials. It also shows that the real-word diagnostic accuracy of the QIAstat-Dx SARS-CoV-2 test was high compared to our composite PCR reference standard.

**Implications of all the available evidence**

Routine POCT for SARS-CoV-2 in hospitalised adults is feasible, accurate and improves the time to results compared to laboratory PCR. POCT 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 POCT for acute admission to secondary care, in preparation for a second wave of COVID-19.