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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

Nathan J Brendish, Ahalya K Malachira, Lawrence Armstrong, Rebecca Houghton, Sandra Aitken, Esther Nyimbili, Sean Ewings, Patrick J Lillie, Tristan W Clark

Summary

Background Respiratory virus infection is a common cause of hospitalisation in adults. Rapid point-of-care testing (POCT) for respiratory viruses might improve clinical care by reducing unnecessary antibiotic use, shortening length of hospital stay, improving influenza detection and treatment, and rationalising isolation facility use; however, insufficient evidence exists to support its use over standard clinical care. We aimed to assess the effect of routine POCT on a broad range of clinical outcomes including antibiotic use.

Methods In this pragmatic, parallel-group, open-label, randomised controlled trial, we enrolled adults (aged ≥18 years) within 24 h of presenting to the emergency department or acute medical unit of a large UK hospital with acute respiratory illness or fever higher than 37·5°C (≤7 days duration), or both, over two winter seasons. Patients were randomly assigned (1:1), via an internet-based allocation sequence with random permuted blocks, to have a molecular POC test for respiratory viruses or routine clinical care. The primary outcome was the proportion of patients who received antibiotics while hospitalised (up to 30 days). Secondary outcomes included duration of antibiotics, proportion of patients receiving single doses or brief courses of antibiotics, length of stay, antiviral use, isolation facility use, and safety. Analysis was by modified intention to treat, excluding patients who declined intervention or were withdrawn for protocol violations. This study is registered with ISRCTN, number 90211642, and has been completed.

Findings Between Jan 15, 2015, and April 30, 2015, and between Oct 1, 2015, and April 30, 2016, we enrolled 720 patients (362 assigned to POCT and 358 to routine care). Six patients withdrew or had protocol violations. 301 (84%) of 360 patients in the POCT group received antibiotics compared with 294 (83%) of 354 controls (difference 0·6%, 95% CI −4·9 to 6·0; p=0·84). Mean duration of antibiotics did not differ between groups (7·2 days [SD 5·1] in the POCT group *vs* 7·7 days [4·9] in the control group; difference −0·4, 95% CI −1·2 to 0·4; p=0·32). 50 (17%) of 301 patients treated with antibiotics in the POCT group received single doses or brief courses of antibiotics (<48 h) compared with 26 (9%) of 294 patients in the control group (difference 7·8%, 95% CI 2·5 to 13·1; p=0·0047; number needed to test=13). Mean length of stay was shorter in the POCT group (5·7 days [SD 6·3]) than in the control group (6·8 days [7·7]; difference −1·1, 95% CI −2·2 to −0·3; p=0·0443). Appropriate antiviral treatment of influenza-positive patients was more common in the POCT group (52 [91%] of 57 patients) than in the control group (24 [65%] of 37 patients; difference 26·4%, 95% CI 9·6 to 43·2; p=0·0026; number needed to test=4). We found no differences in adverse outcomes between the groups (77 [21%] of 360 patients in the POCT group *vs* 88 [25%] of 354 patients in the control group; −3·5%, −9·7 to 2·7; p=0·29).

Interpretation Routine use of molecular POCT for respiratory viruses did not reduce the proportion of patients treated with antibiotics. However, the primary outcome measure failed to capture differences in antibiotic use because many patients were started on antibiotics before the results of POCT could be made available. Although POCT was not associated with a reduction in the duration of antibiotics overall, more patients in the POCT group received single doses or brief courses of antibiotics than did patients in the control group. POCT was also associated with a reduced length of stay and improved influenza detection and antiviral use, and appeared to be safe.

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NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK (N J Brendish MRCP); **Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK** (N J Brendish, R Houghton MRCP, T W Clark MD); **Department of Infection, University Hospital Southampton NHS Foundation Trust, Southampton, UK** (A K Malachira MD, L Armstrong MBBS, R Houghton, P J Lillie PhD, T W Clark); **NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK** (S Aitken BA, E Nyimbili RGN, T W Clark); **and Southampton Statistical Sciences Research Institute, University of Southampton, Southampton, UK** (S Ewings PhD)

Correspondence to:
Dr Tristan William Clark, Southampton General Hospital, Southampton, SO16 6YD, UK
T.W.Clark@soton.ac.uk

Introduction

Acute respiratory tract infections are responsible for a huge burden of disease and are the third most common cause of death worldwide.[1,2] Although bacteria were previously considered to be the principal aetiological agents of severe respiratory tract infections, the global importance of respiratory viruses in this group has been increasingly recognised in recent years.[3–6] Around 700 000 emergency hospital admissions with acute respiratory infection (including exacerbations of chronic lung disease) occurred in England in 2014–15, with approximately 50 000 deaths.[7] Recent, large studies using modern molecular diagnostic tests have shown that respiratory viruses are detectable in around 40–50% of hospitalised adults with acute respiratory illness.[4,8]

Research in context

Evidence before this study

We searched PubMed, the Cochrane Controlled Clinical Trials Register, and ClinicalTrials.gov database for relevant published articles and ongoing trials assessing the clinical effect of rapid molecular testing or molecular point-of-care testing (POCT) for respiratory viruses in hospitalised adults with acute respiratory illness. We used the search terms "point-of-care testing" or "rapid PCR testing" or "rapid testing" or "viral testing" and "respiratory virus" or "influenza" and "hospital" and "adult" and "clinical trial" or "randomised controlled trial" or "study". We limited the search to studies published between Jan 1, 1980, and Nov 1, 2016, in English. We excluded studies using antigen-based tests for respiratory viruses, studies in children, and studies reporting only diagnostic accuracy. We found no Cochrane systematic reviews in adults. We found no high-quality randomised controlled trials of molecular POCT evaluating clinical outcomes. We found one small randomised controlled trial evaluating the effect of rapid (not point-of-care) molecular testing for viruses (combined with procalcitonin testing) on antibiotic use in hospitalised adults with non-pneumonic lower respiratory tract infection. We found one retrospective cohort study evaluating influenza detection and neuraminidase inhibitor use with a rapid (not point-of-care) molecular testing for influenza in hospitalised adults.

Added value of this study

To our knowledge, our study is the first large, randomised, controlled trial evaluating the use of routine molecular POCT for respiratory viruses in hospitalised adults with acute respiratory illness, and the first to report comprehensively on a wide range of clinical outcomes. Its pragmatic design with broad inclusion criteria and a simple intervention make the results highly generalisable to other similar centres and settings.

Implications of all the available evidence

Although POCT was not associated with a reduction in the proportion of patients treated with antibiotics, it did lead to a greater proportion of patients being treated with single doses or brief courses of antibiotics compared with routine clinical care. The findings of our study are consistent with previous studies that suggested potential benefits for rapid molecular testing for respiratory viruses in adults, in terms of reduction of unnecessary antibiotic use, improvements in the detection rate of influenza, and improvements in neuraminidase inhibitor use. Our study suggests that routine POCT leads to improvements in the rate of respiratory virus detection, improved antiviral use for influenza, rationalisation of hospital isolation facilities, reduction in length of stay, and is safe. If these findings are confirmed in other studies and supported by health economic analysis showing cost-effectiveness, routine POCT for respiratory viruses should become part of standard care for adults presenting to hospital with acute respiratory illness.

Testing for respiratory viruses in hospitalised adults is done on the basis of clinical suspicion rather than routinely, and relies on laboratory-based PCR testing. Although highly accurate, the turnaround time of laboratory PCR in the UK is generally 24–48 h, and requires specialist, centralised laboratory facilities. Previously, point-of-care testing (POCT) for respiratory viruses has been mainly limited to antigen-based tests for influenza. These tests have insufficient sensitivity, especially in adults,[9] and randomised controlled trials have failed to show clinical or health economic benefits in hospitalised adults with acute respiratory illness.[10] Rapid molecular testing platforms for respiratory viruses have been developed with broadly equivalent diagnostic accuracy to laboratory PCR, and some of these platforms are potentially deployable as POC tests. One such platform is the US Food and Drug Administration-approved and European Conformity-marked FilmArray Respiratory Panel (BioFire; Salt Lake City, UT, USA), which tests for a comprehensive range of viruses, is relatively simple to use, and gives a result in 1 h.[11–14]

For the **study protocol** see http://eprints.soton.ac.uk/402407

Antimicrobial resistance is arguably one of the greatest threats to global human health and is driven by overuse of antibiotics. Antibiotics are prescribed to most patients hospitalised with acute respiratory illness, including clinical groups in which viruses are strongly implicated in as the cause and no evidence for benefit exists, such as patients with asthma exacerbations[15,16] and some patients with exacerbation of COPD.[17] Diagnostic uncertainty regarding microbial aetiology contributes to this practice, and so the potential benefits of molecular POCT for viruses in hospitals include a reduction in unnecessary antibiotic use.[18] Other important potential benefits of POCT include reductions in hospital length of stay, improvements in influenza detection with subsequent directed rather than empirical antiviral use, and rationalisation of hospital isolation facilities. However, no high-quality evidence exists to support use of molecular POCT. We aimed to address this evidence gap by doing a pragmatic, randomised controlled trial evaluating the effect of routine molecular POCT in adults presenting to hospital with acute respiratory illness, on a broad range of clinical outcomes.

Methods

Study design and participants

We did a large, pragmatic, parallel-group, open-label, single-centre, randomised controlled superiority trial in a large UK hospital. The trial took place over two successive winter seasons in 2014–15 and 2015–16. All patients were recruited from the Acute Medical Unit and Emergency Department of Southampton General Hospital, a large, teaching hospital in the south of the UK serving a population of 650 000 for secondary care and run by the trial sponsor, University Hospital Southampton Foundation

NHS Trust (Southampton, UK). The study was approved by the North West—Preston Regional Ethics Committee (NW/14/1467).

Eligible patients were aged 18 years or older; had the capacity to give informed, written consent and were able and willing to adhere to the study procedures; were a patient in the Southampton General Hospital Acute Medical Unit or Emergency Department; could be recruited to the study within 24 h of first triage by emergency department staff or within 24 h of arrival at the acute medical unit (if admitted directly to the unit); had an acute respiratory illness or fever higher than 37·5°C, or both; and had a duration of illness less than or equal to 7 days. An episode of acute respiratory illness was defined as an 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 COPD, asthma, or bronchiectasis). The exclusion criteria were a palliative approach being taken by the treating clinicians, or patients who declined nasal or pharyngeal swabbing. Previous inclusion in this study was originally an exclusion criterion, but for the second winter season this was modified (July 15, 2015) to permit inclusion of patients previously recruited but re-presenting more than 30 days after hospital discharge. All participants gave written informed consent.

Randomisation and masking

Immediately after enrolment, patients were consecutively assigned a unique participant identification number by study team members (NJB, AKM, LA, RH, SA, and EN), 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. Trial participants, research staff, and clinical care providers were not blinded to group allocation. Data analysts were blinded to group allocation.

Procedures

Participants randomly allocated to the intervention group had a nose and throat swab taken by research staff (NJB, AKM, LA, RH, SA, and EN) according to standard protocols, which was analysed immediately using the FilmArray Respiratory Panel. The panel detects the following viruses: influenza A (H1 and H3), influenza B, respiratory syncytial virus, rhinovirus or enterovirus (without specifying which), human metapneumovirus, parainfluenza virus types 1–4, coronaviruses (OC43, 229E, HKU1, and NL63), and adenovirus. The testing units were located in the acute medical unit and emergency department. If a respiratory virus was detected, the clinical and infection control teams were informed directly, and all results (positive and negative) were recorded in the medical notes. Patients randomly allocated to the control group were managed according to routine clinical care in which use of antibiotics, influenza antivirals, and isolation facilities is based on the judgment of the responsible clinical team, and testing for respiratory viruses by laboratory PCR is at their discretion. Laboratory PCR was done using conventional methods in the centralised laboratory facility and detected the following viruses: influenza A (H1 and H3), influenza B, respiratory syncytial virus, human metapneumovirus, parainfluenza virus types 1–3, and adenovirus. Clinical management decisions were made independently by the responsible clinical team. Demographic and clinical data were collected at recruitment and outcome data were collected retrospectively from paper case notes, electronic medical records, and electronic prescribing systems. All data were collected on a standard case report form.

Outcomes

The primary outcome measure was the proportion of patients treated with antibiotics during hospitalisation or within 30 days of admission if the patient was still hospitalised, whichever was shortest. We chose this outcome after publication of a Cochrane review[19] on the clinical effect of POCT for influenza in children that concluded existing evidence was insufficient to make recommendations and that randomised controlled trials were urgently needed with antibiotic use as an outcome measure. Additionally, small non-randomised studies[20] have suggested reductions in the proportion of patients prescribed antibiotics when tested for influenza with POCT. To capture the entire range of clinically relevant antibiotic changes associated with POCT, we selected the following key secondary outcome measures: duration of antibiotic use (with a cutoff at 30 days), proportion of patients receiving only a single dose of antibiotics, proportion of patients receiving less than 48 h of antibiotics, proportion of patients receiving intravenous antibiotics, and duration of intravenous antibiotics (with a cutoff at 30 days). Because the aim of this trial was to evaluate other potential clinical benefits of POCT for respiratory viruses and not just antibiotic use, non-antibiotic secondary outcome measures were proportion of patients admitted, hospital length of stay, proportion of patients with prolonged inpatient stay (defined as ≥7 days), turnaround time of respiratory virus testing, proportion of patients with viruses detected, proportion of patients with influenza detected, proportion of patients with confirmed influenza treated with neuraminidase inhibitors, proportion of all neuraminidase inhibitor use occurring in patients with confirmed influenza, time to neuraminidase inhibitor use, duration of neuraminidase inhibitor use, proportion of patients admitted to a hospital side room, duration of side room use, and time to isolation or de-isolation. Duration-based endpoints were not prespecified, and choice of mean or median was dependent on various factors, including distribution and sample size, and made after the data had been collected. All outcomes were measured until discharge from hospital or for the first 30 days of hospitalisation, whichever was shorter in duration, and included antibiotics and antivirals that patients were

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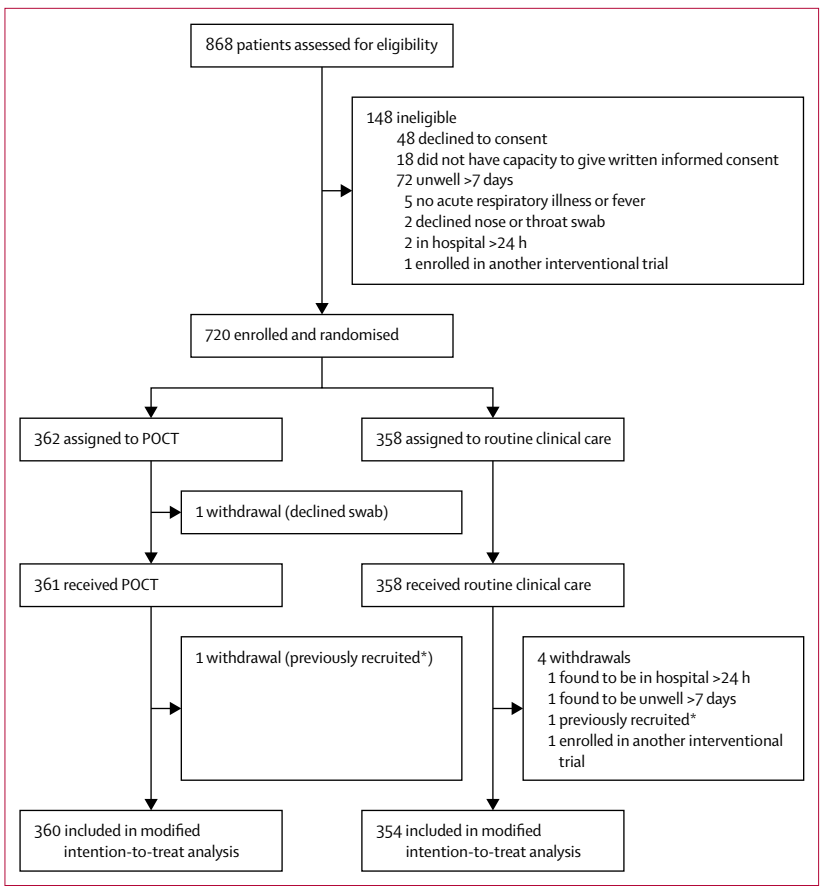

Figure 1: **Trial profile**
POCT=point-of-care testing. *Previous recruitment was an exclusion criterion during the first season (January, 2015, to April, 2015); this was changed for the second season (September, 2015, to April, 2016) to permit inclusion for patients presenting more than 30 days after hospital discharge.

discharged with. Serious adverse events were reported to the sponsor as per regulatory requirement. Safety outcomes were admission to respiratory high-dependency unit or general intensive care unit while hospitalised, re-presentation (without admission) to hospital, re-admission to hospital, and death within 30 days of enrolment.

Statistical analysis

We based our sample size on the primary outcome measure of proportion of patients treated with antibiotics. We assumed that about 75% of patients would be treated with antibiotics.[4] To detect a reduction in antibiotic use of 10%[20] with a power of 0·8 and significance level of 0·05, 326 patients would be required in each group (based on χ^2 test without continuity correction). Allowing for a 10% withdrawal rate, we set target recruitment at 360 patients per group (720 patients in total).

Owing to the small proportion of patients who withdrew after randomisation, and the fact that withdrawals were predominantly due to breaches in inclusion criteria, the decision was made for primary and safety analyses to be modified intention to treat. Analyses were done using Prism version 6.0 (GraphPad Software; La Jolla, CA, USA) and Stata version 13.1 (StataCorp; College Station, TX, USA). Baseline characteristics within each group were summarised using appropriate descriptive statistics. We initially compared the primary outcome—antibiotic use—between groups (intervention and control) using difference in proportions and unadjusted odds ratio. We further assessed the effect of group on the primary outcome using multiple logistic regression to control for the following covariates: demographics (age, sex), influenza vaccination status, duration of symptoms, receipt of antibiotics before presentation, comorbidity, temperature, C-reactive protein concentration, and clinical group. We compared duration of antibiotic use (recorded in hours; analysed and presented in days) between groups using mean difference and unadjusted rate ratio. We further assessed the effect of group using the adjusted rate ratio from multiple negative binomial regression, controlling for the same covariates as for the multiple logistic regression. For other secondary outcomes, we compared the intervention and control groups using differences in proportions for binary data, and *t* tests and Mann-Whitney *U* tests for continuous data (eg, turnaround time), as appropriate; the choice between the latter two tests was based on the distribution of the observed data and the sample size. Where 95% CIs are presented, Stata version 13.1 defaults are used.

In view of the deliberately broad inclusion criteria, we anticipated heterogeneity of treatment effect among different clinical groups a priori, and we did a pre-planned subgroup analysis for the primary and certain key secondary outcome measures on the basis of diagnostic group (eg, exacerbation of asthma, exacerbation of COPD, pneumonia). We assessed results for antibiotic use (including any use, single dose, and use for <48 h duration), duration of antibiotics, admission, and length of hospitalisation separately for each diagnostic subgroup. We assessed the interaction between clinical subgroups and group in both regression models described above. The original analysis plan was to include the interaction between clinical group and trial arm in the multiple logistic regression; however, the model was unstable, possibly due to the size of the subgroups. We instead present unadjusted comparisons of subgroups. Owing to the nature of the analyses, and the many comparisons made, the results should be interpreted cautiously. All results presented here relate to absolute differences in means or proportions.

This study was prospectively registered with ISRCTN, number 90211642.

Role of the funding source

The study was conducted in a hospital in partnership with the study funder. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

	POCT (n=360)	Control (n=354)
Age (years)	63 (41–75)	62 (44–74)
Sex		
Female	183 (51%)	185 (52%)
Male	177 (49%)	169 (48%)
Ethnic origin		
White British	337 (94%)	331 (94%)
Other	23 (6%)	23 (6%)
Current smoker		
Yes	92 (26%)	89 (25%)
No	268 (74%)	265 (75%)
Influenza vaccine*		
Yes	206 (57%)	208 (59%)
No	151 (42%)	143 (40%)
Duration of symptoms (days)	4 (2–6)	4 (3–5)
Antibiotics within 14 days†		
Yes	90 (25%)	91 (26%)
No	270 (75%)	263 (74%)
Antivirals within 14 days†		
Yes	0	0
No	360 (100%)	354 (100%)
Comorbidity		
Cardiovascular disease	132 (37%)	133 (38%)
Respiratory disease	213 (59%)	206 (58%)
Renal disease	20 (6%)	22 (6%)
Liver disease	7 (2%)	2 (1%)
Diabetes	48 (13%)	64 (18%)
Immunocompromised	18 (5%)	21 (6%)
Cancer	23 (6%)	25 (7%)
Observations		
Temperature (°C)	36·9 (36·4–37·7)	37·0 (36·4–37·8)
Temperature ≥38°C	64 (18%)	78 (22%)
Pulse rate (bpm)	100 (85–110)	100 (84–110)
Respiratory rate (bpm)	23 (19–28)	22 (18–26)
O_2 saturations (%)	96 (94–98)	95 (93–97)
Supplementary O_2	96 (27%)	76 (21%)
BP (mm Hg)		
Systolic	130 (118–149)	133 (120–152)
Diastolic	72 (63–81)	72 (64–83)
(Table 1 continues on next column)		

	POCT (n=360)	Control (n=354)
(Continued from previous column)		
Laboratory and radiology		
CRP (mg/L)	40 (12–127)	44 (13–99)
White cell count (×10⁹ per L)	10·8 (8·1–14·8)	10·4 (8·0–14·0)
Neutrophils (×10⁹ per L)	8·4 (5·7–11·0)	7·9 (5·5–11·1)
Chest X-ray done		
Yes	346 (96%)	340 (96%)
No	14 (4%)	14 (4%)
Final diagnosis		
Asthma	62 (17%)	57 (16%)
IECOPD	81 (23%)	83 (23%)
Pneumonia	94 (26%)	98 (28%)
Influenza-like illness/NPLRTI	76 (21%)	69 (19%)
Other‡	47 (13%)	47 (13%)
Location of recruitment		
Emergency department	134 (37%)	147 (42%)
Acute medical unit	226 (63%)	207 (58%)

Data are n (%) or median (IQR). POCT=point-of-care testing. bpm=beats per min. O_2=oxygen. BP=blood pressure. CRP=C-reactive protein. IECOPD=infective exacerbation of COPD. NPLRTI=non-pneumonic lower respiratory tract infection. *Received vaccine for the current influenza season. †Received within 14 days before presentation to hospital. ‡See appendix (p 1) for breakdown of individual clinical diagnoses.

***Table 1*: Baseline characteristics**

Results

We recruited patients in two seasons: between Jan 15, 2015, and April 30, 2015, and between Oct 1, 2015, and April 30, 2016. We assessed 868 patients for eligibility, and stopped the trial when 720 patients had been recruited (figure 1). 362 patients were randomly assigned to receive POCT and 358 were randomly assigned to receive routine clinical care (control). One patient assigned to POCT declined to be swabbed and so did not receive the intervention. One patient in the POCT group and four in the control group were withdrawn due to protocol violations (figure 1). 360 patients in the POCT group and 354 patients in the routine clinical care group were analysed in the modified intention-to-treat analysis (figure 1). Baseline demographics and clinical characteristics seemed similar between groups (table 1).

All patients in the POCT group were tested for respiratory viruses compared with 158 (45%) of 354 patients in the control group (table 2). More patients in the POCT group had a respiratory virus detected than in the control group (table 2). The mean turnaround time (time from the decision to test a patient to the result being available to clinicians) for respiratory virus testing was substantially lower in the POCT groups (table 2). The positive and negative agreement between the POCT results and laboratory PCR (for patients in the POCT group in whom both were done) are given in the appendix (p 2).

See Online for appendix

For the primary outcome, 301 (84%) of 360 patients in the POCT group received antibiotics during their admission compared with 294 (83%) of 354 patients in the control group (difference 0·6% in favour of the control group, 95% CI –4·9 to 6·0; p=0·84; table 3). Multiple logistic regression analysis on the primary outcome altered the direction of the difference but did not change the broader interpretation (table 3; appendix p 3 for full results from the multiple logistic regression model). Mean duration of antibiotics did not differ between groups (difference –0·4, –1·2 to 0·4; p=0·32; table 3), and multiple negative binomial regression analysis did not significantly alter the interpretation of the results (table 3; appendix p 4 for full results from the multiple negative binomial

	POCT (n=360)	Control (n=354)	Difference (95% CI)	Odds ratio (95% CI)	Number needed to test (95% CI)	p value
Patients tested for viruses	360 (100%)	158 (45%)	55·4% (50·1 to 60·0)	..	..	<0·0001
Patients with any virus detected	161 (45%)	52 (15%)	30·0% (23·3 to 36·8)	4·70 (3·28 to 6·74)	4 (2·8 to 4·2)	<0·0001
Influenza A or B	61 (17%)	37 (10%)	6·5% (1·5 to 11·5)	1·75 (1·13 to 2·71)	16 (9 to 68)	0·0124
Rhinovirus or enterovirus (unspecified)*	55 (15%)	..	..	..	..	..
Coronavirus*	18 (5%)	..	..	..	..	..
Human metapneumovirus	14 (4%)	5 (1%)	2·5% (0·1 to 4·8)	..	..	0·060
Parainfluenza	11 (3%)	2 (<1%)	2·5% (0·6 to 4·4)	..	..	0·0214
RSV	9 (3%)	6 (2%)	0·8% (–1·3 to 2·9)	..	..	0·60
Adenovirus	1 (<1%)	2 (<1%)	–0·3% (–1·2 to 0·7)	..	..	0·62
Viral co-detection	8 (2%)	0	2·2% (0·7 to 3·7)	..	..	0·0075
Turnaround time (h)	2·3 (1·4)†	37·1 (21·5)	–34·7 (–38·1 to –31·4)			<0·0001

Data are n (%) or mean (SD). Medians are presented in the appendix for completeness. POCT=point-of-care testing. RSV=respiratory syncytial virus. *Not tested for by laboratory PCR. †Assessed in 356 patients.

***Table 2*: Patients tested for viruses, rate of detection, and turnaround time**

	POCT (n=360)	Control (n=354)	Risk difference (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Number needed to test (95% CI)	p value
All antibiotics							
Antibiotics given	301 (84%)	294 (83%)	0·6% (–4·9 to 6·0)	1·04 (0·70 to 1·54)	0·99 (0·57 to 1·70)	..	0·96*
Single dose only	31/301 (10%)	10/294 (3%)	6·9% (2·9 to 11·0)	3·26 (1·59 to 6·68)	..	15 (9 to 35)†	0·0010
Given for <48 h	50/301 (17%)	26/294 (9%)	7·8% (2·5 to 13·1)	2·05 (1·40 to 3·39)	..	13 (8 to 41)‡	0·0047
Duration (days)	7·2 (5·1)	7·7 (4·9)	–0·4 (–1·2 to 0·4)§	0·95 (0·85 to 1·05)¶	0·91 (0·80 to 1·04)‖	..	0·17*
Intravenous antibiotics							
Intravenous antibiotics given	196 (54%)	183 (52%)	2·7% (–4·6 to 10·0)	1·15 (0·83 to 1·50)	..	..	0·46
Single dose only	50/196 (26%)	37/183 (20%)	5·3% (–3·1 to 14·0)	1·35 (0·84 to 2·19)	..	..	0·22
Given for <48 h	106/196 (54%)	100/183 (55%)	–0·5% (–11·0 to 9·5)	0·98 (0·65 to 1·46)	..	..	0·91
Duration (days)	3·1 (4·6)	2·9 (3·7)	0·3 (–0·6 to 1·1)§	1·09 (0·86 to 1·40)¶	..	..	0·48

Data are n (%) or mean (SD). POCT=point-of-care testing. *Applies to adjusted effect sizes. †Number needed to test to change a standard course to a single dose. ‡Number needed to test to change a standard course to a brief course. §Mean difference. ¶Unadjusted rate ratio. ‖Adjusted rate ratio.

***Table 3*: Comparison of antibiotic use**

regression model). Among patients given antibiotics, a greater proportion of patients in the POCT group received only a single dose of antibiotics than in the control group (table 3). Similarly, a greater proportion of patients in the POCT group received a brief course (<48 h) of antibiotics than in the control group (table 3). The proportion of patients treated with intravenous antibiotics and their duration did not differ between the groups (table 3).

Owing to hospital processes of care, many recruited patients had antibiotics prescribed very early in the course of their assessment and often before they could be randomly allocated or before the POCT results were available to the clinical teams for the POCT group. We therefore did a post-hoc analysis on patients in whom antibiotics had not been prescribed before randomisation and before POCT results were available to the clinical teams. In this subgroup, antibiotics were prescribed in 61 (51%) of 120 patients in the POCT group compared with 107 (64%) of 167 in the control group (difference –13·2%, 95% CI –24·8 to –1·7; p=0·0289; number needed to test to prevent one patient being treated with antibiotics is eight; appendix p 5).

Most patients presenting to secondary care were hospitalised in both groups (table 4). Mean hospital length of stay was shorter in the POCT group than in the control group (table 4). The proportion of patients with a prolonged inpatient stay (≥7 days) did not differ between groups.

Post-hoc analysis of antibiotic duration and hospital length of stay in the intervention group by POCT result showed that patients with positive results received shorter courses of antibiotics (mean 6·2 days [SD 4·8]) than did patients with negative results (8·0 days [5·3]; difference –1·7 days, 95% CI –2·9 to –0·6; p=0·0033) and had a shorter duration of hospitalisation (4·7 days [4·6]) than did patients with negative results (6·5 days [7·2]; difference

	POCT (n=360)	Control (n=354)	Difference (95% CI)	Odds ratio (95% CI)	p value
Admitted	332 (92%)	327 (92%)	−0·2% (−4·1 to 3·8)	0·98 (0·56 to 1·70)	0·94
Length of hospital stay (days)*	5·7 (6·3)	6·8 (7·7)	−1·1 (−2·2 to −0·3)	..	0·0443
Prolonged inpatient stay†	81/327 (25%)	86/311 (28%)	−2·9% (−9·7 to 3·9)	0·86 (0·61 to 1·23)	0·42

Data are n (%) or mean (SD). POCT=point-of-care testing. *Adjusted for in-hospital mortality. †Defined as ≥7 days (adjusted for in-hospital mortality).

***Table 4*: Length of hospital stay**

−1·7 days, 95% CI −3·0 to −0·4; p=0·0085; appendix p 6). The distribution of antibiotic duration and length of hospital stay for both groups and according to POCT results are shown in figure 2.

We explored potentially different treatment effects in prespecified clinical subgroups (table 5, appendix pp 7–8). In the exacerbation of asthma and COPD subgroups, mean duration of antibiotics was lower for patients in the POCT group than in the control group. Non-significant differences were observed in the other subgroups (appendix pp 7–8). For patients with asthma treated with antibiotics, a greater proportion of patients in the POCT group than in the control group received only a single dose of antibiotics (table 5). For patients with infective exacerbation of COPD treated with antibiotics, a greater proportion of patients in the POCT group than in the control group received less than 48 h of antibiotics (for distributions of antibiotic duration for asthma and COPD subgroups, see appendix pp 10–11). For patients with infective exacerbation of COPD, the mean length of hospital stay was lower in the POCT group than in the control group; mean length of hospital stay did not differ within other subgroups (table 5, appendix pp 7–8).

No difference was observed in the number of patients treated with neuraminidase inhibitors (table 6). A greater proportion of patients treated with neuraminidase inhibitors in the POCT group had confirmed influenza infection than in the control group (table 6). In addition, patients treated empirically with neuraminidase inhibitors who then tested negative for influenza received shorter courses of neuraminidase inhibitors in the POCT group compared with the control group (table 6). UK Public Health England guidelines[21] recommend neuraminidase inhibitor treatment for all hospitalised adults with influenza. A greater proportion of hospitalised patients with confirmed influenza in the POCT group were treated with neuraminidase inhibitors than in the control group (table 6). The mean time to starting neuraminidase inhibitor treatment in these patients did not differ between groups (table 6).

Data on isolation facility use were only available for the second year of recruitment (winter of 2015–16) owing to the introduction of a new hospital information system that allowed hospital side room use to be accurately tracked in real time (to the nearest whole day). Overall isolation facility use did not differ between the groups (table 6). However, a greater proportion of patients in the POCT group were isolated for confirmed respiratory virus infection compared with the control group (table 6). The proportion of influenza-positive patients admitted to hospital and staying for at least 6 h who were isolated did not differ significantly between groups (table 6). Mean time to isolation for influenza-positive patients not empirically isolated at presentation was significantly shorter in the POCT group than in the control group, as was mean time to de-isolation for patents initially isolated with suspected influenza but subsequently testing negative (table 6).

We found no differences between the groups in overall rates of adverse outcomes, or in individual rates of high dependency or intensive care unit admissions during hospitalisation, re-presentation, or readmission to hospital within 30 days of discharge, or 30-day mortality (table 7).

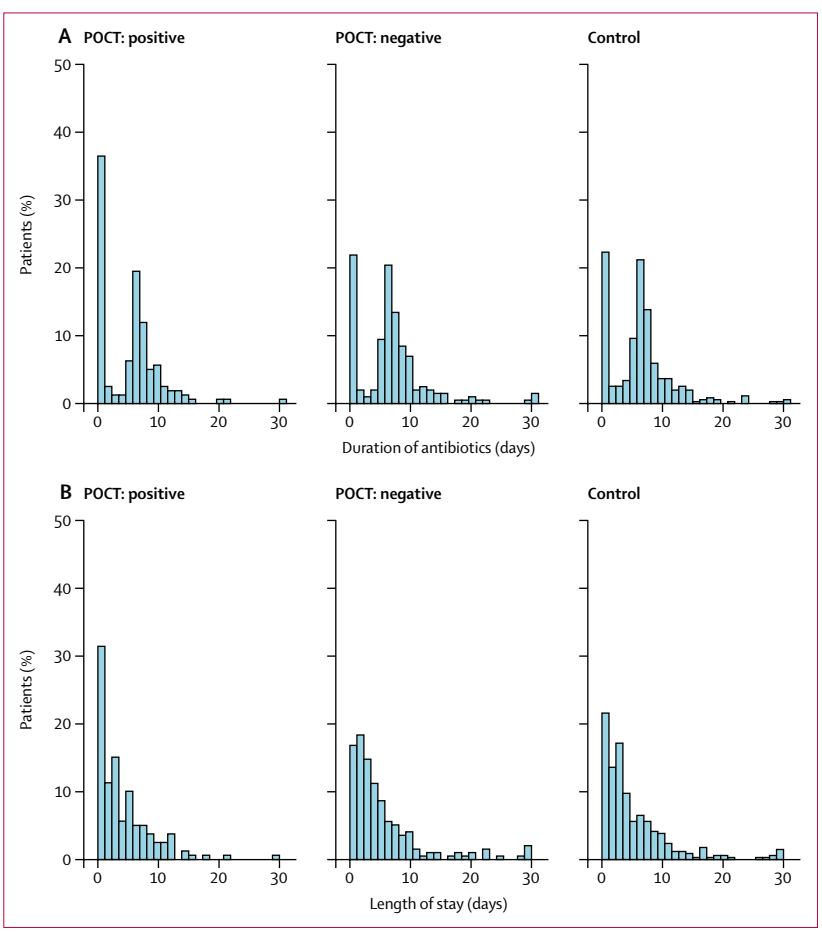

***Figure 2*: Distribution of the (A) duration of antibiotics and (B) length of hospital stay**
Distributions are shown for patients with positive POCT results, patients with negative POCT results, and patients in the control group. POCT=point-of-care testing.

	POCT (n=360)	Control (n=354)	Difference (95% CI)	Odds ratio (95% CI)	p value
Asthma	62 (17%)	57 (16%)	..	..	..
Antibiotics given	43/62 (69%)	36/57 (63%)	6·2% (−10·5 to 22·6)	1·32 (0·62 to 2·83)	0·56
Single dose only	14/43 (33%)	3/36 (8%)	24·2% (6·1 to 40·1)	5·31 (1·38 to 20·41)	0·0125
Given for <48 h	18/43 (42%)	4/36 (11%)	30·8% (11·2 to 47·0)	5·76 (1·73 to 19·20)	0·0026
Duration of antibiotics (days)	3·9 (3·4)	5·3 (2·3)	−1·4 (−2·7 to −0·1)	..	0·0382
Length of hospital stay (days)	3·4 (3·3)	3·9 (3·5)	−0·5 (−1·8 to 0·9)	..	0·49
IECOPD	81 (23%)	83 (23%)	..	..	..
Antibiotics given	75/81 (93%)	75/83 (90%)	2·2% (−6·9 to 11·4)	1·33 (0·44 to 4·03)	0·78
Single dose only	7/75 (9%)	3/75 (4%)	5·3% (−3·2 to 14·4)	2·47 (0·61 to 9·95)	0·33
Given for <48 h	11/75 (15%)	3/75 (4%)	10·7% (1·2 to 20·7)	4·13 (1·10 to 15·50)	0·0462
Duration of antibiotics (days)	6·1 (3·2)	8·0 (5·0)	−1·9 (−3·2 to −0·5)	..	0·0078
Length of hospital stay (days)	4·5 (3·6)	6·3 (6·2)	−1·8 (−3·4 to −0·2)	..	0·0276
Asthma or IECOPD	143 (40%)	140 (40%)	..	..	..
Antibiotics given	118/143 (83%)	111/140 (79%)	3·2% (−6·0 to 12·4)	1·23 (0·68 to 2·24)	0·55
Single dose only	21/118 (18%)	6/111 (5%)	12·4% (4·1 to 20·8)	3·79 (1·47 to 9·78)	0·0041
Given for <48 h	29/118 (25%)	7/111 (6%)	18·3% (9·0 to 27·4)	4·84 (2·02 to 11·59)	0·0002
Duration of antibiotics (days)	5·3 (3·4)	7·1 (4·5)	−1·8 (−2·8 to −0·8)	..	0·0008
Length of hospital stay (days)	4·0 (3·5)	5·4 (5·5)	−1·4 (−2·5 to −0·2)	..	0·0186

Data are n/N (%) or mean (SD). Medians and data on other subgroups are reproduced in the appendix (pp 7–8). POCT=point-of-care testing. IECOPD=infective exacerbation of COPD.

***Table 5*: Antibiotic use and length of stay for asthma and IECOPD clinical subgroups**

	POCT (n=360)	Control (n=354)	Difference (95% CI)	Odds ratio (95% CI)	Number needed to test (95% CI)	p value
Neuraminidase inhibitor use						
Neuraminidase inhibitor used (total)	66 (18%)	51 (14%)	3·9% (−1·5 to 9·4)	1·33 (0·89 to 1·99)	..	0·16
Used in influenza-positive patients	54/66 (82%)	24/51 (47%)	34·7% (17·5 to 52·0)	5·06 (2·20 to 11·65)	3 (1·9 to 5·5)	0·0001
Used in influenza-negative patients	12/66 (18%)	27/51 (53%)	..	..	..	..
Influenza-positive patients treated with neuraminidase inhibitor*	52/57 (91%)	24/37 (65%)	26·4% (9·6 to 43·2)	5·63 (1·80 to 17·60)	4 (2·3 to 10·7)	0·0026
Duration of neuraminidase inhibitor use in influenza-negative patients (doses)†	2·0 (2·6)	6·1 (4·1)	−4·1 (−6·3 to −1·9)	..	..	0·0006
Time to first dose of neuraminidase inhibitor (h)*	8·8 (15·3)	21·0 (28·7)	−12·2 (−24·9 to 0·5)	..	..	0·0597
Isolation facility use‡						
All patients isolated	63/191 (33%)	49/194 (25%)	7·7% (−1·3 to 16·8)	1·45 (0·94 to 2·27)	..	0·12
Isolated with confirmed respiratory virus infection§	32/191 (17%)	17/194 (9%)	8·0% (1·3 to 14·7)	2·10 (1·12 to 3·92)	13 (6·8 to 73·2)	0·0217
Influenza-positive patients isolated*	20/27 (74%)	13/23 (57%)	17·6% (−8·8 to 43·9)	2·20 (0·67 to 7·24)	..	0·24
Time to isolation (days)¶	0·5 (0·5)	1·0 (0·4)	−0·5 (−0·9 to −0·2)	..	..	0·0071
Time to de-isolation (days)‖	1·0 (0·0)	3·1 (2·2)	−2·1 (−3·6 to −0·7)	..	..	0·0057

Data are n (%) or mean (SD). Medians are reported in the appendix for completeness. POCT=point-of-care testing. *For hospitalised influenza-positive patients only. †Oseltamivir is given twice daily. ‡Side room data only available for the second season of the study (PCOT n=191; control n=194). §Includes influenza and respiratory syncytial virus. ¶For patients not empirically isolated at admission, but subsequently found to be influenza positive. ‖For patients isolated empirically on admission for suspected influenza infection, but subsequently found to be influenza negative.

***Table 6*: Neuraminidase inhibitor use and hospital isolation facility use**

Discussion

This large, pragmatic, randomised controlled trial is the first, to our knowledge, to report on the effect of routine molecular POCT for viruses, on a broad range of clinical outcomes including antibiotic use, length of hospital stay, influenza antiviral use, isolation facility use, and safety. The results showed that a routine molecular POCT strategy in adults presenting to secondary care with acute respiratory illness led to a higher detection rate of viruses and a faster turnaround time for results

compared with laboratory PCR, but did not reduce the proportion of patients treated with antibiotics or the overall duration of antibiotics compared with routine clinical care. However, it did lead to an increased proportion of patients receiving single doses and brief (<48 h) courses of antibiotics, without any evidence of harm. The reason that the increase in single doses and brief courses did not translate into an overall reduction in the duration of antibiotics is likely to relate to the uniformly high use of prolonged antibiotics in certain clinical groups, especially patients with pneumonia (mean duration of around 9 days), which was not affected by POCT. Our subgroup analyses suggest that the increase in single doses and brief courses of antibiotics occurred mainly in patients with exacerbation of airways disease, and in these groups POCT was associated with a significant reduction in antibiotic duration. Our analysis also suggests that this reduction in antibiotic use occurs mainly in those patients testing positive for respiratory viruses and that a positive test reduces antibiotic duration by leading clinicians to stop antibiotics earlier, after a single dose or a brief course of 1–2 days, rather than completing a standard 5–7 day course. Although premature discontinuation of an antibiotic course has previously been regarded as inadvisable owing to concerns over generating resistance, evidence suggests that early discontinuation is safe from this perspective and is in fact associated with a reduced risk of drug resistance.[22] Around 200 000 patients are hospitalised with exacerbation of asthma and COPD combined each year in the UK,[7,23] and more than two thirds of these patients are treated with antibiotics; therefore, being conservative regarding the effect size, a reduction in antibiotic duration of around 1 day per patient treated would equate to a total reduction of around 150 000 antibiotic days per year. This reduction would contribute substantially to the antimicrobial reduction targets set by National Health Service (NHS) organisations to address the threat of antimicrobial resistance. Although this trial is the first large randomised controlled trial of molecular POCT for respiratory viruses examining antibiotic use in detail, other smaller studies have suggested the potential of this strategy to reduce antibiotic use.[24]

In addition to the changes in antibiotic use, our study shows that POCT might be associated with a reduction in hospital length of stay, and subgroup analyses suggest that this reduction was also principally in patients with exacerbation of airways disease. Again, our data suggest that this result was due to earlier discharge in patients testing positive for respiratory viruses in the POCT group. Notably, duration of hospitalisation in the COPD control group is consistent with that quoted in a large, contemporaneous UK study.[25] The reduction in length of stay for patients with exacerbation of airways disease was in the order of 1 day, which would equate to around 200 000 bed days saved per year across the NHS with an associated cost saving of around £80 million per year (a formal health economic analysis of our trial will be published separately).[26]

	POCT (n=360)	Control (n=354)	Difference (95% CI)	Odds ratio (95% CI)	p value
Any adverse outcome (total)	77 (21%)	88 (25%)	−3·5% (−9·7 to 2·7)	0·82 (0·6 to 1·2)	0·29
High dependency unit admission	6 (2%)	3 (1%)	0·8% (−1·2 to 2·8)	1·98 (0·5 to 8·0)	0·33
Intensive care unit admission	11 (3%)	7 (2%)	1·1% (−1·2 to 3·4)	1·56 (0·6 to 4·1)	0·36
Died within 30 days	9 (3%)	16 (5%)	−2·0% (−4·7 to 0·6)	0·54 (0·3 to 1·2)	0·15
Re-presented within 30 days*	49 (14%)	49 (14%)	0·2% (−4·8 to 5·2)	0·98 (0·6 to 1·5)	1·00
Readmitted within 30 days	45 (13%)	55 (16%)	−3·0% (−8·3 to 2·1)	0·78 (0·5 to 1·2)	0·28

Data are n (%). POCT=point-of-care testing. *Re-presenting to hospital but not admitted.

***Table 7*: Adverse outcomes**

Routine POCT for respiratory viruses was also associated with an increased rate of detection of influenza cases and an improvement in antiviral use. Although only patients with clinically suspected infection were tested in the control group, the lower detection rate compared with the POCT group suggests that many cases of influenza were missed and remained undiagnosed in this group. This result is unsurprising as physician-diagnosed influenza is well known to be an insensitive method of case detection, even during periods of high influenza activity.[27,28] In view of the potential consequences including nosocomial spread and the unrealised opportunity to benefit from neuraminidase inhibitor treatment in undiagnosed influenza, these data suggest that influenza testing should be routinely done in patients hospitalised with acute respiratory illness during periods of influenza circulation. Neuraminidase inhibitor treatment is recommended by UK Public Health England for all patients hospitalised with influenza,[21] and although treatment is recommended irrespective of the duration of illness, neuraminidase inhibitors are likely to be most effective when administered earlier in the course of infection.[29] Our study shows that POCT for respiratory viruses leads to an increased proportion of influenza-positive patients correctly receiving treatment with neuraminidase inhibitors and suggests a reduced time to administration of the first dose. Additionally, most neuraminidase inhibitor use was directed towards influenza-positive patients in the POCT group, whereas most use was empirical in the control group and led to many influenza-negative patients receiving neuraminidase inhibitors unnecessarily. Neuraminidase inhibitor use in influenza-negative patients was also prolonged in the control group, presumably due to the long turnaround time of laboratory PCR compared with POCT. This unnecessary neuraminidase inhibitor use exposes patients to the side-effects of neuraminidase inhibitors without any chance of associated benefit. The improvements in neuraminidase inhibitor use seen in this study are consistent with the

findings of a previous non-randomised study[30] of hospitalised adults in which similar differences in the turnaround time between rapid testing and laboratory PCR were also noted.

Hospital side rooms, used for isolating potentially infectious patients, are a limited resource in most UK hospitals and, reassuringly, the use of POCT for respiratory viruses did not lead to an overall increase in side room use despite the increased detection rate of respiratory viruses. However, side room isolation for confirmed respiratory virus infection was more common in the POCT group than in the control group. This result reflects the high rate of directed use of side rooms for patients with confirmed influenza and other viruses compared with the empirical use of side rooms in the control group, many of whom subsequently tested negative and were de-isolated. POCT was also associated with other improvements in side room use including reduced time from admission to isolation with confirmed influenza and reduced time to de-isolation in patients isolated with suspected influenza but subsequently testing negative. Rapid and appropriate assignment of hospital side rooms for patients with respiratory virus infection is hugely important to reduce the risk of nosocomial transmission to other vulnerable hospitalised patients and to improve the flow of patients through acute areas within the hospital.

A molecular POCT result for respiratory viruses can therefore be expected to directly influence patient management in several ways. A positive result can identify the need for isolation facility or neuraminidase inhibitor use in the case of influenza. Although the detection of a virus does not rule out the possibility of a bacterial infection or a benefit from antibiotics, a positive result might also allow the premature discontinuation of precautionary antibiotics in patients with exacerbation of airways disease, if not required on the basis of other criteria such as severity of illness. If negative, a POCT result can prevent or shorten the unnecessary use of isolation facilities and neuraminidase inhibitors.

The strengths of our study include the large number of patients recruited, the setting of a typical large acute hospital, and its pragmatic design with broad inclusion criteria representing typical patients admitted to UK secondary care, simple intervention, and comparison to routine clinical care. Our study also took place over two winter seasons with very different patterns of influenza activity. These factors suggest that the findings of this study are likely to be generalisable to other similar UK and international centres.

In retrospect, the choice of primary outcome measure was not ideal to assess the effect of POCT on antibiotic use, because the processes of care for patients with acute respiratory illness presenting to hospital lead to patients being started on antibiotics very early in the course of their assessment and often before the results of POCT could be made available. Therefore, the results of the POCT were not able to influence the primary outcome in a large proportion of patients. The a-priori secondary outcome measures of duration of antibiotic use and proportion of patients treated with single doses or brief courses of antibiotics are arguably more relevant to standard clinical management in this group—antibiotics are started very early in most patients with acute respiratory illness but might subsequently be continued or discontinued based on test results and clinical course. The post-hoc analysis of patients who had not yet been given antibiotics when POCT results were available arguably examines a slightly different population than does the primary outcome: patients in whom clinicians did not feel it necessary to start antibiotics very early on. However, the reduction in antibiotic use in the POCT group compared with the control group in this subgroup gives further credibility to the antibiotic reductions seen in the main study, and suggests that POCT at an even earlier point might reduce unnecessary antibiotic use further.

Our study has the weakness of being a single-centre study, and additionally was not powered specifically to detect differences in the subgroups. No attempt was made at blinding anyone in the study other than the analysts. Because the purpose of the study was to inform the clinical teams of the POCT results, they could not be blinded to which group a participant had been randomised to. Patients and those collecting data could have been blinded with the use of a sham swab; however, we felt that the risk of bias due to non-blinding was very low. Our findings should ideally be replicated in further studies before a definitive conclusion can be made. Because the study took place during winter months when respiratory virus infections are more common, the findings cannot be extrapolated outside of this period. In our trial, POCT was done by research staff rather than clinicians and so uncertainties remain about how such a test could be delivered routinely. Several models of delivery are potentially possible and include training clinicians or nursing staff to do the test (with the attendant consumption of their time) or the development of a POCT hub within acute areas, staffed by dedicated technicians and linked to a centralised laboratory.

In conclusion, routine molecular POCT for respiratory viruses in adults presenting to secondary care with acute respiratory illness improved the turnaround time of results and the detection rate of respiratory viruses but did not reduce the proportion of patients treated with antibiotics or the overall duration of antibiotic use. However, routine molecular POCT was associated with an increased proportion of patients receiving single doses or brief courses of antibiotics, reduced length of hospital stay, improved use of neuraminidase inhibitors for influenza, improved use of hospital isolation facilities, and appeared to be safe. If these findings are reproduced in further studies and are associated with health economic benefit, routine molecular POCT for viruses should be introduced into diagnostic pathways for acute respiratory illness in adults presenting to hospital during the winter months.

Contributors

TWC reviewed the medical literature, conceived of and designed the study, supervised the study, participated in the data analysis and interpretation, and drafted and wrote the manuscript. NJB reviewed the medical literature participated in the trial design, recruited patients, generated and collected data, and drafted and wrote the manuscript. AKM, LA, RH, EN, SA, and PJL recruited patients and generated and collected data. SE designed the statistical analysis and analysed the data. All authors reviewed and contributed to the report during its development.

Declaration of interests

We declare that we have no competing interests.

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