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Clinical impact of a routine, molecular, point-of-care, test-and-treat strategy for influenza in adults admitted to hospital (FluPOC): a multicentre, open-label, randomised controlled trial

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Summary

Background Diagnosis of influenza in patients admitted to hospital is delayed due to long turnaround times with laboratory testing, leading to inappropriate and late antiviral treatment and isolation facility use. Molecular point-of-care tests (mPOCTs) are highly accurate, easy to use, and generate results in less than 1 h, but high-quality evidence for their effect on management and clinical outcomes is needed. The aim of this study was to assess the clinical impact of an mPOCT on influenza detection, antiviral use, infection control measures, and clinical outcomes in adults admitted to hospital with acute respiratory illness.

Methods In this multicentre, pragmatic, open-label, randomised controlled trial (FluPOC), we recruited adults admitted to hospital with acute respiratory illness during influenza seasons from two hospitals in Hampshire, UK. Eligible patients were aged 18 years and older, with acute respiratory illness of 10 days or fewer duration before admission to hospital, who were recruited within 16 h of admission to hospital. Participants were randomly assigned (1:1), using random permuted blocks of varying sizes (4, 6 and 8), to receive mPOCT for influenza or routine clinical care (control group). The primary outcome was the proportion of patients infected with influenza who were treated appropriately with antivirals (neuraminidase inhibitors) within 5 days of admission. Safety was assessed in all patients. Secondary outcomes included time to antivirals, isolation facility use, and clinical outcomes. This study is registered with the ISRCTN registry, ISRCTN17197293, and is now complete.

Findings Between Dec 12, 2017, and May 3, 2019, over two influenza seasons, 613 patients were enrolled, of whom 307 were assigned to the mPOCT group and 306 to the control group, and all were analysed. Median age was 62 years (IQR 45–75) and 332 (54%) of 612 participants with data were female. 100 (33%) of 307 patients in the mPOCT group and 102 (33%) of 306 in the control group had influenza. 100 (100%) of 100 patients with influenza were diagnosed in the mPOCT group and 60 (59%) of 102 were diagnosed though routine clinical care in the control group (relative risk 1.7, 95% CI 1.7–1.7; p<0.0001). 99 (99%) of 100 patients with influenza who were treated appropriately with antivirals (neuraminidase inhibitors) within 5 days of admission. Safety was assessed in all patients. Secondary outcomes included time to antivirals, isolation facility use, and clinical outcomes. This study is registered with the ISRCTN registry, ISRCTN17197293, and is now complete.

Interpretation Routine mPOCT for influenza was associated with improved influenza detection and improvements in appropriate and timely antiviral and isolation facility use. Routine mPOCT should replace laboratory-based diagnostics for acute admissions to hospital during the influenza season.

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Introduction

The influenza virus causes seasonal epidemics of acute respiratory illness every winter in temperate climates, leading to large numbers of admissions to hospital, principally among adults (ie, aged ≥18 years).1,2 Adults who are admitted to hospital with influenza are frequently admitted to critical care units and 3–15% will die in hospital.3 Influenza often remains undiagnosed in patients admitted to hospital due to the absence of universal testing for influenza in patients with acute respiratory illness and the inaccuracy of testing based on clinical suspicion of infection.4 Therefore, many patients infected with the
Research in context

Evidence before this study
We searched PubMed, the Cochrane Controlled Clinical Trials Register, and ClinicalTrials.gov, for relevant published articles and ongoing trials assessing the clinical impact of molecular point-of-care tests (mPOCTs) for influenza in adults (aged ≥18 years) admitted to hospital with acute respiratory illness. We used the search terms (“point-of-care testing” OR “rapid PCR testing” OR “rapid molecular testing”) AND “influenza” AND “hospital” AND “adult” AND (“clinical trial” OR “randomised controlled trial” OR “trial” OR “study”). We restricted our search to studies published between Jan 1, 1980, and Jan 1, 2020, in English. We excluded studies using antigen-based point-of-care tests for influenza (including digital immunoassays), studies in children, and studies reporting only diagnostic accuracy. We found no Cochrane systematic reviews for mPOCT in adults. We found two randomised controlled trials of mPOCT for influenza and other respiratory viruses assessing clinical outcomes and one quasi-randomised trial of low quality. One of these studies did not specifically report the effect of influenza detection on outcomes. The other two studies suggested improvement in use of neuraminidase inhibitors and isolation facilities with mPOCT but were constrained by the low number of patients infected with influenza or other methodological issues. We found several retrospective observational studies in adults admitted to hospital assessing the effect of mPOCT on clinical outcomes including neuraminidase inhibitor use, antibiotics, length of hospital stay, and number of investigations. These studies all broadly suggested improvements in neuraminidase inhibitor use and investigations but did not reliably assess use of isolation facilities and were conflicting regarding the effect on antibiotic use. One study suggested a reduction in nosocomial spread of influenza. No studies reported on the effect of mPOCT for influenza on clinical outcomes other than length of hospital stay. We found a systematic review of studies assessing the clinical impact and diagnostic accuracy of rapid molecular tests for respiratory viruses, only some of which were done at the point of care and all were already identified in our initial literature search.

Added value of this study
To our knowledge, this is the first multicentre, pragmatic, randomised control trial of mPOCT for influenza that was designed and powered to assess influenza-specific outcomes in adults admitted to hospital. Retrospective testing for influenza in all patients in the control group allowed a direct assessment of missed diagnoses and comparison of outcomes in all patients with influenza tested with mPOCT or routine clinical care. The use of clinical outcome measures such as time to clinical improvement, time on supplementary oxygen, and the hospital recovery scale score, allowed assessment of the effect of mPOCT on clinical outcomes in addition to the effect on clinical management (eg, use of antivirals, antibiotics, isolation facilities). Although this study does not definitively exclude the possibility that routine laboratory PCR testing could lead to some of the improvements seen with mPOCTs, such improvements would require substantial reductions in current turnaround times that are unlikely to be achievable in most laboratories due to batch testing and other constraints.

Implications of all the available evidence
Routine mPOCTs for influenza in adults admitted to hospital during influenza season improves the detection rate of influenza, and the appropriate use of influenza antivirals and isolation facilities. Routine use of mPOCTs for influenza should become standard of care in hospitals during the influenza season.

Influenza virus are not identified and treated appropriately with antivirals or isolated correctly in single-room accommodation to prevent the spread of influenza to others. Even when patients are tested for influenza, diagnosis is often delayed due to the long turnaround times of centralised laboratory PCR testing. This delay also contributes to the inappropriate and late use of antivirals and isolation facilities and impairs patient flow through acute areas, reducing hospital operational capacity.

Antiviral treatment with neuraminidase inhibitors is recommended for all patients admitted to hospital with suspected and proven influenza by UK and US national guidelines and evidence suggests that earlier use is associated with better outcomes. New rapid molecular point-of-care tests (mPOCTs) using PCR for influenza are highly accurate, easy to use, and can generate a result in less than 1 h compared with the current turnaround time of approximately 24 h for laboratory-based PCR testing. Routinely testing patients for influenza at the point of care might improve influenza detection and use of antivirals and isolation facilities by allowing confident real-time decision making.

Results of our previous trial suggested that the use of routine mPOCT for respiratory viruses improves the use of antivirals and isolation facilities for influenza, but was hampered by small numbers of patients who were positive for influenza and an absence of universal viral testing in the control group. Several retrospective observational studies have also suggested that mPOCT might improve the detection of influenza, the use of influenza antivirals and isolation facilities, and might reduce nosocomial transmission; however, such studies are highly prone to bias. Because mPOCTs for influenza are now starting to be used in some UK National Health Service (NHS) hospitals and in other countries around the world, high-quality evidence for their clinical impact is urgently needed. We aimed to prospectively assess the effect of a routine molecular point-of-care test-and-treat strategy for influenza in adults admitted to hospital with acute
respiratory illness on clinical management and patient outcomes.

**Methods**

**Study design and participants**

In this multicentre, pragmatic, parallel group, open-label, randomised, controlled trial (FluPOC), patients were recruited from two acute hospitals in Southampton and Winchester, Hampshire, UK. The trial took place over two successive winter seasons in 2017–18 and 2018–19 when influenza was circulating according to national (ie, Public Health England) surveillance systems. All patients were recruited from the acute medical unit and emergency department of Southampton General Hospital, Southampton, UK (a large, acute-care, teaching hospital in the south of the UK serving a population of 650 000 for secondary care) run by University Hospital Southampton Foundation NHS Trust, and from Royal Hampshire County Hospital (Winchester, UK) a large district general hospital in Hampshire run by Hampshire Hospitals Foundation NHS Trust.

Patients were eligible if they: were aged 18 years or older; had the capacity to give informed, written consent, or if the patient did not have the capacity to consent for themselves, consultee assent was obtained; were admitted to the hospital and physically in either the acute medical unit or emergency department; could be recruited to the study within 16 h of admission; had an acute respiratory illness; and had been ill for 10 days or fewer before admission to hospital. An episode of acute respiratory illness was defined as a provisional diagnosis of acute pulmonary illness including pneumonia, bronchitis (non-pneumonic lower respiratory tract infection) and influenza-like illness, or an acute exacerbation of a chronic respiratory illness (including exacerbation of chronic obstructive pulmonary disease, asthma, or bronchiectasis). Patients were excluded if a palliative approach was being taken by the treating clinicians; the patient declined nasal or pharyngeal swabbing; and if they had previously been included in this study and were re-presenting within 30 days of hospital discharge.

The study was approved by the South Central – Hampshire A Research Ethics Committee (reference 17/SC/0368, approved on the Sept 7, 2017). The protocol has been published previously. The protocol was amended once on Nov 23, 2017, to allow the inclusion of a second study site (Hampshire Hospitals Foundation NHS Trust) and this change was communicated to the trial registry.

**Randomisation and masking**

Participants were consecutively assigned a unique participant identification number by study team members (NJB, AKM, SP, CC, SM, KRB, EN, and LP) who then, using an internet-based randomisation service (Sealed envelope, which uses random permuted blocks of varying sizes; 4, 6 and 8) to generate the allocation sequence. Using the allocation code, participants were assigned (1:1) to either the mPOCT group (intervention group) or the routine clinical care group (control group). Due to the nature of the intervention, participants, research staff, and clinical care providers were unmasked to assignment. Data analysts and statisticians (including SE) were masked to group allocation.

**Procedures**

Participants randomly assigned to the intervention (mPOCT) group had a combined nose and throat swab sample (and sputum samples where available) taken by research staff according to standard protocols, which was then analysed immediately using the FilmArray Respiratory Panel 2 (BioFire Diagnostics, a bioMérieux company, Salt Lake City, UT, USA)—ie, the mPOCT. The FilmArray Respiratory Panel 2 uses nested PCR to detect a panel of respiratory viruses and atypical bacteria, including influenza A and B. The BioFire 2.0 testing units were located in the acute medical units and the test took around 45 min to generate a result. The clinical and infection control teams were informed directly of all results (positive
Panel 2) to allow retrospective assessment of missed diagnoses. Clinical management decisions were made independently by the responsible clinical team and if influenza was detected by mPOCT, research teams directed clinical teams to national guidelines for the treatment of influenza.7

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 standardised case report form. Serious adverse events were actively monitored and reported. A serious adverse event was defined as any adverse event that: results in death, was life threatening, required admission to hospital or extension of stay in hospital, resulted in persistent or clinically significant disability or incapacity, or consisted of a congenital anomaly or birth defect. Participants already admitted to an acute medical unit and emergency department but with a decision already made to admit were considered already admitted to hospital. However, an adverse event leading to an extended ongoing stay in hospital was counted as a serious adverse event.

Outcomes

The primary outcome measure was the proportion of patients with confirmed influenza (ie, positive PCR test) who were treated with antivirals (ie, neuraminidase inhibitors) during their hospital stay, within 5 days of admission. This outcome measure was selected because Public Health England guidelines recommend that all adults requiring admission to hospital for influenza should receive neuraminidase inhibitors. This guidance is consistent with that in several other countries.8,9 Although, to our knowledge, no placebo-controlled trials of neuraminidase inhibitors have been done in adults who have been admitted to hospital, there is observational evidence showing that use of neuraminidase inhibitors are associated with improvements in clinical outcomes in this group.10–12

Secondary outcomes were as follows: the proportion of patients with influenza (ie, PCR positive) identified during their time in hospital, turnaround time for respiratory virus testing, proportion of all antiviral (ie, neuraminidase inhibitors) use occurring in patients with influenza and without influenza, time to antiviral commencement, duration of antiviral use in patients with influenza (ie, PCR positive) identified during their time in hospital, proportion of patients with influenza (ie, PCR positive) identified during their time in hospital, proportion of patients with influenza (ie, PCR positive) identified during their time in hospital, proportion of patients with influenza (ie, PCR positive) identified during their time in hospital, proportion of patients with influenza (ie, PCR positive) identified during their time in hospital, and negative). Participants randomly assigned to the control group were managed according to routine clinical care, with testing for respiratory viruses being at the discretion of the responsible clinical team, and any testing was done using laboratory PCR by conventional methods in the on-site laboratory facilities. Patients in the control group also had a nose and throat swab obtained at enrolment and stored for subsequent analysis at least 30 days after enrolment (using the FilmArray Respiratory

|                                | All patients (ITT) | ITT influenza-infected population |
|--------------------------------|--------------------|----------------------------------|
|                                | mPOCT group        | Control group                    | mPOCT group | Control group |
|                                | (n=307)            | (n=306)                          | (n=100)     | (n=102)       |
| Age, years                     |                    |                                  |             |               |
|                               | 62 (41–74)         | 63 (47–76)                       | 63 (42–73)  | 65 (51–78)    |
| Sex                            |                    |                                  |             |               |
| Female                         | 175 (57%)          | 157 (51%)                        | 53 (53%)    | 47 (46%)      |
| Male                           | 132 (43%)          | 148 (48%)                        | 47 (47%)    | 55 (54%)      |
| Missing                        | 0                  | 1 (<1%)                          | 0           | 0             |
| Ethnic origin                  |                    |                                  |             |               |
| White British                  | 285 (93%)          | 284 (93%)                        | 95 (95%)    | 94 (93%)      |
| Other                          | 22 (7%)            | 21 (7%)                          | 5 (5%)      | 7 (7%)        |
| Missing                        | 0                  | 1 (<1%)                          | 0           | 1 (2%)        |
| Current smoker                 |                    |                                  |             |               |
| Yes                            | 71 (23%)           | 70 (23%)                         | 23 (23%)    | 24 (24%)      |
| No                             | 235 (77%)          | 235 (77%)                        | 77 (77%)    | 78 (76%)      |
| Missing                        | 1 (<1%)            | 0                                | 0           | 0             |
| Influenza vaccine              |                    |                                  |             |               |
| Yes                            | 199 (65%)          | 185 (60%)                        | 60 (60%)    | 56 (55%)      |
| No                             | 107 (35%)          | 117 (38%)                        | 40 (40%)    | 46 (45%)      |
| Missing                        | 1 (<1%)            | 4 (1%)                           | 0           | 0             |
| Pregnant                       |                    |                                  |             |               |
| Yes                            | 4 (1%)             | 9 (3%)                           | 1 (1%)      | 2 (2%)        |
| No                             | 302 (99%)          | 297 (97%)                        | 99 (99%)    | 100 (98%)     |
| Missing                        | 1 (<1%)            | 4 (1%)                           | 0           | 0             |
| Duration of symptoms, days†    | 4 (3–6)            | 4 (3–7)                          | 4 (3–7)     | 4 (3–6)       |
| Antibiotics within 14 days before presentation | | | | |
| Yes                            | 95 (31%)           | 99 (33%)                         | 30 (30%)    | 34 (33%)      |
| No                             | 209 (68%)          | 205 (67%)                        | 70 (70%)    | 68 (67%)      |
| Missing                        | 3 (1%)             | 2 (1%)                           | 0           | 0             |
| Antivirals within 14 days before presentation | | | | |
| Yes                            | 0                  | 2 (1%)                           | 0           | 1 (1%)        |
| No                             | 305 (99%)          | 302 (99%)                        | 100 (100%)  | 101 (99%)     |
| Missing                        | 2 (1%)             | 2 (1%)                           | 0           | 0             |
| Comorbidities                  |                    |                                  |             |               |
| Hypertension                   | 82 (27%)           | 89 (29%)                         | 26 (26%)    | 29 (28%)      |
| Cardiovascular disease         | 61 (20%)           | 64 (21%)                         | 22 (22%)    | 17 (17%)      |
| Respiratory disease            | 216 (70%)          | 189 (62%)                        | 60 (60%)    | 49 (48%)      |
| Renal disease                  | 16 (5%)            | 18 (6%)                          | 4 (4%)      | 6 (6%)        |
| Liver disease                  | 2 (1%)             | 6 (2%)                           | 1 (1%)      | 0             |
| Diabetes                       | 36 (12%)           | 57 (19%)                         | 12 (12%)    | 15 (15%)      |
| Cancer                         | 18 (6%)            | 21 (7%)                          | 7 (7%)      | 9 (9%)        |
| Immunosuppression              | 14 (5%)            | 12 (4%)                          | 3 (3%)      | 4 (4%)        |
| Charlson Comorbidity Index score | 4 (4–7)           | 4 (3–8)                          | 4 (0–4)    | 4 (0–7)       |

(Table 1 continues on next page)
reported here), duration of stay in hospital for all patients, time on supplementary oxygen for all patients, time to clinical improvement (originally defined as time to clinical stability in the published protocol20 and subsequently changed to time to clinical improvement, which is a newly developed outcome measure for trials of influenza antivirals; full details and relevant references are provided in the appendix [p 2]), proportion of patients requiring admission to an intensive care unit (ICU) or high dependency unit (HDU), median duration of stay in ICU or HDU (not reported here), proportion of patients re-presenting to hospital within 30 days, proportion of patients readmitted to hospital within 30 days, in-hospital and 30-day all-cause mortality, and 60-day all-cause mortality (not reported here).

Exploratory outcomes reported here were median hospital recovery score at days 4 and 7 (the hospital recovery scale is a 6-point ordinal scale developed as an outcome measure for trials of influenza therapeutics, with higher scores denoting a worse outcome; appendix p 2). Additional exploratory outcomes not reported here are difference in influenza viral load between upper and lower respiratory tract samples; proportion of patients with influenza RNA detected in blood; and changes in influenza viral load over time (kinetics) in respiratory tract samples and blood. These will be reported elsewhere.

All outcomes were measured for the duration of hospital stay or up to 30 days (whichever was shortest) unless otherwise specified and the duration of antimicrobials includes medication (antibiotics and antivirals) that patients were discharged home with.

Statistical analysis

The sample size for our study was based on the primary outcome measure of the proportion of patients testing positive for the influenza virus and treated with neuraminidase inhibitors (within 5 days of hospital admission). We initially aimed to recruit up to 840 participants (420 patients per group) over up to three influenza seasons, on the conservative assumption of a 25% positivity rate for influenza during influenza seasons (based on our previous local studies over several seasons)—ie, approximately 100 patients being positive for influenza in each group. These group sizes would give a 90% power at a 0·05 significance level to detect a difference of 20% in neuraminidase inhibitor use for patients with influenza between the groups (ie, from 65% to 85%).21 Because 100 patients or more with confirmed influenza were recruited to each group by the end of the second season, the trial was stopped at this point.

Analysis was by intention to treat (ITT) and the framework was superiority. Analyses were done by a dedicated statistician from the University of Southampton, Southampton, UK (SE) who was masked to group allocation. We had complete data for the primary outcome and, overall, we had minimal missing data (<1%).

We measured the primary outcome only in patients with influenza (ie, the ITT influenza-infected population). We used difference in proportions and unadjusted risk ratios (ie, relative risk) to compare the groups. We calculated the number needed to treat (1/absolute risk ratio) for the primary outcome to allow assessment of the number of patients required to receive mPOCT to have a clinical impact on one person, above routine care. The prespecified plan was to analyse antiviral use in a logistic regression model; however, the model could not be fitted due to separation, at least partly as a result of only one person testing positive for influenza in the mPOCT not receiving antiviral treatment. No further multivariable analyses were performed.

Table 1: Baseline characteristics of all patients (ITT population) and ITT influenza-infected population

|                          | All patients (ITT) | ITT influenza-infected population |
|--------------------------|--------------------|----------------------------------|
|                          | mPOCT group (n=307) | Control group (n=306)            |
|                          | mPOCT group (n=102) | Control group (n=102)            |
| (Continued from previous page) |

### Observations at admission

| Outcome                  | mPOCT (n=307) | Control (n=306) | mPOCT (n=102) | Control (n=102) |
|--------------------------|---------------|-----------------|---------------|-----------------|
| Temperature, °C          | 37·1 (36·5–38·1) | 37·1 (36·4–37·9) | 37·3 (36·7–38·1) | 37·5 (36·7–38·3) |
| ±38°C                    | 82 (22%)      | 70 (23%)        | 30 (30%)      | 35 (34%)        |
| Pulse rate, beats per min| 100 (88–117)  | 100 (85–115)    | 103 (90–116)  | 100 (85–115)    |
| Respiratory rate, breaths per min | 23 (20–26) | 22 (19–27) | 22 (19–27) | 22 (19–28) |
| Oxygen saturation, %     | 95 (92–97)    | 95 (92–97)      | 95 (93–97)    | 95 (91–97)      |
| Supplemenary oxygen      | 54 (18%)      | 71 (23%)        | 21 (21%)      | 22 (22%)        |
| Blood pressure, mm Hg    | 134 (120–150) | 135 (120–148)   | 135 (122–148) | 136 (117–146)   |
| Systolic                 | 74 (63–84)    | 75 (65–83)      | 71 (64–81)    | 75 (65–84)      |
| Diastolic                | 4 (3–6)       | 4 (3–6)         | 4 (3–7)       | 5 (3–7)         |

### Laboratory and radiology

| Outcome                  | mPOCT (n=307) | Control (n=306) | mPOCT (n=102) | Control (n=102) |
|--------------------------|---------------|-----------------|---------------|-----------------|
| C-reactive protein, mg/L | 48 (13–127)   | 38 (14–99)      | 51 (17–138)   | 49 (18–98)      |
| White blood cell count, 10⁹ per L | 10·5 (7·9–14·6) | 9·9 (7·3–13·3) | 8·7 (6·7–11·5) | 8·1 (5·8–11·0)  |
| Neutrophils, 10⁹ per L   | 8·1 (5·8–12·1) | 7·8 (5·2–10·9)  | 6·6 (5·1–9·6) | 6·0 (4·0–8·1)   |
| Lymphocytes, 10⁹ per L   | 1·1 (0·7–1·6)  | 1·1 (0·7–1·7)   | 0·9 (0·6–1·4) | 0·8 (0·6–1·4)   |
| Chest x-ray              |               |                 |               |                 |
| Yes                      | 302 (98%)     | 299 (98%)       | 98 (98%)      | 102 (100%)      |
| No                       | 5 (2%)        | 25 (8%)         | 2 (2%)        | 0               |
| Chest CT                 |               |                 |               |                 |
| Yes                      | 19 (6%)       | 25 (8%)         | 2 (2%)        | 4 (4%)          |
| No                       | 288 (94%)     | 281 (92%)       | 98 (98%)      | 98 (96%)        |

| Outcome                  | mPOCT (n=307) | Control (n=306) | mPOCT (n=102) | Control (n=102) |
|--------------------------|---------------|-----------------|---------------|-----------------|
| Pulse rate, beats per min|               |                 |               |                 |
| Systolic                 | 74 (63–84)    | 75 (65–83)      | 71 (64–81)    | 75 (65–84)      |
| Diastolic                | 4 (3–6)       | 4 (3–6)         | 4 (3–7)       | 5 (3–7)         |

### Final diagnosis based on hospital discharge summary

| Outcome                  | mPOCT (n=307) | Control (n=306) | mPOCT (n=102) | Control (n=102) |
|--------------------------|---------------|-----------------|---------------|-----------------|
| Asthma                   | 59 (19%)      | 55 (18%)        | 22 (22%)      | 14 (14%)        |
| COPD exacerbation        | 77 (25%)      | 79 (26%)        | 19 (19%)      | 23 (23%)        |
| Exacerbation of another chronic lung disease | 8 (3%) | 9 (3%) | 2 (2%) | 1 (1%) |
| Pneumonia                | 88 (29%)      | 71 (23%)        | 23 (23%)      | 20 (20%)        |
| Influenza-like illness   | 27 (9%)       | 38 (12%)        | 21 (21%)      | 32 (31%)        |
| NPLRTI                   | 31 (10%)      | 38 (12%)        | 12 (12%)      | 11 (11%)        |
| Other                    | 17 (6%)       | 16 (5%)         | 1 (1%)        | 1 (1%)          |

Data are n (%) or median (IQR). COPD=chronic obstructive airways disease. ITT=intention-to-treat. mPOCT=molecular point-of-care test. NEWS2=national early warning score 2. NPLRTI=non-pneumonic lower respiratory tract infection.

*For the current influenza season, before admission to hospital.

See Online for appendix
Table 2: Influenza testing, antiviral use, and isolation facility use in all patients (ITT population)

| Measure                                      | mPOCT group (n=307) | Control group (n=306) | Difference or relative risk (95% CI) | p value |
|----------------------------------------------|---------------------|-----------------------|-------------------------------------|---------|
| Tested for influenza during admission        | 307 (100%)          | 212 (69%)             | 1.4 (1.4 to 1.5)                    | <0.0001 |
| Turnaround time for results, h*              | 1.2 (1.1 to 1.4)    | 22.6 (16.0 to 28.7)   | 21.4 (20.6 to 22.4)                 | <0.0001 |
| Influenza infected                           | 100 (33%)           | 102 (33%)             | 1.0 (0.9 to 1.2)                    | 0.86    |
| Influenza A                                  | 63/100 (63%)        | 76/102 (75%)          |                                    |         |
| Influenza B                                  | 37/100 (37%)        | 24/102 (24%)          |                                    |         |
| Influenza A and B                            | 0/100 (0%)          | 2/102 (2%)            |                                    |         |
| Antiviral use                                |                     |                       |                                    |         |
| Total antiviral use                          | 139 (45%)           | 130 (42%)             | 1.1 (0.9 to 1.3)                    | 0.49    |
| Oseltamivir                                  | 139 (45%)           | 130 (42%)             |                                    |         |
| Other                                        | 0                   | 0                     |                                    |         |
| Patients testing positive for influenza      | 99/139 (71%)        | 63/130 (48%)          | 1.5 (1.2 to 1.8)                    | <0.0001 |
| Duration of antivirals, days                 | 4.7 (0.7 to 5.1)    | 4.5 (1.0 to 5.0)      | -0.2 (-0.5 to 0.0)                  | 0.11    |
| Influenza positive                           | 4.8 (4.6 to 5.5)    | 4.5 (4.2 to 5.0)      | -0.3 (-0.6 to -0.1)                 | 0.0024  |
| Influenza negative                           | 0.1 (0.1 to 0.5)    | 1.5 (0.05 to 4.5)     | 1.4 (0.7 to 2.1)                    | <0.0001 |
| Isolation facility use†                      |                     |                       |                                    |         |
| Isolated at presentation                     | 30 (10%)            | 26 (9%)               | 1.2 (0.7 to 1.9)                    | 0.58    |
| Isolated at any time                         | 106 (35%)           | 67 (22%)              | 1.6 (1.2 to 2.1)                    | 0.0006  |
| Influenza positive                           | 70/106 (66%)        | 39/67 (58%)           | 1.1 (0.9 to 1.5)                    | 0.33    |
| Duration of isolation, days                  | 2.5 (1.3 to 4.5)    | 1.8 (1.0 to 4.4)      | -0.7 (-0.9 to 0.3)                  | 0.29    |
| All isolated patients                         | 2.8 (1.9 to 4.5)    | 2.4 (1.0 to 4.7)      | -0.4 (-1.2 to 0.3)                  | 0.21    |
| Influenza positive                           | 1.4 (0.5 to 3.5)    | 1.4 (1.0 to 3.9)      | 0.0 (-0.5 to 0.8)                   | 0.42    |

Data are n(%) or median (IQR) unless otherwise stated. p values were calculated using Y² test or Fisher’s exact test. ITT=intention-to-treat. mPOCT=molecular point-of-care test. *Based on those that were tested; for mPOCT group, this is the turnaround time for mPOCT results; for the control group, it is for laboratory PCR results. Isolation facility use relates to the use of single-room accommodation or dedicated influenza cohort beds for patients.

The ITT influenza-infected population comprised 100 (33%) of 307 patients in the mPOCT group and 102 (33%) of 306 patients in the control group who were infected with influenza. 100 (100%) of 100 patients with influenza in the mPOCT group were diagnosed with influenza while in hospital (all by PCR testing) but only 60 (59%) of 102 in the control group were diagnosed while in the hospital, of whom 55 (54%) were PCR positive and five (5%) had a clinical diagnosis of influenza but had no confirmatory test performed (relative risk 1.7 [95% CI 1.7 to 1.7]; p<0.0001; table 3). 42 patients in the control group not diagnosed during admission were retrospectively attempted given the strong signal. Secondary outcome measures were measured both in all patients (ITT population) and in the ITT influenza-infected population as appropriate. Difference in proportions was assessed using the Y² test or Fisher’s exact test as appropriate, depending on group size. For secondary outcomes, we compared the intervention and control groups for equality of proportions for binary data and used Student’s t tests or Mann-Whitney U tests for continuous data (eg, turnaround time), as appropriate; the choice between these two analyses was based on the distribution of the observed data and the sample size. Time-to-event analysis data were compared using the log-rank test. Where 95% CIs are presented, we used Stata defaults.

We did a post-hoc analysis to assess median time to receipt of antivirals, excluding patients treated empirically, and the proportion of patients isolated, excluding those discharged rapidly or nursed in areas without isolation facilities.

All analyses were done using Prism version 7.0 (GraphPad Software, La Jolla, CA, USA) and Stata version 16.0. This study was prospectively registered with the ISRCTN registry, ISRCTN17197293.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data and the final responsibility to submit for publication.

Results

Between Dec 12, 2017, and May 3, 2018, and between Dec 3, 2018, and May 3, 2019, over two influenza seasons, 973 patients were assessed for eligibility and 613 were randomly assigned to the mPOCT (n=307) or routine clinical care group (n=306; figure 1). Because 100 or more patients with confirmed influenza were recruited to each group by the end of the second season, the trial was stopped at this point. Overall the median age of study population was 62 years (IQR 45–75) and 332 (54%) of 612 participants were female (data missing for one patient). Baseline characteristics for all patients (ITT population) and influenza-infected patients (ITT influenza-infected population) are shown in table 1.

In the analysis of all patients (ie, the ITT population), the median turnaround time for influenza test results was 1.2 h (IQR 1.1–1.4) in the mPOCT group and 22.6 h (16.0–28.7) in the control group (difference of 21.4 h [95% CI 20.6–22.4; p<0.0001]; table 2). All antiviral use was with the neuraminidase inhibitor oseltamivir and no difference was seen in the proportion of patients given antivirals between the groups (relative risk 1.1 [95% CI 0.9–1.3; p=0.49]; table 2); however, more patients given antivirals in the mPOCT group than in the control group tested positive for influenza (99 [71%] of 139 vs 63 [48%] of 130; relative risk 1.5 [95% CI 1.2–1.8; p<0.0001]; table 2). Patients who tested negative for influenza who were given antivirals had a median course length of 0.1 days (IQR 0–1.0) in the mPOCT group versus 1.5 days (0.5–4.5) in the control group (difference of 1.4 days [95% CI 0.7–2.1; p<0.0001]; table 2). Information on antibiotic use in the mPOCT and control groups can be found in the appendix (p 4).

The ITT influenza-infected population comprised 100 (33%) of 307 patients in the mPOCT group and 102 (33%) of 306 patients in the control group who were infected with influenza. 100 (100%) of 100 patients with influenza in the mPOCT group were diagnosed with influenza while in hospital (all by PCR testing) but only 60 (59%) of 102 in the control group were diagnosed while in the hospital, of whom 55 (54%) were PCR positive and five (5%) had a clinical diagnosis of influenza but had no confirmatory test performed (relative risk 1.7 [95% CI 1.7 to 1.7; p<0.0001]; table 3). 42 patients in the control group not diagnosed during admission were retrospectively assessed as influenza-negative; their median time to diagnosis, excluding patients tested empirically, was 5.0 days (IQR 3.8–7.2) versus 2.2 days (1.8–2.8) in the mPOCT group (p<0.0001; table 3).
diagnosed with influenza after testing of their stored samples using the FilmArray Respiratory Panel 2.

For the primary outcome, 99 (99%) of 100 patients with influenza in the mPOCT group were given antiviral treatment within 5 days versus 63 (62%) of 102 in the control group (relative risk 1·6 [95% CI 1·4 to 1·9; p<0·0001]; number needed to test was 2·7; table 3). Median time to receipt of antivirals was 1·0 h (0·0 to 2·0) in the mPOCT group versus 6·0 h (0·0 to 12·0) in the control group (difference of 5·0 h [95% CI 0·0 to 6·0; p=0·0039; table 3, figure 2). In a post-hoc analysis, excluding patients treated empirically (ie, before results were available) the median time to receipt of antivirals was 2·0 h (IQR 1·0 to 3·0) in the mPOCT group versus 5·0 h (IQR 2·0–12·0) in the mPOCT group versus 32·0 h (IQR 16·0 to 55·0) in the control group (difference of 27·0 h [95% CI 17·0–33·0; p<0·0001]; table 3). Patients in the mPOCT group received antibiotics for less than 24 h versus seven (7%) of 98 in the control group (relative risk 0·9 [95% CI 0·8 to 1·1; p=0·10]; table 3). Time to antiviral use, excluding those treated empirically, h

| Treatment | mPOCT group | Control group | Difference or relative risk (95% CI) | p value |
|-----------|-------------|---------------|------------------------------------|---------|
| Isolated empirically at presentation | 10 (10%) | 9 (9%) | 1·1 (0·5 to 2·7) | 0·77 |
| Isolated during hospital stay | 70 (70%) | 39 (38%) | 1·8 (1·4 to 2·4) | <0·0001 |
| Isolated during hospital stay, excluding exceptions | 70 (70%) | 39 (39%) | 2·1 (1·7 to 2·8) | <0·0001 |
| Time to isolation, h | 4·5 (1·9 to 9·8) | 25·0 (3·6 to 45·1) | 10·5 (6·0 to 26·5) | 0·0003 |
| Time to isolation, excluding those isolated empirically, h | 5·0 (2·0 to 12) | 32·0 (16·0 to 55·0) | 27·0 (10·0 to 33·0) | <0·0001 |

### Antibiotic use

| Antibiotic use (any) | 90 (90%) | 98 (96%) | 0·9 (0·9 to 1·0) | 0·089 |
|----------------------|----------|----------|-----------------|-------|
| Duration of antibiotics, days | 6·1 (4·1 to 7·2) | 5·8 (4·2 to 7·4) | 0·3 (0·8 to 0·8) | 0·96 |
| Single dose of antibiotics only | 9·9 (10%) | 9·3 (8%) | 0·9 (0·9 to 1·1) | 0·32 |
| Antibiotics given for <24 h | 13·9 (14%) | 7·9 (7%) | 0·9 (0·8 to 1·1) | 0·10 |
| Intravenous antibiotics | 68 (68%) | 69 (68%) | 1·0 (0·8 to 1·2) | 0·96 |
| Duration of intravenous antibiotics, days | 0·5 (0·1 to 1·8) | 1·1 (0·1 to 2·0) | 0·6 (0·0 to 0·5) | 0·31 |
| Single dose of intravenous antibiotics only | 29·6 (43%) | 19·6 (28%) | 0·8 (0·6 to 1·0) | 0·064 |
| Intravenous antibiotics given for <24 h | 40·6 (59%) | 34·6 (50%) | 0·8 (0·6 to 1·2) | 0·26 |

(Tables 3 continues on next page)
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Figure 2: Antiviral use over time in patients with influenza (ITT influenza-infected population)

Table 3: Outcomes in patients in the ITT influenza-infected population

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Data are n (%), n/N (%), or median (IQR) unless otherwise stated. P values for the difference between proportions were calculated using the χ2 or Fisher’s exact test as appropriate, and for continuous variables (ie, difference in medians) using the Mann-Whitney U test. ITT-intention-to-treat. NA-not applicable. *A clinical diagnosis of influenza is defined as either influenza listed as a diagnosis on the discharge summary or a full 5-day course of oseltamivir given, in the absence of diagnostic testing being done. †Empirical antiviral use denotes antivirals started in patients with a presumptive clinical diagnosis of influenza before diagnostic results were available. ‡Directed course of oseltamivir given, in the absence of diagnostic testing being done. §Isolation facility use relates to the use of single room accommodation or dedicated influenza cohort bays for patients. ¶Exceptions are patients discharged rapidly or nursed in areas without isolation facilities.

Table 3: Outcomes in patients in the ITT influenza-infected population

Data are n (%), n/N (%), or median (IQR) unless otherwise stated. P values for the difference between proportions were calculated using the χ2 or Fisher’s exact test as appropriate, and for continuous variables (ie, difference in medians) using the Mann-Whitney U test. ITT-intention-to-treat. NA-not applicable. *A clinical diagnosis of influenza is defined as either influenza listed as a diagnosis on the discharge summary or a full 5-day course of oseltamivir given, in the absence of diagnostic testing being done. †Empirical antiviral use denotes antivirals started in patients with a presumptive clinical diagnosis of influenza before diagnostic results were available. ‡Directed course of oseltamivir given, in the absence of diagnostic testing being done. §Isolation facility use relates to the use of single room accommodation or dedicated influenza cohort bays for patients. ¶Exceptions are patients discharged rapidly or nursed in areas without isolation facilities.

Discussion

The routine use of a molecular point-of-care test-and-treat strategy for influenza during influenza season led to improved detection of patients infected with influenza who had been admitted to hospital and delivery of results in near real time to clinical and infection control teams. Use of neuraminidase inhibitors and isolation facilities were improved with mPOCT, such that patients testing positive for influenza were rapidly treated with antivirals and appropriately isolated. Additionally, routine mPOCT was also associated with improvements in the exploratory clinical outcome measure of hospital recovery scale in patients with influenza.

The high proportion of patients with influenza who remained undiagnosed in the control group is likely to relate to low rates of test requests by clinicians in patients not displaying the classic symptoms or signs of influenza. Influenza testing in most institutions is not done routinely but is based on clinical suspicion of influenza, which is known to be highly inaccurate, even during periods of intense transmission. The risk of nosocomial transmission of influenza from patients who are undiagnosed to staff and other patients is high, and undiagnosed patients do not have the opportunity to benefit from antiviral therapy. These factors make a compelling argument for health-care centres to institute routine mPOCT for influenza in all patients admitted to hospital with acute respiratory illness during influenza season.

Our study showed rapid time to results with mPOCT of just over 1 h compared with almost 1 day with laboratory PCR in the control group, a typical laboratory turnaround time reported in other studies. The importance of rapid turnaround times in improving clinical management has been shown in several studies and is supported by similar findings in studies of other diagnostics in emergency departments. Some of the benefits associated with mPOCT in this study might also be achieved by routine laboratory PCR testing if turnaround times could be substantially reduced. However, because turnaround times of 1 h or less are unlikely to be achievable in most laboratory settings, testing for influenza in hospitals should move to the point of care.
The mPOCT platform used in this study generated a result in 45 min but other mPOCT platforms can generate results within 20 min or less (eg, GeneXpert [Cepheid, Sunnyvale, CA, USA] and the Cobas Liat [Roche Diagnostics, Basel, Switzerland]) and might further reduce time to therapeutic and infection control interventions.

The use of influenza antivirals was significantly improved with routine mPOCT compared with routine clinical care, such that nearly all patients with influenza were given appropriate antiviral treatment within a few hours of admission. Patients not initially suspected to have influenza who subsequently had a positive mPOCT were rapidly started on neuraminidase inhibitors compared with a delay of over 24 h in the control group. Conversely, patients who were started on neuraminidase inhibitors empirically because of clinical suspicion of them having influenza, but who subsequently tested negative by mPOCT, had their neuraminidase inhibitors stopped after a single dose compared with an extended duration of unnecessary drug use in the control group. These findings are consistent with previous randomised controlled trials and observational studies of mPOCT for influenza that consistently show improved use of directed neuraminidase inhibitors in patients tested by mPOCT. With the use of even faster mPOCTs than that used in this study, done at the time of presentation, the need for empirical therapy could be removed altogether without compromising the speed of administration of antivirals and ushering in an era of real-time pathogen-directed therapy for influenza and other infections.

Single-room accommodation in hospitals, used for isolating patients who are potentially infectious, is a scarce resource in most UK hospitals. Our study shows that in routine clinical care most patients with influenza are not isolated appropriately in single-room accommodation or in influenza cohort bays, and are hence a high risk for nosocomial transmission to other patients. In comparison, most patients with influenza in the mPOCT group were correctly isolated. Additionally, patients with influenza in the control group who were not initially isolated but subsequently had a positive laboratory PCR result for influenza were only isolated after a delay of nearly 1-5 days (reflecting the long turnaround time of laboratory PCR tests) compared with just a few hours in the mPOCT group. The rational and appropriate use of isolation facilities is hugely important for UK hospitals to prevent nosocomial transmission of influenza and to maintain patient flow through acute areas during periods of intense influenza activity.

Routine mPOCT use was not associated with major reductions in antibiotic use in patients with influenza in this trial and most patients with influenza in both groups were given antibiotics, consistent with other similar trials. Other studies of mPOCT for respiratory viruses have shown similar results with either no effect on antibiotic use or only slight reductions. The identification of a virus by PCR does not by itself rule out the presence of a concomitant bacterial infection and so clinicians tend to continue to treat patients admitted to hospital with an acute respiratory illness with antibiotics. Alternative strategies to reduce unnecessary antibiotics are still urgently needed in this group and include combining pathogen detection with biomarker measurement (such as C-reactive protein or procalcitonin) or with other markers of host response, all integrated in a robust antibiotic stewardship programme.

In addition to observing the above improvements in clinical management, to our knowledge, this is the first randomised trial to show improvements in clinical outcomes in patients with influenza through the use of mPOCTs. Although this study cannot directly attribute the cause of these changes, the possible trend towards improvement in time to clinical improvement and the improvement in hospital recovery score are likely to
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relate to the rapid and near universal use of oseltamivir in patients infected with influenza in the mPOCT group compared with frequently absent or delayed use with routine care. Although no placebo controlled trials of neuraminidase inhibitors for influenza have ever been done in adults admitted to hospital, our findings are consistent with a large body of observational evidence showing that use of neuraminidase inhibitors is associated with improvements in clinical outcomes, including length of stay and mortality, in this group and that early use of neuraminidase inhibitors is associated with the best outcomes.

The strengths of this study include the multicentre and pragmatic design of the study, that it was run over two influenza seasons, the broad inclusion criteria representing typical patients admitted to UK secondary care, the simple intervention, and comparison to routine clinical care. These factors suggest that the findings of this study are likely to be generalisable to other similar UK and international centres. The trial was designed and powered to assess influenza-specific outcomes in adults admitted to hospital and universal sampling with retrospective testing for influenza in the control group using the same platform allowed a direct assessment of missed diagnoses and comparison of outcomes in all patients with influenza. The use of clinical outcome measures such as time on supplementary oxygen, time to clinical improvement, and hospital recovery score allowed the assessment of the effect of mPOCT on clinical outcomes in addition to changes in clinical management.

Our study has several limitations. Because the study took place only during winter months when influenza was circulating, the findings cannot be extrapolated to times outside of this period, when mPOCT for influenza is unlikely to have an effect. We made no attempt to mask clinical teams or participants to the allocated groups. Because the study required clinical teams to be informed of the mPOCT results in real time, they could not be masked to which group a participant had been randomly assigned. In our trial, the mPOCT was done by research staff rather than clinicians, and so uncertainties remain about how testing should be best delivered in routine care. Various implementation models exist including physician-delivered or nurse-delivered testing and technician-delivered testing in a POCT hub, embedded in an acute admission area. These models should be studied in implementation trials alongside obtaining real-world data to confirm the clinical impact of mPOCTs. Another uncertainty regarding the implementation of mPOCTs is the choice between syndromic testing for a comprehensive panel of respiratory viruses or testing for influenza viruses alone. Our previous work suggests that the effect on antibiotic use and length of stay in hospital will be greatest when the syndromic approach is used, although this approach must be balanced against the current higher cost and longer turnaround times of most current systemic panels than tests for influenza alone.

In summary, a routine molecular point-of-care test-and-treat strategy for influenza in adults who have been admitted to hospital with an acute respiratory illness improved detection of influenza, appropriate use of influenza antivirals, and the rational use of isolation facilities, and was associated with improvements in clinical outcomes in patients infected with influenza. Routine mPOCT for influenza should become the standard of care in hospitals during the influenza season.

Contributors

TWC reviewed the medical literature, conceived of and designed the study, oversaw the conduct of the study, participated in the collection of data and interpretation of results, and drafted and wrote the manuscript. RRB reviewed the medical literature, participated in the trial design, recruited patients, generated and collected data, and assisted with drafting the manuscript. NJB, AKM, SM, CC, SP, EN, and LP screened and recruited patients and collected data. NC acted as principal investigator for the second trial site and oversaw the running of the study there. SE designed the statistical analysis plan and analysed the data. All authors reviewed and contributed to the manuscript during its development. TWC and SE verified the underlying data for this study.

Declaration of interests

TWC has received speaker fees, honoraria, travel reimbursement, and equipment and consumables free of charge for the purposes of research outside of this submitted study, from BioFire Diagnostics and bioMérieux; received consultancy fees from Synairgen Research, Randox Laboratories, and Cidara therapeutics; is a member of an advisory board for Roche and of two independent data monitoring committees for trials sponsored by Roche; and has acted as the UK chief investigator for an investigational medicinal product study sponsored by Janssen. SM has received speaker fees and travel reimbursement from bioMérieux. 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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