Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and *Streptococcus pneumoniae* infection on the management of acute admissions in the elderly and high-risk 18- to 64-year-olds

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Declared competing interests of authors: Karl G Nicholson has been an ad hoc consultant to GlaxoSmithKline and Novartis. He has received funding to speak at meetings organised by Novartis, Baxter, Berna Biotech, Esteves, and the European Scientific Working Group on Influenza, and H5 vaccines from Novartis to support an MRC-funded research project, and H1N1 vaccines from Baxter AG and GlaxoSmithKline to support an NIHR-funded research project. A colleague in Karl G Nicholson's Department has received research funding from Roche. Maria Zambon has been an investigator of clinical trials sponsored by Novartis, Baxter, Sanofi Pasteur and CSL Australia Ltd. Keith R Abrams has acted as a paid consultant to the health-care industry generally (for the provision of advice and short courses), but specifically has not advised any organisation as regards diagnostics. Tristan W Clark has been an investigator of clinical trials sponsored by Novartis and Roche.

Published May 2014
DOI: 10.3310/hta18360

Scientific summary

S. pneumoniae infection on the management of acute admissions

Health Technology Assessment 2014; Vol. 18: No. 36
DOI: 10.3310/hta18360

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

In 2007, for the first time, the population at state pension age exceeded the number of children. Despite increases to state pension age, the number of pensioners is projected to exceed the number of children of < 16 years by over 2 million in 2031. People aged > 60 years accounted for almost half of all the 16.8 million hospital admissions from 2009 to 2010. During 2009–10, infections of the respiratory tract accounted for about 1 in 20 of the 51.5 million bed-days. Preparation for this population growth and its effects is of paramount importance.

With increasing severity of acute respiratory infection (ARI) in older people, the number of hospitalisations for acute lower respiratory infections in England is about three times higher in those > 75 years than in younger people. The average length of stay for acute respiratory conditions increases progressively with age. The annual number of pneumonia and influenza deaths in England and Wales increases with increasing age. Strategies that prevent acute lower respiratory infections, ameliorate their severity, or shorten the average duration of stay will have the greatest benefit in the elderly.

In this study, we evaluate rapid diagnostic technologies for three target pathogens: influenza, respiratory syncytial virus (RSV) and *Streptococcus pneumoniae*. Collectively, they are responsible for considerable morbidity and mortality in the elderly. A number of diagnostic tests are available for these pathogens but they have drawbacks.

The overall aim of our study was to improve the detection, treatment and control of these respiratory infections in at-risk people in the hospital setting, using new diagnostics tests to see if they improved patient care and cut duration of hospital stay. The tests chosen were two promising point-of-care tests (POCTs) for influenza A and B, and *S. pneumoniae*, and polymerase chain reaction (PCR) tests for influenza A and B and RSV A and B. The study involved an evaluation of diagnostic accuracy of immunoassays for the detection of influenza nucleoproteins, and the C polysaccharide cell wall antigen common to all *S. pneumoniae* strains, as well as PCR tests and conventional diagnostic tests in adult at-risk patients who were hospitalised over a three-winter period with acute cardiopulmonary illness. We evaluated the clinical effectiveness of three investigation strategies to reduce antibiotic prescribing and improve clinical outcomes. We carried out a systematic review and meta-analysis of POCTs for influenza, evaluated the ease and speed of use of the different tests, evaluated the cost-effectiveness of the three diagnostic strategies and, finally, considered the implications of our research for further research.

Objectives

1. To determine whether randomisation of patients to one of two study groups – (1) POCTs for influenza and pneumococcal antigens and (2) laboratory-based PCRs for influenza and RSV – has any impact on prescribing outcomes, clinical outcomes, quality of life (QoL) or use of single-room accommodation in comparison with (3) traditional culture methods.
2. To compare the diagnostic accuracy of PCR for influenza and RSV, and POCTs for influenza, and *S. pneumoniae* with the diagnostic accuracy of traditional culture methods.
3. To conduct a systematic review to (1) determine the diagnostic accuracy of POCTs for influenza; (2) estimate the heterogeneity of published studies; and (3) conduct subgroup-specific estimates using study-level covariates.

4. To evaluate the ease and speed of use of the three diagnostic strategies used in the study: (1) POCTs for influenza and pneumococcal antigens; (2) laboratory-based PCRs for influenza and RSV; and (3) traditional culture methods.
5. To conduct a trial-based cost-effectiveness analysis.

Methods

We conducted the clinical trial in the acute medical admissions units and medical wards of two teaching hospitals (Glenfield Hospital and Leicester Royal Infirmary) in the University Hospitals of Leicester NHS Trust. We recruited people with an acute exacerbation of chronic cardiopulmonary illness of ≤ 168 hours' (7 days') duration *or* an acute cardiopulmonary illness of ≤ 7 days' duration [including pneumonia, 'influenza'/influenza-like illness, exacerbations of chronic obstructive pulmonary disease (COPD), bronchitis, asthma, congestive heart failure or cardiac arrhythmia], who satisfied the study inclusion and exclusion criteria, and could be recruited to the study within a 16-hour period of initial assessment by the patient's medical team. Participants were then randomly allocated to one of three diagnostic study groups: (1) near-patient tests for pneumococcal infection and influenza; (2) rapid molecular tests for influenza and RSV; or (3) conventional laboratory diagnostic tests. Identical diagnostic samples were taken from each person but were processed differently depending on the randomisation. We assessed QoL using the EuroQoL European Quality of Life-5 Dimensions (EQ-5D) tool. We captured basic demographic data information on prescribed medication, oxygen and intravenous fluids, investigations, isolation status, complications, transfer to the intensive care unit, duration of stay, deaths, QoL, and the timing of specimen collection and test results. Eventually, all tests were undertaken on all specimens.

The diagnostic accuracy study used the diagnostic results obtained in the above randomised controlled trial (RCT). Data on diagnostic performance of the various tests [viral culture, sputum culture, PCR, Quidel POCT for influenza A and B (Quidel® QuickVue Influenza A + B: Quidel, San Diego, CA, USA) and BinaxNOW® (Portland, ME, USA) POCT for pneumococcal antigen] were summarised as (1) percentage diagnostic agreement; (2) sensitivity (percentage of true positives correctly identified); (3) specificity (percentage of true-negatives correctly identified); (4) positive and negative predictive values; or (5) area under receiver operating characteristic (ROC) curve (the probability that two patients, one diseased and one not diseased, would be both correctly classified by the test). We undertook analyses using different reference standards to enable comparison between the results from our study and those found in the literature.

We conducted a systematic review to determine the sensitivity and specificity of POCTs for influenza. Pooled sensitivities and specificities were estimated using a bivariate mixed-effects meta-analysis model. Heterogeneity was assessed using the I^2 measure and explored using subgroup analyses using study-level covariates.

We examined the speed of use of the tests used in this study from data collected in the RCT. The time of specimen collection was recorded in the case report forms by the study nurses, as was the time that the test result was entered into the continuation sheets in the patients' case-notes. All other times were derived from the intranet record of test results, and times when details of positive blood culture and virus culture results were communicated to clinicians. We assessed the ease of use (EoU) of the tests using a modification of the US Clinical Laboratory Improvement Amendments (CLIA) Categorization Criteria, which grade specific laboratory test systems, assays and examinations for level of complexity by assigning scores of 1, 2 or 3 for each of seven criteria: (1) knowledge; (2) training and experience; (3) reagents and materials preparation; (4) characteristics of operational steps; (5) calibration, quality control and proficiency of testing materials; (6) test system troubleshooting and equipment maintenance; and (7) interpretation and judgement. We combined (1) and (2) above, and included five additional criteria: (1) test site requirements; (2) equipment; (3) storage and disposal of waste test materials and reagents; (4) health and safety implications; and (5) time to reporting of results. As in the CLIA system, a score of 1 indicates the

lowest level of complexity, and a score of 3 indicates the highest level. Sensitivity analysis was also undertaken.

We analysed resource-use data collected prospectively during the RCT while the patient was in hospital and retrospectively from a 28-day follow-up. An incremental cost-effectiveness analysis was undertaken, with cost per quality-adjusted life-year (QALY) using the EQ-5D data recorded during the RCT. Markov chain Monte Carlo methods were used to estimate the uncertainty surrounding outcome measures, and calculate the probability of strategies being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY, together with the probability of error for any strategy adopted.

Results

The main results reported are based on the first admission for 1172 patients. The RCT found no difference in prescribing outcomes between diagnostic groups for time from admission to first narrow-spectrum antibiotic, time from admission to first oral antibiotic, or time from admission to cessation of antibiotics. Similarly, there was no difference in clinical outcome between groups for length of hospital stay among survivors, fever duration, supplemental oxygen dependence, continuous positive airway pressure dependence or deaths. The number of patients requiring intensive treatment unit and ventilator support was too small for statistical analysis. Use of isolation facilities did not differ between groups, nor was there a significant difference in EQ-5D scores.

The accuracy study found that the Quidel Influenza A + B POCT detected 24.4% of influenza infections compared with PCR but the specificity was almost 98%. The BinaxNOW pneumococcal POCT detected 57% of pneumococcal infections compared with blood culture, and its specificity was 92.5%. Sputum culture detected 100% of pneumococcal infections compared with blood culture, and its specificity was 97%.

In the systematic review and meta-analysis study, we found that the headline sensitivity for influenza POCTs was 74% [95% confidence interval (CI) 67% to 80%] and specificity was high [99% (95% CI 98% to 99%)]. There was a high level of heterogeneity between studies for both outcomes, and further analyses showed that the pooled estimate of sensitivity was considerably lower for some subgroup combinations than others. We found that the sensitivity was 86% in children and adolescents but 67% in populations of mixed age. We found evidence of reduced sensitivity for infection caused by the 2009 H1N1 virus. Finally, analysis of five studies that included both adults and children and compared the Quidel POCT with PCR revealed a sensitivity of 34% (95% CI 14% to 62%), which was similar to the result found in our study [24.4% (95% CI 16% to 31.6%)].

In the ease and speed of use study, we found that both POCTs gave results quickly and were rated as straightforward and undemanding to use. The median time to reporting the real-time PCR for influenza A and B was approximately 29 hours. EoU analysis showed that PCR is complex and demanding in requirements. Viral culture was extremely slow with a median turnaround time exceeding 3 weeks; it was also rated as complex. The median times for reporting growth of *S. pneumoniae* in blood and sputum culture were similar at 84 hours and 71 hours, respectively. Blood culture was rated as moderately complex; sputum culture was rated as complex.

There were no statistically significant differences in the distributions of total costs, or QALYs associated with each of the three diagnostic groups. Formal incremental analysis shows that traditional laboratory culture testing is dominated; PCR has lower average total cost but also lower QALY gain than POCT. The associated incremental cost-effectiveness ratio of POCT compared with PCR is £734,717, and the probability of POCT being a cost-effective strategy at a willingness-to-pay threshold of £20,000 per QALY is only 18.3%. Conversely, the probability of adopting a PCR-based diagnostic strategy as the most cost-effective strategy when, in fact, either POCT or traditional laboratory culture should be adopted at a willingness-to-pay

threshold of £20,000 per QALY is only 21.7%. Very few patients were admitted within a period that would permit treatment with a neuraminidase inhibitor (NI) according to National Institute for Health and Care Excellence guidance.

Conclusions

Although the study was powered to enable *both* clinical effectiveness (in terms of length of stay) and diagnostic performance to be evaluated with sufficient power/precision, we found no evidence that POCTs for influenza or *S. pneumoniae* infection, or PCR for influenza A and B and RSV A and B, influenced either the prescribing of antibiotics by clinicians providing care or clinical outcome. All tests had limitations – poor sensitivity, complexity, demands, test turnaround times or a combination of these. The total costs and QALYs of each diagnostic strategy were similar, though incrementally PCR was the most cost-effective strategy with a probability of being so of 78.3% at a willingness-to-pay threshold of £20,000 per QALY. Results of sensitivity analyses indicated that this conclusion appeared to be warranted. The analysis does not support routine testing with POCTs for either influenza or pneumococcal antigen for adults presenting with acute cardiopulmonary conditions. Our findings suggest that conventional viral culture for clinical diagnosis should be replaced by PCR.

Recommendations for research

1. We recommend a systematic review and meta-analysis of published data relating to the treatment of patients hospitalised with influenza with NIs to assess the evidence in support of treatment of patients hospitalised with influenza complications at > 48 hours after symptom onset.
2. Most patients with influenza complications in this study were unable to receive antiviral therapy because of delayed presentation. Patients risk serious outcomes from acute respiratory illness unless they are seen sooner. Research is needed to determine how widespread delayed presentation is, why it occurs, and whether it can be reduced.
3. Because of the high specificity of POCTs for influenza, research is needed to determine their effectiveness in general practice surgeries (or a commercial pharmacy setting) for people at risk of serious complications owing to age and chronic ill heath during declared outbreaks.
4. There is good evidence that influenza virus exacerbates asthma, COPD, cystic fibrosis, and is causally associated with community-acquired pneumonia and acute bronchitis. Uncertainty about the role of NI treatment of patients presenting with these complaints during influenza outbreaks will remain until trials have shown clear benefits.
5. Controversy about the benefits of treatment with neuraminidase of patients presenting to hospital at > 48 hours (up to 6 days) after onset of symptoms will remain until clinical trials have established clear benefits. We recommend that this research includes assessments of quantitative viral shedding and biomarkers to evaluate their role in guiding patient management.

Trial registration

This trial is registered as ISRCTN21521552.

Funding

Funding for this project was provided by the NIHR Health Technology Assessment programme for the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.804

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 03/39/18. The contractual start date was in November 2005. The draft report began editorial review in January 2012 and was accepted for publication in April 2013. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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