Clinical impact of syndromic molecular point-of-care testing for gastrointestinal pathogens in adults hospitalised with suspected gastroenteritis (GastroPOC): a pragmatic, open-label, randomised controlled trial

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# Summary

## Background

Single-occupancy isolation rooms are a limited resource in UK hospitals but are critical in preventing transmission of infection. Patients with suspected gastroenteritis are nursed in single-occupancy rooms but delays in laboratory testing lead to non-infectious patients remaining isolated for prolonged periods unnecessarily. Rapid molecular test panels for gastrointestinal pathogens have a run time of around 1 hour but their clinical impact is unknown.

## Methods

In this pragmatic, randomised controlled trial, we enrolled adults hospitalised with suspected gastroenteritis in a large UK hospital. Patients were randomly allocated (1:1) to receive syndromic molecular point-of-care testing (mPOCT) of stool or rectal samples, or to routine clinical care (control) with laboratory testing. The primary outcome was the duration of time in single-occupancy rooms. Secondary outcomes included the time to results, time to de-isolation, antibiotic use, and safety outcomes. The study was registered (ISRCTN88918395) and is complete.

## Findings

Between March 20, 2017 and March 17, 2020, we enrolled 278 patients, 138 assigned to mPOCT (one withdrawal) and 140 to the control group. The duration (geometric mean) of single-occupancy room isolation was 1∙8 days (95%CI 1∙5 to 2∙2) in the mPOCT group compared with 2∙6 (2∙2 to 3∙0) days in the control group (exponentiated coefficient 0·70 [95%CI 0·56 to 0·87]; p=0·0017). The median (IQR) time to results was 1∙7 hours (1∙5 to 2∙0) for mPOCT and 44∙7 hours (21∙2 to 66∙1) for the control group (p<0∙0001). Time to de-isolation was 0·6 days (0·3 to 1·8) in the mPOCT group compared with 2·2 days (1·2 to 3·2) in the control group, (p<0·0001). Antibiotics were given in 89 (65%) of 137 in the mPOCT group and 66 (47%) of 140 in the control group (p=0·0028). There were no differences in length of stay, re-admission, or mortality between groups.

## Interpretation

mPOCT for gastrointestinal pathogens in patients with suspected gastroenteritis returned results more rapidly than conventional testing and was associated with a reduction in single-occupancy room use. However, these benefits need to be balanced against a potential increase in antibiotic use.

## Funding

University Hospital Southampton NHS Foundation Trust.

# Introduction

Worldwide, diarrhoeal illness causes over 1.6 million deaths annually, and is the eighth most common cause of death.1 Gastrointestinal illness accounts for over 1 million visits to Emergency Departments, and at least 130,000 hospital admissions, in England each year.2,3 Diarrhoea can be caused by a wide range of gastrointestinal pathogens and also by many other illnesses and medications, and is therefore a non-specific symptom with a wide differential diagnosis.2 Additionally, centralised laboratory testing of stool samples is associated with a long turnaround time to results.4–7 Patients presenting to hospital with diarrhoea are routinely nursed in single-occupancy rooms (called ‘side rooms’ in the NHS) along with associated infection control measures. There are only about 40,000 single-occupancy rooms out of about 111,000 acute hospital beds in the NHS in England and only around 1700 of these are dedicated isolation rooms.8,9 The COVID-19 pandemic has put further pressure on this limited resource, therefore patients presenting with diarrhoea to hospital represent a diagnostic challenge, experience delays in diagnosis, and stretch limited healthcare resources.

Testing for gastrointestinal pathogens is further delayed by the need to wait for the patient to produce a stool sample which is the standard sample type used for laboratory testing. However, rectal swabs have been shown to have broadly equivalent diagnostic performance compared to conventional stool samples for the molecular detection of gastrointestinal pathogens.10–12 Additionally, the use of rectal swabs for diagnosis is supported by US guidelines when stool samples cannot be collected in a timely manner, and in European guidelines for *Clostridioides difficile* diagnosis.13,14 Rectal swabs therefore provide an opportunity to expedite current testing for gastrointestinal pathogens.

Syndromic molecular test platforms for the detection of gastrointestinal pathogens are highly accurate, test for a comprehensive range of pathogens, and selected platforms are easy to use ‘sample-to-answer’ type platforms, with a run time of about an hour. These have the potential to be deployed as near-patient or point-of-care tests in acute care areas.6,15–17 Because some syndromic molecular panels test comprehensively for gastrointestinal pathogens in a single test, negative test results can lead to confident de-isolation decisions. The use of rectal swabs combined with syndromic molecular point-of-care tests (mPOCT) may therefore reduce the current delays associated with laboratory testing, and lead to improved use of single-occupancy rooms in patients presenting to hospital with diarrhoea. Other potential benefits include improved diagnosis and treatment of patients with diarrhoea through increased pathogen detection, although the detection of pathogens by molecular test may not always represent the cause of patient’s illness and concern exist around the potential for overtreatment of colonising or non-pathogenic organisms.18

The UK’s National Institute for Health and Care Excellence diagnostic assessment programme has previously reviewed molecular panels for gastrointestinal pathogens and identified key research priorities for assessing the impact of their use. Suggested outcome measures included length of time in single-occupancy room, length of hospital stay, and change of treatment as a result of testing.19

We aimed to address this evidence gap by performing a pragmatic, randomised controlled trial of mPOCT for gastrointestinal pathogens on stool samples and/or rectal swabs in adult patients presenting to hospital with suspected gastroenteritis and evaluating the impact upon single-occupancy room use, antibiotic use, and a range of other outcome measures.

# Methods

## Study design

We did a single-centre, pragmatic, open-label, parallel group randomised controlled trial (GastroPOC). Patients were recruited from the acute medicine unit, acute surgical unit, emergency department, and other acute clinical areas within Southampton General Hospital, a large acute teaching hospital in the UK. The hospital serves a secondary care population of 650,000 people, and is run by University Hospital Southampton NHS Foundation Trust, which was the trial sponsor.

The study was approved by the West Midlands – Solihull Research Ethics Committee (REC) on January 9, 2017 (reference 16/WM/0515). The study protocol was amended once (REC approval on June 19, 2018) to: change the study from a pilot to a full study, increase the sample size from 200 to 300 participants, allow three years for participant recruitment, and add additional patient de-isolation measures as secondary outcome measures. The study was prospectively registered on an international trials database (ISRCTN88918395) and has completed. The study protocol is available online (<https://eprints.soton.ac.uk/449770/>).20

## Participants

Patients were eligible if: they had an acute diarrhoeal illness and/or vomiting of ≤14 days duration, were ≥18 years old, had capacity to provide informed written consent, and were able to adhere to study procedures, were located in the Emergency Department (ED), Acute Medicine Unit (AMU), Acute Surgical Unit (ASU), or inpatient ward. Patients had to be recruited within 48 hours of first triage in ED, or within 48 hours of arrival in AMU, ASU, or inpatient ward if they were admitted directly from the community. Acute diarrhoeal illness was defined as the having three or more loose stools for a least one day. Patients were excluded if: a palliative approach was being taken by the treating clinicians, they were previously included in the study and were re-presenting within 30 days after hospital discharge, or they declined to give a stool sample and/or rectal swab. All participants gave written informed consent.

## Randomisation and masking

Patient-participants were consecutively assigned a unique participant identification number by study staff who then used the internet-based randomisation service Sealed Envelope, which uses random permuted blocks of sizes 4, 6, and 8, to generate the allocation sequence, and assigned the participants (1:1) to either the intervention group or control group. Data analysts and statisticians were masked to group allocation. Due to the nature of the intervention, research staff, participants, and the clinical teams were not masked to group allocation.

## Procedures

Patients randomly allocated to the intervention group had a stool sample and/or rectal swab obtained (both in Carey-Blair media: Remel, Thermo Fisher Scientific, Kansas, USA, and FecalSwab, Copan, Brescia, Italy) and analysed immediately using the FilmArray Gastrointestinal Panel (BioFire Diagnostics, bioMérieux, Salt Lake City, USA) at the point-of-care. Clinical staff caring for the patient, and the hospital infection control team, were informed of the mPOCT result directly. The FilmArray testing units were located in dedicated areas within the AMU and ASU. If a rectal swab was obtained, a subsequent stool sample was obtained whenever possible. The mPOCT analysers were operated by members of the research team.

Patients randomly assigned to receive routine clinical care (control group) had stool testing performed by standard laboratory testing at the discretion of the clinical team. In addition, all patients in the control group also had a stool sample and/or rectal swab taken (into Carey-Blair media) and frozen at -80°C, and subsequently analysed using the FilmArray Gastrointestinal Panel (at least 30 days after collection) to allow direct comparison for pathogens not detected by routine clinical care.

The FilmArray Gastrointestinal Panel gives a result in about 60 minutes and detects 22 pathogens: Bacteria: *Campylobacter* (*jejuni, coli* and *upsaliensis*), *Clostridioides difficile* (toxin A/B), *Plesiomonas shigelloides*, *Salmonella sp*, *Yersinia enterocolitica*, *Vibrio* (*parahaemolyticus*, *vulnificus*, *and cholerae*), Diarrhoeagenic *E. coli/Shigella*: Enteroaggregative *E. coli* (EAEC), Enteropathogenic *E. coli* (EPEC), Enterotoxigenic *E. coli*(ETEC), Shiga-like toxin-producing *E. coli* (STEC) stx1/stx2, *E. coli O157*, *Shigella*/Enteroinvasive *E. coli* (EIEC); Parasites: *Cryptosporidium*, *Cyclospora cayetanensis*, *Entamoeba histolytica*, *Giardia lamblia*; Viruses: Adenovirus F40/41, Astrovirus, Norovirus GI/GII, Rotavirus A, and Sapovirus (I, II, IV and V).16

The on-site microbiology laboratory used a variety of diagnostic methods for the detection of gastrointestinal pathogens including: culture for *Salmonella, Shigella, Campylobacter*, and *E. coli* O157; the EntericBio PCR system (Serosep, Ireland/UK) for bacterial pathogens (*Salmonella, Shigella, Campylobacter, Verotoxigenic E. coli, plus Cryptosporidium and Giardia*), *Clostridioides difficile (in addition to toxin detection by enzyme immunoassay)*, and separate norovirus GI/GII PCR; microscopy for ova, cysts and parasites; and antigen testing for adenovirus and rotavirus (bioNexia Rota-Adeno, bioMérieux, France).

## Outcomes

The primary outcome measure was the duration of time in a single-occupancy room (known as a ‘side room’ in the NHS). This was chosen as single-occupancy rooms are a finite hospital resource and vital for preventing transmissions of infection between patients, and was suggested by the National Institute for Health and Care Excellence diagnostic assessment programme review of this technology as detailed above.19 The duration of time in a side room was measured for the whole of the admission to hospital, regardless of the time of gastrointestinal pathogen testing.

Secondary outcome measures included: duration of time in a side room for pathogen positive patients (days), duration of time in a side room for pathogen negative patients (days), proportion of patients isolated in a side room, proportion of pathogen positive patients isolated in a side room, proportion of pathogen negative patients isolated in a side room, proportion of pathogen negative patients de-isolated, proportion of pathogen positive patient de-isolated, time to de-isolation in pathogen negative patients (days), proportion of patients treated with antibiotics, duration of antibiotics (days), duration of hospitalisation (days), proportion of patients with a pathogen detected, proportion of patients with a bacterial pathogen detected, and the proportion of patients with missed diagnoses, concordance between results obtained from rectal swab and stool culture, and time from sampling to availability of results (hours). Safety outcome measures included: ICU admissions, 30-day mortality, and representation (without admission) and readmission to hospital. Patient satisfaction scores and other medication use were exploratory outcomes and are not reported here. Complications including acute kidney injury and the time to treatment with antibiotics were planned as outcome measures but data were unobtainable. Time to patent isolation was a planned outcome but was not analysed as almost all patients were isolated at enrolment (table 1). Where appropriate, all outcomes were measured until discharge from hospital or the first 30 days of hospitalisation, whichever was shorter, however antibiotic duration included what the patient was discharged with. Serious adverse events were reported to the sponsor.

For the *post hoc* additional secondary outcome analysis of inappropriate antibiotic use, antibiotic prescriptions were reviewed by two independent infectious diseases physician researchers, with any disagreements adjudicated by a third infectious diseases researcher. Appropriateness was based on a retrospective assessment as to the clinical relevance of the pathogens detected, the use of antibiotics recommended by national and international guidelines and on pathogen detection from FilmArray gastrointestinal panel testing used either as mPOCT or retrospectively performed on frozen samples in the control group, in addition to pathogens detected by routine laboratory testing where this was performed.13,21 Antibiotics not active against *Clostridioides difficile* and prescribed for gastrointestinal illness when *C. difficile* was detected and deemed to be causing disease were termed inappropriate. Antibiotics given for gastrointestinal illness when no pathogen or only a viral pathogen was detected were deemed inappropriate.

The proportion of patients with bacterial gastroenteritis treated with antibiotics, and proportion of patients without bacterial gastroenteritis treated with antibiotics were originally planned as secondary outcome measures. After review, this data was instead analysed *post hoc* as antibiotic use by clinical diagnosis and according to individual pathogens detected, due to the complexities caused by pathogen co-detection and other factors.

Hospital infection control policy would permit immediate de-isolation based on test results. The research team members had no influence over decisions relating to de-isolation, antibiotic management, or other clinical or patient-flow decisions.

## Sample size

The initial phase of this study was designed as an internal pilot study so as to derive data to inform the sample size of the full study. After recruiting 100 patients (50 per group) we generated data on the duration of single-occupancy room use, and withdrawal rate, allowing us to calculate the sample size based on the primary outcome. 141 patients per group were required to provide 90% power, at a 0·05 significance level, to detect a 1 day reduction in the mean duration of single-occupancy room use, from 3 to 2 days (with a variance of 6·7 days). We considered this reduction significant from an institutional and economical perspective. Allowing for a ~5% withdrawal rate we aimed to recruit 150 patients per group (300 in total).

## Statistical analysis

The trial design framework was superiority. Analysis was by intention-to-treat. Statistical analyses were performed by a trial statistician independent from the study team who was masked to group allocation. 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 as missing data was below this threshold. There was no missing data for the primary outcome and missing data was <1% overall.

Descriptive statistics were used to summarise baseline demographic and clinical variables. For continuous variables, the mean and standard deviation was used for normally distributed data. For non-normally distributed data, the median and interquartile range were calculated. Categorical or binary variables were summarised as frequency and percentage of total.

The primary outcome was compared between groups using Student’s t-test. The distribution of time in a single-occupancy room was right-skewed (appendix p 2), and log-transformation of this variable was found to yield a normal distribution. This was verified using the Sharpiro-Wilk and skewness and kurtotis tests. A multiple regression model with a range of explanatory variables (age, sex, presence of inflammatory bowel disease, duration of diarrhoea, time from admission to recruitment and whether a pathogen was detected) was used to estimate the effects of these key variables upon the primary outcome of (log transformed) time in a single-occupancy room. This model also included an interaction term in order to investigate whether the relationship between time in a single-occupancy room and intervention group differed depending on pathogen status.

For secondary outcomes, we compared the intervention and control groups for equality of proportions using the two-sample test of proportions for binary data using the z-test. For continuous data, we used the appropriate regression model. Time-to-event analysis data were compared using the log-rank test. No differences were expected between the sexes and therefore no analyses were done disaggregated by sex. All analyses were done using Prism version 9·4·1 (GraphPad Software, La Jolla, CA, USA) and Stata version 17·0 (StataCorp, College Station, Texas).

## Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

# Results

Between March 20, 2017, and March 17, 2020, 455 patients were assessed for eligibility, and 278 were enrolled and randomly assigned to either the mPOCT group (n=138) or to routine clinical care group (n=140). One patient randomised to the intervention group did not receive the intervention (as they could not produce a stool sample and declined a rectal swab) and so was withdrawn from the study leaving 137 and 140 in the modified intention-to-treat analysis. Although the desired number of recruited participants was not achieved (150 per group), because of resource constraints due to the COVID-19 pandemic the study recruitment period could not be extended. The trial profile is shown in figure 1. Baseline characteristics for all patients are shown in table 1 and were well matched between the groups. 130 (95%) of 137 patients in the mPOCT group and 132 (94%) of 140 patients in the control group were isolated in single-occupancy rooms at the time of study enrolment. 136 (99%) of 137 patients and 140 (100%) of 140 patients in the mPOCT and control groups respectively were isolated at any time during their admission.

The duration (geometric mean) of time in a single-occupancy room in the mPOCT group was 1·8 (95%CI 1·5 to 2·2) days compared with 2·6 (2·2 to 3·0) days in the control group (exponentiated coefficient 0·70 [95%CI 0·56 to 0·87], p=0·0017, table 2). The interpretation of the exponentiated coefficient is that the time in a single-occupancy room was reduced by 30% overall in the intervention group (100 x (1 - 0·70). The difference between the groups for the primary outcome remained significant when adjusting for multiple co-variates (appendix p 3).

Patients with no pathogen detected had a shorter duration of time in a single-occupancy room in the mPOCT group, 1·3 (1·0 to 1·6) days, compared with the control group, 2·5 (2·1 to 2·9) days, (exponentiated coefficient 0·51 [95% CI 0·39 to 0·67]; p<0·0001, table 2). There was no difference in the duration of time in a single-occupancy room between the groups in patients who had a pathogen detected, 2·8 (2·1 to 3·5) days, in the mPOCT group compared with 2·9 (2·2 to 3·9) days in the control group (exponentiated coefficient 0·94 [95%CI 0·64 to 1·39]; p=0·76). Time-to-event analyses further demonstrate that patients in the mPOCT group had a shorter time in single-occupancy isolation rooms, that de-isolation occurred promptly after mPOCT, and that patients in the mPOCT group with no pathogen detected were the reason for the shorter duration of time in isolation between the groups overall (figure 2).

The median time from study enrolment to results being available to clinicians was 1·7 (1·5 to 2·0) hours in the mPOCT group and 44·7 (21·2 to 66·1) hours in the control group (difference of -43·9 [95%CI -49·3 to -38·4]; p<0·0001, table 3).

A higher proportion of patients in the mPOCT group were de-isolated (moved from single-occupancy room accommodation to a shared bay area) during their hospitalisation compared to the control group, 58 (43%) of 136 versus 38 (27%) of 140 (difference of 16% [95%CI 4 to 27]; p=0·0069, table 3). Patients with no pathogen detected were more likely to be de-isolated during their hospital stay in the mPOCT group than in the control group, 54 (73%) of 74 versus 35 (34%) of 104 (difference of 39% [95%CI 26 to 53]; p<0·0001) whereas there was no difference between the groups in patients with a pathogen detected, 4 (6%) of 62 versus 3 (8%) of 36 (difference of -2% [95%CI -13 to 9]; p=0·73).

The median time from study enrolment to de-isolation was 0·6 (0·3 to 1·8) days in the mPOCT group compared with 2·2 (1·2 to 3·2) days in the control group (difference -1·5 (95% CI -2·2 to -0·8); p<0·0001). This difference in time to de-isolation was again due to patients with no pathogen detected in the mPOCT group compared with the control group, 0·6 (0·3 to 1·3) days compared to 2·2 (1·2 to 3·2) days (difference of -1·6 [-2·2 to -0·9]; p<0·0001) and there was no difference in time to de-isolation in patients with pathogens detected (p=1·0).

There was no difference in the length of hospital stay between the mPOCT group and the control group, 3·3 (2·1 to 7·9) days versus 3·0 (2·0 to 7·0) days (difference of 0·3 [95%CI -0·7 to 1·3]; p=0·55) and there were no differences between groups in mortality, intensive care unit admission, representation to hospital (without admission), or readmission to hospital (table 3).

A higher proportion of patients had pathogens detected in the mPOCT group, 62 (45%) of 137 patients, compared to the control group (with laboratory testing), 36 (26%) of 140 (difference of 20% [95%CI 9 to 31]; p=0·0007; table 3). *Campylobacter* was the most frequently detected pathogen in both groups (appendix p 4). mPOCT detected a greater number of pathogens (71 detections versus 36) and range of pathogens (14 different pathogens versus 10), compared to the control group. In addition, co-detection of pathogens was also more common in the mPOCT group and involved detection of EPEC in all cases (appendix p 4). The details of pathogens detected in the control group by retrospective testing of frozen stored samples using the FilmArray Gastrointestinal panel are shown in the appendix, p 5. 30 (21%) of 140 patients were found to have had at least one pathogen that was not detected via routine clinical care, including: *Campylobacter* (5), norovirus (5), EPEC (11), *C. difficile* (4), and *Shigella/*EIEC (2).

89 (65%) of 137 patients in the mPOCT group received an antibiotic at any point in their hospitalisation compared with 66 (47%) of 140 patients in the control group (difference of 18% [95%CI 6 to 29]; p=0·0028, table 4). Patients with a final diagnosis of gastroenteritis were more frequently treated with antibiotics in the mPOCT group, 45 (65%) of 69 versus 40 (48%) of 83 in the control group (p=0.049). Antibiotic treatment of *Campylobacter* and EPEC was more common in the mPOCT group, although EPEC was frequently co-detected with other pathogens (including *Campylobacter*), appendix p6.

Of patients receiving antibiotics, there was no difference in the proportion of patients who received inappropriate antibiotics, 34 (38%) of 89 in the mPOCT group versus 35 (53%) of 66 in the control group (difference of -15% [95%CI -31 to 0·9]; p=0·066), however patients in the mPOCT group received a shorter median duration of inappropriate antibiotics compared to the control group, 0·5 (0·0 to 1·8) days compared to 4·2 (0·7 to 6·5) days (difference -3·7 [95% CI -5·6 to -1·9], p=0·0002; table 4). Further details of inappropriate antibiotic use and the antibiotic agents used are shown in the appendix, p 7-8. Empiric use of broad-spectrum intravenous antibiotics (e.g. cefuroxime and metronidazole) was common in patient with gastroenteritis including in those patients subsequently testing positive for *Campylobacter*, and in patients without pathogens detected. The patients in the mPOCT group and the control group had similar proportions of different categories of final diagnoses based on discharge ICD-10 codes (appendix p 9).

There was high concordance in pathogens detected between paired rectal swabs and stool samples collected at the same time and tested on the FilmArray Gastrointestinal Panel, with rectal swabs having a negative predictive value of 91% (95%CI 80 to 97) (appendix p 9). Five (56%) out of nine discordant rectal swabs occurred in samples with multiple pathogen detections (appendix p 9).

# Discussion

In this study, routine syndromic molecular point-of-care testing for gastrointestinal pathogens in adults hospitalised with suspected gastroenteritis led to a faster time to results, identified more pathogens, and reduced the duration of single-occupancy isolation room use, compared with routine clinical care using conventional laboratory testing. The reduced time in single-occupancy rooms was driven by pathogen-negative patients being appropriately de-isolated a day and half earlier in the course of their hospitalisation.

Single-occupancy isolation rooms are a limited resource in the NHS, and many other healthcare systems, and most hospital beds are located in shared bays.22 Around 130,000 hospital admissions for potentially infectious diarrhoeal illnesses occur in England each year.3 This study suggests that a molecular point-of-care testing strategy for these patients could reduce unnecessary single-occupancy room use and overall decrease use by around 30% (i.e. around 40,000 single-occupancy rooms saved per year) therefore improving patient flow and operational capacity within NHS hospitals.

Overall antibiotic use was higher in the mPOCT group compared to the control group by 18% which is potentially concerning for overtreatment of colonising organisms including *C. difficile* due toincreased detection. Our data show that increased antibiotic use was due to a higher proportion of patient with gastroenteritis in the mPOCT group receiving antibiotics, including those with *Campylobacter* and EPEC but not *C. difficile*. Not all patients with *Campylobacter* require antibiotics and so the impact of this increase in treatment is difficult to ascertain. Similarly, most of the patients with EPEC who were treated with antibiotics were co-infected with another pathogen (most frequently *Campylobacter*) and so the likely impact of this is unclear.

Inappropriate antibiotic use was very common in both groups with broad spectrum antibiotics commonly being given empirically, likely representing diagnostic uncertainty at the point of admission and before results were available. The duration of inappropriate antibiotics was reduced by almost four days in the mPOCT group demonstrating that clinicians acted on mPOCT results by switching to appropriate agents based on pathogen detected or by stopping antibiotics, representing a powerful antibiotic stewardship intervention. Use of mPOCT even earlier in the patient pathway may overcome this issue and could lead to even greater clinical benefits and true pathogen-directed therapy.

A single small previous study has demonstrated that using mPOCT in the emergency department was associated with improvements in pathogen-directed antibiotic use but did not evaluate impact on infection control measures.23 The only randomised controlled trial of laboratory-based molecular testing in hospitalised adults enrolled around half the number of patients in our study and found no difference in isolation facility use or other clinical outcomes which is unsurprising given the delays in obtaining laboratory results compared to mPOCT.24 In addition, in a randomised controlled trial in children in Botswana, a test-and-treat strategy with rapid molecular laboratory testing was not associated with improved outcomes, although this study was significantly underpowered.25 That there was no difference in the length of hospital stay or other clinical outcome measures between groups in our study may suggests that other factors, such as age and comorbidity, are more important determinants, although it is important to note that our study was not powered specifically to evaluate these endpoints. In our study about a quarter of participants were patients with known inflammatory bowel disease (IBD) and studies of mPOCT use in IBD rapid access clinics with outcome measures including admission avoidance, antibiotic and steroid use are warranted.

The concordance of pathogen detection in rectal swabs and stool samples tested on the FilmArray platform was high and comparable with previously reported studies.10–12 In particular, the negative predictive value of rectal swabs was high in this study suggesting that routine rectal swab use in clinical practice is reasonable and can safely facilitate rapid diagnosis, as its use is likely to negate the significant delays associated with obtaining a stool sample.

Patients in the mPOCT group had more pathogens detected than those in the control group. The reasons for this are multifactorial. Firstly, all patients in the mPOCT group were tested for gastrointestinal pathogens whereas only 84% were tested in the control group as stool samples were not always sent for laboratory testing. This is likely to be due to the inability of some patient to produce stool samples when requested and the inability to use rectal swabs to overcome this as part of routine diagnostic testing. Secondly, it is due to the wider range of pathogens detectable on the syndromic molecular panel compared to laboratory testing, including pathogens that the in-house laboratory methods did not test for (for example EPEC). Thirdly, it was due to patients in the mPOCT group always being tested for all pathogens (i.e. the ‘syndromic approach’) whereas patients in the control group were often tested for only one type of pathogen (i.e. bacterial, viral, or *C. difficile*) depending on the clinical details provided to the laboratory. The retrospective testing of patients in the control group using the FilmArray Gastrointestinal Panel allowed an objective assessment of pathogens not detected by the processes of routine clinical care and demonstrated frequent missed detections of pathogens including norovirus, *Campylobacter*, and *C. difficile.* Finally, the increased detection of pathogens in the mPOCT group may also reflect the greater sensitivity of molecular methods compared with the culture or antigen-based testing that were sometimes used in the control group.

Whilst the increased detection of pathogens may improve diagnosis and management of patient with gastroenteritis, the higher sensitivity of molecular testing compared to traditional laboratory methods may also result in detection of low levels of genetic material found in stool from past infection or asymptomatic carriage. This may lead to over-diagnosis of some pathogens, particularly in *C. difficile* where detection by PCR alone often represents carriage. Similarly, some targets on molecular panels such as EPEC and EAECare not always pathogenic and their detection may be unrelated to patients’ illnesses. Both of these situations have the potential to result in unnecessary antibiotic treatment and, as discussed above, highlight the importance of integrating robust diagnostic and antibiotic stewardship when introducing new molecular test such as gastrointestinal panels.

Despite the increased pathogen detection by mPOCT, a higher proportion of patients were de-isolated during their hospitalisation in the mPOCT group than the control group. This suggests that the rapid turnaround time of results and subsequent rapid de-isolation of patients who do not have infectious diarrhoea more than offsets the effect of increased pathogen detection by mPOCT on single-occupancy room use. However, the increased frequency of pathogen detection by molecular testing has the potential to increase the use of single-occupancy rooms in institutions where patients hospitalised with diarrhoea are not routinely isolated. The use of the limited number of single-occupancy rooms for isolation of patients with COVID-19, influenza, and other contagious diseases could therefore be further pressured by the introduction of molecular gastrointestinal testing, although this may be managed by pragmatic infection control policies and skilled co-ordination of patient flow.

To our knowledge, this is the first randomised controlled trial to evaluate the clinical impact of molecular point-of-care testing for gastrointestinal pathogens on isolation facility use in addition to a wide range of other clinically relevant outcomes. The study recruited standard adult medical patients presenting to hospital over a 3-year period, limiting bias from any gastrointestinal pathogen outbreaks or epidemics. Other strengths of the study include the pragmatic trial design, with comparison to routine clinical care, and broad inclusion criteria. Therefore, the study results are likely to be generalisable to other UK and international centres.

The limitations of the study include that it was a single-centre non-blinded study, and that we could not extend study recruitment to obtain the original target sample size due to the COVID-19 pandemic. Despite this, our achieved sample size was able to detect clinically significant differences between the groups for both the primary and for several key secondary outcome measures. The patient, clinical teams, and researchers could not be blinded to group allocation and intervention result, as it was required that these groups were informed of the mPOCT results to evaluate the effects of these results on patient management. Adjudicating antibiotic appropriateness is prone to subjectivity and so may potentially introduce bias despite prescriptions being compared to guideline-based advice. Furthermore antibiotic treatment guidelines are based on pathogen detection by traditional diagnostic methods rather than highly sensitive molecular testing, and do not consider the potential that detection represents non-pathogenic colonisation rather than infection, therefore our adjudication of appropriateness may unduly favour molecular testing. The FilmArray system is not marketed as a point-of-care test platform and is not CLIA-waived in the US for this purpose. A health economic analysis is needed to understand the cost implications of mPOCT implementation. Although molecular panel tests are more expensive than conventional laboratory testing, these costs are likely to be offset by the improvements seen in isolation facility use as this may improve patient flow and operational capacity in hospital, and potentially prevent nosocomial outbreaks.

The use of molecular point-of-care testing for respiratory viruses including SARS-CoV-2 in hospital pathways now has a robust evidence base, and has been associated with improvements in antibiotic use, length of stay, patient flow through the hospital, and isolation facility use.26–29 Many NHS hospital trusts and hospitals internationally have now developed POCT or near-patient testing infrastructure to allow rapid molecular SARS-CoV-2 testing.29­–31 Therefore widespread implementation of gastrointestinal pathogen detection at the point-of-care may be feasible. Although the optimal delivery model for mPOCT services will depend upon the circumstances of individual institutions, all such services must be embedded within a comprehensive quality management system provided by local pathology services in order to ensure the accuracy and reliability of results.

In conclusion, molecular point-of-care testing for gastrointestinal pathogens on stool and rectal swabs in adults hospitalised with suspected gastroenteritis was associated with a faster time to results and reduced the unnecessary use of single-occupancy isolation rooms. This is likely to have a significant impact on hospital infection control capacity and patient flow though acute areas. mPOCT was also associated with the detection of more pathogens and an increase in antibiotic use. Whilst the duration of inappropriate antibiotics appears reduced, the overall increase in antibiotic use has an unclear impact on clinical outcome and is potentially concerning from an antimicrobial stewardship perspective. Further studies are needed to examine the effects of mPOCT on antibiotic use and clinical outcomes in greater detail.

# Contributors

TWC reviewed the medical literature, conceived of and designed the study, oversaw the conduct of the study, collected data, interpreted results, and wrote the manuscript. NJB reviewed the medical literature, participated in the trial design, recruited patients, generated and collected data, interpreted results, and drafted and wrote the manuscript. KRB reviewed the medical literature, participated in the trial design, recruited patients, and generated and collected data. AKM recruited patients, and generated and collected data. ART and LS-N generated and collected data. MG and JRFC participated in the trial design and assisted with study oversight. HEM designed the statistical analysis plan and analysed the data. All authors contributed to, reviewed, and approved the final manuscript and had final responsibility for the decision to submit for publication. TWC and NJB verified the underlying data for this study.

# Declaration of interests

TWC has received speaker fees, honoraria, travel reimbursement, and equipment and consumables at discount or free of charge for the purposes independent of research, outside of this submitted study, from BioFire diagnostics, BioMerieux and QIAGEN. He has received consultancy fees from Cepheid, Synairgen research, Randox laboratories and Cidara therapeutics. He has received honoraria for participation in advisory boards from Cepheid, Roche, Janssen and Shionogi. He is a member of an independent data monitoring committee for a trial sponsored by Roche. He has acted as the UK chief investigator for a study sponsored by Janssen. All other authors declare no competing interests.

# Data sharing

All de-identified participant data analysed and presented in this study are available from the corresponding author following publication, on reasonable request.

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The molecular analysers and the test kits were provided without cost by the manufacturer (BioFire Diagnostics, a bioMérieux company, Salt Lake City, Utah, USA). The manufacturer had no role in the study conception, design, data analysis, or manuscript preparation.

The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

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# Figure legends

**Figure 1: Trial profile.**

**Figure 2: Time-to-event analyses showing time in a single-occupancy room for (a) mPOCT group and control groups and (b) mPOCT group and control groups, by pathogen detection.**

# Panel: Research in context

## Evidence before this study

We searched PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and the ISRCTN trial database for relevant published articles and ongoing trials assessing the clinical impact of molecular point-of-care testing for gastrointestinal pathogens in hospitalised adults. We used the search terms “point-of-care test\*” OR “rapid PCR testing” OR “rapid molecular testing’’, AND “diarrhoea” OR “gastroenteritis”. Word variations for British English or American English spellings were also done. To widen the search, we also included the names of PCR panel manufacturers. We limited the search to studies published between January 1, 1980, and October 1, 2022, and also to articles in English. We excluded studies reporting only diagnostic test accuracy, studies in outpatients, studies enrolling patients presenting without gastrointestinal illness, studies using antigen-based tests, studies requiring endoscopy or ultrasound, studies assessing faecal occult blood testing, and studies only in children.

Eight studies were identified that that used rapid syndromic PCR for gastrointestinal pathogens in the laboratory, rather than at the point-of-care, and reported on the clinical impact beyond turnaround time of results. Only one study was a randomised controlled trial and the others were observational. The randomised controlled trial was smaller than the study presented here and did not find any difference in isolation facility use or the limited range of other clinical outcomes measured.

Only one study (a small randomised controlled trial conducted in the emergency department) was identified that used syndromic PCR for gastrointestinal pathogens at the point-of-care, however, this study was terminated due to the COVID-19 pandemic after including only 74 patients. This study showed an improvement in appropriate antibiotic prescriptions but did not report on isolation facility use. We found no systematic reviews evaluating the impact of molecular point-of-care testing for gastrointestinal pathogens.

## Added value of this study

To our knowledge, this is the first large randomised controlled trial of molecular point-of-care testing of gastrointestinal pathogens in adults presenting to hospital, evaluating the impact on isolation facility use in addition to other outcome measures.

## Implications of all the available evidence

Routine molecular point-of-care testing for gastrointestinal pathogens by rectal swabs and/or stool samples in adults presenting to hospital with suspected gastroenteritis is associated with improved the time to results and reduced time non-infectious patients spend in single-occupancy isolation rooms, by accelerating the time to de-isolation from single-occupancy isolation rooms to bays. Use of mPOCT also reduces the use of inappropriate antibiotics in patients and appears safe.